Orginal Article Open Access
Iranian Journal of Diabetes and Obesity (IJDO)

Predictors of Mortality among Intensive Care Unit (ICU) Hospitalized Diabetic Patients with COVID-19

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Abstract

Objective: Diabetic patients with COVID-19 are at the higher risk of clinical complications and intensive care unit (ICU) admission. There is limited information available on the risk factors of mortality in diabetic patients with COVID-19 admitted to the ICUs. The aim of this study was identifying the mortality risk factors in diabetic patients with COVID-19 who are admitted to the ICU.

Materials and Methods: In this study, we conducted a descriptive-analytical observational analysis on 391 patients admitted to the ICU for 18 months. We assessed the demographic, clinical, pharmaceutical, laboratory and imaging data of diabetic patients and statistically analyzed them to identify mortality risk factors.

Results: The study found 156 (39.89%) diabetic out of 391 patients. The group of diabetic patients had significantly higher rates of endotracheal intubation ($P< 0.001$), mortality ($P< 0.001$), and complications during hospitalization due to COVID-19, including secondary bacterial infections ($P = 0.005$), venous thrombosis ($P = 0.008$), and gastrointestinal bleeding ($P = 0.011$), compared to the nondiabetic patient.

Conclusion: Patients with diabetes who also have COVID-19 tend to experience more severe clinical outcomes and a higher mortality rate when admitted to the intensive care unit. The likelihood of mortality in these patients is closely associated with factors such as stroke occurrence, oxygenation levels, and the presence of secondary infections at the time of admission.

Keywords: Diabetes, COVID19, Mortality, Intensive care unit, Patient

QR Code:

Citation: Gholinataj Jelodar M, Mirzaei S, Haji Maghsoudi M. Predictors of Mortality among Intensive Care Unit (ICU) Hospitalized Diabetic Patients with COVID-19. IJDO 2024; 16 (2) :78-89

URL: http://ijdo.ssu.ac.ir/article-1-871-en.html

10.18502/ijdo.v16i2.15707

Article info:

Received: 25 December 2023
Accepted: 26 March 2024
Published in May 2024

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[DOI: 10.18502/ijdo.v16i2.15707]

Introduction

In recent years, exposure to the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) led to the Coronavirus disease 2019 (COVID-19) pandemic (1,2). The first case of this disease was reported in Wuhan, China, in December 2019, and since then, it has rapidly spread worldwide (2). The current pandemic is the first since the 1918 influenza outbreak (3). Even though some individuals may be symptom-free or only have mild symptoms, it can escalate to a severe form that requires ICU hospitalization (4).

The older age and chronic diseases were related to severity and mortality in hospitalized COVID-19 patients (5-13). It was discovered that diabetes played a significant role in determining outcomes for those infected with acute respiratory syndrome (14).

The diabetes is a risk factor of developing the severe form of COVID-19 (15,16). According to the studies (16-18), diabetic patients have a higher risk of experiencing complications and hospitalization in the ICU if they contract with COVID-19.

The exact explanation for why virus infections result in varying degrees of severity among patients with specific risk factors is still not fully understood (19). It is known that diabetes increases susceptibility and worsens prognosis compared to nondiabetic individuals (20).

The diabetes is more prevalent in Yazd (21). A systematic review and meta-analysis by Singh et al (2020) on 18 studies showed that the prevalence of diabetes in patients with COVID-19 is 11.5% [95% CI (9.7, 13.4)] (15). According to two other review studies, people with diabetes have a relative risk (RR) of 2.11, [95% CI (1.40-3.19)] for developing severe COVID-19 (22,23). We previously found that diabetes with OR=3.84 is a risk factor for mortality among COVID-19 patients who were hospitalized in the ICU (24). As a result, enhancing the treatment and care of diabetic patients with COVID-19 is crucial in preventing complications or fatalities (15).

Furthermore, additional investigation is necessary to reveal the connection between DM and the aftermath of COVID-19. Currently, there is limited information on the mortality risk factors for ICU-admitted diabetic COVID-19 patients. Improved comprehension of clinical complications and risk factors in specific clinical groups can assist in planning and organizing health services during acute situations. To determine the mortality risk factors, the study focused on diabetic patients with COVID-19 in Yazd, Iran, who were hospitalized in the ICU from March 20, 2020, through September 1, 2021.

Material and methods

This study is an observational, analytical research that aimed to describe and analyze ICU patients at Shahid Rahnemoon Hospital in Yazd during 18 months. The study examined patients who had a positive COVID-19 PCR test from March 20, 2020, through September 1, 2021.

The patients' files were reviewed to collect data on demographics (age, gender, comorbidities) as well as clinical, pharmaceutical, laboratory, and imaging data. This information was gathered upon admission to the ICU, throughout the treatment, and upon discharge. The clinical data gathered for each patient included the percentage of their oxygen saturation, any significant complications experienced during treatment, the need for invasive or non-invasive mechanical ventilation support, the duration of their stay in the ICU, and any instances of death.

The severity and type of pulmonary involvement were determined using HRCT imaging upon the patient's arrival at the ICU. Two methods were used to assess the extent of involvement in HRCT. The initial approach comprised a general CT scan observation and calculation of the overall involvement percentage. In the second method, the scoring system outlined by the Fleischner Society's glossary (25) was used. Lung lobe

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involvement was evaluated using a scoring system that assigns a value between 0 and 5, based on the percentage of involvement. No involvement receives a score of 0; while up to 5% lobar involvement receives a score of 1. Lobar involvement ranging from 5% to 25% is assigned a score of 2, whereas involvement ranging from 25% to 50% is given a score of 3. In cases where lobar involvement ranges from 50% to 75%, a score of 4 is assigned. If the involvement exceeds 75%, a score of 5 is given. The total score is calculated by adding the scores for each of the five lung lobes. The patient's drug information was reviewed, including medications such as Favipiravir, Hydroxychloroquine, Remdesivir, Interferon beta-1a, Lopinavir/ Ritonavir, and Tocilizumab for COVID-19 treatment.

Furthermore, we assessed the patient's usage of additional medications, including antidiabetic agents [Biguanides, Insulin, dipeptidyl peptidase-4 inhibitor (DPP-4 I), Sulfonylurea, Sodium-glucose co-transporter-2 (SGLT2) inhibitors included empagliflozin].

The abovementioned factors were initially compared between the diabetic and non-diabetic groups. Afterward, the diabetic patients were divided into two groups depending on their mortality status. Following that, a comparison was conducted between the two groups using the same criteria. The analysis of risk factors for mortality was finally done using statistical methods.

Data analysis was performed using the statistical software SPSS version 26.0. The quantitative data were expressed as mean (± standard deviation). Two groups were compared using an independent T-test for continuous variables. Numerical data was represented using percentages, and group differences were compared using the chi-square test or exact probability method. The researchers investigated the factors that increase mortality risk in diabetic patients with COVID-19.

The investigation involved the use of bivariate analysis and multivariate regression. Only factors with a P= 0.05 or less in the bivariate analysis were considered by the researchers for the multivariate analysis. Furthermore, a separate examination of the survival rate was done by the Kaplan – Meier test.

Ethical considerations

The study was approved by Clinical Research Development Center at Shahid Rahnemoon Hospital, Yazd, Iran. assigne to the code IR.SSU.SRH. REC.1402.022

Results

The study examined 391 COVID-19 patients who were admitted to the ICU. Totally, 156 patients (39.89%) were diabetics. Diabetic patients exhibited significantly increased rates of complications during hospitalization (Table 1).

The imaging (Score of lung involvement, Type of CT) data and laboratory of the patients are shown in Table 2.

Table 3 provides a comprehensive overview of the patient's medical history, including significant differences in variables such as CVA, remdesivir drug usage, secondary complications (infection, venous thrombosis, intubation), and O2 saturation upon entering the ICU. Additionally, the table displays comparisons of demographic, clinical, and pharmaceutical data for these patients.

Based on other findings, the initial laboratory results (NLR, AST, ALT, LDH), the percentage of lung involvement upon entering the ICU showed significant differences with death (Table 4).

The impact of background and clinical factors on the mortality rate of diabetic patients with COVID-19 was investigated using logistic multivariate regression in this study. The Hosmer-Lemeshow test yielded a p-value of 0.323. After fitting the logistic regression model, the researchers discovered significant predictor variables, including a history of CVA, use of remdesivir, infection and venous thrombosis, and NLR, AST, BS, ALT, LDH, O2 saturation, and percentage of lung involvement. The last phase of the model

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Table 1. Demographics, baseline characteristics, and Outcomes & Complications of patients

Variables	General data	DM (N=156) N (%)	Non-DM (N=235) N (%)	*P*-value
Age	<=60 y	37 (23.7)	119 (50.6)	<0.001*
	>60 y	119 (76.3)	116 (49.4)	
	Mean (±SD)	68.79 (±15.74)	60.14 (±18.21)	<0.001*
Sex	Male	86 (55.1)	138 (58.7)	0.482*
	Female	70 (44.9)	97 (41.3)	
O2Sat, Baseline	O2 < 88%	138 (88.5)	178 (75.7)	0.007*
	92% > o2 >=88%	14 (9.0)	45 (19.1)	
	O2 >= 92%	4 (2.6)	12 (5.1)	
	Mean (±SD)	76.59 (±10.86)	78.64 (±11.94)	0.085**
Comorbidities	HTN	97 (62.2)	65 (27.7)	<0.001*
	IHD	36 (23.1)	46 (19.6)	0.405*
	CHF	10 (6.4)	22 (9.4)	0.297*
	CKD	42 (26.9)	39 (16.6)	0.014*
	COPD	22 (14.1)	32 (13.6)	0.892*
	CVA	19 (12.2)	21 (8.9)	0.300*
	DLP	28 (17.9)	10 (4.3)	<0.001*
	ESRD	8 (5.1)	16 (6.8)	0.498*
	Brain. Hemorrhage	16 (10.3)	7 (3.0)	0.003*
	Cancer	9 (5.8)	3 (1.3)	0.014*
	Hypothyroidism	3 (1.9)	6 (2.6)	0.485*
	Seizure	4 (2.6)	5 (2.1)	0.515*
	IPF	5 (3.2)	2 (0.9)	0.093*
	Cirrhosis	1 (0.6)	4 (1.7)	0.337*
	Trauma	1 (0.6)	2 (0.9)	0.650*
	Parkinson	2 (1.3)	1 (0.4)	0.350*
	Rheumatoid arteritis	0 (0)	2 (0.9)	0.364*
	Sickle cell	0 (0)	2 (0.9)	0.361*
	MS	2 (1.3)	0 (0)	0.159*
	LAM	0 (0)	1 (0.4)	0.601*
COVID19 Drugs	Tocilizumab	22 (14.1)	55 (23.4)	0.024*
	Favipiravir	15 (7.7)	18 (9.6)	0.496*
	Hydroxychloroquine	17 (10.9)	14 (6)	0.077*
	Remdesivir	78 (50)	125 (53.2)	0.536*
	Lopinavir/Ritonavir	48 (30.8)	52 (22.1)	0.055*
	Interferon beta-1a	45 (28.8)	49 (20.9)	0.070*
Outcomes & complications	Intubation	90 (57.7)	62 (26.4)	<0.001*
	Death	92 (59.0)	57 (24.3)	<0.001*
	Secondary bacterial Infection	31 (19.9)	23 (9.8)	0.005*
	GI. Bleeding	17 (10.9)	10 (4.3)	0.011*
	Venous thrombosis	12 (7.7)	5 (2.1)	0.008*
O2Sat, discharge with supplementary o2	O2 < 88%	5 (7.6)	6 (3.4)	0.30*
	92% > o2 >=88%	33 (50)	83 (47.2)	
	O2 >= 92%	28 (42.4)	87 (49.4)	
	Mean (±SD)	92.27 (±3.03)	92.76 (±3.09)	0.278**
Hospital length of stay	Mean (±SD)	12.85 (±8.77)	12.89 (±9.76)	0.969**
ICU length of stay	Mean (±SD)	10.80 (±8.77)	11.02 (±9.87)	0.825**

N: Number; SD: Standard Deviation; DM: Diabetes Mellitus; HTN: Hypertension; IHD: Ischemic Heart Disease; DLP: Dyslipidemia; COPD: Chronic Obstructive Pulmonary Disease; CVA: cerebral vascular accident; ESRD: End Stage Renal Disease; IPF: Idiopathic Pulmonary Fibrosis; MS: Multiple sclerosis; LAM: Lymphangioleiomyomatosis; O2Sat: Oxygen Saturation.
*: Chi-squared test, **: Independent T-test

showed that O2 saturation upon ICU admission (OR= 0.948, *P*= 0.035*)*, secondary bacterial infection (OR= 0.030, *P*= 0.002*)*, NLR (OR=1.147, *P*= 0.001*)*, and AST (OR=1.037, *P*= 0.001*)* are autonomous predictors of mortality in diabetic COVID-19 patients.

The Kaplan-Meier survival rate with SPSS V.26 is displayed in Figure 1.

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Table 2. Laboratory and Imaging findings of patients

Variable	General Data		DM(N=156) N(%)	Non-DM (N=235) N (%)	*P*-value
Imaging Result (score of lung involvement) at baseline	Mild (0-8)		26(16.7)	55 (23.4)	0.156*
	Moderate (9-16)		75 (48.1)	93 (39.6)	
	Severe (17-25)		55 (35.3)	87 (37.0)	
	Mean (± SD)		14.17 (±5.76)	13.93 (±6.22)	0.695**
Type of CT	consolidation		53 (34.0)	80 (34.0)	0.989*
	GGO		43 (27.6)	57 (24.3)	0.463*
	Nodular		8 (5.1)	15 (6.4)	0.606*
	Reticular		7 (4.5)	16 (6.8)	0.421*
	Fibrosis		2 (1.3)	10 (4.3)	0.081*
	PE		11 (7.1)	22 (9.4)	0.421*
	Crazy Paving		5 (3.2)	18 (7.7)	0.067*
Laboratory findings	CRP, N (%)	Negative	25 (16)	53 (22.6)	0.118*
		+	36 (23.1)	41 (17.4)	
		++	47 (30.1)	84 (35.7)	
		+++	48 (30.8)	57 (24.3)	
	WBC		8.92 (±5.39)	9.40 (±5.70)	0.319**
	ESR		46.95 (±28.51)	45.46 (±29.06)	0.616**
	BS		173.43 (±64.30)	135.84 (±35.34)	<0.001**
	NLR		10.01 (±7.36)	10.64 (±9.43)	0.487**
	PLT		196.23 (±80.66)	208.22 (±98.40)	0.206**
	BUN	Mean± (SD)	64.16 (±42.86)	58.88 (±57.09)	0.325**
	Cr		1.81 (±1.48)	1.72 (±2.12)	0.652**
	AST		57.19 (±55.16)	81.18 (±170.21)	0.090**
	ALT		50.55 (±58.89)	72.86 (±157.94)	0.092**
	ALP		214.95 (±111.21)	215.16 (±128.87)	0.986**
	LDH		713.45 (±453.56)	798.58 (±580.03)	0.123**

N: Number; SD: Standard Deviation; DM: Diabetes Mellitus; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; CPK: Creatine Phosphokinase ; LDH: Lactate Dehydrogenase; WBC: White Blood Cells; NLR: Neutrophil-Lymphocyte Ratio; AST: Aspartate Transaminase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; BS: Blood Sugar; Cons: Considerations; GGO: Ground-glass opacification; PE: pleural effusion; y:year; N: Number; *: Chi-squared test, **: Independent T-test

Discussion

The study revealed that diabetic patients who were admitted to the ICU had a higher need for endotracheal intubation, and invasive mechanical ventilation, as well as higher mortality rates compared to nondiabetic patients. It has been demonstrated that individuals with type 2 diabetes have an approximately 20% higher risk of mortality when experiencing severe COVID-19. This risk seems to be independent of age, gender, ethnicity, obesity, and other major comorbidities (26). In a study by Yang X et al, among 52 patients with life-threatening medical conditions, diabetes was found in 10% (2.20) of and 22% (7.32) of survivors and non-survivors patients, respectively (17). Notably, the diabetic patients in the study had a higher average age and a higher prevalence of comorbidities, including HTN, CKD, cancer, and cerebral hemorrhage, which may have influenced the observed disparities between the two groups. Elderly people experience chronic inflammation, causing higher levels of pro-inflammatory cytokines and worsen COVID-19 symptoms (27,28).

Immunosenescence, associated with old age, refers to the decline in immune system function, resulting in reduced pathogen response and increased morbidity and mortality in patients (29). A retrospective observational study found that COVID-19 patients with a history of cancer experience more severe disease upon hospital admission (30).

Furthermore, cancer survivors with COVID-19 are more likely to need mechanical ventilation. These findings have been corroborated by other studies as well (31-33). Old age, along with concurrent diseases and immunosuppression in patients with cancer, are influential factors in aggravating COVID-19 in these people (34).

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Table 3. Association between Demographic, Primary, and Outcomes of clinical with death in diabetes Patient

Variable			Death		Total	*P*-value
			Yes	No		
Sex, N (%)		Male	56 (60.90)	30 (46.9)	86	0.084*
		Female	36 (39.10)	34 (53.1)	72	
Age, N (%)		<=60	26 (28.3)	11 (17.2)	37	0.110*
		>60	66 (71.7)	53 (82.8)	119	
		Mean (±SD)	68.7 (±16.75)	68.92 (±14.28)	156	0.930**
Comorbidity, N (%)	**HTN**	Yes	56 (60.9)	41 (64.1)	97	0.686*
	IHD		20 (21.7)	16 (25)	36	0.634*
	DLP		15 (16. 3)	13 (20.3)	28	0.521*
	CKD		28 (30.4)	14 (21.9)	42	0.236*
	COPD		15 (16.3)	7 (10.9)	22	0.343*
	Hypothyroidism		3 (1.9)	0(0)	3	0.202*
	Parkinson		1 (1.1)	1 (1.6)	1	0.654*
	Seizure		3 (3.3)	1 (1.6)	4	0.509*
	CVA		17 (18.5)	2 (3.1)	19	0.003*
	ESRD		5 (5.40)	3 (4.7)	8	0.571*
	Cancer		8 (8.7)	1 (1.6)	9	0.057*
	Trauma		1 (1.1)	0 (0)	1	0.590*
	MS		1 (1.1)	1 (1.60)	2	0.654*
	Cirrhosis		1 (1.1)	0 (0)	1	0.590*
	IPF		4 (4.3)	1 (1.6)	5	0.316*
Drugs N (%)	**DPP-4 I**	Yes	36 (39.1)	22 (34.4)	58	0.545*
	Sulfonylurea		34 (37)	25 (39.1)	59	0.790*
	Biguanides		74 (80.4)	43 (67.2)	117	0.060*
	SGLT2 inhibitor		32 (34.8)	24 (37.5)	56	0.728*
	Insulin		48 (52.2)	26 (40.6)	74	0.155*
COVID19 Drugs	**Tocilizumab**	Yes	12 (13)	10 (15.6)	21	0.649*
	Favipiravir		9 (9.8)	6 (9.4)	15	0.932*
	Hydroxychloroquine		11 (12)	6 (9.4)	17	0.611*
	Remdesivir		37 (40.2)	41 (64.1)	78	0.003*
	Lopinavir/Ritonavir		26 (28.3)	22 (34.4)	48	0.416*
	Interferon beta-1a		23 (25)	22 (34.4)	45	0.204*
Outcomes & Complications	**Secondary bacterial Infection**	Yes	30 (32.6)	1 (1.6)	31	<0.001*
	Venous thrombosis		11 (12)	1 (1.6)	12	0.014*
	GI. Bleeding		12 (13)	5 (7.8)	17	0.302*
	Intubation		85 (92.4)	5 (7.8)	91	<0.001*
O2 saturation ranges at baseline, N (%)		O2 < 88%	87 (94.6)	51 (79.7)	138	0.007*
		92% > o2 >=88%	5 (5.4)	9 (14.1)	14	
		O2 >= 92%	0 (0)	4 (6.3)	4	
		Mean (±SD)	73.51 (±11.29)	81.02 (±8.49)	156	<0.001**
ICU length of stay		Mean (±SD)	11.12 (± 9.48)	10.34 (±7.67)	156	0.589**
Hospital length of stay		Mean (±SD)	13.21 (± 9.5)	12.33 (±7.62)	156	0.540**

N: Number; SD: Standard Deviation; DM: Diabetes Mellitus; HTN: Hypertension; IHD: Ischemic Heart Disease; DLP: Dyslipidemia; COPD: Chronic Obstructive Pulmonary Disease; CVA: cerebral vascular accident; ESRD: End Stage Renal Disease; IPF: Idiopathic Pulmonary Fibrosis; MS: Multiple sclerosis; DDPI: Dipeptidyl peptidase-4 inhibitor; SGLT2:Sodium-glucose co-transporter-2; O2Sat: Oxygen Saturation; ***** chi-square test**,** **: Independent T-test

Compared to nondiabetic patients, diabetic patients were found to have a higher occurrence of inpatient complications, including secondary bacterial infections, GI bleeding, and venous thrombosis.

These complications may have played a role in the higher mortality rate among diabetic patients. Hospital infections were found to be the leading cause of death for Covid-19 patients (35). The lungs can be damaged by severe coronavirus-2 infection, resulting in disrupted gas exchange, loss of surfactant, and increased bacterial growth (36). The risk of secondary bacterial infections is higher for ICU patients due to the severity of their primary viral disease and increased use of invasive procedures (37). According to our research, the need for endotracheal intubation and mechanical ventilation was more common in diabetic patients than in nondiabetic patients.

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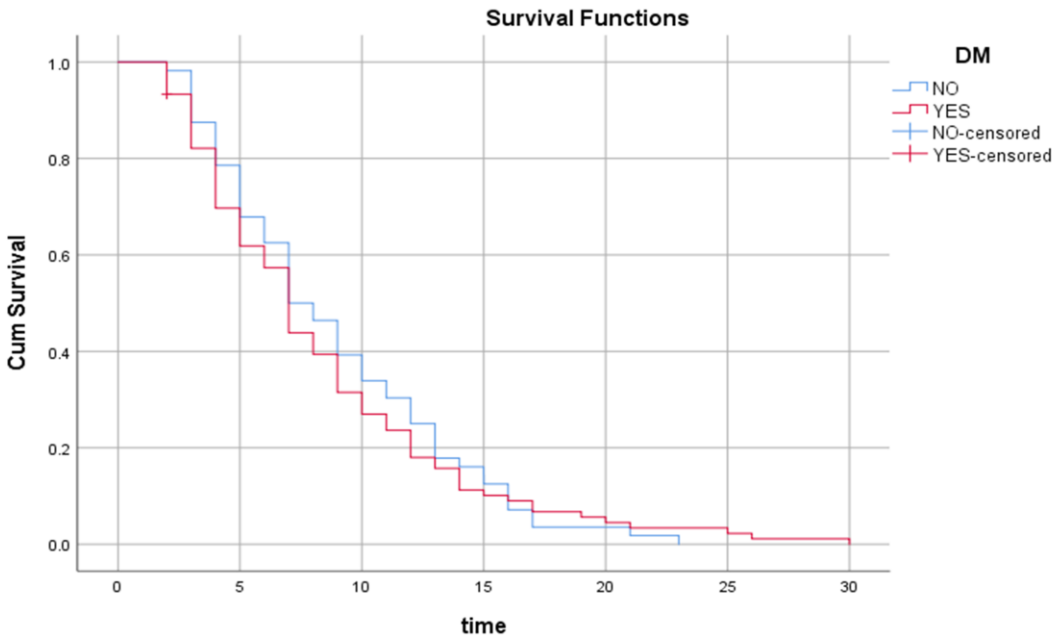
Table 4. Association between Imaging findings and Laboratory with death in diabetes Patient

Variable			Death		Total	*P*-value
			Yes	No		
Type of CT	Consolidation	Yes	27 (29.3)	26 (40.6)	53	0.144*
	GGO		25 (27.2)	18 (28.1)	43	0.896*
	Nodular		5 (5.4)	3 (4.7)	8	0.835*
	Reticular		7 (7.6)	0 (0)	7	0.023*
	Fibrosis		2 (2.2)	0 (0)	2	0.346*
	PE		6 (6.5)	5 (7.8)	11	0.757*
	Crazy. Paving		3 (3.3)	2 (3.1)	5	0.962*
Score of lung involvement at baseline, N (%)		0-8	20 (21.7)	6 (9.4)	26	0.001*
		9-16	32 (34.8)	43 (67.2)	75	
		17-25	40 (43. 5)	15 (23.4)	55	
		Mean (±SD)	14.71 (±6.49)	13.45 (±4.39)	156	0.181**
CRP, N (%)		-	18 (19.6)	7 (10.9)	25	0.403*
		+	19 (20.7)	17 (26.6)	37	
		++	29 (31.5)	18 (28.1)	47	
		+++	26 (28.3)	22 (34.4)	48	
Laboratory Findings at baseline	ESR	Mean (±SD)	46.10 (±28.08)	48.17 (±29.31)	156	0. 656**
	WBC		9.28 (± 5.22)	8.40 (± 5.62)	156	0.321**
	NLR		11.78 (±8.06)	7.48 (± 5.33)	156	<0.001**
	PLT		196.27 (±77.25)	196.17 (±85.95)	156	0.994**
	BUN		68.02 (±39.10)	58.60 (±47.52)	156	0.178**
	Cr		1.82 (±1.33)	1.79 (±1.68)	156	0.890**
	BS		184.97 (±68.72)	156.84 (±53.63)	156	0.007**
	AST		70.50 (±66.49)	38.06 (±21.71)	156	<0.001**
	ALT		60.17 (±66.62)	36.72 (±42.34)	156	0.014**
	ALP		221.75 (±123.49)	205.17 (±90.75)	156	0.362**
	LDH		788.04 (±544.58)	606.23 (±240.70)	156	0.013**

N: Number; SD: Standard Deviation; DM: Diabetes Mellitus; Disease; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; CPK: Creatine Phosphokinase ; LDH: Lactate Dehydrogenase; WBC: White Blood Cells; NLR: Neutrophil-Lymphocyte Ratio; AST: Aspartate Transaminase; ALT: AlanineTransaminase; BS: Blood Sugar; ALP: Alkaline Phosphatase; O2Sat: Oxygen Saturation.; Cons: Considerations; GGO: Ground-glass opacification; PE: pleural effusion; ***** chi-square test**,** **:Independent T-test



Log Rank (Mantel-Cox), x^2:0 .192, *P*-value:0.661

Figure 1. diabetic patients-survival rate in diabetic and non Meier diagram-Kaplan

Diabetic patients experience worsening of the disease and increased susceptibility to complications and secondary infections from the ventilator. Some studies have established a

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[DOI: 10.18502/ijdo.v16i2.15707]

solid synergistic effect that intensifies lung damage in the presence of both coronavirus and bacterial infections (38,39).

In the interaction of bacterial and viral pathogens, numerous pro-inflammatory cytokines are released, particularly in severe cases of COVID-19 (40). Infections of the respiratory tract by viruses lead to dysbiosis and compromised immune response, allowing secondary infections to thrive. Some observe through studies show that diabetic patients with COVID-19 have a higher abundance of pathogens and opportunistic microorganisms than both nondiabetic patients (41,42) and the control group (38,39).

The destruction of normal flora in the oral cavity and nasopharynx puts COVID-19 patients at a higher risk of secondary infections (39,40). Antimicrobial substances produced by the normal flora play a crucial role in preventing the activity of pathogenic bacteria (43). The absence of this protective mechanism raises the likelihood of secondary infections.

The study revealed a significant increase in venous thrombosis among diabetic patients compared to nondiabetic patients. It has been found that COVID-19 patients in intensive care units have a higher likelihood of developing VTE events, and the occurrence of venous thrombosis in these patients is associated with a decline in their clinical prognosis (44).

According to a meta-analysis, venous thrombosis is associated with a 161% increase in mortality and a 190% rise in severe COVID-19 cases (45). Calvisi and his colleagues (46) discovered a higher risk of thromboembolism in COVID-19 patients with diabetes or hyperglycemic stress, resulting in worse clinical outcomes.

The current study shows that the type of medication for blood glucose management does not significantly affect diabetic patient mortality. Previous studies in this area have presented contrasting results, unlike our findings. According to a network meta-analysis conducted by Chen et al. (47), the use of metformin, DPP-4I, SGLT2I, or GLP1RA can decrease the mortality risk in COVID-19 patients, whereas insulin use can increase it. Notably, a significant number of the reviewed studies did not mention clinical outcomes in severe cases of COVID-19. The restricted population we studied, consisting of ICU patients with severe disease, could be a key factor in the disparity of our findings.

Among the COVID-19 drugs given to the patients in the study, it was found that diabetic patients who took remdesivir had a lower mortality rate. However, the multivariate regression did not reveal significant use of this drug. A meta-analysis performed by Amstutz et al. (2023) showed that remdesivir reduces mortality in hospitalized COVID-19 patients without respiratory support, but the evidence was inconclusive for those on mechanical ventilation (48). Remdesivir, the first approved antiviral agent for COVID-19, has been proven to reduce recovery time, hasten clinical improvement, and decrease discharge time (49).

Patients with elevated blood glucose upon ICU admission have a greater likelihood of mortality, as indicated by the study. Evidence suggests that, despite undergoing comprehensive treatment for COVID-19, patients with hyperglycemia showed higher D-dimer levels during hospitalization than patients with normo-glycaemia (50). Thus, increased blood glucose levels can trigger inflammation and abnormal blood clotting, resulting in severe COVID-19 and mortality. Additionally, it has been demonstrated that IL-6 and D-dimer levels remain elevated in hyperglycemic patients during hospitalization at the hospital (51,52).

Hence, stringent control of blood glucose levels mainly serves to protect hyperglycemic patients with COVID-19 infection (53). The cytokine level returns to normal after insulin infusion and the resolution of the hyperglycemic crisis, reducing the risk of death (50).

The study found that diabetic individuals with a history of stroke, lower oxygen

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saturation levels at ICU admission, severe lung involvement on chest CT scan, higher NLR, secondary bacterial infection, venous thromboembolism, and elevated AST, ALT, and LDH had a significantly higher mortality rate. Regression analysis showed that initial arterial O2 saturation, NLR, incidence of infection, and higher AST are significant factors affecting the mortality of diabetic patients in the ICU. Hence, it is crucial to thoroughly evaluate these factors during the admission of diabetic patients with COVID-19.

This will help identify high-risk diabetic patients and allow for closer monitoring of their clinical condition and optimal treatment. It is crucial to highlight that diabetic patients admitted to the ICU face the highest risk of mortality from secondary bacterial infections. Consequently, it is of utmost importance to take extraordinary measures to prevent these infections in the ICU.

Careful consideration should be given to strict adherence to infection control measures for diabetic COVID-19 patients in the ICU. The prompt detection and treatment of infections can significantly decrease patient mortality rates. It has been reported in several studies that an increase in NLR upon admission of COVID-19 patients independently predicts disease severity and mortality (54,55).

The present study found no significant difference in average survival days for diabetic and nondiabetic groups. Diabetes may not be the sole reliable predictor for mortality and survival in COVID-19 patients in the ICU, as other risk factors could also have a significant impact.

The present study has certain limitations that should be noted. Although patients were examined for a relatively long time, this study was retrospective and single-center. Additionally, the study results may have been affected by different variants of the coronavirus with varying levels of virulence. Furthermore, the introduction of better treatments and vaccines for COVID-19 has resulted in improved clinical outcomes for patients.

The status of chronic blood glucose control and HbA1C levels in patients, which we had no information on, may have influenced their prognosis and led to secondary complications.

Conclusion

Diabetic patients who contact with COVID-19 are at a greater risk of experiencing severe clinical consequences and a higher mortality rate when admitted to the intensive care unit. Mortality in these patients is closely linked to factors such as O2 saturation, NLR levels, and secondary infections. Careful attention to prevention, patient monitoring, and prompt treatment of secondary infections are crucial to reducing mortality rates.

Acknowledgments

The authors express their sincere gratitude to the authorities at Shahid Sadoughi University of Medical Sciences for their invaluable assistance throughout the study.

Funding

This study was approved by Clinical Research Development Center at Shahid Rahnemoon Hospital, Yazd, Iran.

Conflict of Interest

The authors declare that they have no Conflicts of interest.

Authors' contributions

M. GhJ: conceived and designed the analysis and wrote initial draft of the manuscript.

S. M: conceived and designed the analysis, collected the data, and performed the analysis.

M. H: conceived and designed the analysis and interpreted of data.

All authors have accepted responsibility for the entire content of this manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work

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[DOI: 10.18502/ijdo.v16i2.15707]

are appropriately investigated and resolved and approved the version to be published.

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