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Evaluation of the Effects of Being Over 65 Years of Age on Different Clinical Outcomes in Diabetic Patients with COVID-19

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Abstract

Objective: The Coronavirus disease-2019 (COVID-19) pandemic has affected the entire population, with the most damaging effects among the elderly. The elderly, especially those with diabetes, are at the highest risk for adverse outcomes. We aimed to evaluate the laboratory findings of diabetic patients with COVID-19 from different clinical courses, and to investigate whether being over or under 65 years of age has an effect on the clinical outcome.

Materials and Methods: The demographic data and biochemical results of the patients were examined and recorded. Clinical outcomes, namely hospital discharge, transfer to intensive care unit (ICU) and death, were recorded at the end of the study period. The patients were divided into two groups according to being over or under 65 years of age.

Results: Overall, 122 participants (47 females, 75 males; mean age: 57±13.5 years) were included in the analyses. Age and lactate dehydrogenase (LDH) values were significantly higher in the death group than in the discharged group ($p<0.05$). Ferritin, D-dimer and C-reactive protein (CRP) values of the death and ICU groups were statistically significantly higher than the discharge group ($p<0.05$). The hemoglobin a1c (Hba1c) values of the ICU group were found to be significantly higher than those of the discharged group ($p<0.05$). D-dimer and CRP values were significantly higher in diabetic patients aged >65 years ($p<0.05$). >65 age group, the CRP value of the death group was statistically significantly higher than the discharge group, while the Hba1c value of the ICU group was higher than those of the discharged group. The Spearman correlation analysis showed that there was a negative correlation between HbA1c and lymphocyte ($r=-0.23$, $p=0.030$), HbA1c and white blood cells ($r=-0.22$, $p=0.042$) in patients aged >65 years ($p<0.05$). Age, ferritin, D-dimer, CRP, LDH and Hba1c values of the death/ICU transfer group were significantly higher than the discharged group ($p<0.05$). According to the logistic regression analysis; age, D-dimer, CRP and Hba1c values were found as a statistically significant risk factors for death and transfer to the ICU.

Conclusion: Early intervention and treatment are vital, especially in the presence of elevated inflammatory parameters in uncontrolled diabetic patients aged >65 years with COVID-19 to prevent poor clinical outcomes.

Keywords: Diabetes, COVID-19, older adults

Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), defined as a new type of coronavirus, is a curse that causes coronavirus disease (COVID-19), which threatens human public health all over the world and has become a pandemic (1). Patients with COVID-19 have clinical manifestations ranging from mild upper respiratory tract infection symptoms to possibly fatal outcomes due to diffuse respiratory disorders and multi-organ complications (2). The complexity of COVID-19 results from the unpredictable clinical course of the disease, and therefore it is crucial to identify risk factors associated with poor clinical outcomes. Various studies have been carried out in order to predetermine vulnerable groups that may have a poor clinical course of COVID-19 and to reverse the process with early intervention (2). In the face of this pandemic that has taken hold of the world, the need to put an end to the vulnerability

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to the serious COVID-19 disease faced by elderly and chronically ill adults is essential since age has been shown to be a risk factor of poor outcomes of patients with COVID-19 (3). Elderly patients have relatively higher mortality and morbidity than younger patients infected with SARS-CoV-2 (4,5). This can be attributed to the physiological changes of aging; comorbidities such as cardiopulmonary disease, diabetes, neurodegenerative diseases, demantia: and associated polypharmacy are factors that contribute to negative health outcomes. Moreover, immune aging, characterized by reduced ability to mount an adequate immune response to infection and susceptibility to an inflammatory condition, also contributes to the advanced vulnerability of older adults (6,7).

Elderly patients with COVID-19 are very frail and have a high complication burden due to their variable comorbidities. One of the most serious comorbidities accompanying elderly patients is diabetes mellitus (DM) (8). Actually, DM is another pandemic characterized by chronic hyperglycemia, multiple organ dysfunctions, and systemic complications involving the cardiovascular, nervous and renal systems. Inflammation and endothelial dysfunction are the main pathophysiological disorders in the development of DM and associated cardiovascular complications (9). The fact that SARS-CoV-2 causes inflammatory cascades, cytokine storms and coagulation cascade activation through pathogenetic mechanisms after entering the human body, and the aggressive inflammatory responses in SARS-CoV-2 infection cause damage to the airways (10), results in poor clinical outcomes in diabetic patients with COVID-19 (11,12). Both COVID-19 itself and the treatment modalities given impair glucose regulation and complicate glycemic control (13,14). It is known that DM increases the severity and mortality of COVID-19, especially in patients with uncontrolled hyperglycemia (15). In addition, mortality in diabetic patients with COVID-19 is 3 times higher than that in patients without diabetes (16).

Identifying cases that may lead to potentially serious complications and death with rapid progression of the disease is critical for prompt initiation of treatment in high-risk elderly patients. Therefore, in this study, we aimed to investigate whether being over or under the age of 65 has an effect on clinical outcome in COVID-19 patients with DM.

Materials and Methods

Study population and design

This study was carried out by retrospectively scanning the data of 122 patients with DM, who were followed up due to the SARS-CoV-2 infection in the Internal Medicine Clinic of İstanbul Aydın University Hospital between 1.11.2020 and 1.11.2021. The demographic data and biochemical results of the patients were examined and recorded. Clinical outcomes, namely hospital discharge, transfer to intensive care and death, were recorded until the end of the study period. SARS-CoV-2 infection was confirmed by real-time reverse transcription polymerase chain reaction analysis of nasal and pharyngeal swab samples at admission. The patients were divided into two groups according to being over or under 65 years of age.

Patients with a history of acute and/or chronic inflammatory, autoimmune or infectious disease, hematological disease, malignancy, renal and hepatic injury, documented cardiovascular disease, and a history of major surgery or trauma were not included in the study.

In order to prevent the effect of antiviral treatment on laboratory results, laboratory results at the time of first admission before the start of treatment were evaluated. Laboratory blood tests including complete blood count, glucose, hemoglobin a1c (Hba1c), total cholesterol (TC), triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), aspartat aminotransferase, alanine aminotransferase, ferritin, D-dimer, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels were evaluated. The time elapsed since the first diagnosis of diabetes was recorded as diabetes age (years).

Statistics

The data were collected by the relevant researchers through clinical studies, transferred to the Microsoft Excel program, organized, cleaned and made suitable for analysis. Data analyzes were tested using the IBM SPSS Statistics 26.0 (Statistical Package for Social Science) package programs. Descriptive statistics were expressed as numbers and percentages for categorical variables, mean, standard deviation, minimum and maximum values for numerical variables. In the normality test applied to the variables in age groups, while age, Hb, Hct, TC, LDL-C, and glucose were normally distributed in the <65 age group ($p>0.05$), in the >65 age group, age, Hb, Hct, monocytes, CRP, ESR, TC, LDL-C, HDL-C and Hba1c were normally distributed ($p>0.05$). It was determined that other variables were not normally distributed in both age groups ($p<0.05$). According to these results, parametric tests were used in the analysis of normally distributed variables, and non-parametric tests were used in the analysis of non-normally distributed variables. T-test, Mann-Whitney U test, ANOVA, Kruskal-Wallis, Tukey post-hoc, Dunn-Benforonni post-hoc and Spearman correlation test was used in the analysis. Multivariable logistic regression modeling was used to explore independent risk factors for death and transfer to the ICU. We performed a receiver operating characteristic (ROC) curve analysis to evaluate accuracy of risk factors. The area under the curve (AUC) was then estimated with a 95% confidence interval (CI) p-value of <0.05 was considered statistically significant.

Results

Overall, 122 participants (47 females, 75 males; mean age: 57±13.5 years) were included in the analyses. 27% (n=33) of patients included in the analyzes were over 65 years of age, while 73% (n=89) of the patients were under 65 years old. Of the patients included in the study, 4.1% (n=5) were dead and 7.4% (n=9) were admitted to the intensive care unit (ICU), while 88.5% (n=108) were discharged. The mean age of patients who died was 71.4±11.5. The mean age of diabetes was 6 years. Of the patients under 65 years of age, 2 (2.2%) died, 5 (5.6%) were transferred to the ICU, and 82 (92.1%) were discharged. As for patients over 65 years of age, 3 (9.1%) died, 4 (12.1%) were transferred to the ICU and 26 (78.8%) were discharged.

Demographics and laboratory findings of diabetic patients with COVID-19 in terms of clinical outcomes were shown in Table 1. There was a significant difference in terms of age, ferritin, and D-dimer, CRP, LDH and Hba1c between the groups who were discharged, admitted to the ICU, and died (p<0.05). Age and LDH values were significantly higher in the death group than in the discharged group (p<0.05). Ferritin, D-dimer and CRP values of the death and ICU groups were statistically significantly higher than the discharge group (p=0.002, p=0.000, p=0.000, respectively). The Hba1c values of the ICU group were found to be significantly higher when compared to the Hba1c values of the discharged group (p=0.009).

Table 2 demonstrates the demographic and laboratory findings of diabetic patients with COVID-19 according to being under or over the age of 65. There was a significant difference between these age groups in D-dimer, CRP and onset of diabetes years variables (p<0.05). D-dimer, CRP values, and onset of diabetes years were significantly higher in the group over 65 years of age (p=0.008, p=0.008 p<0.001, respectively).

Diabetic patients under 65 years of age with COVID-19 were examined according to their clinical outcome. As shown in Table 3, statistically significant differences were found in lymphocyte, ferritin, D-dimer, CRP, ESR, LDH and Hba1c variables between clinical groups ≤65 years of age. Ferritin, ESR and CRP values of the death group were significantly higher than the discharge group, while the lymphocyte value was lower (p<0.05). D-dimer and LDH values of the death and ICU groups were significantly higher than those of the discharged group (p<0.05). The Hba1c and CRP values of the ICU group were statistically significantly higher than the discharged group (p<0.05). As shown in Table 4, for the >65 age group, the CRP value of the death group

Table 1. Demographics and laboratory findings of diabetic patients with COVID-19 in terms of discharge, intensive care unit and death

Laboratory results, mean ± SD	All patients (n=122)	Discharge (n=108)	Intensive care unit (n=9)	Death (n=5)	p
Age (years)	56.95±13.56	55.79±13.04	62.89±15.81	71.4±11.5	0.015
Hemoglobin, g/dL	13.32±1.75	13.28±1.72	13.68±2.21	13.38±1.76	0.810
Hemotocrit %	39.88±4.97	39.74±4.78	41.4±7.12	40.2±5.47	0.626
WBC, 10^3/µL	7.69±3.7	7.56±3.68	7.09±2.22	11.6±4.55	0.133
Neutrophil, 10^3/µL	6.44±7.1	6.33±7.43	5.43±2.19	10.56±4.03	0.065
Lymphocyte, 10^3/µL	2.63±4.41	2.75±4.57	1.17±0.41	2.73±4.92	0.145
PLT, 10^3/µL	232.75±81.02	230.02±76.83	210.44±59.89	331.8±141.17	0.124
Monocyte, 10^3/µL	0.44±0.24	0.45±0.24	0.45±0.19	0.25±0.15	0.081
AST, IU/L	35.73±26.11	36.42±27.29	30.11±14.87	31±12.08	0.986
ALT, IU/L	42.43±32.76	43.55±34.27	35.22±16.24	31.4±14.99	0.907
Ferritin, ng/mL	489.92±569.21	425.74±528.41	744.33±596.14	1418.21±535.92	**0.002**
D-dimer, mg/L	902.62±1594.26	632.9±895.18	2745.78±3421.54	3411.02±3816.1	**<0.001**
CRP, mg/L	57.33±61.42	48.22±55.69	113.38±36.25	153.3±87.74	**<0.001**
ESR, mm/h	30.6±21.35	29.25±20.34	35.78±23.71	50.4±31.67	0.196
LDH, U/L	274.37±119.87	260.89±109.63	337.67±124.95	451.6±169.45	**0.004**
Glucose, mg/dL	160.89±61.27	156.73±54.81	210.11±95.65	162±94.88	0.164
HbA1c, %	7.98±1.69	7.81±1.56	9.89±2.15	8.14±1.75	**0.009**
TC, mg/dL	163.23±40.55	165.06±41.56	143.78±22.87	158.6±38.94	0.310
LDL-C, mg/dL	99.74±31.52	100.75±31.81	89.82±25.59	95.9±37.37	0.588
TG, mg/dL	149.91±104.23	154.05±108.56	105.56±36.54	140.4±75.63	0.348
HDL-C, mg/dL	37.38±11.85	37.9±12.01	30.26±6.51	39.04±13.57	0.160

COVID-19: Coronavirus disease-2019, SD: Standard deviation, WBC: White blood cell, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, HbA1c: Hemoglobin A1c, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, significant p-values are bolded. P<0.05 was considered statistically significant. Data are presented as mean ± standard deviation

Table 2. Demographics and laboratory findings of diabetic patients with COVID-19 by age groups

Laboratory results, (mean ± SD)	All patients (n=122)	≤65 years (n=89)	>65 years (n=33)	p
Sex Male (%) Female (%)	 75 (61.5%) 47 (38.5%)	 56 (62.9%) 33 (37.1%)	 19 (57.6%) 14 (42.4%)	 0.087
Hemoglobin g/dL	13.32±1.75	13.48±1.62	12.87±2.01	0.087
Hemotocrit %	39.88±4.97	40.34±4.44	38.64±6.09	0.094
WBC, 10^3/µL	7.69±3.7	7.69±3.78	7.68±3.52	0.809
Neutrophil, 10^3/µL	6.44±7.1	6.61±8.07	5.98±3.38	0.547
Lymphocyte, 10^3/µL	2.63±4.41	2.71±4.68	2.43±3.64	0.568
PLT, 10^3/µL	232.75±81.02	228.18±74.35	245.06±97	0.682
Monocyte, 10^3/µL	0.44±0.24	0.45±0.24	0.42±0.22	0.665
AST, IU/L	35.73±26.11	34.29±24.99	39.61±28.97	0.234
ALT, IU/L	42.43±32.76	45.06±34.84	35.36±25.51	0.184
Ferritin, ng/mL	489.92±569.21	463.64±564.64	560.79±584.19	0.146
D-dimer, mg/L	902.62±1594.26	825.99±1643.52	1109.29±1456.75	**0.008**
CRP, mg/L	57.33±61.42	49.96±59.35	77.22±63.38	**0.008**
ESR, mm/h	30.6±21.35	28.55±20.01	36.12±24.08	0.095
LDH, U/L	274.37±119.87	265.85±123.47	297.33±107.99	0.082
Glucose, mg/dL	160.89±61.27	165.73±60.76	147.82±61.67	0.081
HbA1c, %	7.98±1.69	8.16±1.74	7.49±1.47	0.059
Onset of diabetes, years	5.93±4.81	4.92±3.97	8.67±5.79	**<0.001**
TC, mg/dL	163.23±40.55	165.37±42.29	157.45±35.36	0.340
LDL-C, mg/dL	99.74±31.52	101.41±32.67	95.24±28.13	0.339
TG, mg/dL	149.91±104.23	155.1±108.09	135.91±93.13	0.590
HDL-C, mg/dL	37.38±11.85	37.2±11.81	37.86±12.15	0.714

COVID-19: Coronavirus disease-2019, SD: Standard deviation, WBC: White blood cell, PLT: Platelet; AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, HbA1c: Hemoglobin A1c, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride. Significant p-values are bolded. P<0.05 was considered statistically significant. Data are presented as mean ± standard deviation or n (%).

was statistically significantly higher than the discharge group, while the Hba1c value of the ICU group was higher than that of the discharged group. The Spearman correlation analysis of associated factors for HbA1c by age groups was given in Table 5. Correlation analysis showed that there was a negative correlation between HbA1c and lymphocyte (r=-0.23, p=0.030), HbA1c and white blood cell (WBC) (r=-0.22, p=0.042) in patients >65 years (p<0.05). Lastly, there was a positive high-level (r=0.69) significant correlation between Hba1c and glucose in >65 years patients (p<0.05).

Table 6 demostrates the analysis of biochemical variables by clinical groups of death/ICU transfer and discharged. There was a significant difference between clinical groups in age, ferritin, D-dimer, CRP, LDH and Hba1c variables (p<0.05). Ages, ferritin, D-dimer, CRP, LDH and Hba1c values of the death/ICU transfer group were significantly higher than the discharged group. According to the logistic regression analysis; age [Odds ratio (OR) 21.515 (95%) confidence interval (CI) 1.898-243.912, p=0.013], D-dimer [OR 1.001, (95%) CI 1.000-1.001, p=0.003], CRP [OR 1.038, (95%) CI 1.016-1.061, p=0.001] and Hba1c [OR 4.128, (95%) CI 1.792-9.509, p=0.001] values were found as a statistically significant risk factor for death and transfer to the ICU (Table 7).

A ROC curve analysis was undertaken. We demonstrated that the area under the ROC curve (AUC) of age 0.716 (p=0.009, 95% CI 0.569-0.862), Hba1c 0.720 (p=0.007, 95% CI 0.579-0.860), CRP 0.842 (p<0.001, 95% CI 0.762-0.922) and D-dimer 0.830 (p<0.001, 95% CI 0.725-0.934) (Figure 1).

Discussion

Identifying potential risk factors predicting the course of COVID-19, effectively triage patients, and individualizing treatment are of great benefit to healthcare professionals to ensure optimal clinical outcomes. Various studies have revealed that advanced age, comorbidities, and a wide range of different laboratory parameters are associated with a poor clinical course of the disease (3,4). As age has been shown to be one of the major risk factors for poor outcomes of COVID-19 patients, the vulnerability of the elderly and chronically ill adults to the serious COVID-19 disease faced should be taken seriously, and it

Table 3. Demographics and clinical findings of diabetic patients with COVID-19 by age of ≤65 years according to the clinical outcomes

Laboratory results, mean ± SD	All patients (n=89)	Discharge (n=82)	Intensive care unit (n=5)	Death (n=2)	p
Age (years)	50.58±9.31	50.21±9.14	53±12.47	60±4.24	0.287
Hemoglobin, g/dL	13.48±1.62	13.49±1.63	13.14±1.84	13.85±1.34	0.851
Hemotocrit %	40.34±4.44	40.35±4.46	39.68±5.23	41.4±3.39	0.896
WBC, 10^3/µL	7.69±3.78	7.61±3.84	7.73±2.93	11.12±1.11	0.253
Neutrophil, 10^3/µL	6.61±8.07	6.54±8.36	6.14±2.83	10.62±0.72	0.171
Lymphocyte, 10^3/µL	2.71±4.68	2.86±4.85	1.1±0.32	0.37±0.28	**0.046**
PLT, 10^3/µL	228.18±74.35	224.67±72.1	231.2±70.5	364.5±85.56	0.110
Monocyte, 10^3/µL	0.45±0.24	0.45±0.24	0.46±0.25	0.13±0.11	0.075
AST, IU/L	34.29±24.99	34.46±25.69	36.4±17.24	22±1.41	0.506
ALT, IU/L	45.06±34.84	45.17±36.2	47.6±7.2	34±12.73	0.427
Ferritin, ng/mL	463.64±564.64	415.05±533.72	811.2±643.62	1587±59.4	**0.022**
D-dimer, mg/L	825.99±1643.52	531.29±592.18	3690.6±4374.23	5747.5±6013.94	**0.009**
CRP, mg/L	49.96±59.35	43.98±54.99	107.72±27.22	150.65±148.99	0.017
ESR, mm/h	28.55±20.01	26.16±17.48	47.2±26.68	80±11.31	**0.012**
LDH, U/L	265.85±123.4	252.15±108.67	380.6±150.32	541±248.9	**0.015**
Glucose, mg/dL	165.73±60.76	162.98±57.61	220.4±90.62	142±80.61	0.103
HbA1c, %	8.16±1.74	7.99±1.58	10.43±2.67	9.05±1.91	**0.048**
Onset of diabetes, years	4.92±3.97	5.1±4.06	2.4±2.07	4±1.41	0.286
TC, mg/dL	165.37±42.29	166.43±43.33	142.8±23.57	178.5±12.02	0.439
LDL-C, mg/dL	101.41±32.67	101.81±33.3	87.44±22.96	120±7.07	0.460
TG, mg/dL	155.1±108.09	159.21±111.27	99.4±24.32	126±66.47	0.383
HDL-C, mg/dL	37.2±11.81	37.54±11.81	30.94±4.43	38.8±26.16	0.508

COVID-19: Coronavirus disease-2019, SD: Standard deviation, WBC: White blood cell, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, HbA1c: Hemoglobin A1c, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride. Significant p-values are bolded. P<0.05 was considered statistically significant. Data are presented as mean ± standard deviation

Table 4. Demographics and clinical findings of diabetic patients with COVID-19 by age of >65 years according to the clinical outcomes

Laboratory results, mean ± SD	All patients (n=33)	Discharge (n=26)	Intensive care unit (n=4)	Death (n=3)	p
Age (years)	74.12±6.34	73.38±5.79	75.25±9.64	79±6.24	0.334
Hemoglobin, g/dL	12.87±2.01	12.62±1.87	14.35±2.73	13.07±2.21	0.283
Hemotocrit %	38.64±6.09	37.8±5.3	43.55±9.37	39.4±7.18	0.212
WBC, 10^3/µL	7.68±3.52	7.4±3.17	6.28±0.36	11.92±6.35	0.388
Neutrophil, 10^3/µL	5.98±3.38	5.68±3.01	4.54±0.5	10.52±5.68	0.304
Lymphocyte, 10^3/µL	2.43±3.64	2.39±3.63	1.27±0.54	4.3±6.25	0.892
PLT, 10^3/µL	245.06±97	246.88±89.64	184.5±36.37	310±185.52	0.305
Monocyte, 10^3/µL	0.42±0.22	0.43±0.24	0.44±0.09	0.33±0.12	0.748
AST, IU/L	39.61±28.97	42.58±31.6	22.25±6.7	37±12.49	0.284
ALT, IU/L	35.36±25.51	38.42±27.29	19.75±7.72	29.67±18.9	0.287
Ferritin, ng/mL	560.79±584.19	459.46±520.12	660.75±615.3	1305.68±724.68	0.089
D-dimer, mg/L	1109.29±1456.75	953.36±1467.26	1564.75±1535.9	1853.37±1393.9	0.167
CRP, mg/L	77.22±63.38	61.58±56.84	120.45±48.95	155.07±65.47	**0.014**
ESR, mm/h	36.12±24.08	39±25.49	21.5±7.77	30.67±21.94	0.380
LDH, U/L	297.33±107.99	288.45±110.17	284±67.78	392±114.58	0.335
Glucose, mg/dL	147.82±61.67	137.04±39.66	197.25±114.25	175.33±118.7	0.396
HbA1c, %	7.49±1.47	7.22±1.33	9.22±1.32	7.53±1.7	**0.035**
Onset of diabetes, years	8.67±5.79	9.08±6.29	7.25±4.35	7±1.73	0.916
TC, mg/dL	157.45±35.36	160.77±35.84	145±25.5	145.33±47.96	0.598
LDL-C, mg/dL	95.24±28.13	97.4±26.69	92.8±31.96	79.83±42.43	0.597
TG, mg/dL	135.91±93.13	137.77±99.83	113.25±51.29	150±94.25	0.822
HDL-C, mg/dL	37.86±12.15	39.01±12.79	29.4±9.23	39.2±5.11	0.342

COVID-19: Coronavirus disease-2019, SD: Standard deviation, WBC: White blood cell, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, HbA1c: Hemoglobin A1c, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride. Significant p-values are bolded. P<0.05 was considered statistically significant. Data are presented as mean ± standard deviation

Table 5. Spearman correlation analysis of associated factors for Hba1c by age groups (r (p))

	hba1c (r (p)) >65 years (n=33)	hba1c (r (p)) ≤65 years (n=89)
Age (years)	0.17 (p=0.116)	0.32 (p=0.071)
Hemoglobin, g/dL	-0.12 (p=0.256)	0.18 (p=0.311)
Hemotocrit %	-0.15 (p=0.153)	0.21 (p=0.252)
WBC, 10^3/µL	-0.23 (p=0.030)	-0.11 (p=0.539)
Neutrophil, 10^3/µL	-0.12 (p=0.258)	-0.12 (p=0.492)
Lymphocyte, 10^3/µL	-0.22 (p=0.042)	0.18 (p=0.323)
PLT, 10^3/µL	-0.07 (p=0.502)	-0.02 (p=0.920)
Monocyte, 10^3/µL	-0.19 (p=0.082)	0.07 (p=0.713)
AST, IU/L	0.01 (p=0.891)	-0.14 (p=0.450)
ALT, IU/L	-0.06 (p=0.596)	-0.16 (p=0.374)
Ferritin, ng/mL	-0.08 (p=0.464)	0.05 (p=0.775)
D-dimer, mg/L	-0.06 (p=0.596)	-0.01 (p=0.947)
CRP, mg/L	0.00 (p=0.963)	0.11 (p=0.552)
ESR, mm/h	0.20 (p=0.059)	-0.18 (p=0.319)
LDH, U/L	0.00 (p=0.979)	-0.26 (p=0.144)
HbA1c, %	-	-
Onset of diabetes, years	0.09 (p=0.378)	-0.15 (p=0.411)
TC, mg/dL	-0.13 (p=0.215)	-0.09 (p=0.610)
LDL-C, mg/dL	-0.16 (p=0.146)	-0.13 (p=0.454)
TG, mg/dL	-0.07 (p=0.515)	-0.16 (p=0.374)
HDL-C, mg/dL	-0.06 (p=0.573)	-0.04 (p=0.822)

WBC: White blood cell, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, HbA1c: Hemoglobin A1c, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride. Significant p-values are bolded. P<0.05 was considered statistically significant

is important to understand the mechanisms underlying this age-related vulnerability. Age-related immune system remodeling or immune aging is considered the main cause of increased susceptibility to infection, particularly respiratory infections (6).

In this study, demographic and laboratory data of patients with diabetic COVID-19 and the variability of laboratory parameters in different clinical outcomes in patient groups over and under 65 years of age were examined. The results of our study revealed that age, ferritin, D-dimer, CRP and LDH values were higher in the death and ICU groups than in those who were discharged. In addition, D-dimer and CRP were higher in diabetic COVID-19 patients aged >65 years compared to those aged ≤65 years. In addition, Hba1c was found to be higher in the ICU group than in those discharged, and this result was valid for diabetic COVID-19 patients in the ICU group both under and over the age of 65. Moreover, ages of the patients who died and were transferred to the ICU were higher than those who were discharged. According to the logistic regression analysis, we obtained the result that the patient's age over 65 increased the risk of death/transfer to the ICU 21.5 times.

Vasculitic processes that develop on the background of organ damage caused by activation of inflammatory cascades, complement activation and proinflammatory cytokines in severe COVID-19 patients have been described. Vasculitic injury causes pulmonary edema and acute respiratory distress syndrome and plays an important role in cardiovascular and brain injuries such as ischemia, deep vein thrombosis and pulmonary thromboembolism (6). Various studies have been conducted to investigate the roles of inflammatory parameters in predicting disease progression (3,4). In this study, we showed that ferritin, D-dimer, CRP and LDH values were higher in the patient groups who died and needed ICU. Supporting our study in the literature, various studies indicate that laboratory parameters such as CRP, ferritin, LDH and D-dimer, which are associated with death, are higher in patients with poor prognosis (17,18).

When patients were classified according to whether they were elderly or not, D-dimer and CRP values were higher in diabetic COVID-19 patients over 65 years of age compared to younger patients. Moreover, CRP values were higher in patients who died >65 years than those who were discharged. Therefore, according to this study, it can be suggested that age is associated with an increased risk of inflammation and death. The results of our study are similar to previous studies in the literature (19-21). However, we obtained another interesting result that was beyond our expectation. In the general population of our study, ferritin, D-dimer, CRP and LDH values were higher in patients who died and required ICU, compared to patients who were discharged without complications. Actually, our expectation was that these higher values would be more pronounced over the age of >65. However, contrary to our hypothesis, interestingly, these values, excluding CRP, were higher in the group of patients ≤65 years of age who died and/or were admitted to the ICU. This unexpected result can be attributed to the relatively small sample size of our study and the smaller number of elderly participants.

DM is a chronic, progressive disease that is common in society with lifetime effects on patients. DM is one of the most common comorbidities of COVID-19, with a prevalence ranging from 6% to 50% (13). Diabetes has been associated with increased mortality in previous viral outbreaks such as the SARS-CoV-1 and Middle East respiratory syndrome coronavirus outbreak (22,23). Data from other viral outbreaks such as SARS and influenza H1N1 have shown that patients with poor glycemic control have a higher risk of mortality (22,24). As for SARS-CoV-2 pandemic, data on the impact of diabetes on the prognosis of COVID-19 patients are inconclusive and controversial, as some studies suggest that diabetes is a risk factor for the poor prognosis of COVID-19 (25,26), while some studies have reported that patients with diabetes do not appear to have a higher risk of mortality (27,28). In our study, regardless of the age group, HbA1c levels were found to be higher in both age groups who died and needed intensive care. Thus, our results revealed an

Table 6. Analysis of biochemical variables by clinical groups (mean ± SD/median-range)

	Death/intensive care unit transfer (n=14)	Discharged (n=108)	Total (n=122)	p
Age (years)**	65.93±14.58/65-52	55.79±13.04/55-58	56.95±13.56/57-58	0.008*
Hemoglobin, g/dL **	13.57±2/13.25-6.7	13.28±1.72/13.35-8.7	13.32±1.75/13.3-9.3	0.565
Hemotocrit %**	40.97±6.39/39.75-22.2	39.74±4.78/39.9-24.1	39.88±4.97/39.9-29.1	0.385
WBC, 10^3/µL	8.7±3.8/7.29-12.43	7.56±3.68/6.7-17.65	7.69±3.7/6.7-17.65	0.225
PLT, 10^3/µL	253.79±109.46/229.5-371	230.02±76.83/217-417	232.75±81.02/218.5-453	0.697
Monocyte, 10^3/µL	0.38±0.2/0.38-0.73	0.45±0.24/0.41-1.3	0.44±0.24/0.41-1.32	0.429
Neutrophil, 10^3/µL	7.26±3.8/5.78-11.65	6.33±7.43/4.79-72.39	6.44±7.1/4.87-72.39	0.131
Lymphocyte, 10^3/µL	1.73±2.85/0.99-11.33	2.75±4.57/1.34-24.47	2.63±4.41/1.32-24.63	0.069
Ferritin, ng/mL	985±647.57/910-1915	425.74±528.41/248.63-1990.67	489.92±569.21/281-1990.67	0.001*
D-dimer, mg/L	2983.37±3434.31/1342-9724	632.9±895.18/361-7690	902.62±1594.26/445.16-9990	0.000*
CRP, mg/L	127.64±59.76/119.25-210.7	48.22±55.69/21.5-196.8	57.33±61.42/31.75-255.8	0.000*
ESR, mm/h	41±26.59/36.5-82	29.25±20.34/24-106	30.6±21.35/25.5-106	0.107
LDH, U/L	378.36±147.15/357.5-527	260.89±109.63/243-639	274.37±119.87/257.5-639	0.002*
TC, mg/dL **	149.07±29.03/151-97	165.06±41.56/164.5-182	163.23±40.55/163-182	0.166
LDL-C, mg/dL **	91.99±29.01/86.3-106.4	100.75±31.81/97.7-155.1	99.74±31.52/97.35-163.4	0.330
TG, mg/dL	118±53.68/97.5-188	154.05±108.56/134-553	149.91±104.23/131-553	0.278
HDL-C, mg/dL	33.39±10.09/32.15-37.3	37.9±12.01/34.9-56.7	37.38±11.85/34.4-56.7	0.219
AST, IU/L	30.43±13.46/25.5-53	36.42±27.29/27.5-163	35.73±26.11/27-163	0.942
ALT, IU/L	33.86±15.33/34-45	43.55±34.27/32-157	42.43±32.76/32-157	0.772
Glucose, mg/dL	192.93±94.73/158-282	156.73±54.81/142-242	160.89±61.27/150-297	0.251
HbA1c, %	9.27±2.13/9.04-7.9	7.81±1.56/7.41-7.9	7.98±1.69/7.53-9.4	0.007*
Onset of diabetes, years	5±3.4/4.5-11	6.06±4.96/5-25	5.93±4.81/5-25	0.646

WBC: White blood cell, PLT: Platelet, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, HbA1c: Hemoglobin A1c, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase. *Statistically significant at the 0.05 level. **T-test, all other variables were analyzed with Mann-Whitney U test

Table 7. Effect of variables on clinical groups (death/intensive care unit transfer and discharged) - logistic regression analysis

	B	S.E.	Wald	df	p	OR	95% CI
Age groups (65+)	3.069	1.239	6.136	1	0.013*	21.515	1.898-243.912
D-dimer	0.001	0.000	8.826	1	0.003*	1.001	1.000-1.001
CRP	0.037	0.011	11.650	1	0.001*	1.038	1.016-1.061
Hba1c	1.418	0.426	11.089	1	0.001*	4.128	1.792-9.509

*Statistically significant at the 0.05 level, CI: Confidence interval, CRP: C-reactive protein, OR: Odds ratio, HbA1c: Hemoglobin

increased risk of disease worsening in COVID-19 patients with diabetes. Liu et al. (25) found that COVID-19 patients with diabetes had a higher risk of worsening, especially those with poorly-controlled HbA1c, with an optimal cut-off value of 8.6%. In another study, it was demonstrated that high HbA1c level was associated with inflammation, hypercoagulability, and low SaO_2 in COVID-19 patients, and the mortality rate (27.7%) was higher in patients with diabetes (29). In that study, there was a linear negative correlation between SaO_2 and HbA1c, while there was a linear positive correlation between serum ferritin, CRP, fibrinogen, and ESR levels and HbA1c. Besides, it has been shown that generally decreased lymphocytes in severe COVID-19 patients with DM, especially in T and B subgroups, are closely associated with poor prognosis and disease severity (29). In our study, variables that could correlate with Hba1c were examined in the groups above and below 65 years of age, and it was observed that Hba1c was negatively correlated with WBC and lymphocytes in the >65 age group. It is of great importance to state that this correlation did not appear in diabetic patients with COVID-19 under the age of <65 years.

In this study, when we divided the patients into death/ICU transfer and discharge groups and analyzed the analysis of demographic and biochemical variables, we observed that the patients in the death/ICU transfer group had higher age, ferritin, D-dimer, CRP, LDH and Hba1c variables compared to those in the discharged group. Moreover, in the logistic regression analysis that we created to evaluate the effect of the variables on the death/intensive care transfer and discharge clinical groups, we obtained the result that the patient's age over 65 increased the risk of death/transfer to the ICU 21.5 times. Clinical experience

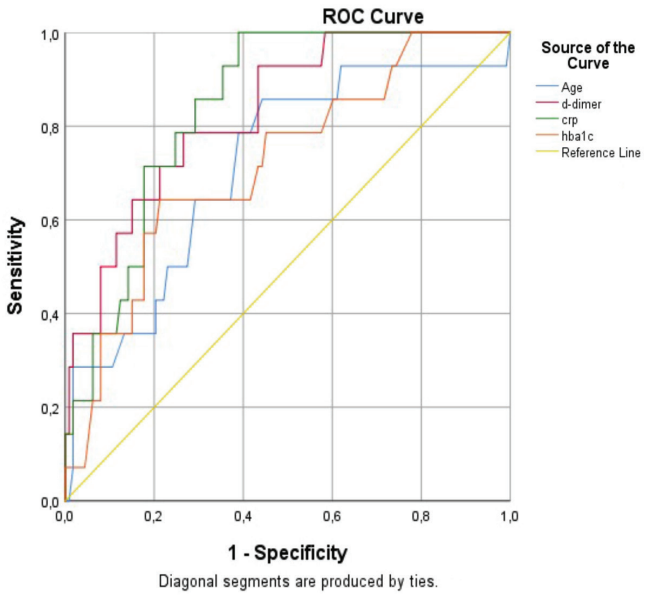

Figure 1. Receiver-operating characteristic (ROC) curve analysis of variables on death and transfer to the intensive care unit. Area under the ROC curve (AUC) for age 0.716 (p=0.009, 95% CI 0.569-0.862), for hba1c 0.720 (p=0.007, 95% CI 0.579-0.860), for CRP 0.842 (p<0.001, 95% CI 0.762-0.922), for D-dimer 0.830 (p<0.001, 95% CI 0.725-0.934)

CI: Confidence interval, CRP: C-reactive protein

to date shows that COVID-19 is highly heterogeneous, ranging from asymptomatic and mild to severe and fatal. Host factors, including age, gender, and comorbid conditions, are key determinants of disease severity and progression. Aging itself is a leading risk factor for serious illness and death from COVID-19. Age-related decline and dysregulation of immune function, i.e. immune aging and inflammation, is thought to play an important role in contributing to the increased vulnerability to serious COVID-19 outcomes in older adults (27,28). The results of our study mentioned above are consistent with previous studies showing that advanced age is a risk factor for worsening clinical outcome (4,6,19,20). Surely, there is much to learn about immune responses to COVID-19. Studies that separate and evaluate all immunological outcome data by age are needed to better understand disease heterogeneity and aging. Taken together, it is clear that aging is an important risk factor for adverse health outcomes, particularly severe COVID-19 disease and the need for hospitalization and ICU.

Study Limitations

This study has several limitations. First, the interpretation of our results might be limited by the small sample size and less number of older participants. Second, medical history was not taken in detail in all patients.

Conclusion

In conclusion, advanced age, Hba1c and inflammatory parameters including D-dimer and CRP are associated with poor clinical outcome such as death and transfer to ICU in COVID- 19 patients with diabetes. Furthermore, since there were increased Hba1c levels in the patient group requiring ICU, the increase in Hba1c levels, which is accepted as an indicator of uncontrolled diabetes, is associated with the need for transfer to the ICU. Finally, aging is an important risk factor for adverse health outcomes, particularly severe COVID-19 disease with diabetes and the need for hospitalization and ICU. In the light of all this information, early intervention and treatment are vital, especially in the presence of elevated inflammatory parameters in uncontrolled diabetic patients aged >65 years with COVID-19 to prevent poor clinical outcomes.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2973).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.U.A., D.A., Design G.U.A., Data Collection or Processing: G.U.A., D.A., Analysis or Interpretation: D.A., Literature Search: G.U.A., D.A., Writing: G.U.A., D.A.

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