

# The Effect of Diabetes Mellitus on Mortality in Patients Hospitalized Intensive Care Unit in Covid-19 Pandemic

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**Abstract** *Background and aim:* There are many studies on the effects of Diabetes Mellitus on the clinical course in COVID-19 patients. Factors that increase the risk of contracting COVID-19 disease and increase disease progression have been caused, and diabetes mellitus is one of them. We aimed to evaluate the incidence of Diabetes Mellitus in patients treated in the intensive care unit in respiratory failure due to COVID-19 pneumonia, and the effect of Diabetes Mellitus on the length of stay in intensive care and mortality. *Methods:* Our study is a single-center retrospective study. The study includes patients hospitalized in our COVID intensive care unit between March 16, 2019, and May 16, 2020. Patients over 18 years of age with and without a history of Diabetes Mellitus were compared in 2 groups. Demographic data of the patients, length of stay in the intensive care unit, respiratory support methods, presence of other comorbid diseases, effects of Diabetes Mellitus to mortality in ICU were recorded. *Results:* The information of 150 patients was obtained in the COVID-19 intensive care units of our hospital. Diabetes Mellitus was detected in 49 of the patients hospitalized in intensive care. 34.7% of these patients were female and 65.3% were male. There was no significant difference in survival in both groups ( $p = 0.942$ ). The BMI of the patients with Diabetes Mellitus was  $27.07 \pm 2.55$ , significantly higher ( $p = 0.005$ ). Intensive care stay periods were similar in both groups. The presence of hypertension was significantly higher in those with Diabetes Mellitus ( $p = 0.000$ ). There was no statistically significant difference between respiratory support methods. *Conclusions:* Diabetes Mellitus did not affect the duration of stay in the intensive care unit and mortality in patients who were followed up and treated in the intensive care unit due to COVID-19 pneumonia. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** COVID-19, Diabetes Mellitus, ICU, Mortality

## Introduction

Sars-CoV-2 virus, which first appeared in Wuhan, China, at the end of 2019, rapidly spread worldwide and turned into a pandemic. The World Health Organization (WHO) announced the outbreak as COVID - 19 on February 11, 2020. Clinical findings of cases infected with Sars-CoV-2 can range from mild upper respiratory tract infection to severe pneumonia. In the

later stages of the disease, kidney failure, multi-organ dysfunction and even death may develop.

Although the pathophysiological mechanisms are still not fully understood, the most severe and fatal cases of COVID-19 are seen in the elderly or patients with underlying comorbidities, especially those with cardiovascular disease, Diabetes Mellitus (DM), chronic lung and kidney disease, hypertension and cancer (1-4).

Diabetes is a chronic inflammatory condition characterized by multiple metabolic and vascular abnormalities. It is known that the risk of severe disease increases in people with Diabetes in COVID-19, and that measures to optimize glycemic control and prevent disease spread is critical (5).

In our study, we aimed to evaluate the incidence of DM in patients treated in the intensive care unit due to respiratory failure due to COVID-19 pneumonia and the effect of DM on the length of stay in the intensive care unit and mortality.

## Methods

Our study is a single-center, observational, retrospective study. Approval letter dated 07/07/2020 and numbered 1559 was received from the Ministry of Health and the ethics committee of our hospital. The study includes patients over 18 years old hospitalized in our covid intensive care unit because of respiratory failure between March 16, 2019 and May 16, 2020. Polymerase Chain Reaction (PCR) tests performed with a nasopharyngeal swab taken from the person, which is the standard diagnostic method, and the diagnosis of infection symptoms, risk factors and thoracic CT scans indicating pneumonia was diagnosed. Retrospective records were examined by examining the electronic data files of the patients. Patients whose hospital records could not have sufficient data were excluded from the study.

Patients over 18 years of age with and without a medical history of DM in their history were identified and compared in two groups.

Demographic data such as age, gender, Body Mass Index (BMI) of all patients, presence of another comorbid disease (Hypertension, Coronary Arterial Disease (CAD), Chronic Obstructive Pulmonary Disease (COPD)), blood glucose values, Ferritin, C-Reactive Protein (CRP) values and respiratory support methods (nasal oxygen, nasal high flow, noninvasive mechanical ventilation, intubation) were recorded during the first admission to intensive care. In addition, the length of stay in the intensive care unit and mortality were recorded.

Statistical analyses were performed with the Scientific Package for Social Science (version 27.0; SPSS Inc., Chicago, IL, USA). Continuous variables were

given as mean  $\pm$  standard deviation if they distributed typically or as median (interquartile range) if they were distributed abnormally. Qualitative variables were given as a percentage. Comparison of normally distributed data was performed by independent samples t-test. Abnormally distributed data compared with the Mann-Whitney U test. The Chi-Square test compared categorical variables. Differences were considered statistically significant for p values less than 0.05. Survival analysis has been performed by Kaplan-Meier curve. Also multiple analysis of the independent variables that have a significant relationship with the dependent variables, the patient's ferritin level and age, were also performed with multiple logistic regression analysis.

## Results

The information of 150 patients treated in the COVID-19 intensive care units of our hospital between March 16, 2019 and May 16, 2020 was reached. Diabetes Mellitus was detected in 49 of the patients hospitalized in intensive care. Statistical analysis was performed on the data of 150 patients.

Females made up 34.7 % of the patients, while males made up 65.3 %. In terms of the gender distribution of the groups, no statistically significant differences were discovered. Patients with DM had a higher average age ( $p = 0.028$ ) than patients without DM. The BMI of diabetic individuals was greater than that of the control group ( $p = 0.005$ ) (Table 1).

The presence of hypertension was significantly higher in those with DM ( $p = 0.000$ ). There was no statistically significant difference between other comorbidity conditions (Table 2).

There was no statistically significant difference between the respiratory support methods between the groups (Table 3).

The group DM group's median mean of glucose values was 190 mg / dl (119-270), while it was 136 mg / dl (111-160) in the non-DM group. The average glucose values of the patients with DM were higher than the patients without DM ( $p = 0.001$ ). There was no significant difference between inflammatory markers C-reactive protein ( $p = 0.370$ ) and Ferritin values ( $p = 0.269$ ) (Table 4).

**Table 1.** Demographic details of all patients.

Parameter	All patients n=150	Diabetes mellitus		p
		Yes n=49	No n=101	
Age, years, mean±standard deviation	65.47±13.68	69.26±10.67	64.04±14.66	0.028
Female patients N (%)	26.7	34.7	22.8	0.122
Male patients N (%)	73.3	65.3	76.2	
Body mass index, kg/m <sup>2</sup> , mean± standard deviation	26.08±3.01	27.07±2.55	25.60±3.11	0.005

(n: Number of patients, p: statistically significant difference, <0,05)

Table 1 shows that age and BMI are statistically correlated with the patients' death.

**Table 2.** Comorbidities.

Parameter	All patients n=150	Diabetes mellitus		p
		Yes n=49	No n=101	
Hypertension (%)	49.3	71.4	38.6	0.000
CAD (%)	26	30.6	23.8	0.370

(n: Number of patients, p: statistically significant difference, <0,05)

Table 2 shows that Hypertension and CAD are not correlated with the patients' death.

**Table 3.** Respiratory support.

Parameter	All patients n=150	Diabetes mellitus		p
		Yes n=49	No n=101	
Nasal oxygen First day (%)	31.3	34.7	27.7	0.382
All time (%)	39.3	44.9	36.6	
High flow nasal oxygen First day (%)	16	22.4	13.9	0.186
All time (%)	26	30.6	23.8	
NIMV First day (%)	5.6	4.1	5.9	0.635
All time (%)	7.3	8.2	6.9	
IMV First day (%)	47.2	38.8	48.5	0.261
All time (%)	68.7	61.2	72.3	

(n: Number of patients, p: statistically significant difference, <0,05)

Table 3 shows that the respiratory support techniques were not correlated with the patients' death.

**Table 4.** Laboratory values.

Parameter	All patients n=150	Diabetes mellitus		p
		Yes n=49	No n=101	
Glucose, mg/dl, median (interquartile range)	142.5 (112.7-191)	190 (119-270)	136 (111-160)	0.001
Ferritin, ng/ml, median (interquartile range)	426 (138-918)	275 (109-906)	476 (172-939)	0.269
C reactive protein, mg/L, median (interquartile range)	152.5 (101.1-	135 (84.5-207.5)	162 (105-225)	0.370

(n: Number of patients, p: statistically significant difference, <0,05)

Table 4 shows that the glucose levels of the patients were correlated with the patients' death.

There was no significant difference between the groups in terms of length of stay in the intensive care unit (p = 0.809) (Figure 1) and survival (p = 0.942) (Table 5).

Table 5 shows that survival comparisons between DM group and non-DM group. According to the effect of significant independent variables, ferritin and age, with multiple logistic regression analysis on the mortality rate of patients hospitalized in the intensive care unit, the combined ferritin level and age of the patient explain only 8% of deaths (R square = 0.081) (Table 6).

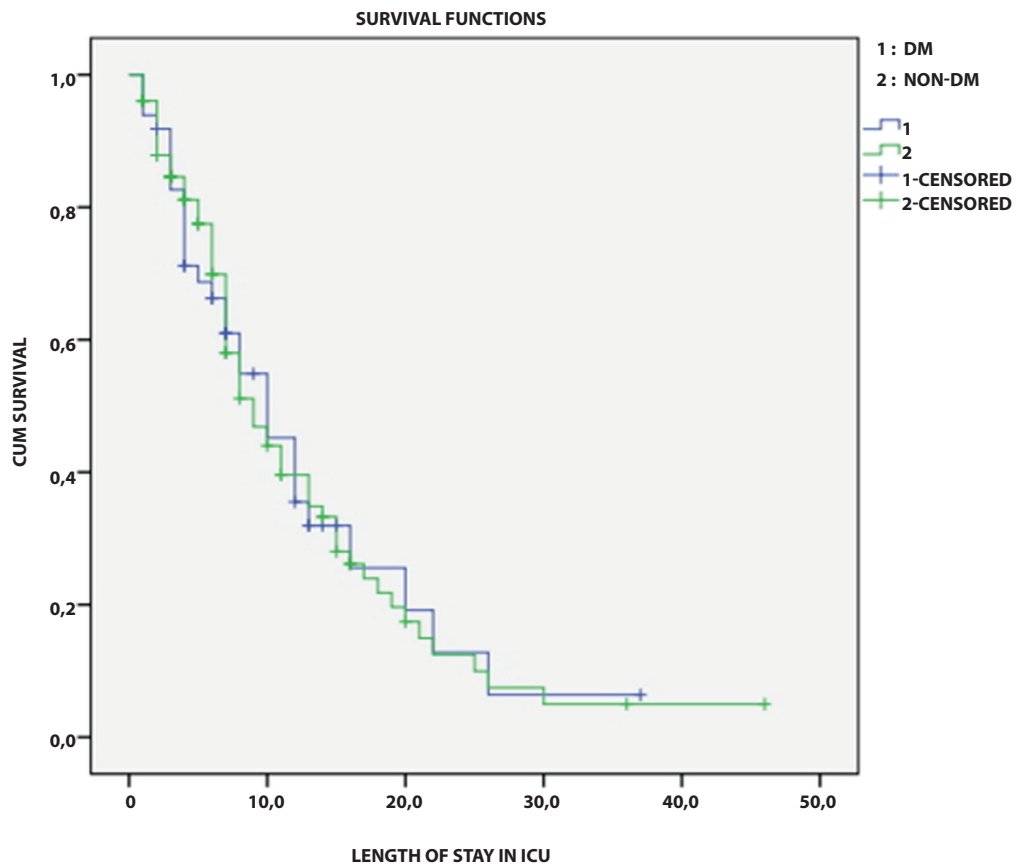


Figure 1. Survival Functions

Table 5. Survival Comparisons

	Chi-Square	df	Sig
Log Rank (Mantel-Cox)	0.005	1	0.942

Table 6. Ferritin and age

	R	R Square	Adjusted R square	Std Error of the Estimate
Ferritin/age	0.308 <sup>a</sup>	0.095	0.081	0.46013

(a. Predictors: Ferritin, Age)

Table 6. shows that increases in the Ferritin and Age together are responsible for the 8,1% of survival.

**Conclusion**

Individuals with DM, hypertension and severe obesity (BMI 40kg / m2) have been claimed to have a higher rate of infection with COVID-19 and the

risk of complications and death from COVID-19 (1,3,4,6,7,8).

About Diabetes, the first of three components that does not cause a higher rate of infection with COVID-19 and the risk of complications and death from COVID-19, according to a meta-analysis conducted by Zeng-hong Wu et al., it significantly raises the mortality of COVID-19 patients. These findings showed that the COVID-19 patients had an abnormal blood glucose level (9). While pathophysiology is uncertain, it has been found that in the elderly or patients with possible complications, particularly those with Diabetes, the most severe and fatal cases of COVID 19 occur (2). Diabetes and elevated blood glucose levels, according to sources, are potent determinants of the severity and mortality of patients compromised with viral pathogens, including SARS-CoV and MERS-CoV (4,10). In the meta-analysis published by Kumar A et al. (11); the prevalence of Diabetes in

COVID-19 patients was approximately 10%, similar to the prevalence in the population. They also concluded that the risk of developing severe disease and mortality in COVID-19 patients with Diabetes was more than twice that of the average population. They stated that whether the relationship of Diabetes with COVID-19 mortality is independent of other comorbidities should be investigated further. The different results may be the small sample size, the presence of only intensive care patients in the study, the poor general condition of the patients with or without diabetes mellitus admitted to the intensive care unit despite medical treatment, and respiratory failure.

Moving on, about hypertension, which we found in our study to cause a higher rate of infection with COVID-19 and no risk of complications and death from COVID-19, according to Richardson et al., the most common comorbidities in individuals with COVID-19 that need hospitalization are hypertension and Diabetes. 5,700 patients (average age 63 years; 39.7% female) were included in a case-series sample, with the most common comorbidities being hypertension (56.6%), obesity (41.7%), and Diabetes (33.8%) (12). Furthermore, Zuin et al. shown in their trials that patients with COVID-19 and hypertension had a significantly increased chance of death than non-hypertensives (13). The rate of comorbidity (71.4%) of hypertension in DM patients is significantly higher than the group without DM (38.6%) supports these studies. However, the same cannot be said for its effect on mortality.

About obesity, which we found in our study to cause a higher rate of infection with COVID-19 and no risk of complications and death from COVID-19, Hussain et al. reported in their published article in 2020 that it is a risk factor for mortality in Covid-19, as well as Huang J.F. et al., added that another notable finding was that patients who were obese needed more advanced respiratory assistance substantially (14,15). The results of our study; The fact that BMI is significantly higher in DM patients compared to non-DM patients; however, according to our findings, overweight did not significantly affect mortality.

In a 2019 systematic study and meta-analysis, the amount of Ferritin in severe patients was substantially increased compared to the level in non-severe patients.

In comparison with those of survivors, non-survivors have had somewhat higher levels of Ferritin. This led to a weak prognosis of Ferritin, and the deterioration of COVID-19 could be forecast (16). Similarly, in our study, in patients with severe COVID-19 with Diabetes, CRP and Ferritin were higher. Median survival times from hospitalization in severe COVID-19 patients with and without Diabetes were found to be 10 days and 18 days, respectively. Consequently, there was no statistical difference in Ferritin, C-reactive protein, which are among the inflammatory markers, between patients with DM and patients without DM. However, given the CRP literature, in particular, the research conducted in 2020 demonstrated that CRP is closely related to disease development and that it provides an early indicator for severe COVID-19 (17,18).

There are at least two specific mechanisms that may play a role in COVID-19 infection. First, to enter its target cells, the SARS-CoV-2 virus hijacks an endocrine pathway that plays an essential role in blood pressure regulation, metabolism, and inflammation (19).

Yongli Yan et al. (18) study is similar to our study in terms of sample size and parameters examined. This is a single-center, retrospective, observational study, and the clinical and laboratory characteristics of 193 patients with severe COVID-19 were collected. While 48 (24.9%) patients with severe COVID-19 had Diabetes, Diabetes was not detected in 145 patients. They found that 68.8% of the diabetic patients were male, and the average age was high. They also found that the need for mechanical ventilation and ICU was higher, and the mortality was higher for DM group. Similar results of our study to this study: Patients with DM are older (mean age of the patients with DM  $69.26 \pm 10.67$ , the average age of patients without DM  $64.04 \pm 14.66$ ) male gender is more in the group with DM. According to the findings in our study, there was no significant difference in the rate of attachment to mechanical ventilation and mortality in both groups. The length of hospital stay was similar in both groups as 7 (3-12) days.

In a retrospective analysis with laboratory-confirmed COVID-19, most patients were admitted to the ICU in Lombardy, Italy. Whether or not the mortality rate is DM or not, absolute mortality has been high (20).



The role of angiotensin-converting enzyme 2 (ACE2) in the relationship between DM and COVID-19 is plausible. ACE2 is a type 1 integral membrane glycoprotein structurally expressed by epithelial cells of the lungs, kidneys, intestines and blood vessels. In normal physiology, ACE2 divides angiotensin-II and, to a lesser extent, angiotensin-I into small peptides, angiotensin (1-7) and angiotensin (1-9), respectively (3). The ACE2 / Ang (1-7) system plays a significant anti-inflammatory and antioxidant role, protecting the lung against ARDS; indeed, ACE2 is protective against the deadly avian influenza A H5N1 infection (4). ACE2 expression is decreased in patients with DM, possibly due to glycosylation; this may increase susceptibility to severe lung injury and ARDS with COVID-19 (21).

ACE2 has been identified as the receptor for the coronavirus spike protein. ACE2 has protective effects primarily related to inflammation. COVID-19 reduces ACE2 expression, which induces infection, cellular damage, hyper inflammation and respiratory failure. Acute hyperglycemia has been shown to upregulate ACE2 expression on cells, which can facilitate viral cell entry. However, chronic hyperglycemia is known to downregulate ACE2 expression, making cells vulnerable to the inflammatory and deleterious effects of the virus (6). We attributed the fact that the mean glucose median value of 190 mg/dl in the patient group with DM included in our study was not bad in glyce-mic control; this may be due to reasonable glyce-mic control in the intensive care unit or the patients being under a suitable follow-up and treatment due to DM before being infected with SARS-COV 2. When we look at the median glucose values, although the values are higher in the patient group with DM, the glucose values below 200 g / dl suggest that blood sherry control is primarily achieved. The fact that the HbA1C values of a sufficient number of patients are not exam-ined due to the patient density during the pandemic course limits our knowledge about long-term glucose regulation.

In our study, we emphasized that DM does not affect mortality; the reasons for the different results from other conducted studies may be the small sample size, the presence of only intensive care patients in the study, the poor general condition of the patients with

or without diabetes mellitus admitted to the intensive care unit despite medical treatment, and respiratory failure.

The limitation of our study; It is retrospective, includes a small number of patients; we have been able to calculate the rates of hospitalization in intensive care because we cannot reach the number of patients with DM admitted throughout the hospital, and we have sufficient data on HbA1C levels and end-organ dam-age of DM.

In summary, our findings showed that the need for invasive mechanical ventilation and mortality did not increase in COVID-19 patients hospital-ized in the intensive care unit with DM compared to COVID-19 patients without DM. It has been re-vealed that the male gender dominates COVID-19 patients with DM and that patients in this group are older.

In conclusion, DM was not effective in inten-sive care stay and mortality in patients who were fol-lowed up and treated in the intensive care unit due to COVID-19 pneumonia.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a con-flict of interest in connection with the submitted article.

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