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ORIGINAL ARTICLE

Association between Hb A_{1c} and Severity of COVID-19 Patients

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ABSTRACT

This study aimed to examine the relationship between Hb A_{1c} levels and the clinical course of coronavirus-19 (COVID-19) patients. Sixty-six COVID-19(+) patients with high Hb A_{1c} and 46 with average Hb A_{1c} and 30 COVID-19(–) patients with average Hb A_{1c} were included. Hb A_{1c} levels and parameters examined in COVID-19(+) patients were compared between groups, and correlation analysis was performed between these parameters and Hb A_{1c} levels. The effect of Hb A_{1c} levels on intensive care unit (ICU) admission and mortality rate in COVID-19 patients was analyzed with the χ^2 test. It was observed that hemoglobin (Hb) and arterial oxygen saturation (SaO_2) levels of the COVID-19 (+) groups was lower than the COVID-19 (–) group, while ferritin, D-dimer, procalcitonin (PCT), and C-reactive protein (CRP) levels were higher. The COVID-19 (+) group with high Hb A_{1c} had higher lactate dehydrogenase (LDH), PCT and D-dimer levels than the other two groups, while Hb, partial arterial oxygen pressure (PaO_2) levels were lower. The Hb A_{1c} levels of the COVID-19 (+) groups were positively correlated with absolute neutrophil count (ANC), LDH, PCT and (K^+) levels, while negatively correlated with Hb and PaO_2 levels. Hb A_{1c} was found to be associated with the inflammation process, coagulation disorders and low PaO_2 in COVID-19 patients. The COVID-19 patients with high Hb A_{1c} levels had a higher mortality rate than other COVID-19 patients. Using Hb A_{1c} measurements with other prognostic markers would contribute to the patient's risk of death assessment.

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Introduction

The coronavirus-19 (COVID-19) pandemic, which was caused by acute respiratory syndrome coronavirus-2, designated SARS-CoV-2, from the coronavirus family, is a highly contagious disease that first appeared in the People's Republic of China (PRC) at the end of 2019. The COVID-19 affected almost all countries within weeks. As a result, it was declared to be a pandemic by the World Health Organization [1].

Diabetes mellitus (DM), another global epidemic, is a chronic inflammatory disease characterized by metabolic and cardiovascular complications affecting approximately 9.3% of the world population (463 million) in the 20-79 age group, according to 2019 data [2]. While pathophysiological changes in diabetic patients predisposed to infectious diseases, any infection in diabetic patients also causes hyperglycemia. Diabetes mellitus itself also causes a pro-inflammatory state. Bacterial and viral respiratory tract infections are quite common in diabetic patients due to neutrophil dysfunction, decreased T cell response and irregular humoral immunity [3].

Interferon response is critical in the fight against viruses. In COVID-19 infections, early interferon responses are suppressed, then secondary maladaptive, delayed and exaggerated interferon responses lead to cytokine storm, resulting in organ damage. Impaired endothelial-epithelial barrier functions and hypercoagulability in the microvascular bed, triggered by the cytokine storm, are responsible for the disease's poor prognosis [3]. When COVID-19 and diabetes coexist, the possibility of a cytokine storm resulting in organ damage increases exponentially in diabetic patients. Interleukin-6 (IL-6), fibrinogen, ferritin, D-dimer and C-reactive protein (CRP) levels were found to be significantly higher in diabetic patients with COVID-19 infection than non diabetic subjects [2]. Exaggerated increase in lactate dehydrogenase (LDH), CRP, ferritin, D-dimer levels, low lymphocyte counts and more common computer tomography (CT) findings, are indicators of poor prognosis of the disease, especially in diabetic patients [4].

Hb A_{1c} [glycated hemoglobin (Hb)] is a marker used in routine patient follow-up, showing an average of 2-3 months glycemic level and predicting diabetic complications development risk. Most studies examining the relationship between blood glucose control, Hb A_{1c} levels (a determinant of this control), and the disease severity and mortality in diabetic individuals with COVID-19, demonstrated that good blood glucose control and at or near-target (Hb A_{1c}) levels were associated with favorable prognosis, shorter hospitalization, and again, lower mortality rates [5,6].

In our study, Hb A_{1c} values of COVID-19 (+) diabetic (with high Hb A_{1c} level), non diabetic (normal Hb A_{1c} level)

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Table 1. Laboratory findings in the three groups of COVID-19 patients.

Parameters	nonDM/COVID19(+) ($n=66$)	DM/COVID19(+) ($n=46$)	DM/COVID19(−) ($n=30$)
Hb A_{1c} (%)	5.58 ± 0.43	11.68 ± 2.91	9.50 ± 2.64
SaO_2 (%)	67.84 ± 16.03	63.80 ± 16.27	76.64 ± 11.13
PaO_2 (mmHg)	47.52 ± 15.09	39.63 ± 15.26	57.53 ± 9.63
Hb (g/dL)	11.89 ± 1.32	11.16 ± 1.40	12.72 ± 0.90
K^+ (mmol/L)	4.09 ± 0.44	4.44 ± 0.64	4.35 ± 0.50
Inflammatory Biomarkers			
ESR (mm/hr)	39.59 ± 23.81	46.07 ± 23.52	30.50 ± 18.42
PCT (mg/L)	0.34 ± 0.82	0.66 ± 0.88	0.30 ± 0.01
Ferritin (ng/mL)	464.12 ± 254.20	578.23 ± 539.18	282.07 ± 237.61
CRP (mg/L)	92.87 ± 78.28	111.73 ± 101.52	53.54 ± 60.77
LDH (U/L)	277.89 ± 105.12	381.50 ± 235.88	272.80 ± 105.37
Lymphocyte (10^9/L)	1.25 ± 0.73	1.11 ± 0.88	1.36 ± 0.67
Neutrophil (10^9/L)	6.85 ± 4.92	9.29 ± 5.72	7.47 ± 3.51
Coagulopathy Biomarker			
D-dimer (μg/mL)	0.97 ± 0.80	1.88 ± 2.92	0.49 ± 0.26

COVID-19: coronavirus-19; DM: diabetes mellitus; SaO_2: arterial oxygen saturation; PaO_2: partial arterial oxygen pressure; Hb: hemoglobin; K^+: potassium; ESR: erythrocyte sedimentation rate; PCT: procalcitonin; CRP: C-reactive protein; LDH: lactate dehydrogenase.

and COVID-19 (−) diabetic patients who were followed in our hospital ward and intensive care unit (ICU), together with Hb, ferritin, LDH, CRP, procalcitonin (PCT), erythrocyte sedimentation rate (ESR), D-dimer, potassium (K^+), arterial oxygen saturation (SaO_2), partial arterial oxygen pressure (PaO_2) and lymphocyte, absolute neutrophil count (ANC), levels and mortality rates were compared. Correlation analysis was performed to see the relationship between the Hb A_{1c} level of COVID-19 (+) patients and other parameters analyzed. Moreover, the Hb A_{1c} levels affect on the need of ICU admissions and mortality rate in COVID-19 (+) patients was examined. This study aimed to examine the relationship between Hb A_{1c} levels and the clinical course and outcome of COVID-19 patients.

Materials and methods

One hundred twelve patients who were followed at the Health Sciences University Samsun Training and Research Hospital, Samsun, Turkey COVID-19 service or ICU, between June and September 2020, were included. These 112 patients were divided into two groups according to their Hb A_{1c} levels: group 1 [nonDM/COVID19(+)] patients with normal Hb A_{1c} levels (4.0-6.0%) ($n=66$), group 2 [DM/COVID19(+)] patients with high Hb A_{1c} levels (>6.0%) ($n=46$). In addition, as a third group [DM/COVID19(−)] patients with high Hb A_{1c} levels (>6.0%) ($n=30$), were included in the study. Because this is a retrospective study, patient characteristics, medical history, signs and symptoms, laboratory examination results, at admission, and final clinical outcomes, were collected from the hospital information management system for analysis. Hb A_{1c}, SaO_2, PaO_2, Hb, K^+ levels and inflammatory process biomarkers ESR, PCT, ferritin, CRP, LDH levels, neutrophil and lymphocyte counts, and as a coagulopathy biomarker D-dimer values were taken into account in this study.

All laboratory parameters were studied following the manufacturer's recommendations using appropriate materials and methods: Hb A_{1c} by high performance liquid chromatography method on a PREMIER 9120 device (Trinity Biotech USA Inc., Kansas City, MO, USA); neutrophil and lymphocyte counts using an DXH800 (Beckman Coulter Inc., Miami, FL, USA) device; ferritin by electrochemiluminescence method on a Cobas E411 (Roche Diagnostics GmbH, Mannheim, Germany) device; D-Dimer by particle enhanced immunoturbidometric assay using a Ca-7000 (Sysmex Corp., Kobe, Japan) device; LDH by spectrophotometric, CRP by turbidimetric and K^+ by ion-selective electrode (ISE) methods using a AU5800 (Beckman Coulter Inc., Brea, CA, USA) device; ESR using the Westergren method in a VACUPLUS ESR-110 (Sistat, Ankara, Turkey; https://sistat.com.tr/) device; SaO_2 and PaO_2 as blood gas parameters in an ABL90 FLEX (Radiometer, Brønshøj, Denmark) device. This study was approved by the Health Sciences University Samsun Training and Research Hospital Ethics Committee [2020–05-05T14_19_43; decision no: KAEK2020/4/4].

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22 (hpps://ibm.com/spss/statistics). A p values of <0.05 was considered to be statistically significant. Categorical variables were expressed as frequency and percentage and compared using the χ^2 test. Continuous variables were expressed as mean ± SD and compared in pairs with the Mann-Whitney U test. Spearman correlation was performed to see the relationship between the Hb A_{1c} level of COVID-19 (+) patients and other parameters analyzed.

Results

The study groups were assigned as follows: the nonDM/COVID19(+) group included non DM COVID-19 (+) patients with normal Hb A_{1c} levels, and the DM/COVID19(+) group included DM COVID-19 (+) patients with high Hb A_{1c} levels. The third group, DM/COVID19(−), included DM COVID-19 (−) patients with high Hb A_{1c} levels.

In our study, the mean age and gender distribution of the three groups were as follows: the nonDM/COVID19(+) group ($n=66$; 28 females; 38 males), mean age 55.59 ± 14.36; DM/COVID19(+) group ($n=46$; 25 females; 21 males), mean age 65.02 ± 11.61; DM/COVID19 (−) group ($n=30$; 17 females; 13 males), mean age 57.76 ± 15.92. The laboratory findings of the groups (as mean ± SD) are shown in Table 1.

The mean corpuscular volume (MCV) values of the patients included in the study were 83.44 ± 8.04 and the red cell distribution width (RDW) values were 14.41 ± 1.87 [from the complete blood count (CBC), along with neutrophil and lymphocyte counts]. Average MCV and RDW values obtained were within the reference ranges. Therefore, as no hemoglobinopathy was suspected in the patients, additional evaluations were not required.

Table 2. Comparison of intensive care and mortality rates of two groups of COVID-19 (+) patients.

	Total ($n = 112$)	nonDM/COVID19(+) ($n = 66$)	DM/COVID19 (+) ($n = 46$)	Results of χ^2 Test
Service (*n*)	78	47	31	
ICU (*n*)	34	19	15	0.187
ICU rate (%)	30.36	28.79	32.61	
Alive (*n*)	90	61	29	
Deceased (*n*)	22	5	17	14.825
Mortality rate (%)	19.64	7.58	39.96	

COVID-19: coronavirus-19; DM: diabetes mellitus; ICU: intensive care unit.

Group parameters were compared in paired groups using the Mann-Whitney U test. Hb A_{1c} levels were higher in the DM/COVID19(+) group than the other two groups ($p < 0.01$) and were higher in the DM/COVID19(–) group than in the nonDM/COVID19(+) group ($p < 0.001$). The SaO_2 levels were higher in the DM/COVID19(–), group than the other two groups ($p < 0.01$). The PaO_2 levels were lower in the DM/COVID19(+) group than the other two groups ($p < 0.01$). Hemoglobin levels were lower in the DM/COVID19(+) group than the other two groups ($p < 0.01$) and lower in the nonDM/COVID19(+) group than the DM/COVID19(–) group ($p < 0.001$). The K^+ levels were lower in the nonDM/COVID19(+) group than the other two groups ($p < 0.01$).

Comparisons of inflammatory process biomarkers were as follows: ESR levels were higher in the DM/COVID19(+) group than the DM/COVID19(–) group ($p = 0.003$). The PCT levels were higher in the DM/COVID19(+) group than the other two groups ($p < 0.001$) and higher in the nonDM/COVID19(+) group than the DM/COVID19(–) group ($p = 0.003$). Ferritin levels were lower in the DM/COVID19(–) group than the other two groups ($p < 0.01$). The CRP levels were lower in the DM/COVID19(–) group than the other two groups ($p < 0.01$). The LDH levels were higher in the DM/COVID19(+) group than the other two groups ($p < 0.05$). Lymphocyte count was lower in the DM/COVID19(+) group than DM/COVID19(–) group ($p = 0.043$). Neutrophils count was higher in the DM/COVID19(+) than nonDM/COVID19(+) ($p = 0.001$).

As a coagulopathy process biomarker, D-Dimer levels were higher in the DM/COVID19(+) group than the other two groups ($p < 0.01$) and higher in the nonDM/COVID19(+) group than the DM/COVID19(–) group ($p = 0.004$). The nonDM/COVID19(+) and the DM/COVID19(+) groups had lower SaO_2 and Hb levels and higher ferritin, D-Dimer, PCT and CRP levels than the DM/COVID19(–) group. As expected, the two diabetic groups had higher Hb A_{1c} and K^+ levels than the nonDM group regardless of COVID-19 condition. The DM/COVID19(+) group had higher Hb A_{1c}, LDH, PCT and D-Dimer levels and had lower PaO_2 and Hb levels than the other two groups.

A total of 112 COVID-19 (+), 66 nonDM and 46 DM patients were hospitalized, and 78 of them were followed in service and 34 in the ICU. According to the χ^2 test results, there was no significant difference in the ICU hospitalization rate ($p > 0.05$) between the two groups, while there was a significant difference in the mortality rate ($p < 0.001$) (Table 2). The nonDM/COVID19(+) and DM/COVID19(+) groups were divided into subgroups according to death status, and χ^2 analysis was performed within the group. Hb A_{1c} levels in the nonDM/COVID19(+) group were insignificant ($p > 0.05$), while the Hb A_{1c} levels in the DM/COVID19(+) group were evaluated as significant ($p = 0.005$).

Spearman correlation was performed to see the relationship between the Hb A_{1c} level of COVID-19 (+) patients and other parameters analyzed. According to the result of the Spearman correlation, Hb A_{1c} level was positively correlated with neutrophil count ($r = 0.280$, $p = 0.003$), LDH ($r = 0.242$, $p = 0.010$), PCT ($r = 0.229$, $p = 0.015$) and K^+ ($r = 0.222$, $p = 0.019$) levels, while negatively correlated with PaO_2 ($r = -0.266$, $p = 0.005$), and Hb ($r = -0.250$, $p = 0.008$) levels.

Spearman correlation was also performed for the relationship between Hb A1c levels and other parameters only in the DM/COVID19(+) group. According to the analysis result, Hb A_{1c} levels of this group showed positive correlation with lymphocyte count ($r = 0.323$, $p = 0.029$) and PCT ($r = 0.473$, $p = 0.001$), while negatively correlated with neutrophil count ($r = -0.400$, $p = 0.006$), D-dimer ($r = -0.316$, $p = 0.034$) and *Hb* ($r = -0.483$, $p = 0.001$) levels. Compared to the general correlation in the DM/COVID19(+) group, Hb A_{1c} was more highly correlated with PCT and Hb. In addition, lymphocyte and D-dimer values started to show correlation, and the correlation with neutrophil count turned negative from positive.

Discussion

While pathophysiological changes in diabetes patients predisposed to infectious diseases, any infection in these patients also causes hyperglycemia. Regardless of the type of diabetes, susceptibility to infections and related complications increases. Dysregulation of the innate immune response, endothelial dysfunction and impaired barrier structure based on chronic diabetes, causes pro-inflammatory hypercoagulability, susceptibility to infections and a more severe course of the disease [7]. Irrespective of the agent, pneumonia is associated with increased morbidity and mortality risk in diabetic patients [7]. In hyperglycemia, a diabetes indicator, adhesion molecules mediating tissue inflammation, glycation end products, pro-inflammatory cytokine synthesis and oxidative stress level are known to be increased. This inflammatory process is thought to be the underlying mechanism that diabetic patients are more prone to COVID-19 infection [8, 9]. C-reactive protein and ferritin levels, which were among the biomarkers associated with inflammation, were found to be significantly higher in DM/COVID19(+) patients than non diabetic subjects. This situation suggests that the inflammation process is more severe in diabetic patients [2,9]. In another study, it was stated that an exaggerated increase of LDH, CRP, ferritin, D-dimer, and low lymphocyte counts were indicators of poor prognosis in DM/COVID19(+) patients [4]. With diabetes triggering mechanisms that lead to cytokine storm, a worse

inflammatory effect would occur in diabetic patients in the presence of the COVID-19 infection.

Because the cytokine storm would increase insulin resistance, the glycemic state will worsen [10]. With the hyperglycemia predisposing to cytokine storm and the cytokine storm deepening hyperglycemia by increasing insulin resistance, patients enter a vicious circle, and their condition worsens.

Diabetes is also associated with increased coagulopathy and thrombosis. Similarly, the COVID-19 infection is linked to thrombotic mechanisms and coagulation disorders. Diabetic patients with COVID-19 have a higher D-dimer level than non diabetics. Therefore, diabetes is associated with a worse prognosis in SARS-CoV-2 infection [10,11].

In our study, SaO_2 levels were lower in the two groups with COVID-19 (+) than the COVID-19 (–) group, while ferritin, D-dimer and CRP levels were higher ($p < 0.01$). This situation suggested that the inflammatory process was severe in COVID-19 (+) cases, and the coagulation disorder was present. Moreover, in the comparison of the two COVID-19 (+) groups, the neutrophil and D-Dimer levels of the DM/COVID19(+) group were higher than the nonDM/COVID19(+) group ($p < 0.01$). The addition of diabetes comorbidity (high Hb A_{1c}) to COVID-19 triggered the inflammatory process to be more severe and the coagulation disorder to be more intense.

Insulin resistance is generally thought to worsen in association with hypokalemia in patients with COVID-19 with diabetes. It has been reported that hypokalemia may adversely affect glucose control and decreased regulation of pulmonary angiotensin-converting enzyme 2 (ACE-2) in diabetic patients, associated with the disruption of angiotensin II and increased aldosterone secretion [12]. In our study, it was observed that two DM groups had higher Hb A_{1c} and K^+ levels than the non DM group 1 ($p < 0.01$). Our findings contradicted previous studies of K^+ levels. In addition, in the comparison of two groups with high Hb A_{1c} levels, it was observed that the lymphocyte levels of the two COVID-19(+) groups were lower, and the ESR levels were higher than the COVID-19(–) group. This situation shows that when patients with high Hb A_{1c} levels got COVID-19 disease, the inflammatory process was more severe. Thus, it could be inferred that high Hb A_{1c} levels are one of the determinants in COVID-19 disease and poor prognosis.

In our study, it was observed that the Hb A_{1c}, LDH and D-Dimer levels of the DM/COVID19(+) group with high Hb A_{1c} levels were higher than the other two groups, while PaO_2 levels were lower than the other two groups. It suggested that in COVID-19 (+) cases, Hb A_{1c} elevation was one of the determinants in the more severe inflammatory process, more intense coagulation disorder and worse prognosis.

It was shown in meta-analysis studies that the mortality rate increased in diabetic COVID-19 patients [13]. The presence of diabetes has been associated with a poor prognosis in these patients. It was reported in records of a hospital in Wuhan, PRC that 15 (18.3%) of 82 patients who died due to COVID-19 were also diabetic [14]. When male patients, 73.0% of infected patients, were examined, it was observed that 32.0% had comorbid diseases, and diabetes accounted for 20.0% of these comorbidities [15]. The report published by the Chinese Center for Disease Control and Prevention, showed that mortality was approximately three-times higher in people with diabetes (7.3%) than those without diabetes (2.3%) in 72,314 COVID-19 cases [16].

Plasma glucose elevation alone is a risk factor for organ failure mortality and morbidity. The additional effect of COVID-19 further increases the risk for organ damage in diabetic people. It has been reported that the diabetes prevalence in COVID-19 patients was high, ranging from 7.4–20.0% in different regions of the PRC [4]. The diabetes prevalence in COVID-19 patients hospitalized in Italy was 8.9%, which was above the diabetes prevalence in the 55-75 age range (6.2%) in Italy [17]. In another study, it was reported that exaggerated inflammatory response was seen in diabetic COVID-19 patients with poor prognosis, and diabetes should be considered one of the most critical risk factors for death in severe COVID-19 patients [18]. In a meta-analysis of 33 studies, it was determined that the presence of comorbid diabetes in COVID-19 patients was associated with a doubly increased risk of mortality [5].

In our study, the inpatient's number in the ICU was 19 (28.79%) in the nonDM/COVID19(+) group, while it was 15 (32.61%) in the DM/COVID19(+) group. In the χ^2 test, no significant difference was found between the two groups in the number of inpatients in the ICU. In contrast, the number of patients who died was five (7.58%) in the nonDM/COVID19(+) group and 17 (39.96%) in the DM/COVID19(+) group. In the χ^2 test, there was a significant difference between the two groups in the number of patients who died. The nonDM/COVID19(+) and DM/COVID19(+) groups were divided into subgroups according to death status. Within subgroups (alive/deceased) χ^2 analysis revealed that the Hb A_{1c} levels in the nonDM/COVID19(+) group were insignificant, while they were significant in the DM/COVID19(+) group. In this study, while there was no difference in ICU hospitalization rates (disease severity-according to ICU acceptance criteria defined by the Ministry of Health in Turkey) between diabetic and non diabetic patients, there was a significant difference between high Hb A_{1c} level and mortality rates. Although it was found that diabetes did not significantly affect the disease severity in our study, it significantly increased the mortality rates. Therefore, in COVID-19 (+) patients with comorbid diabetes, we considered that measuring Hb A_{1c} during hospitalization would contribute to the patient's risk of death assessment. It constitutes a simple marker option that can be applied in any laboratory condition in predicting the probability of death, early detection and intervention of at-risk patients.

Our study tested the relationship between the Hb A_{1c} level of COVID-19 (+) patients and the other parameters analyzed with Spearman correlation. According to the Spearman correlation analysis, Hb A_{1c} level was positively correlated with neutrophil, LDH and K^+ levels, while negatively correlated with the PaO_2 level. Our study also

demonstrated the association between the Hb A_{1c} with inflammatory processes and PaO_2 used to assess the patient's oxygenation.

In conclusion, in our study, Hb A_{1c} was associated with the inflammation process, coagulation disorders and low PaO_2 in COVID-19 patients, and the mortality rate was higher in diabetic COVID-19 patients. We considered that simultaneous Hb A_{1c} measurements with other prognostic markers would contribute to the patient's risk of death assessment. We concluded that evaluating DM/COVID19(+) patients by Hb A_{1c} measurements and other prognostic markers could lead to early and advanced treatment options, thus decreasing the mortality rate of the diabetic patient group is achieved. With large-scale studies, the Hb A_{1c} cut-off value should be determined for mortality risk assessment to increase the clinical availability of Hb A_{1c}.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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