RESEARCH ARTICLE

The effect of underlying diabetes disease on clinical outcome and survival in patients with Covid-19: a propensity score matching study

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Abstract

Purpose Coronavirus increases mortality rate in people with underlying disease. The purpose of the present research was to compare the clinical outcomes in Covid-19 patients with and without underlying diabetes disease using propensity score matching.

Methods A matched case–control study was conducted on 459 diabetic patients with Covid-19 (case group) and 459 non-diabetic patients with Covid-19 (control group). Matching in two groups was performed using propensity score matching method. The effect of covariates on the clinical outcome of the patients (recovery-death) was assessed using logistic regression and the associations of factors with the patients' survival were determined using Cox proportional hazards regression model. Data were analyzed using R software.

Results The mean (standard deviation) age of patients in the case and control groups were 65.77 (12.2) and 65.8 (12.24), respectively. 196 patients (43%) in the case group, and 249 patients (54%) in the control group were male (with P-value < 0.05). The logistic regression model showed that the variables of age, level of blood oxygen (SpO2), ICU admission, length of hospitalization, cancer and diabetes affected patients' death. Furthermore, the resuts of the Cox regression showed that the variables of age, level of blood oxygen (SpO2), ICU admission, cancer and diabetes were related to survival of the patients. It was found that diabetes was significantly associated with mortality from COVID-19 with odds ratio of 2.88 (95% CI: 1.80–4.69; P < 0.01) and hazard ratio of 1.45 (95% CI: 1.01–2.03; P = 0.05).

Conclusion The underlying diabetes significantly increases the mortality among patients with Covid-19, so special care should be taken for this high risk group if they develop Covid-19.

Keywords Diabetes · Covid-19 · Logistic regression · Cox regression · Matching · Propensity score

Introduction

Covid-19 first appeared in China in December 2019 and spread rapidly worldwide, causing a global pandemic [1]. Coronavirus increases mortality in people with underlying disease [2–4]. Because COVID-19 is a new disease and the virus is changing day by day, knowledge about this disease is still incomplete and evolving. Many studies have shown that diabetic patients may experience a more severe clinical course and a higher mortality rate compared to others when

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they are infected by COVID-19 [5]. These studies identified diabetes as an important risk factor that increases mortality among Covid-19 patients [6, 7]. In recent decades, diabetes has been considered as one of the growing epidemics [8, 9]. Moreover, diabetes is one of the most common underlying diseases for patients with Covid-19 and about 20% of Covid-19 patients suffer from diabetes [10, 11]. Diabetes is an important public health problem, and uncontrolled diabetes can lead to many complications in other organs, including loss of vision and kidney dysfunction, heart attacks, strokes, and lower limb amputation, which can lead to disability and death [12]. Therefore, diabetic patients are more prone to certain infectious diseases, probably due to defects in their immune systems [13, 14]. Previous studies have reported that underlying diseases increase the risk of death in patients with Covid-19 [15].

Many studies have been conducted on risk factors of mortality rate among patients with diabetes, nevertheless their results are predisposed to high levels of bias because patients vary in terms of demographic variables, especially age. According to studies [16–18] and experts, the age variable is one of the most important demographic variables in COVID-19 disease. Therefore, the present study aimed to investigate the effect of diabetes on patients' treatment outcomes and assess their affecting factors among patients with Covid-19, using matching patients based on a case–control study in Hamadan.

Materials and methods

Subjects

In total, 2459 patients were hospitalized in Sina Hospital in Hamadan, Iran from February 2020 to October 2020 due to COVID-19 disease, of them 459 patients had diabetes (case group). Also, a number of 459 patients out of other 2000 COVID-19 patients who did not have diabetes were selected using the matching method based on age (control group). All demographic characteristics, clinical data, underlying diseases and disease symptoms were extracted from patients' medical records. Moreover, laboratory findings were performed during hospitalization. In this study, two outcomes were considered Including a binaryclinical outcome (death or recovery) and survival time. Survival time was considered as the time from admission to the hospital to death or discharge from the hospital (in days).

Statistical analysis

Quantitative variables with normal distribution were described by mean and standard deviation (SD), and their means were compared by independent samples t-test.

Qualitative variables were described by frequency (%) and compared by the Chi-square test or Fisher's exact test in two groups. To minimize any known confounding due to selection bias, the propensity score matching was done. Propensity score matching was performed by the nearest neighbor method with a ratio of (1:1) based on age variable aiming at to achieve a balanced distribution of all the covariates in the propensity score matched (PSM) cohort. "MatchIt" package (version 4.3.0) was used in R software version 3.6.2 for the propensity score matching, "survival" and "survminer" packages were used for survival analyses. Cox regression model was used to compare the survival of patients in case and control groups and to estimate the hazard ratios (HR). Univariate and multivariate logistic regression was used to estimate the odds ratio (OR) of patients' death and to explore the risk factors of death from COVID-19 among patients with diabetes disease, using "GLM" package. Stepwise regression using backward selection (Wald) method was also utilized to conduct variable selection. The final model only included the variables that contributed signifcantly to the model. Kaplan–Meier curves were plotted (before and after matching) for the time from admission to death (in days) for patients who died. The significance level of the tests was set in 5%.

Results

In the present matched case–control study, out of 2000 non-diabetic patients, using propensity score matching, 459 non-diabetic patients (control group) compared with 459 diabetes patients (case group). There were 196 men among diabetic patients (case group) and 249 men among non-diabetic patients (control group) (42.7% vs 54/2%, $P < 0.001$). Hypertension (58.4% vs 39.2%, $P < 0.001$) and heart disease (28.3% vs 16.1%, $P < 0.001$) were more frequent in patients with diabetes,while the median blood oxygen (SpO2) was lower (86% vs 88%, $P = 0.018$) in patients with diabetes. The median length of hospital stay and ICU stay were 6 (5) and 3 (1) days, respectively, in the case (control) group ($P < 0.001$). The rate of ICU admission, oxygentherapy, intubation, and death were significantly higher in patients with diabetes compared with the control group ($P < 0.001$ for all). There were statistically significant differences in variables of clinical signs of asthma, nausea and vomit ($p < 0.05$). There were no significant differences in other variables after matching (Table 1).

In this study, after data matching, un-adjusted logistic regression was used to identify significant variables associated with the patients' clinical outcomes in two groups (Table 2).

Multivariate logistic regression models were utilized using stepwise backward elimination of insignificant

Table 1 Demographic and clinical characteristics of the patients

Characteristics ID	Case group (n = 459)	Control group (n = 459)	p-value
mean(SD))) Age	65.77(12.24)	65.77(12.24)	1
Sex (male(%))*	196(0.43)	249(0.54)	<0.01
Temperature (mean(SD))	37.29(0.76)	37.37(0.74)	0.10
Hypertension (yes(%))*	268(0.58)	180(0.39)	<0.01
Systolic BP (mean(SD))	126.25(22.14)	124.21(19.34)	0.14
Diastolic BP (mean(SD)	76.65(12.96)	76.34(12.25)	0.71
Smoking(yes(%))	28(0.06)	44(0.09)	0.06
Length of hospitalization (mean(SD))*	8.05(5.91)	6.42(4.47)	<0.01
SpO2 (mean(SD))*	82.49(10.84)	84.17(10.70)	0.02
ICU admission (yes(%))*	166(0.36)	125(0.27)	<0.01
Oxygentherapy (yes(%))*	446(0.97)	416(0.91)	<0.01
Mechanical ventilation (yes(%))*	106(0.23)	50(0.11)	<0.01
Length of ICU stay (mean(SD))*	2.88(5.47)	1.63(3.54)	<0.01
Heart disease (yes(%))*	130(0.28)	74(0.16)	<0.01
pulmonary disease (yes(%))	54(0.12)	60(0.13)	0.62
Kidney failure (yes(%))	31(0.07)	21(0.04)	0.20
Cancer (yes(%))	14(0.03)	17(0.04)	0.71
Other diseases(yes(%))	190(0.41)	172(0.37)	0.25
Asthmatic(yes)(%)*	254(0.55)	297(0.65)	<0.01
Diarrhea(yes)(%)	43(0.09)	31(0.07)	0.18
Dry cough(yes)(%)	174(0.38)	189(0.41)	0.34
Sputum cough(yes)(%)	79(0.17)	86(0.19)	0.61
Muscles pain(yes)(%)	189(0.41)	177(0.38)	0.46
Fever(yes)(%)	230(0.50)	219(0.48)	0.51
Chills(yes)(%)	199(0.43)	196(0.43)	0.89
Sore throat(yes)(%)	15(0.03)	27(0.06)	0.08
Nausea(yes)(%)*	120(0.26)	83(0.18)	<0.01
Headache(yes)(%)	60(0.13)	77(0.17)	0.14
Fatigue(yes)(%)	15(0.03)	16(0.03)	0.99
Vomit(yes)(%)*	105(0.23)	66(0.14)	<0.01
Runny nose(yes)(%)	0	3(0.01)	0.25
Death(%)*	103(0.22)	48(0.11)	<0.01

*statistically significant

variables. In this way, variables with relaxed P-value ≤ 0.20 were included in the multivariate analysis with backward selection approach. The results of multivariate logistic regression were shown in Table 3. The results showed that having chronic diabetes is a factor influencing the clinical outcome of patients with Covid-19. The odds of death in diabetic patients was 2.88 times higher than that of the non-diabetic patients. Also, according to the results of the adjusted regression, in addition to diabetes, variables of age, having cancer, being admitted in ICU, length of hospitalization and SpO2 were significantly associated with mortality of the patient ($p < 0.05$), so that the odds of death in patients admitted to the ICU were 23.97 times higher than that of the other patients, and the odds of death was 3.32 times higher in patients with cancer compared with the noncancer patients.

Also, a decrease in one unit in blood oxygen (SpO2) level was associated with an increase in the odds of mortality by 4%, and with every one year increase in age and also with every one day increase in the length of hospitalization, the odds of death increasedby 5%. In the above interpretations, other variables in the model were considered to be constant.

Cox regression model was used to examine the effect of diabetes on the survival of patients with Covid-19 considering the time from admission to death (in days). The results of the univariate Cox regression model for the diabetes underlying disease were given in Table 4. Moreover, the results of the multivariate Cox regression model using stepwise backward variable selection method were provided in Table 5. According to the results, the variables of diabetes, age, having cancer, SpO2 and ICU admission were significantly

Table 2 Evaluating the effect of covariates on clinical outcome (mortality) of patients with Covid-19 using univariate logistic regression

Characteristics ID	OR	95% CI		p-value
		Lower	Upper	
*Age	1.06	1.04	1.07	<0.01
Sex	1.03	0.72	1.45	0.89
Smoking	1.14	0.58	2.04	0.70
Hypertension(yes)*	1.64	1.15	2.32	0.01
Temperature	0.97	0.76	1.22	0.79
Length of hospitalization*	1.06	1.03	1.09	<0.01
SpO2*	0.93	0.92	0.94	<0.01
ICU admission*	26.57	16.30	45.60	<0.01
Oxygentherapy*	5.64	1.73	34.70	0.02
Mechanical ventilation*	385.25	195.42	819.26	<0.01
Length of ICU stay*	1.18	1.14	1.22	<0.01
pulmonary disease(yes)	1.45	0.89	2.23	0.12
Kidney failure(yes)	1.85	0.90	3.59	0.07
Diabetes(yes)*	2.50	1.72	3.57	<0.01
Heart disease(yes)*	2.38	1.64	3.45	<0.01
Cancer(yes)	2.44	0.92	5.88	0.06
Other diseases(yes)	1.35	0.94	1.92	0.10
Asthmatic(yes)	1.28	0.89	1.85	0.18
Diarrhea(yes)	0.78	0.37	1.49	0.48
Dry cough(yes)*	0.64	0.44	0.93	0.02
Muscles pain(yes)	0.71	0.48	1.02	0.06
Fever(yes)	1.01	0.88	1.43	0.98
Chills(yes)	0.97	0.68	1.37	0.86
Sore throat(yes)	0.67	0.42	1.61	0.23
Nausea(yes)	1.12	0.73	1.69	0.58
Vomit(yes)	0.89	0.55	1.39	0.63
Fatigue(yes)	1.82	0.75	4.00	0.16
Headache(yes)	0.85	0.50	1.39	0.53
Sputum cough(yes)	0.75	0.45	1.19	0.23

*statistically significant

Table 3 Evaluating the adjusted effect of covariates on clinical outcome (mortality) of patients with Covid-19 using multivariate logistic regression

Characteristics	OR	95% CI		p-value
		Lower	Upper	
Age*	1.05	1.03	1.08	<0.01
SpO2*	0.96	0.94	0.98	<0.01
Diabetes(yes)*	2.88	1.80	4.69	<0.01
Cancer(yes)	3.32	0.93	11.27	0.06
ICU admission*	23.97	13.86	43.51	<0.01
Length of hospitalization*	0.96	0.92	0.99	0.02

*statistically significant

Table 4 The results of the univariate Cox regression model

Characteristics ID	HR	95% CI		p-value
		Lower	Upper	
*Age	1.04	1.02	1.05	<0.01
Sex	1.06	0.77	1.46	0.72
Smoking	1.08	0.61	1.90	0.80
Hypertension(yes)	1.24	0.90	1.72	0.19
Temperature	0.96	0.77	1.19	0.69
SpO2*	0.96	0.95	0.97	<0.01
ICU admission*	7.73	4.71	12.68	<0.01
Oxygentherapy	2.27	0.56	9.23	0.25
Mechanical ventilation*	33.96	19.49	59.18	<0.01
pulmonary disease(yes)	1.37	0.89	2.09	0.15
Kidney failure(yes)	1.74	0.96	3.15	0.06
Diabetes(yes)*	1.45	1.02	2.05	0.03
Heart disease(yes)*	1.44	1.03	2.01	0.03
Cancer(yes)	1.99	0.93	4.27	0.07
Other diseases(yes)	1.28	0.93	1.76	0.13
Asthmatic(yes)	1.10	0.79	1.54	0.56
Diarrhea(yes)	0.81	0.43	1.54	0.52
Dry cough(yes)*	0.69	0.49	0.98	0.04
Muscles pain(yes)	0.72	0.51	1.01	0.06
Fever(yes)	0.97	0.71	1.34	0.86
Chills(yes)	0.93	0.67	1.29	0.67
Sore throat(yes)	0.90	0.37	2.20	0.81
Nausea(yes)	0.87	0.60	1.27	0.47
Vomit(yes)	0.71	0.46	1.08	0.11
Fatigue(yes)	1.64	0.80	3.35	0.18
Headache(yes)	0.92	0.57	1.47	0.73
Sputum cough(yes)	0.88	0.56	1.38	0.58

*statistically significant

Table 5 Evaluating the adjusted effect of covariates on clinical outcome of patients (death, alive) with Covid-19 using multivariate Cox regression model

Characteristics ID	HR	95% CI		p-value
		Lower	Upper	
*Age	1.04	1.02	1.05	<0.01
SpO2*	0.96	0.95	0.97	<0.01
Diabetes(yes)*	1.45	1.01	2.03	0.05
Cancer(yes)*	3.03	1.37	6.66	<0.01
ICU admission*	7.48	4.97	11.56	<0.01

*statistically significant

associated with the survival of the patient ($P < 0.05$). The death risk of COVID-19 among the patients with the underlying diabetes was 1.45 times higher than that without diabetes. With every one-year increase in the patient's age and with every one unit increase in the blood oxygen (SpO2)

level, the risk of death increased by 4%, considering other variables constant. The death risk among the patients who were admitted to the ICU were 7.48 times higher than that of the other patients. Furthermore, the survival of the patients before (Fig. 1) and after (Fig. 2) matching in the case and control groups was displayed using the Kaplan–Meier survival analysis plots for the time since admission to death (days) for patients who died from COVID-19. Figure 2 shows that survival rates vary across the two groups after matching, with the diabetes disease patients having lower survival rates. There were 103 deaths among 459 diabetic patients and 48 deaths among 459 non-diabetic patients (22% vs 11%, $P < 0.001$). The mortality rates of the patients with Covid-19 for other significant variables were shown in Fig. 3. It can be seen from the Fig. 3 that the patients with diabetes, concurrent cancer, being admited to ICU, older than 80 years and having oxygen levels below 80 had higher mortality rates.

Discussion

Underlying diabetes disease was an important risk factors of mortality in patients with COVID-19.

Because they are a vulnerable population with a higher mortality rate than the general population and need special cares, so in this study, identifyingspecific risk factors of mortality and survival of these patients was performed using appropriate statistical analysis method.

In this study, the clinical outcome in 459 diabetic patients with Covid-19 (case group) was compared with 459 non-diabetic patients (control group) matched using the propensity score method. In the present study, in the univariate model, before adjusting the effect of other variables, the odds of mortality in diabetic patients was 2.50 times higher than that of the non-diabetic patients, so that 103 deaths were observed in diabetic patients and 48 deaths in non-diabetic patients. Various studies from different nations around the world have reported different mortality rates ranging from 8 to 60% in COVID-19 patients with diabetes underlying disease [19–23]. But none of these studies used data matching methods. Furthermore, some studies have confirmed the relationship between chronic diabetes and mortality in patients with COVID-19 [24, 25]. Guan et al. concluded that COVID-19 patients with any underlying disease had a lower prognosis than other patients [2]. Yan et al. showed that the incidence of death in patients with COVID-19, who also had underlying diseases such as diabetes, hypertension, and heart disease, was significantly higher compared with others [26]. Other studies have also shown that chronic underlying diseases such as hypertension and diabetes may be risk factors for death in patients with COVID-19 [27]. Numerous

Fig. 1 Survival time(day) from admission to death (before PSM)
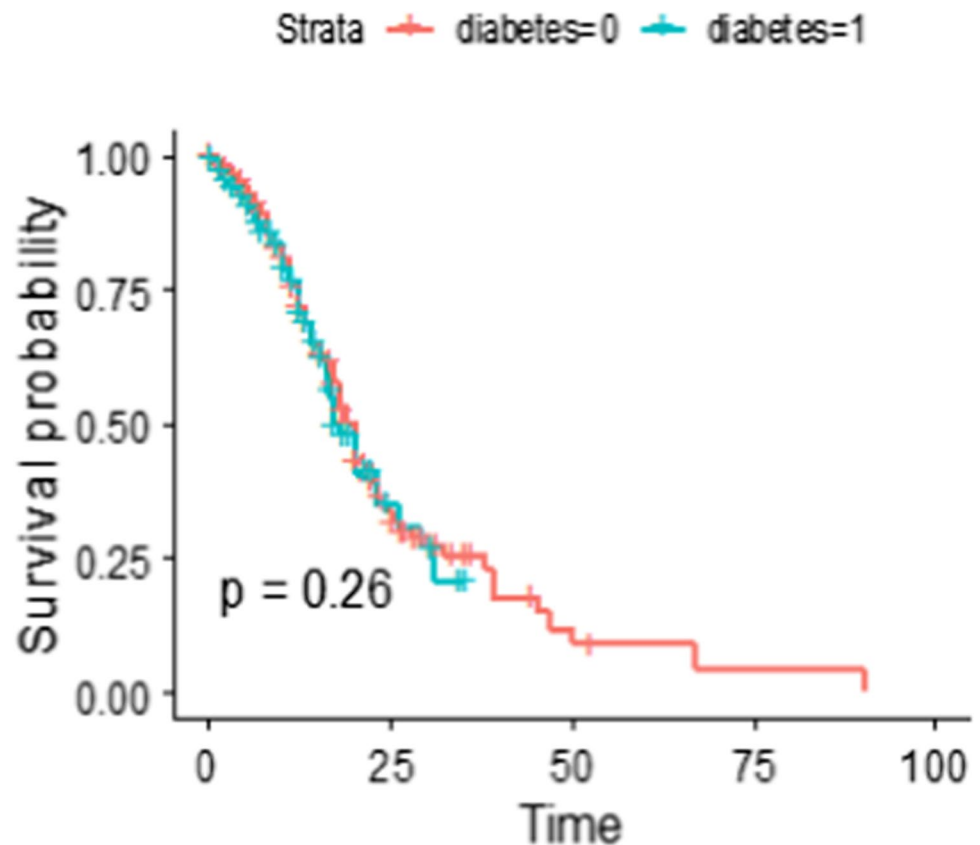
Fig. 2 Survival time from(day) admission to deat (after PSM)
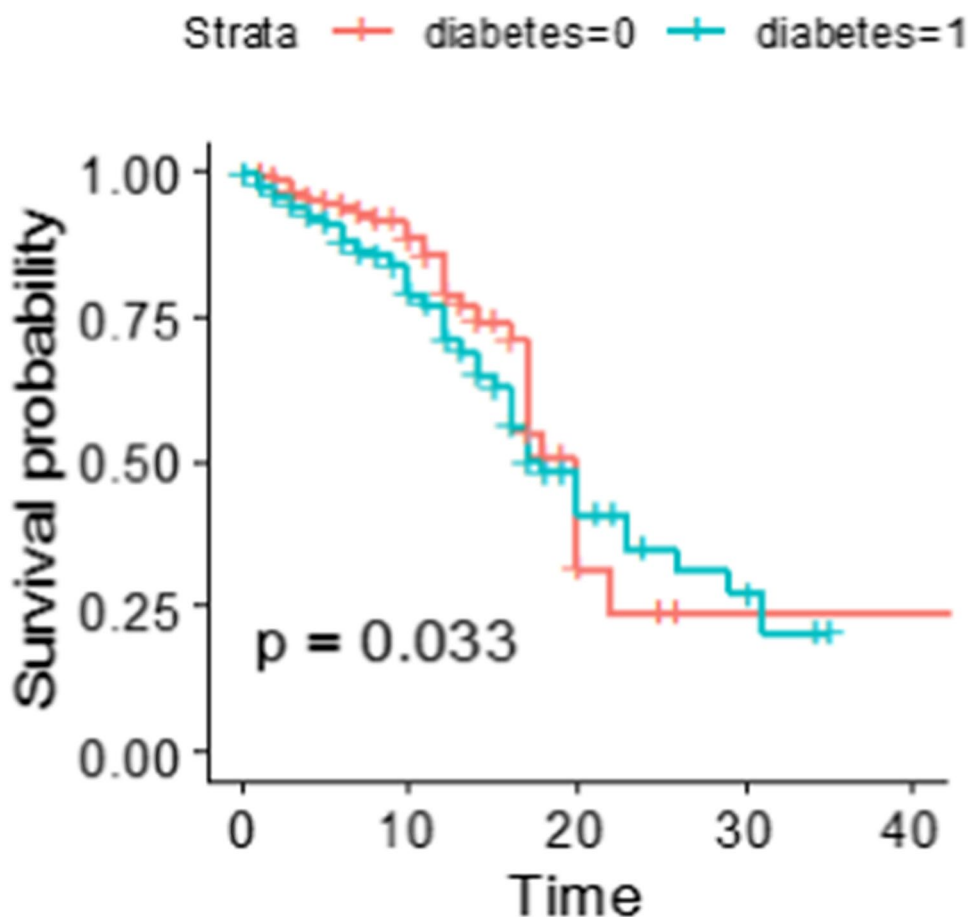
studies have shown that diabetes increases mortality ratein COVID-19 patients [28–32]. Kumar et al. showed that diabetes significantly increases mortality in patients with COVID-19. They indicated that the mortality rate in these patients is 2.16 times higher than the other patients [33]. In this study, despite adjusting the heart disease, cancer, and blood pressure in the case and control groups, the mortality rate of diabetic patients was 2.88 times higher than that of the non-diabetic patients. Rawshani et al. showed that hazard of diabetic patients is 1.50 times higher than that of the non-diabetic patients [34]. In the Sonmez et al. study the hazard ratio of diabetic patients was 1.75 [35]. Also, in the present study, after adjustment of all demographic and clinical variables, the hazard of death in diabetic patients was 1.45 times higher than that of non-diabetic patients.

Our findings, also, showed that ICU admission and length of hospitalization were significantly associated with the mortality of the patients with COVID-19. Moreover, Sonmez et al. showed that length of hospitalization and ICU admission were important variables on patient mortality [35].

Some studies have shown that there is no significant relationship between mortality in patients with COVID-19 and diabetes and the most important cause of mortality in these patients was age [36, 37]. Older people and people

with underlying diseases are more likely to be infected with COVID-19 virus [38, 39]. In the present study, age was associated with increasing risk of death among patients with COVID-19. However, age was matched between the two groups. Despite matching of age in both diabetic and non-diabetic groups, it was concluded that there was a significant relationship between mortality of patients with COVID-19 and age. This may be due to the fact that with increasing age, the immune function of the body decreases [40].

The results of the present study, also, showed that gender was not associated with mortality, which was consistent with the findings of other studies [41–46].

In some studies, clinical signs of patients have been considered as factors affecting patient survival [47]. In some studies, fever and dry cough have been the most important clinical symptoms in patients with COVID-19 [25, 48, 49]. In our study, the most important clinical symptoms of patients were shortness of breath and fever. None of the clinical signs had a significant relationship with the outcome of treatment.

In the present study, the results of logistic regression and also Cox regression showed that blood oxygen (SpO2) levels affect patients' survival. Similarly, Park et al. showed that symptoms such as fever and dry cough are the primary
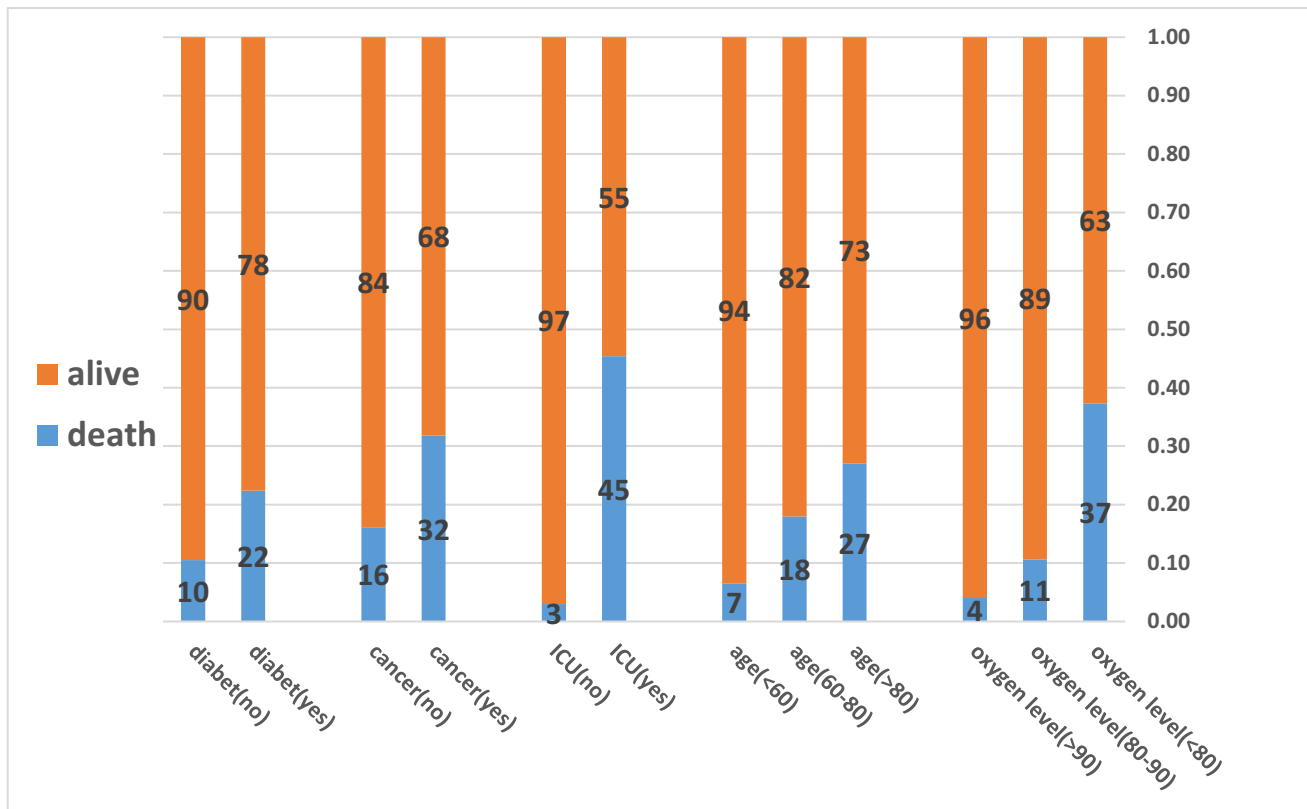
Fig. 3 The percentage of mortality among patients with Covid-19 in term of significant risk factors

causes of COVID-19 disease, but when symptoms become worse and more severe, respiratory symptoms such as shortness of breath and lack of saturated oxygen can cause death [50].

Conclusion

The results of evaluating the effect of diabetes on the outcome of treatment in patients with COVID-19 after adjusting the clinical and paraclinical characteristics of the variables showed that diabetes affects the mortality of patients. Therefore, they are a vulnerable population with a higher mortality rate than the general population. Thus, screening and identifying these patients and vaccinating them can reduce the mortality rate in these patients.

of the results. All authors contributed to the final version of the manuscript. All authors contributed to the final version of the manuscript and approved the final version of the manuscript.

Data availability The data and materials that supporting the findings of this study are available from the corresponding author, upon request.

Declarations

Consent to publication All individual participants included in the study gave their informed consent for the inclusion in the study and for publication of the manuscript.

Competing interests We declare no competing interests.

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