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Original article

Clinical Characteristics and Outcomes in Diabetic and Non-Diabetic Patients Hospitalized for COVID-19: A Multicenter Cross-Sectional Study in Southwestern Iran

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SUMMARY

Background. Diabetes is one of the most common diseases among hospitalized patients due to COVID-19. Therefore, this study aimed to identify the clinical characteristics of diabetic and non-diabetic patients with COVID-19 that may lead to death.
Methods. A multicenter cross-sectional study was conducted among patients admitted to hospitals due to COVID-19. The data, including demographic data, symptoms and signs, underlying diseases, patient progress, and outcomes were obtained from 38 hospitals in the registry system of Khuzestan province (the southwest of Iran) between January 19, 2020 and March 8, 2021. The Cox proportional hazards regression was used to analyze the data.
Results. Data from 23,447 hospitalized patients due to COVID-19 were included in the study. Four thousand three hundred and forty participants (18.5%) with a mean age of 62 years had diabetes and 14.72% of them died. A multivarible Cox regression showed that the variables of age (Hazard Ratio (HR) = 2.65; 95% CI: 1.78- 3.95; P < 0.001), sex (HR = 1.16; 95% CI: 1.001 - 1.35; P = 0.049) and comorbidities such as cancer (HR = 1.89; 95% CI: 1.24 - 2.89; P = 0.003) and cardiovascular disease (HR = 1.2; 95% CI: 1.24 - 2.89; P = 0.032) were associated with mortality in diabetic patients with COVID-19.
Conclusion. This study showed that COVID-19 mortality was higher in men, the elderly, and people with cardiovascular disease and cancer. Therefore, the management and prevention of COVID-19 in diabetic patients with these characteristics are vital.

Keywords: **COVID-19, diabetes, mortality, prognostic factors, Iran**

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INTRODUCTION

In December 2019, a new kind of coronavirus called COVID-19 emerged in Wuhan, China, which spread rapidly around the world and was classified as a pandemic on March 11, 2020, by the World Health Organization (1). Although more than two years have passed since the onset of the pandemic and the vaccination of more than three billion people globally, the spread of the disease has not slowed down. The occurrence of multiple mutations in the virus, including Delta and Omicron, has caused great concern internationally. It has become a new challenge and has involved many countries, including Iran, in multiple peaks (2). According to the latest statistics, until March 5, 2022, more than 440 million cases of COVID-19 and more than 6 million deaths have been reported worldwide. In addition, there have been more than 6 million cases in Iran and more than 130 thousand deaths (3). Since the beginning of the COVID-19 pandemic, one of the issues of health care systems has been how to deal with patients with severe symptoms and need for hospitalization, which has added a heavy burden on the care system around the world, particularly in poor and developing countries. Therefore, the identification of risk factors leading to death, which are related to the severity of the disease, can help prevent and control the disease more effectively. According to studies, various factors such as old age, male gender, illness duration, muscle pain, high body mass index (BMI), hypoalbuminemia, lymphopenia, as well as the underlying diseases such as hypertension, cardiovascular disease, chronic respiratory failure, and diabetes are associated with the severity of illness and death due to COVID-19 (4 - 6).

Studies about COVID-19 showed that diabetes was one of the most common diseases among patients hospitalized due to COVID-19 (7, 8). The relationship between diabetes and the occurrence of infectious diseases, especially respiratory infections, has long been accepted in such a way that diabetic patients were more at risk of death due to infection (9). Viral infections lead to the activation of integrated stress responses, for example, the activation of serine/threonine-protein kinase such as PKR and PERK, which is associated with increased insulin resistance and thus increased disease severity (10). Coronavirus binds to angiotensin-converting enzyme2 (ACE2) receptors in major metabolic-rate organs and tissues, including pancreatic beta cells, adipose tissue, small intestine, and kidneys, causing polytropic changes in metabolism. Glucose can complicate the pathophysiology of diabetes or lead to new disease mechanisms (11). On the other hand, hyperglycemia stimulates the immune and inflammatory agents, and as a result, diabetics patients with COVID-19 can be at high risk of disease (12). Studies have indicated that COVID-19 was more severe in patients with diabetes and led to severe metabolic complications such as diabetic ketoacidosis and hyperosmolarity (13, 14). In many cases, COVID-19 accompanied by diabetes has caused admission to intensive care units (15, 16). In addition, diabetes has been suggested as an independent predictor of death in patients with COVID-19, and evidence has suggested that diabetes patients with COVID-19 were at a high risk of death (17 - 19). A recent study by Shi Q et al. in China found that 20 - 30% of dead patients due to COVID-19 had underlying diabetes, therefore, COVID-19 in diabetic patients has a poor prognosis (17). Recent studies have shown that several factors, including age, sex, race, comorbidities such as hypertension, cardiovascular diseases, chronic renal failure, and obesity, have been associated with poor prognosis in diabetes patients with COVID-19 (19, 20). However, further studies are needed to determine whether the poor prognosis in these cases is due to the nature of diabetes or other risk factors. Furthermore, a review of studies has shown that significant gaps remain in identifying the factors associated with disease severity and risk factors leading to death (10). Knowing these factors is essential to manage the patients better and reduce their complications. Therefore, this study aimed to evaluate the risk factors associated with death and to evaluate demographic and clinical characteristics in hospitalized diabetic and non-diabetic patients with COVID-19 using the Cox proportional hazards regression model.

METHODS

Sample collection

Thirty-eight hospitals affiliated with Ahvaz Jundishapur University of Medical Sciences (AJUMS), located in Khuzestan province in southwestern Iran, participated in this retrospective cross-sectional study. Since the outbreak of COVID-19 has occurred, AJUMS established a COVID-19 registry system in Khuzestan province

to record data of outpatients and inpatients, including those who had the suspected coronavirus (based on clinical signs) or confirmed (based on PCR test results) referred to the affiliated hospitals. The data were extracted from the registry system, as mentioned earlier. The system covered demographic data such as age and sex, underlying diseases (including chronic liver disease, chronic respiratory disease, chronic kidney disease, cardiovascular disease, asthma, cancer, hypertension, rheumatism, and history of stroke), symptoms and signs (including fever, cough, muscle pain, respiratory distress, loss of consciousness, olfactory disorder, taste disorder, seizures, abdominal pain, nausea, vomiting, diarrhea, anorexia, swallowing disorder, gastrointestinal bleeding, constipation, dry mouth, headache, confusion, paralysis, chest pain, skin disorders, chills, weakness and lethargy, sweating, sore throat, drowsiness, runny nose, and hemoptysis), PCR test results, CT scan results, pregnancy status, patient progress, and outcomes. In addition, data about admitting to the ICU and intubated patients were recorded. The inclusion criteria for choosing a record from the registry system included age over 20 years, a definitive diagnosis of COVID-19 (positive PCR-RT test re-

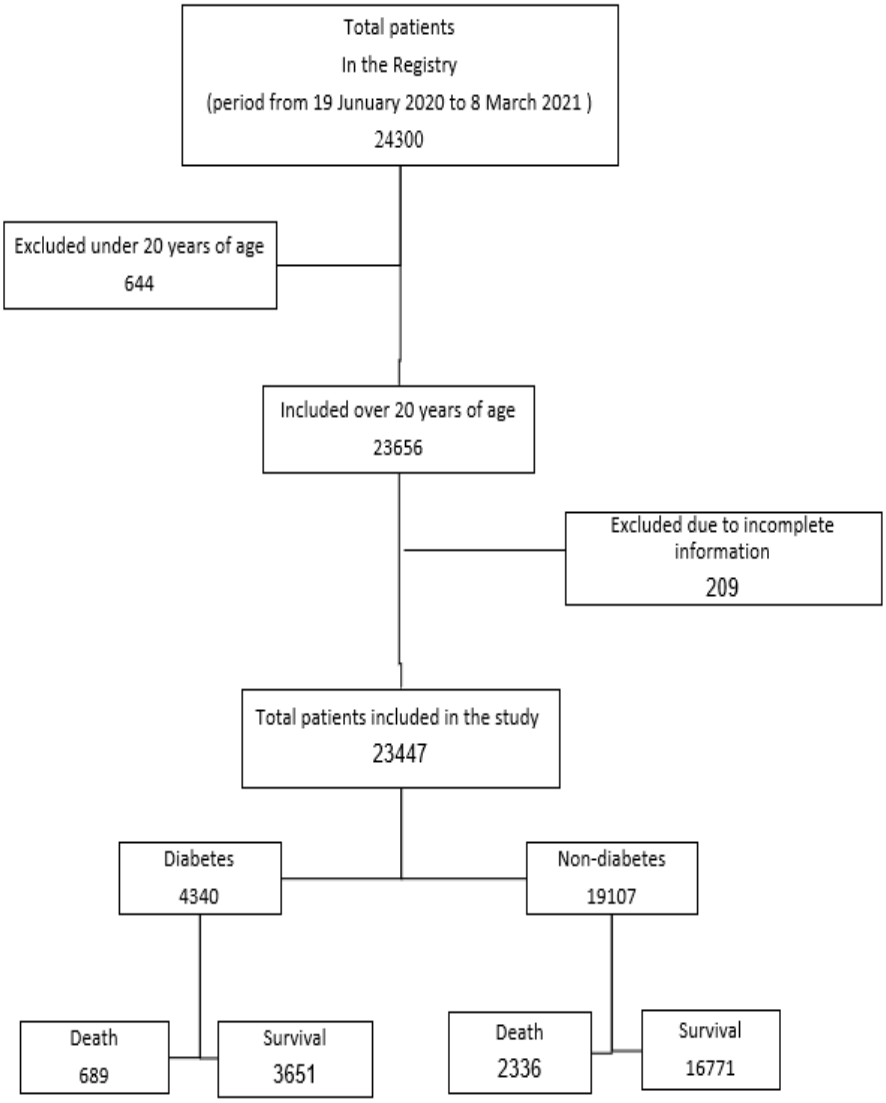

Figure 1: *Flowchart of patients' selection and study path*

sult), and complete data. Therefore, the records of 24,300 patients with a definitive diagnosis of COVID-19 between January 1, 2020, and March 8, 2021, were extracted from the registry system by two researchers. Of these, 853 records (644 under 20 years old and 209 incomplete) were excluded from the study. Finally, 23,447 records (4,340 diabetic and 19,107 non-diabetic) were included in the final analysis (Figure 1).

Statistical analysis

Categorical variables were presented as numbers, and percentages (%) and continuity variables were described using mean and standard deviation. The differences between the two groups (survivors and non-survivors) were compared by using the Pearson x 2 test, or Fisher's exact test, as appropriate. Otherwise, the Mann-Whitney U test was applied for continuous variables. A multivariate Cox proportional hazard regression model as the predictor variable for all-cause mortality was used to estimate hazard ratios (HR) with a 95% confidence interval (CI). A multivariate model was developed using a backward stepwise method, including all variables with $p < 0.2$ on the univariate analysis. The Kaplan-Meier method and log-rank test were used to compare the prognosis of COVID-19 patients in different groups (the analysis was applied to all patients, including diabetic patients). SPSS software version 26 and R version 4.1.1. were used to analyze the data. This study was approved by the Ethics Committee of Behbahan Faculty of Medical Sciences (IR.BHN.REC.1399.062).

RESULTS

The mean age of patients included in the study was 55.81 ± 16.89 years, with a range of 20 to 109 years at the time of diagnosis. The participants included 12,520 men (53.40%) and 10,927 women (46.60%), of which 3,025 (12.9%) participants died due to COVID-19 and 20,422 (87.1%) were cured. The most common symptoms at the admission were respiratory distress (56%), cough (53.88%), fever (39.28%), and muscle pain (27.43%). Among the underlying diseases, hypertension with 3,907 patients (16.66%) and cardiovascular diseases with 2,980 (12.7%) had the highest frequency. Also, more than 19% of patients were admitted to the ICU, and 9.58% were intubated.

As shown in Table 1, of the records (23,447 cases) included in the study, 18.5% had diabetes, and 81.5% were not diabetic. When comparing the diabetic and non-diabetic groups, diabetic patients were older than non-diabetic ones (mean age 62.19 vs. 54.37 years). For instance, 43.69% of diabetic patients were over 65 years old. In addition, most of the patients with diabetes were female (53.4% vs. 46.77%), while most non-diabetics patients were male (54.90% vs. 45.10%). Furthermore, the results indicated that the ratio of diabetic patients with hypertension (43.71% vs. 10.52%) and cardiovascular disease (27.47% vs. 9.36%) was significantly higher than in non-diabetic patients ($P < 0.05$). Also, diabetic patients were admitted to the ICU more than non-diabetics (24.03% vs. 18.22%). Furthermore, the intubation rate in diabetic patients was higher than in non-diabetics (10.81% vs. 9.3%). Moreover, some clinical manifestations such as muscle pain, loss of consciousness, olfactory disorder, taste disorder, seizures, abdominal pain, nausea, vomiting, anorexia, confusion, paralysis, chest pain, weakness, and lethargy as well as the presence of underlying diseases such as chronic liver disease, chronic kidney disease, rheumatism and history of stroke were significantly different between the two groups (diabetic and non-diabetic).

Additionally, the study results showed that of the diabetic patients with COVID-19 (4,340 cases) who participated in the study, 14.72% died, 85.28% survived, and the deceased patients were older than the survivors (67.95% vs. 61.11%). Typically, the highest number of deaths were in the population 65 years and above. Also, the number of COVID-19 cases was higher for males (53.40%) than females (46.60%). However, the number of deaths was almost the same in both sexes ($P > 0.05$). Moreover, the results indicated a statistically significant difference between the dead and survivors in having some conditions such as respiratory distress (71.70% vs. 52.40%), loss of consciousness (22.79% vs. 3.04%), admission in the ICU (59.94% vs. 17.22%), and intubation (52.54% vs. 2.93%), and also, cough, muscle pain, anorexia, headache, dizziness, and underlying diseases such as cancer, chronic kidney disease, chronic lung disease, rheumatism and hypertension (Table 2).

Table 1. *Baseline demographics and clinical characteristics of hospitalized patients with COVID-19, N = 23,447*

Variables	Total n = 23447, n (%)	With diabetes n = 4340, n (%)	Without diabetes n = 19107, n (%)	p-value
Age, (M ± SD)	55.81 ± 16.89	62.19 ± 13.09	54.37 ± 17.32	< 0.001
≤ 44	6635 (28.30)	405 (9.33)	6230 (32.61)	
45 - 64	9162 (39.08)	2039 (46.98)	7123 (37.28)	< 0.001
≥ 65	7650 (32.62)	1896 (43.69)	5754 (30.11)	
Sex				
Male	12520 (53.40)	2030 (46.77)	10490 (54.90)	< 0.001
Female	10927 (46.60)	2310 (53.23)	8617 (45.10)	
Current smoker	291 (1.24)	59 (1.36)	232 (1.21)	0.435
Hospitalized in ICU	4523 (19.29)	1042 (24.03)	3481 (18.22)	< 0.001
Intubation	2246 (9.58)	469 (10.81)	1777 (9.3)	< 0.0001
Symptoms				
Fever (temperature ≥ 37,5°C)	9209 (39.28)	1702 (39.22)	7507 (39.29)	0.929
Cough	12629 (53.86)	2331 (53.23)	10298 (53.90)	0.824
Myalgia	6432 (27.43)	1257 (28.96)	5177 (27.09)	0.013
Dyspnea	13130 (56.00)	2407 (55.46)	10723 (12.60)	0.429
Loss of consciousness	1130 (4.82)	268 (6.18)	862 (4.51)	< 0.001
Dysosmia	384 (1.64)	45 (1.04)	339 (1.77)	0.001
Dysgeusia	293 (1.25)	34 (0.78)	259 (1.36)	0.002
Seizure	84 (0.36)	17 (0.39)	67 (0.35)	0.683
Abdominal pain	433 (1.85)	98 (2.26)	335 (1.75)	0.026
Nausea	1387 (5.92)	313 (7.21)	1074 (5.62)	< 0.001
Vomit	1103 (4.70)	242 (5.57)	861 (4.51)	0.003
Diarrhea	790 (3.37)	148 (3.41)	642 (3.36)	0.869
Loss of appetite	2281 (9.73)	519 (11.96)	1762 (9.22)	< 0.001
Headache	1610 (6.87)	313 (7.21)	1297 (6.79)	0.319
Confused	749 (3.19)	182 (4.19)	567 (2.97)	< 0.001
Chest pain	989 (4.22)	223 (5.14)	766 (4.01)	0.001
Skin symptoms	26 (0.11)	6 (0.14)	20 (0.10)	0.549
Fever shakes	315 (1.34)	70 (1.64)	245 (1.28)	0.088
Weakness	1336 (5.70)	389 (8.96)	947 (4.96)	< 0.001
Sweating	56 (0.24)	10 (0.23)	46 (0.24)	0.900
Sore throat	207 (0.88)	33 (0.76)	174 (0.91)	0.339
Drowsiness	15 (0.06)	4 (0.09)	11 (0.06)	0.416
Rhinitis	43 (0.18)	8 (0.18)	35 (0.18)	0.987
Hemoptysis	33 (0.14)	8 (0.18)	25 (0.13)	0.396
Comorbidity				
Parkinson's disease	15 (0.06)	5 (0.12)	10 (0.05)	0.139
Cancer	317 (1.35)	61 (1.41)	256 (1.34)	0.735
Cronic liver diseases	119 (0.51)	32 (0.74)	87 (0.46)	0.018
Cardiovascular disease	2980 (12.70)	1192 (27.47)	1788 (9.36)	< 0.0001
Chronic kidney disease	619 (2.64)	236 (5.44)	383 (2.00)	< 0.0001
Asthma	494 (2.10)	104 (2.40)	390 (2.04)	0.141
Other chronic lung disease	323 (1.34)	66 (1.52)	257 (1.35)	0.370
History of stroke	46 (0.18)	10 (0.23)	36 (0.19)	0.572
Rheumatoid arthritis	62 (0.26)	13 (0.30)	49 (0.26)	0.030
Hypertension	3907 (16.66)	1897 (43.71)	2010 (10.52)	< 0.001
Death	3028	689 (15.87)	2339 (12.24)	0.001

Table 2 . *Characteristics of subjects with COVID-19 by their outcomes, (with and without diabetes) N = 23,447*

Variables	Patients with diabetes			Patients without diabetes		
	Death (n = 689)	Survival (n = 3651)	p- value	Death (n = 2306)	Survival (n = 16801)	p- value
Age, (M ± SD)	67.95 ± 12.68	61.11 ± 12.88	< 0.001	66.21 ± 16.03	52.74 ± 16.85	< 0.001
≤ 44	26 (3.77)	379 (10.38)	< 0.001	266 (11.54)	5964 (35.50)	< 0.001
45 - 64	244 (35.41)	1795 (49.17)		689 (29.88)	6434 (38.30)	
≥65	419 (60.82)	1477 (40.45)		1351 (58.59)	4403 (26.21)	
Sex, n (%)						
Male	345 (50.07)	1965 (53.82)	0.062	1373 (59.54)	9117 (54.26)	< 0.001
Female	344 (49.93)	1686 (46.18)		933 (40.46)	7684 (45.74)	
Current smoker	12 (1.74)	47 (1.29)	0.341	26 (1.13)	206 (1.23)	0.435
Hospitalized in ICU	413 (59.94)	629 (17.22)	< 0.001	1335 (57.89)	2146 (12.77)	< 0.001
Intubation	362 (52.54)	107 (2.93)	< 0.001	1286 (55.77)	491 (2.92)	< 0.001
Symptoms						
Fever (temperature ≥ 37,5° C)	292 (42.38)	1410 (38.62)	0.064	875 (37.94)	6632 (39.47)	0.156
Cough	337 (48.91)	1994 (54.62)	0.005	990 (42.93)	9308 (55.40)	< 0.001
Myalgia	158 (22.93)	1099 (30.10)	< 0.001	429 (18.60)	4748 (28.26)	< 0.001
Dyspnea	494 (71.70)	1913 (52.40)	< 0.001	1680 (72.85)	9043 (53.82)	< 0.001
Loss of consciousness	157 (22.79)	111 (3.04)	< 0.001	549 (23.81)	313 (1.86)	< 0.001
Dysosmia	9 (1.31)	36 (0.99)	0.452	15 (0.65)	324 (1.93)	< 0.001
Dysgeusia	5 (0.73)	29 (0.79)	0.854	13 (0.56)	246 (1.46)	< 0.001
Seizure	5 (0.73)	12 (0.33)	0.131	20 (0.87)	47 (0.28)	< 0.001
Abdominal pain	11 (1.60)	87 (2.38)	0.172	25 (1.08)	310 (1.85)	< 0.001
Nausea	44 (6.39)	269 (7.37)	0.355	92 (3.99)	982 (5.84)	< 0.001
Vomit	35 (5.08)	207 (5.67)	0.464	79 (3.43)	782 (4.65)	< 0.001
Diarrhea	17 (2.47)	131 (3.59)	0.122	42 (1.82)	600 (3.57)	< 0.001
Loss of appetite	63 (9.14)	456 (12.49)	0.027	187 (8.11)	1575 (9.37)	0.049
Headache	22 (3.19)	291 (7.97)	p < 0.001	73 (3.17)	1224 (7.29)	< 0.001
Confused	14 (2.03)	168 (4.60)	0.003	36 (1.56)	531 (3.16)	< 0.001
Chest pain	37 (5.37)	186 (5.09)	0.771	94 (4.08)	672 (4.00)	0.860
Skin symptoms	3 (0.44)	3 (0.08)	0.054	1 (0.04)	19 (0.11)	0.332
Fever shakes	9 (1.31)	61 (1.67)	0.482	14 (0.61)	231 (1.37)	0.002
Weakness	51 (7.40)	338 (9.26)	0.154	115 (4.99)	832 (4.95)	0.942
Sweating	0 (0.00)	10 (0.27)	0.175	2 (0.09)	44 (0.26)	0.108
Sore throat	8 (1.16)	25 (0.68)	0.198	8 (0.35)	166 (0.99)	0.002
Drowsiness	1 (0.15)	3 (0.08)	0.68	5 (0.22)	6 (0.04)	0.001
Rhinitis	2 (0.29)	6 (0.16)	0.57	1 (0.04)	34 (0.20)	0.097
Hemoptysis	1 (0.15)	7 (0.19)	0.82	5 (0.22)	20 (0.12)	0.223
Comorbidity						
Cancer	22 (3.19)	39 (1.07)	p < 0.0001	83 (3.60)	173 (1.03)	< 0.001
Chronic liver disease	7 (1.02)	25 (0.68)	0.355	19 (0.82)	68 (0.40)	0.005
Cardiovascular disease	243 (35.27)	949 (25.99)	< 0.001	326 (14.14)	1462 (8.70)	< 0.001
Chronic kidney disease	66 (9.58)	170 (4.66)	< 0.001	93 (4.03)	290 (1.73)	< 0.001
Asthma	15 (2.18)	89 (2.44)	0.671	38 (1.65)	352 (2.10)	0.154
Other chronic lung diseases	22 (3.19)	44 (1.21)	< 0.001	57 (2.47)	200 (1.19)	< 0.001
History of stroke	2 (0.29)	8 (0.22)	0.722	12 (0.52)	24 (0.14)	< 0.001
Rheumatoid arthritis	5 (0.73)	8 (0.22)	0.035	9 (0.39)	40 (0.24)	0.175
Hypertension	341 (49.49)	1556 (42.62)	0.001	329 (14.27)	1681 (10.01)	< 0.001

Also, of non-diabetics patients with COVID-19 (19107), 12.07% died, and 87.93% survived. A comparison of the two groups (deceased and survivors) indicated that subjects in the deceased group were older (66.21vs. 52.74), with a larger number of men than women (59.54vs. 40.46) as well as respiratory distress (72.85% vs. 53.82%) and loss of consciousness (23.81% vs. 1.86%). In addition, admission in the ICU (57.89% vs. 12.77%) and intubations (55.77% vs. 2.92%) were significantly more common in the deceased group. A significant difference was also observed between the groups of the deceased and survivors in having some symptoms such as cough, muscle pain, olfactory disorder, taste disorder, seizures, abdominal pain, nausea, vomiting, anorexia, headache, dizziness, chills, sore throat, drowsiness, cancer, chronic liver disease, chronic heart disease, chronic kidney disease, chronic lung disease, and hypertension (Table 2).

For diabetic patients with COVID-19 in the univariate model, variables of age, sex, cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, and hypertension with a p-value less than 0.2 entered the final model. Multivariable Cox regression showed that the variables of age, sex, cancer, and cardiovascular disease were associated with mortality in diabetic patients with COVID-19.

The results showed that the risk of death in diabetic patients over 65 years with COVID-19 was 2.65 times higher than in those under 44 years (HR = 2.65; 95% CI: 1.78- 3.95; P < 0.001). Also, the risk of

Table 3. *Univariable and multivariable Cox regression for risk factors associated with in-hospital death of COVID-19 patients with and without diabetes*

	Patients with diabetes		**Patients without diabetes**	
	Univariable HR (95% CI) p- value	**Multivariable HR (95% CI) p- value**	**Univariable HR (95% CI) p- value**	**Multivariable HR (95% CI) p- value**
Age (Ref: ≤ 44)				
45 - 64	1.5 (1 - 2.24) **0.05**	1.47 (0.98 - 2.21) 0.063	1.74 (1.51 - 2.01) **< 0.001**	1.72 (1.49 - 1.98) **< 0.001**
≥ 65	2.74 (1.85 - 4.08) **< 0.001**	2.65 (1.78 - 3.95) **< 0.001**	3.94 (3.45 - 4.49) **< 0.001**	3.94 (3.45 - 4.49) **<0.001**
Sex	1.13 (0.97 - 1.31) **0.111**	1.16 (1.001 - 1.35) **0.049**	1.17 (1.07 - 1.27) **< 0.001**	1.17 (1.08 - 1.27) **< 0.001**
Cancer	1.8 (1.79 - 2.76) **0.007**	1.89 (1.24 - 2.89) **0.003**	2.03 (1.63 - 2.53) **< 0.001**	2.21 (1.77 - 2.75) **< 0.001**
Chronic liver disease	1.17 (0.55 - 2.46) **0.689**		1.35 (0.86 - 2.12) **0.192**	1.71 (1.09 - 2.69) **0.019**
Cardiovascular disease	1.34 (1.15 - 1.57) **< 0.001**	1.20 (1.02- 1.39) **0.032**	1.48 (1.32 - 1.67) **< 0.001**	
Chronic kidney disease	1.38 (1.07 - 1.78) **0.022**		1.37 (1.11 - 1.68) **0.011**	
Asthma	0.859 (0.52 - 1.43) **0.562**		0.19 (0.59 - 1.11) **0.19**	
Other chronic lung diseases	1.52 (0.99 - 2.32) **0.061**		1.68 (1.28 - 2.17) **<0.001**	1.48 (1.14 - 1.93) **0.003**
History of stroke	0.77 (0.19 - 3.10) **0.713**		3.08 (1.75 - 5.43) **< 0.001**	2.16 (1.22 - 3.80) **0.008**
Rheumatoid arthritis	1.49 (0.62 - 3.62) **0.371**		1.07 (0.56 - 2.06) **0.842**	
Hypertension	1.27 (1.09 - 1.47) **0.002**		1.32 (1.73 - 1.48) **< 0.001**	
Current smoker	0.92 (0.52 - 1.64) **0.821**		1.12 (0.76 - 1.65) **0.561**	

death was 1.16 times higher in males than in females (HR = 1.16; 95% CI: 1.001 - 1.35; P = 0.049). In addition, the risk of death in diabetic patients with cardiovascular disease or cancer due to COVID-19 was 1.2 and 1.89 times higher than in patients without cardiovascular disease (HR = 1.2; 95%; CI: 1.02-1.39; P = 0.032) or cancer (HR = 1.89; 95% CI: 1.24 - 2.89; P = 0.003), respectively.

Also, the results of the univariate model for non-diabetic patients showed that variables such as age, sex, cancer, chronic liver diseases, cardiovascular disease, chronic kidney disease, asthma, chronic lung disease, history of stroke, and hypertension had a p-value less than 0.2. In addition, the multivariate Cox proportional hazard regression model showed that the variables including age, sex, cancer, chronic liver diseases, chronic lung disease, and history of stroke were associated with mortality due to COVID-19 in non-diabetic patients.

In addition, the results were as follows for non-diabetic patients with COVID-19: the hazard of death in patients over 45 years was 3.94 (HR = 3.94; 95% CI: 1.3.45- 4.49; P < 0.001). It was 1.72 times higher than in those under 44 years (HR = 1.72; 95% CI: 1.49 - 1.98; P < 0.001). Moreover, the hazard of death was 1.17 times higher in males than females (HR = 1.17; 95% CI: 1.08 - 1.27; P < 0.001). Also, the hazard of death in patients with chronic liver disease was 2.21 times higher than in patients without chronic liver diseases (HR = 2.21; 95% CI: 1.77 - 2.75; P < 0.001). In addition, patients with cancer had a 1.71 times higher hazard of death than patients without cancer (HR = 1.71; 95% CI: 1.09 - 2.69; P = 0.019). The hazard of death in patients who had chronic lung disease was 1.48 times higher than in patients without the disease (HR = 1.48; 95% CI: 1.14 - 1.93; P < 0.001); also, the hazard of death in patients with a history of stroke was 2.16 times higher than in patients without it (HR = 2.16; 95% CI: 1.22 - 3.80; P = 0.008) (Table 3).

Furthermore, according to the results obtained from the log-rank test and Kaplan-Meier curves (vertical distance), the probability of survival of diabetic patients over 65 years with COVID-19 who had an underlying disease such as cardiovascular disease, hypertension, cancer, chronic lung disease, and chronic kidney disease was less than in those without the diseases. Also, according to the horizontal distance of the Kaplan-Meier curves results, patients with COVID-19 who had diabetes and comorbidity, including cardiovascular disease, hypertension, cancer, chronic lung disease, and chronic kidney disease, were at high-level risk of death (Table 4 and Figure 1).

Table 4. *Results of log-rank test in diabetic patients with COVID-19*

Demographic feature	Chi-square	df	p-value
Age	74.72	2	< 0.001
Gender (ref: Male)	7.77	1	0.099
Cardiovascular disease	13.55	1	< 0.001
Hypertension	9.48	1	0.002
Cancer	7.76	1	0.005
Chronic kidney disease	6.12	1	0.013
Other chronic lung diseases	5.7	1	0.051
Asthma	0.36	1	0.55
Chronic liver disease	0.17	1	0.68
Rheumatoid arthritis	0.85	1	0.36
History of stroke	0.14	1	0.71
Current smoker	0.07	1	0.79

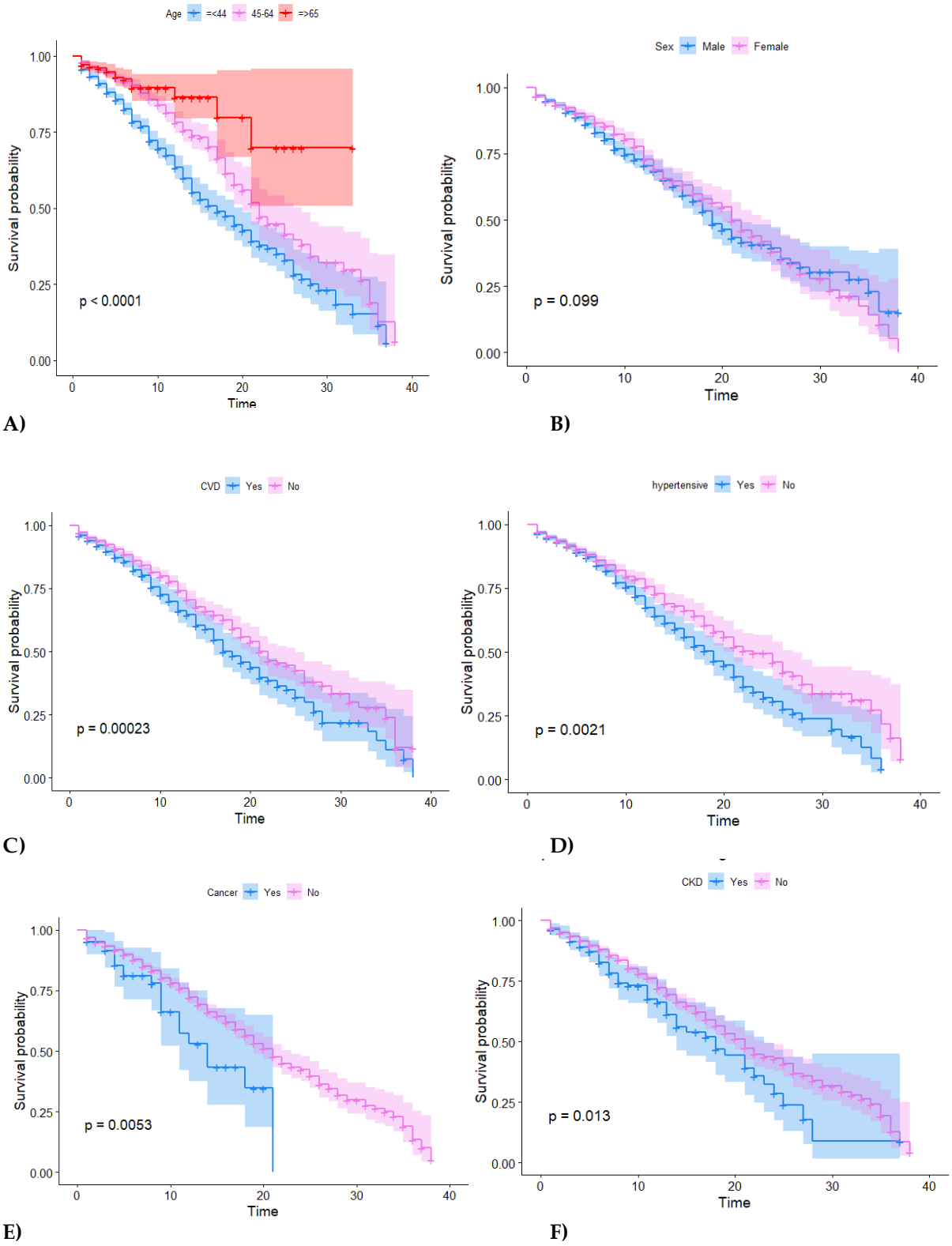

Figure 2. *Kaplan-Meier curve for demographic variables and underlying diseases in diabetic patients with COVID-19 in Ahvaz, Iran. (a) Age of COVID-19 diabetic patients; (b) Gender of COVID-19 patients; (c) CVD patients with COVID-19; (d) hypertension patients with COVID-19; (e) Cancer patients with COVID-19; (f) CKD patients with COVID-19;*

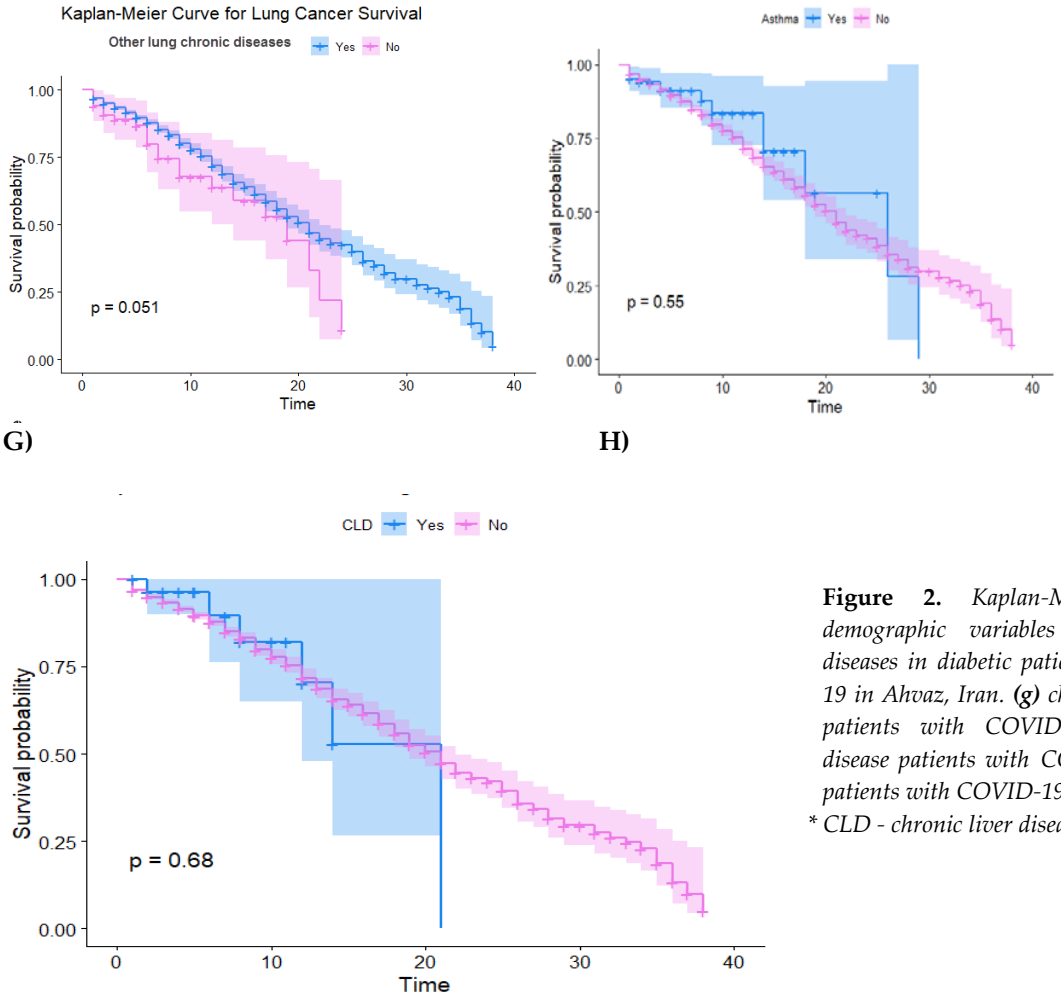

Figure 2. *Kaplan-Meier curve for demographic variables and underlying diseases in diabetic patients with COVID-19 in Ahvaz, Iran.* ***(g)*** *chronic lung disease patients with COVID-19;* ***(h)*** *Asthma disease patients with COVID-19;* ***(i)*** *CLD patients with COVID-19*

* *CLD - chronic liver disease*

DISCUSSION

This study aimed to investigate the risk factors of death in diabetic patients with COVID-19. This study showed that the most common symptoms at the time of hospitalization were shortness of breath, cough, fever, and muscle pain. These results were consistent with the results of some recent studies (17, 18, 21).

In addition, the majority of the hospitalized patients were males. The results of studies have confirmed that men were at high risk of receiving coronavirus infection (21, 22). It may be for reasons such as men being less concerned for health than women. Also, the mortality rate in diabetic men with COVID-19 was higher than in women, which is consistent with most studies in this field (18, 23). Studies have indicated that a higher prevalence of smoking among men can be one of the leading causes significantly associated with the severity of COVID-19 (24, 25). However, the present study showed a low percentage of smokers among the participants and did not confirm a significant difference in mortality rate between smokers and non-smokers. This finding is consistent with the results of a systematic review study with a meta-analysis that examined the association of smoking with COVID-19 (26). Moreover, the results of a retrospective study examining the causes of mortality in patients with diabetes over 18 years in Iran showed that overall mortality rates per 1000 person were higher in men than women, which indicates a higher prevalence of death among diabetic males than females (27). Of course, other factors may be involved in the difference in the mortality rate between males and females that require more research.

This study also showed that most diabetic patients hospitalized due to coronavirus disease were over 45 years old; diabetes type II was also

higher in this range. Therefore, the results were not surprising. In addition, the results of the present study showed higher mortality in elderly patients with diabetes. In addition, according to the multivariate regression results, the risk of death in patients over 65 years was 2.65 times higher than under 44 years. These results were consistent with many similar studies (17, 22). Old age seems to be one of the strongest predictors of death in diabetic patients with COVID-19. However, a study in the UK showed that the mortality rate of patients with diabetes decreases with age (28). Therefore, more studies are needed to interpret the relationship between age and the mortality rate of diabetes. Furthermore, the present study showed that diabetic patients with COVID-19 who have comorbidities, especially cardiovascular disease and cancer, had a higher mortality rate than those without it. These results were significant because cardiovascular disease after hypertension was the most common underlying disease among the patients, which is consistent with some recent studies (17, 18). In addition, many recent studies have noticed an association between cardiovascular diseases with severe COVID-19 and death in patients with diabetes (18, 29). Also, studies indicated that diabetes and cardiovascular disease were often closely related, and their simultaneousness increased the risk of mortality in patients with COVID-19 (17). Moreover, although a low percentage of diabetic patients had cancer in the present study, the results of multivariable regression analysis showed that the hazard ratio in diabetic patients with cancer was 89% higher than in non-cancerous diabetic patients. These results suggested that co-occurrence of cancer and diabetes can be a risk factor and significantly increases the mortality rate of diabetic patients with COVID-19.
Furthermore, recent studies have reported that cancer was significant underlying comorbidity in patients with COVID-19 and was associated with severity and mortality in these patients (30, 31).

One of the strengths of the present study was the large sample size and data collection from several hospitals. In addition, the data were obtained from a comprehensive information system in the center of Khuzestan province, one of the largest provinces in Iran with different ethnic groups, so the collected data could be a suitable representative of patients in this region. However, we could not access the medical records to gather all related data, including laboratory and pharmacological data. Therefore, we could not investigate the paraclinical data related to the severity of the disease and mortality in the patients.

CONCLUSION

The present study showed that diabetes could be a risk factor for coronavirus disease exacerbation and inpatient mortality. According to the current study results, mortality was high in diabetic male, the elderly, as well as in diabetic patients with underlying cardiovascular disease and cancer. These results can be considered for the management and prevention of COVID-19 in patients with diabetes.

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References

1. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet (London, England). 2020;395(10224):565-74. https://doi.org/10.1016/S0140-6736(20)30251-8

2. The Omicron variant: sorting fact from myth: WHO 2022. Available from: https://www.euro.who.int/en/health-topics/health-emergencies/pages/news/news/2022/01/the-omicron-variant-sorting-fact-from-myth .

3. COVID-19 Coronavirus Pandemic, live update: Worldometer; 2022. Available from: https://www.worldometers.info/coronavirus

4. Zali A, Gholamzadeh S, Mohammadi G, et al. Baseline Characteristics and Associated Factors of Mortality in COVID-19 Patients; an Analysis of 16000 Cases in Tehran, Iran. Arch Acad Emerg Med 2020;8(1):e70.

5. Parohan M, Yaghoubi S, Seraji A, et al. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. AGING MALE : 2020;23(5):1416-24. https://doi.org/10.1080/13685538.2020.177474

6. Ahmadi A, Ardeshiri S, Nezhadi VR, et al. Risk Factors for Mortality in Hospitalized Patients with COVID-19: A Cross-Sectional Study in Southwestern Iran. Iran Red Crescent Med J 2021;23(9).

7. Silverii GA, Monami M, Cernigliaro A, et al. Are diabetes and its medications risk factors for the development of COVID-19? Data from a population-based study in Sicily. Nutr Metabolism Cardiovascular Dis 2021;31(2):396-8. https://doi.org/10.1016/j.numecd.2020.09.028

8. Carrasco-Sánchez FJ, López-Carmona MD, Martínez-Marcos et al. Admission hyperglycaemia as a predictor of mortality in patients hospitalized with COVID-19 regardless of diabetes status: data from the Spanish SEMI-COVID-19 Registry. Ann Med 2021;53(1):103-16. https://doi.org/10.1080/07853890.2020.1836566

9. Kim EJ, Ha KH, Kim DJ, Choi YH. Diabetes and the Risk of Infection: A National Cohort Study. Diabetes Metab J 2019;43(6):804-14. https://doi.org/10.4093/dmj.2019.0071

10. Santos A, Magro DO, Evangelista-Poderoso R, Saad MJA. Diabetes, obesity, and insulin resistance in COVID-19: molecular interrelationship and therapeutic implications. Diabetology Metab Syndr 2021;13(1):23. https://doi.org/10.1186/s13098-021-00639-2

11. Rubino F, Amiel SA, Zimmet P, et al. New-onset diabetes in Covid-19. New England J Med 2020;383(8):789-90. https://doi.org/10.1056/NEJMc2018688

12. Lim S, Bae JH, Kwon H-S, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol 2021;17(1):11-30. https://doi.org/10.1038/s41574-020-00435-4

13. Li J, Wang X, Chen J, et al. COVID-19 infection may cause ketosis and ketoacidosis. Diabetes, Obes Metab 2020;22(10):1935-41. https://doi.org/10.1111/dom.14057

14. Ren H, Yang Y, Wang F, et al. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. Cardiovascular Diabetol 2020;19(1):1-8. https://doi.org/10.1186/s12933-020-01035-2

15. Weinberger DM, Chen J, Cohen T, et al. Estimation of excess deaths associated with the COVID-19 pandemic in the United States, March to May 2020. JAMA 2020;180(10):1336-44. https://doi.org/10.1001/jamainternmed.2020.3391

16. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of hospitalized adults with COVID-19 in an integrated health care system in California. JAMA 2020;323(21):2195-8. https://doi.org/10.1001/jama.2020.7202

17. Shi Q, Zhang X, Jiang F, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study. Diabetes Care 2020;43(7):1382-91. https://doi.org/10.2337/dc20-0598

18. Yan Y, Yang Y, Wang F, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Res Care. 2020;8(1):e001343. https://doi.org/10.1136/bmjdrc-2020-001343

19. Holman N, Knighton P, Kar P, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinology 2020;8(10):823-33. https://doi.org/10.1016/S2213-8587(20)30271-0

20. Apicella M, Campopiano MC, Mantuano M, et al. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinology 2020;8(9):782-92. https://doi.org/10.1016/S2213-8587(20)30238-2

21. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507-13. https://doi.org/10.1016/S0140-6736(20)30211-7

22. Alkundi A, Mahmoud I, Musa A, et al. Clinical characteristics and outcomes of COVID-19 hospitalized patients with diabetes in the United Kingdom: a retrospective single centre study. Diabetes Res Clin Pract 2020;165:108263. https://doi.org/10.1016/j.diabres.2020.108263

23. Belice T, Demir I. The gender differences as a risk factor in diabetic patients with COVID-19. Iran J Microbiol 2020;12(6):625. https://doi.org/10.18502/ijm.v12i6.5038

24. Cai H. Sex difference and smoking predisposition in patients with COVID-19. Lancet Respiratory Med 2020;8(4):e20. https://doi.org/10.1016/S2213-2600(20)30117-X

25. Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Res J 2020;55(5). https://doi.org/10.1183/13993003.00688-2020

26. Farsalinos K, Barbouni A, Poulas K, et al. Current smoking, former smoking, and adverse outcome among hospitalized COVID-19 patients: a systematic review and meta-analysis. Ther Adv Chronic Dis 2020;11:2040622320935765. https://doi.org/10.1177/2040622320935765

27. Salehidoost R, Mansouri A, Amini M, et al. Diabetes and all-cause mortality, a 18-year follow-up study. Sci Rep 2020;10(1):1-8. https://doi.org/10.1038/s41598-020-60142-y

28. Dennis JM, Mateen BA, Sonabend R, et al. Type 2 diabetes and COVID-19-Related mortality in the critical care setting: a national cohort study in England, March-July 2020. Diabetes Care 2021;44(1):50-7. https://doi.org/10.2337/dc20-1444

29. Orioli L, Servais T, Belkhir L, et al. Clinical characteristics and short-term prognosis of in-patients with diabetes and COVID-19: a retrospective study from an academic center in Belgium. Diabetes & Metabolic Syndrome: Clin Res Rev 2021;15(1):149-57. https://doi.org/10.1016/j.dsx.2020.12.020

30. Meng Y, Lu W, Guo E, et al. Cancer history is an independent risk factor for mortality in hospitalized COVID-19 patients: a propensity score-matched analysis. J Hematol Oncol 2020;13(1):1-11. https://doi.org/10.1186/s13045-020-00907-0

31. Yang K, Sheng Y, Huang C, et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19

in Hubei, China: a multicentre, retrospective, cohort study. Lancet Oncol 2020;21(7):904-13. https://doi.org/10.1016/S1470-2045(20)30310-7

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Kliničke karakteristike i ishodi kod bolesnika sa dijabetesom i bez dijabetesa hospitalizovanih zbog kovida 19: multicentrična studija poprečnog preseka sprovedena u jugozapadnom Iranu

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SAŽETAK

Uvod. Dijabetes je jedna od najčešćih bolesti kod hospitalizovanih zbog kovida 19. Stoga je cilj ove studije identifikacija kliničkih karakteristika koje su mogle da dovedu do smrtnog ishoda kod obolelih od kovida 19 sa dijabetesom i bez dijabetesa.
Metode. Multicentrična studija poprečnog preseka uključila je bolesnike hospitalizovane zbog kovida 19. Demografski podaci, simptomi i znaci, postojeće bolesti, podaci o stanju bolesnika i ishodu lečenja dobijeni su iz 38 bolnica u registarskom sistemu Khuzestan provincije (jugozapadni Iran), u periodu od 19. januara 2020. do 8. marta 2021. godine. Za analizu podataka korišćena je Koksova proporcionalna regresiona analiza.
Rezultati. Podaci 23.447 bolesnika hospitalizovanih zbog kovida 19 uključeni su u studiju. Četiri hiljade trista četrdeset učesnika (18,5%), prosečne starosti 62 godine, imalo je dijabetes, a 14,72% njih je umrlo. Multivarijabilna Koksova regresiona analiza pokazala je da su varijable godina (*Hazard Ratio* (HR) = 2,65; 95% CI: 1,78–3,95; P < 0,001), pola (HR = 1,16; 95% CI: 1,001–1,35; P = 0,049) i komorbiditeta poput kancera (HR = 1,89; 95% CI: 1,24–2,89; P = 0,003) i kardiovaskulranih bolesti (HR = 1,2; 95% CI: 1,24–2,89; P = 0,032) bili udruženi sa mortalitetom kod dijabetičara sa kovidom 19.
Zaključak. Ova studija je pokazala da je mortalitet zbog kovida 19 bio veći kod muškaraca, kod starije populacije i osoba sa kardiovaskularnom bolešću i kancerom. Stoga su lečenje i prevencija kovida 19 kod dijabetičara sa navedenim karakteristikama od vitalnog značaja.

Ključne reči: **kovid 19, dijabetes, mortalitet, prognostički faktori, Iran**