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RESEARCH ARTICLE

Factors associated with the poor outcomes in diabetic patients with COVID-19

Hadith Rastad[1] · Hanieh-Sadat Ejtahed[2,3] · Armita Mahdavi-Ghorabi[4] · Masoud Arzaghi[5] · Anis Safari[6] · Ehsan Shahrestanaki[6] · Mohammad Rezaei[7] · Mohammad Mahdi Niksima[7] · Akram Zakani[8] · Seyede Hanieh Dehghan Manshadi[7] · Fatemeh Ochi[7] · Shabnam Saedi[7] · Zeinab Khodaparast[9] · Neda Shafiabadi Hassani[10] · Mehdi Azimzadeh[11] · Mostafa Qorbani[11,12]

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Abstract

Purpose Diabetic's patients are supposed to experience higher rates of COVID-19 related poor outcomes. We aimed to determine factors predicting poor outcomes in hospitalized diabetic patients with COVID-19.

Methods This retrospective cohort study included all adult diabetic patients with radiological or laboratory confirmed COVID-19 who hospitalized between 20 February 2020 and 27 April 2020 in Alborz province, Iran. Data on demographic, medical history, and laboratory test at presentation were obtained from electronic medical records. Diagnosis of diabetes mellitus was self-reported. Comorbidities including cancer, rheumatism, immunodeficiency, or chronic diseases of respiratory, liver, and blood were classified as "other comorbidities" due to low frequency. The assessed poor outcomes were in-hospital mortality, need to ICU care, and receiving invasive mechanical ventilation. Self-reported. Multivariate logistic regression models were fitted to quantify the predictors of in-hospital mortality from COVID-19 in patients with DM.

Results Of 455 included patients, 98(21.5%) received ICU care, 65(14.3%) required invasive mechanical ventilation, and 79 (17.4%) dead. In the multivariate model, significant predictors of "death of COVID-19" were age 65 years or older (OR (95% CI): 2.0 (1.16–3.44), chronic kidney disease (CKD) (2.05 (1.16–3.62), presence of "other comorbidities" (2.20 (1.04–4.63)), neutrophil count $\geq 8.0 \times 10^9$/L)6.62 (3.73–11.7 ((, Hb level < 12.5 g/dl (2.05 (1.13–3.72) (, and creatinine level ≥ 1.36 mg/dl (3.10 (1.38–6.98)). (All p –values <0.05). Some of these factors were also associated with other assessed poor outcomes, e.g., need to ICU care or invasive mechanical ventilation.

Conclusion Diabetic patients with age 65 years or older, comorbidity CKD, "other comorbidities", as well as neutrophil count $\geq 8.0 \times 10^9$/L, Hb level < 12.5 g/dl, and creatinine level ≥ 1.36 mg/dl, were more likely to dead after COVID-19. Presence of hypertension and cardiovascular disease were associated with none of the poor outcomes.

Keywords Diabetes · COVID-19 · Mortality · Risk factor

Abbreviations

DM	Diabetes mellitus
ACEIs	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin II receptor blockers
CVD	Cardiovascular disease
CKD	Chronic kidney disease
AST	Aspartate transaminase
ALT	Alanine transaminases
Hb	Hemoglobin
LDH	Lactate dehydrogenase
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
Cpk	Creatine phosphokinase
Cp-MB	Creatine kinase myocardial band
ICU	Intensive care unit
SD	Standard deviation
IQR	Interquartile range
ROC	Receiver operating curve
AUC	Under the curve
Cis	Confidence interval
HTN	Hypertension

✉ Mostafa Qorbani
mqorbani1379@yahoo.com

Extended author information available on the last page of the article

PT	Prothrombin time
WBC	White blood cell
ACEIs	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin II receptor blockers

Introduction

The coronavirus 2019 disease (COVID-19) has become to a serious global public health challenge. So far, more than 5.3 million new cases and 342 thousand deaths of COVID-19 has reported worldwide [1]; the pandemic continues to expand despite intensive global preventive efforts. As with previous viral pandemics, [2] patients with underlying conditions are supposed to experience higher rates of COVID-19 related morbidity and mortality [3–5].

Diabetes mellitus (DM) is one of the most common underlying conditions found among patients with COVID-19 [6, 7]. Besides, the presence of DM has been associated with a higher risk of poor outcome in these patients [8–10]. However, up to our knowledge, a few previous studies intended to identify patients' factors on initial presentation that could predict poor outcome in diabetic patients with COVID-19 [11].

Hence, the present study has attempted to ascertain factors associated with poor outcome in hospitalized diabetic patients with COVID-19.

Materials and methods

Study design and population

This retrospective study included all diabetic patients aged 18 years or older with COVID-19 hospitalized between 20 February 2020 and 27 April 2020 in the Alborz province, Iran. Clinical diagnosis of COVID-19 was confirmed if patients met one of the two following criteria: I) a positive RT–PCR result, or II) a positive pulmonary abnormality on chest CT based on the radiological criteria of COVID-9 infection. We excluded patients who were still hospitalized ($n = 19$). Diabetes was ascertained through self-reporting.

Data collection

Demographic and clinical characteristics including age, gender, medical history, having any comorbidities, disease symptoms (caught, fever, shortness of breath, tiredness and lack of consciousness), O_2 saturation and drug history (statins, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs)) were collected at the first day of hospitalization. The asked comorbidities included hypertension, cardiovascular disease (CVD), chronic kidney disease (CKD), cancer, chronic liver diseases, psychological disorder, chronic respiratory disease, asthma, thyroid dysfunction, immunodeficiency, autoimmune diseases, hematologic disease, and neurological disorder.

Laboratory testing

Laboratory parameters on admission (fasting blood glucose level, white blood cell count, lymphocyte count, neutrophil count, concentrations of aspartate and alanine transaminases (AST, ALT), hemoglobin (Hb), creatinine, lactate dehydrogenase (LDH), albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatine phosphokinase (Cpk) and creatine kinase myocardial band (Cpk-MB) were collected.

Outcome

The primary outcome of this study was in-hospital mortality and poor outcomes including need to intensive care unit (ICU) and being ventilated during hospitalization in COVID-19 patients with diabetes. The study population was classified into two groups: discharged (survivors) or dead (non-survivors). Cured patients were discharged from hospital according to the following criteria: lack of fever for at least 72 h, clinical alleviation, and improvement in pulmonary abnormalities on chest CT imaging.

Statistical analyses

Descriptive statistics, mean (standard deviation (SD)) or median (interquartile range (IQR)), respectively for continuous variables and frequency (percentage) for categorical variables, were used to summarize demographic, clinical, and laboratory data of the cohort. Characteristics of survivors and non-survivors were compared using two-tailed t-tests, Mann–Whitney U tests or Chi-square tests.

The receiver operating curve (ROC) analysis was performed to compare the predictive abilities of blood parameters for predicting death of COVID-19; area under the curve (AUC) and its 95% confidence interval (CIs) are presented. The optimal cut points that provided the maximum sensitivity and specificity for each blood parameter to predict death of COVID-19 were identified using the maximal Youden Index. Then, the blood parameters were converted into a binary variable based on these identified optimal outpoints. Univariable and Multivariable logistic regression models were used to assess the association of predictor factors with each poor outcomes of COVID-19. Results are presented as crude and adjusted ORs and (95% CIs). We also performed a log-rank test to determine if there were differences in the survival distribution between males and females and two age groups ≥65 years and < 65 years.

We considered a P value of less than 0.05 as statistically significant. We conducted all statistical analyses using SPSS

Version19.0, (SPSS Chicago, IL, USA) or STATA version11 (Stata Corp LP, College Station, TX, USA).

Results

The study population was 455 hospitalized diabetic patients with COVID-19. Table 1 shows characteristics and disease-related symptoms in the study population on admission, overall and by survivor status. Overall, the mean age (SD) of patients was 63.8 (13.5), and 190 (41.8%) were male. The most common comlaints at prsentaion were shortness of breath (56.7%), caugh (45.9%), fever (37.4%), and tiredness (23.3%). At admission, lack of consciousness and O2 saturation less than 93% were observed in 5.7% (26) and 58.0% (264) of patients, respectively. Overall, 69.5% (316) of patients reported at least one comorbidity; the common comorbidities, in order of frequency, were HTN (54.0%), CVD (43.7%) and CKD (22.2%). The use of ACEIs /ARBs and statins was reported in 42.9% (190) and 28.9% (117) of patients, respectively.

During hospitalization, out of 455 patients, 98(21.5%) received ICU care, 65(14.3%) required invasive mechanical ventilation, and 79 (17.4%) dead. The median time from admission to discharge was 3 days (IQR: 1–6 days), and the median time to death was 4 days (2–8 days).

ompared to survivors, patients who dead (non-survivors) were significantly older (mean (SD) age: 69.4 years (12.2) vs. 62.6 years (13.5); $P < 0.001$), were more likely to have underlying comorbidity CKD (35.4% (28) vs. 19.4% (73); $P = 0.002$). In terms of numbers of comorbidities, a higher percentage of non-survivors had 3 or more comorbidities (22.8 vs. 12.5%; $P = 0.008$) than survivors.

Non-survivors were more likely to present with lack of consciousness (16.5% vs. 3.5%) and O2 saturation less than 93% (88.6% vs. 51.6%) than survivors. (Both p –values <0.001).

The frequency of the common complaints, ACEIs /ARBs and statins users, also the comorbidities HTN and CVD all

Table 1 Characteristics and disease-related symptoms in the study population on admission, overall and by survivor status

Characteristics	Total *N* = 455	Non-survivors *N* = 79	Survivors *N* = 376	P –value
Age Mean (SD)	63.8 (13.5)	69.4 (12.2)	62.6 (13.5)	**< 0.001**
Age ≥ 65 years, % (N)	47.9% (218)	65.8% (52)	44.1% (166)	**< 0.001**
Gender: Male, % (N)	41.8% (190)	49.4% (39)	40.2% (151)	0.131
Symptoms, % (N)				
Caught	45.9% (209)	36.7% (29)	47.9% (180)	0.070
Fever	37.4% (170)	39.2% (31)	37.0 (139)	0.704
Shortness of breath	56.7% (258)	62.0% (49)	55.6% (209)	0.294
Tiredness	23.3% (106)	16.5% (13)	24.7% (93)	0.114
Lack of consciousness, % (N)	5.7% (26)	16.5% (13)	3.5% (13)	**< 0.001**
O2 saturation < 93%	58.0% (264)	88.6% (70)	51.6% (194)	**< 0.001**
% (N)				
Comorbidities, % (N)				
HTN	54.0% (239)	60.5% (46)	52.6% (193)	0.206
CVD	43.7% (199)	51.9% (41)	42.0% (158)	0.108
CKD	22.2% (101)	35.4% (28)	19.4% (73)	**0.002**
Other*	10.1% (46)	16.7% (13)	8.8% (33)	**0.036**
Number of Comorbidities, % (N)				
0	30.5% (139)	22.8% (18)	32.2% (121)	**0.008†**
1	25.7% (117)	21.5% (17)	26.6% (100)	
2	29.5% (134)	32.9% (26)	28.7% (108)	
≥ 3	14.3% (65)	22.8% (18)	12.5% (47)	
Drug History				
ACEIs or ARBs	42.9% (190)	50.0% (38)	41.4% (152)	0.169
Statins	28.9% (117)	34.3% (24)	27.8% (93)	0.273

ACEIs angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *CKD* Chronic Kidney diseases, *CVD* Cardiovascular diseases, *HTN* Hypertension, *IQR* Inter quartile range, *ICU* Intensive care unit

*Cancer, rheumatism, immunodeficiency, or chronic diseases of respiratory, liver, and blood

†: linear-by-linear association test

were similar between survivors and non-survivors. (All p –values >0.05).

Laboratory findings on admission of the study population are presented in Table 2, overall and by survivor status. A lower lymphocyte count (median (IQR): 1.14 (0.78–1.8) vs. 2.25 (1.52–2.87); *P* value <0.001), but a higher count of WBC (9.8 (6.7–13.4) vs. 7.1 (5.4–9.2), P value = 0.004) and neutrophil (8.34 (7.70–8.71) vs. 7.00 (6.20–7.75); P value <0.001) was observed in non-survivors compared to survivors. Also, Non-survivors significantly had a higher concentration of serum creatinine, CRP, and LDH, CPK, CPK-MB, but a lower concentration of Hb than survivors (all *P* values <0.05).

Table 3 presents AUC and its 95% confidence interval (CI) of laboratory parameters for predicting COVID-19 death and optimal cutoff points of these parameters. Among assessed parameters, neutrophil count (AUC (95% CI): 0.76 (0.69–0.82)), lymphocyte count (0.75 (0.68–0.81)) and LDH level (0.74 (0.64–0.84)) had the highest diagnostic accuracy for the early detection of COVID-19 death, respectively. Besides, the concentrations of ALT and Esr were non-significant predictors of COVID-19 death.

The optimal cutoff point (sensitivity; specificity) of lymphocyte count, neutrophil count, and LDH level to discriminate between survivors and non-survivors was 1.51×10^9/L (72.1, 70.3), 8.0×10^9/L (67.2, 74.3), and 544 U/L (71.9, 72.8), respectively.

The WBC count had significantly lower predictive ability compared to neutrophil and lymphocyte count. ($p < 0.001$) Fig. 1.

Table 4 presents predictors for poor outcomes of COVID-19 separately, including death, need to ICU care, and invasive mechanical ventilation in diabetic patients based on the results of logistic regression models.

In the multivariate model, significant predictors of "death of COVID-19" were age 65 years or older (OR (95% CI): 2.0 (1.16–3.44), comorbidity CKD (2.05 (1.16–3.62), presence of other comorbidity (2.20 (1.04–4.63)), neutrophil count ≥8.0×10^9/L)6.62 (3.73–11.7 ((, Hb level < 12.5 g/dl (2.05 (1.13–3.72) (, and creatinine level ≥ 1.36 mg/dl (3.10 (1.38–6.98)). (All p –values <0.05).

Patients with age ≥ 65 years, 2 or more comorbidities, lymphocyte count <1.51×10^9/L, neutrophil count ≥8.0×10^9/L, Hb level < 12.5 g/dl, AST level ≥ 39 U/L, creatinine level ≥ 1.36 mg/dl, LDH level ≥ 544 U/L, and Cpk level ≥ 81.4 U/L had significantly higher odds for requiring ICU care than others. (All p –values <0.05).

Also, patients with age 65 years or older, comorbidity CKD, neutrophil count ≥8.0×10^9/L, AST level ≥ 39 U/L, creatinine level ≥ 1.36 mg/dl, LDH level ≥ 544 U/L were more likely to require invasive mechanical ventilation than others. (All p –values <0.05).

Based on log-rank test results, the difference in the survival distributions between two age groups ≥65 years and < 65 years were statistically significant ($\chi 2(1) = 8.73$, $p = 0.003$); but, the differences between males and females did not reach statistical significance ($\chi 2(1) = 2.88$, $p = 0.09$) (Figs. 2 and 3).

Table 2 Laboratory findings on admission of the study population, overall and by survivor status

Characteristics	Total Median (IQR*)	Non-survivors Median (IQR*)	Survivors Median (IQR*)	P value
WBC count, × 10^9/L	7.3 (5.4, 10.5)	9.8 (6.7–13.4)	7.1 (5.4–9.2)	**0.004**
Lymphocyte count,× 10^9/L	2.01 (1.21–2.87)	1.14 (0.78–1.8)	2.25 (1.52–2.87)	**<0.001**
Neutrophil count,× 10^9/L	7.29 (6.22–8.23)	8.34 (7.70–8.71)	7.00 (6.20–7.75)	**<0.001**
AST, U/L	36.0 (26.0–51.0)	33.5 (20.25–54.0)	29.0 (18.0–43.0)	0.087
ALT, U/L	30.0 (18.0–43.5)	45.5 (31.0–83.0)	34.0 (25.0–46.5)	0.118
Creatinine, mg/dl	1.1 (0.9–1.5)	1.4 (0.9–2.2)	1.1 (0.9–1.4)	**0.020**
LDH, U/L	474.0 (356.7–629.4)	674.0 (487.0–932.0)	437.0 (350.0–587.0)	**0.002**
Hb, g/dL	12.65 (11.30–14.1)	12.1 (10.9–13.3)	12.8 (11.6–14.1)	**0.008**
Esr, mm/h	44.5 (23.75–75.0)	43.5 (29.5–84.0)	44.5 (22.0–74.5)	0.872
CRP, mg/l	25.0 (7.0–73.0)	53.8 (21.0–79.0)	25.0 (5.75–72.0)	**0.015**
Cpk, U/L	88.5 (58.4–151.0)	115.0 (70.0–222)	81.7 (58.0–150.0)	**0.016**
Cpk-MB, IU/L	22.0 (15.0–30.0)	27.4 (19.0–40.3)	20.0 (14.0–29.0)	**0.019**
FBS, mg/dl	174 (138.0–224)	192.0 (153.0–262.0)	166.0 (134.0–216.0)	0.061

*IQR = Inter quartile range

ALT Alanine transaminases, *AST* Aspartate transaminases, *CRP* C-reactive protein, *CPK* Creatine phosphokinase, *CK-MB* creatine kinase myocardial band, *Esr* Erythrocyte sedimentation rate, *FBS* fasting blood sugar *Hb* Hemoglobin, *LDH* Lactate dehydrogenase, *PT* Prothrombin time, *WBC* White blood cell

Table 3 AUC and Optimal Cut Points of Laboratory test for predicting COVID-19 death in Diabetic patients

Test	AUC (95% CI)	P value	Optimal cutoff point	Sensitivity %	Specificity %
WBC count, × 10^9 /L	0.66 (0.59–0.73)	**<0.001**	8.1	60.0	61.7
Lymphocyte count,× 10^9/L	**0.75 (0.68–0.81)**	**<0.001**	1.51	72.1	70.3
Neutrophil count,× 10^9/L	**0.76 (0.69–0.82)**	**<0.001**	8.0	67.2	74.3
Hb, g/dL	0.61 (0.54–0.68)	**0.003**	12.5	64.3	57.2
Creatinine, mg/dl	0.60 (0.52–0.69)	**0.010**	1.36	52.0	74.6
AST, U/L	0.64 (0.53–0.74)	**0.010**	39	61.1	62.4
ALT, U/L	0.57 (0.47–0.68)	**0.151**	–	–	–
LDH, U/L	**0.74 (0.64–0.84)**	**<0.001**	544	71.9	72.8
Cpk-MB, IU/L	0.66 (0.55–0.76)	**0.004**	23	67.7	60.0
Cpk, U/L	0.61 (0.51–0.71)	**0.027**	81.4	70.7	55.0
CRP, mg/l	0.61 (0.53–0.68)	**0.012**	39.0	60.4	61.0
Esr, mm/h	0.55 (0.46–0.64)	**0.287**	–	–	–
FBS, mg/dl	0.62 (0.53–0.70)	**0.006**	179	60.0	57.0

Discussion

In this retrospective observational study, we compared the characteristics of hospitalized diabetic patients with COVID-19 between survivors and non-survivors and investigated the predicting factors for poor outcomes including need to ICU care and invasive mechanical ventilation and in-hospital death.

Based on our results, age 65 years or older, neutrophil count ≥8.0 × 10^9/L, and creatinine level ≥ 1.36 mg/dl were significant predictors for all poor outcomes of COVID-19 including need to ICU care, invasive mechanical ventilation, and death in diabetic patients. Among predictors of COVID-19 death, Hb level < 12.5 g/dl and the presence of comorbidity CKD were also associated with need to ICU care and invasive mechanical ventilation, respectively. However, AST level ≥ 39 U/L, LDH level ≥ 544 U/L, Cpk level ≥ 81.4 U/L, lymphocyte count <1.51 × 10^9/L, were associated with need to ICU care and / or invasive mechanical ventilation but not with COVID-19 death.

Shi et al. also observed infected patients with diabetes who died were older, were more likely to have hypertension and CVD and presented more dyspnea compared with survivors although frequency of CKD was probable between groups [11]. It should be noted that there were no significant difference in frequency of hypertension and CVD as well as

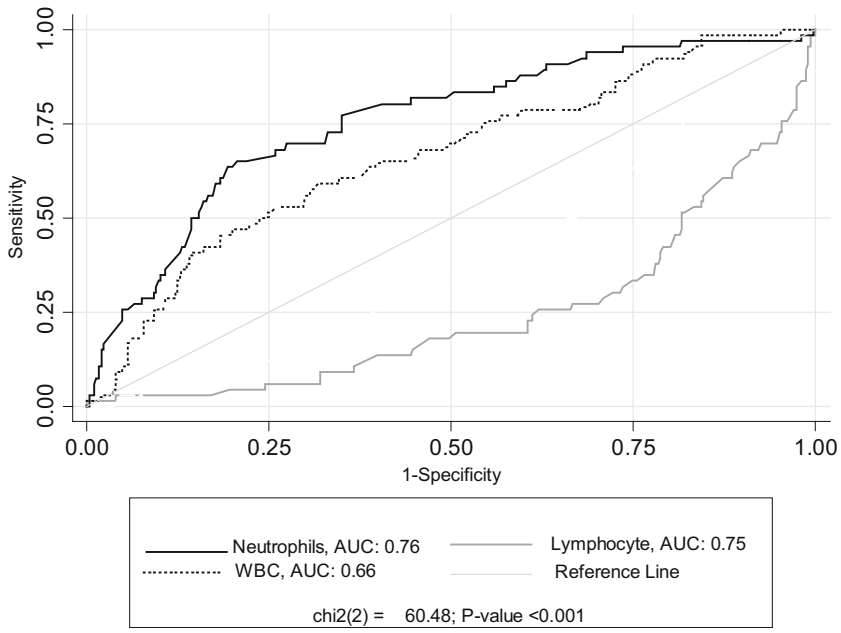

Fig. 1 Receiver operating characteristic curves of Hematologic parameters for predicting COVID- 19 death

Table 4 Predicting factors for death of the COVID-19 in patients with diabetes mellitus (DM): Logistic Regression Analysis

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Demographic and clinical characteristic	Variable	Need to ICU		Being ventilated during hospitalization $N = 65$		Death $N = 79$	
		Crude OR OR(95% CI)	Adjusted§ OR(95% CI)	Crude OR OR(95% CI)	Adjusted§ OR(95% CI)	Crude OR OR(95% CI)	Adjusted§ OR(95% CI)
	Age (≥65/< 65)	**2.34 (1.48–3.72)**	**1.72 (1.02–2.94)**	**2.40 (1.38–4.17)**	**2.40 (1.35–4.28)**	**2.44 (1.47–4.05)**	**2.0 (1.16–3.44)**
	Sex (M/F)	1.24 (0.79–1.95)	–	1.42 (0.84–2.41)	–	1.45 (0.85–2.36)	–
	Comorbidities						
	HTN	**1.75 (1.10–2.80)**	–	1.15 (0.67–1.96)	–	1.38 (0.84–2.29)	–
	CVD	**1.89 (1.21–2.97)**	–	**1.86 (1.09–3.19)**	–	1.49 (0.91–2.42)	–
	CKD	**2.30 (1.41–3.77)**	–	**2.58 (1.48–4.52)**	2.09 (1.16–3.75)	**2.27 (1.34–3.86)**	**2.05 (1.16–3.62)**
	Other comorbidity*	**2.40 (1.26–4.59)**	–	**2.42 (1.18–4.96)**	–	**2.08 (1.04–4.16)**	**2.20 (1.04–4.63)**
	Number of co.; Reference category: No comorbidity						
	1	1.88 (0.94–3.76)	1.61 (0.72–3.60)	1.21 (0.52–2.80)	–	1.14 (0.56–2.33)	–
	2	**2.61 (1.36–5.0)**	**2.23 (1.04–4.78)**	**2.42 (1.16–5.06)**	–	1.62 (0.84–3.11)	–
	≥ 3	**4.80 (2.33–9.88)**	**4.08 (1.78–9.34)**	**3.46 (1.52–7.83)**	–	**2.57 (1.23–5.37)**	–
	Drug history						
	ACEIs or ARBs (yes/no)	**1.70 (1.08–2.67)**	–	1.45 (0.86–2.46)	–	1.41 (0.86–2.32)	–
	Statins(yes/no)	**1.76 (1.01–2.76)**	–	1.10 (0.61–1.99)	–	1.35 (0.78–2.35)	–
Laboratory finding,	**Hematological, Biochemistry and Isoenzymes parameters**						
	WBC, ≥ 8.1/< 8.1(× 10^9 per L)	**2.27 (1.41–3.67)**	–	**2.56 (1.46–4.47)**	–	**2.36 (1.39–3.99)**	–
	Lymphocyte, <1.51/ ≥ 1.51 (× 10^9/L)	**4.33 (2.60–7.19)**	**2.28 (1.01–5.15)**	**4.67 (2.59–8.47)**	–	**5.84 (3.27–10.44)**	–
	Neutrophil, ≥ 8.0 / < 8.0 (× 10^9/L))	**4.55 (2.74–7.57)**	**2.32 (1.04–5.24)**	**5.02 (2.82–8.93)**	**5.00 (2.82–8.94)**	**6.65 (3.75–11.80)**	**6.62 (3.73–11.75)**
	Hb, <12.5/ > 12.5(g/dl)	**2.38 (1.45–3.88)**	**2.03 (1.20–3.43)**	**1.87 (1.04–3.15)**	–	**2.21 (1.30–3.77)**	**2.05 (1.13–3.72)**
	AST, ≥ 39 / < 39 (U/L)	**2.32 (1.46–5.46)**	**2.39 (1.12–5.13)**	**2.65 (1.26–5.61)**	**2.40 (1.25–5.69)**	**2.62 (1.26–5.44)**	–
	Creatinine, ≥1.36/<1.36 (mg/dl)	**2.57 (1.55–4.24)**	**2.67 (1.25–5.58)**	**2.63 (1.49–4.66)**	**2.64 (1.12–6.21)**	**3.18 (1.83–5.53)**	**3.10 (1.38–6.98)**
	CRP, ≥39/<39 (mg/dl)	1.65 (0.96–2.81) ‡	–	1.30 (0.70–2.40)	–	**2.22 (1.25–3.94)**	–
	FBS, ≥179/<179 (mg/dl)	**1.72 (1.03–2.88)**	–	1.63 (0.89–2.95)	–	1.72 (0.97–3.05)	–
	LDH, ≥544/<544(U/L)	**4.0(1.95–8.17)**	**4.31 (1.36–13.68)**	**3.74 (1.64–8.49)**	**3.45 (1.36–9.27)**	**7.04 (3.05–16.26)**	6.53 (2.51–16.97)
	Cpk, ≥81.4/<81.4(U/L)	**2.54 (1.25–5.18)**	**3.67 (0.96–14.23)**	**2.78 (1.23–6.27)**	–	**2.44 (1.17–5.09)**	–
	Cpk-MB, ≥23/<23(IU/L)	**3.09 (1.45–6.56)**	–	**2.69 (1.12–6.06)**	–	**3.18 (1.47–6.89)**	–

†P- value <0.05 ‡ P- value <0.20; § in each class, all variables with $p < 0.2$ in the univariaite model were included in multivariate model

OR Odds Ratio, *CI* Confidence Interval;

ACEIs angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *CKD* Chronic Kidney diseases, *CVD* Cardiovascular diseases, *HTN* Hypertension, *ICU* Intensive care unit

ALT Alanine transaminases, *AST* Aspartate transaminases, *CRP* C-reactive protein, *CPK* Creatine phosphokinase, *CK-MB* creatine kinase myocardial band, *Esr* Erythrocyte sedimentation rate, *FBS* fasting blood sugar, *Hb* Hemoglobin, *LDH* Lactate dehydrogenase, *PT* Prothrombin time, *WBC* White blood cell

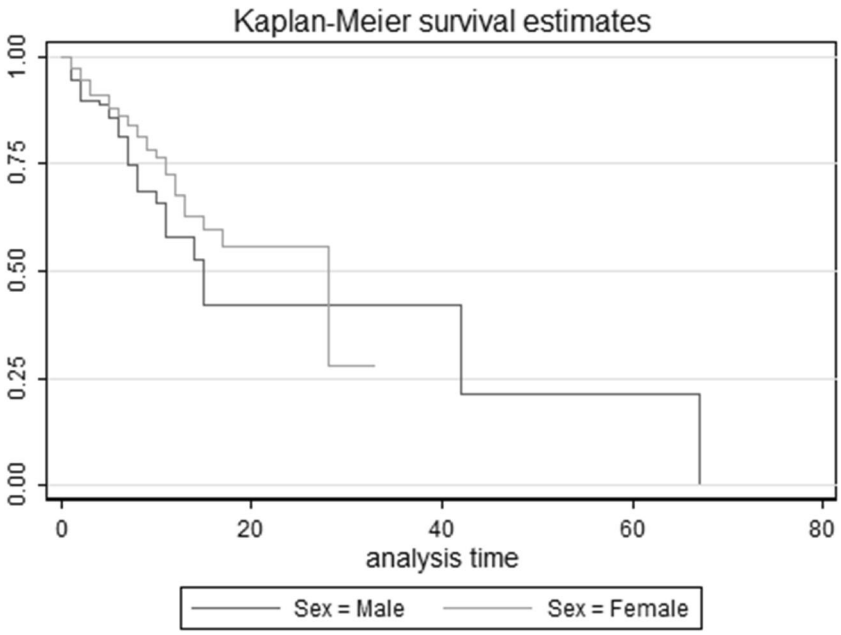

Fig. 2 Survival Curve in Diabetic Patients with COVID-19 by gender status (Kaplan Meier & log rank test)

percentage of ACEIs/ARBs and statins consumption between survivors and non-survivors in our study. Contrary to the recent hypothesis which related severity of COVID-19 infection to elevated expression of ACE2 in those treated with ACEI/ARB drugs [12–14], we did not observe any significant differences in use of these drugs between survivor and non-survivor groups.

According to the laboratory findings, non-survivors had lower lymphocyte count and higher counts of WBC and neutrophil besides higher concentration of serum creatinine, CRP, LDH, CPK and CPK-MB, but lower concentration of Hb compared to survivors, reflecting severe inflammatory response and cardiac and renal impairments in non-survivors. Our findings were in agreement with previous observations in COVID-19 patients [11, 15–17]. These biochemical abnormalities point to that covid-19 infection may be lead to progressive systemic injuries and consequently death in diabetic patients. The mechanisms linking diabetes with high risk of mortality were pulmonary dysfunction and deleterious inflammation which has been indicated in results of comparison

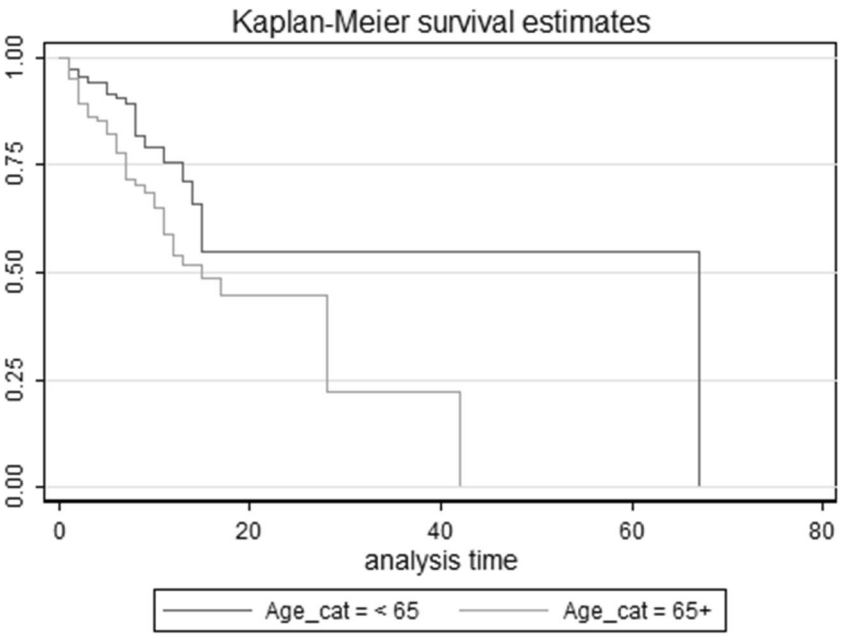

Fig. 3 Survival Curve in Diabetic Patients with COVID-19 by Age – group (Kaplan Meier& log rank test)

between survivors and non-survivors [15, 18]. Chen et al. indicated CRP as the only risk factor for mortality in diabetic patients with COVID-19 as a clinical manifestation of systemic inflammation [19]. This imbalance between pro-inflammation and anti-inflammation process could partly explained the reported association between diabetes and low pulmonary function [20].

Regard to baseline FBS, concentration of blood glucose was higher in non-survivors in comparison with survivors, although it is not statistically significant, it has clinically importance. Zhu et al. retrospectively studied nearly 1000 COVID-19 patients with diabetes in China; they showed that fatality rate in patients with well-controlled blood glucose (1.1%) was lower compared to patients with poorly-controlled blood glucose (11%). Patients with good glycemic control had lower incidence of ARDS, multi-organ injuries and septic shock relative to the patients with poor glycemic control [21]. Glycemic variability was indicated as a probable predictor for severe complications and mortality in COVID-19 infected patients with diabetes. It has been reported that hyperglycemia may reduce the defensive capacity of respiratory tract through increasing glucose level in airway epithelial secretions [22] as well as increase risk of mortality in infected patients via overproduction of advanced glycation end products and dysfunction of immunoglobulins [23]. Moreover, Covid-19 which was reported to bind ACE2 receptor, may damage pancreatic function and lead to worse glycemic status via binding to this receptor in pancreas [15, 24].

Previous studies have been indicated diabetes as a risk factor for poor outcomes and high fatality in COVID-19 patients [8, 25, 26]; however no study focused on biochemical indicators as predicting factors for death in diabetic infected patients, presenting the optimal cutoff points to discriminate between survivors and non-survivors. Among laboratory parameters for predicting death, neutrophil and lymphocyte count as indicators for immune function and LDH level as a marker of tissue breakdown had the highest diagnostic accuracy in infected diabetic patients.

According to the results of logistic regression models, older age, CKD, high neutrophil count and creatinine level were significant predictors of death, requiring ICU care and invasive mechanical ventilation. Moreover, low lymphocyte count and high LDH and Cpk level were associated with higher odds of ICU care. Our observations were in line with previous findings as Shi et al. declared advanced age as an independent risk factor for in-hospital death among COVID-19 patients with diabetes [11]. Totally, old age was demonstrated as an independent predictor of death in COVID-19 patients due to age-dependent decrease in immune function as we observed more lymphopenia in critically ill patients too [27, 28]. Concordant with previous studies, lymphopenia has been shown as a key characteristic of COVID-19 infection, specifically in critically ill and deceased patients [16, 29]. Furthermore, it should be noted that diabetes has additive destructive effects on innate and adaptive immunity [30]. Moreover, our results showed that underlying comorbidities like CKD could be associated with poor outcomes in patients with diabetes. Therefore, diabetic patients with underlying renal failure should attract more attention.

The present study is among the first studies with the approach of exploring the predictors of poor prognosis and mortality in COVID-19 patients with diabetes. Due to the retrospective nature of this study, it has some limitations. First, we could not retrieve the pre-hospital status of diabetic patients including their glycemic control which could be significantly associated with numerous clinical risk factors for the poor outcomes. Therefore, the confounding effects of these factors cannot be excluded. Also, given this lack of pre-hospital data, it was not possible for us to access the trend of blood glucose change. Second, participants of this study were relatively severe cases which needed hospitalization. Therefore, the rate of mortality was higher to some extent and might influence the interpretation of the results. Third, we did not consider the drugs which have been used for COVID-19 treatment during hospitalization in analysis. So we cannot rule out its confounding effects. Moreover, we missed the data about antidiabetic treatments of patients which might lead to bias in analysis and interpretation, as indicated by Chen et al. that insulin users had poor prognosis of COVID-19 [19]. Furthermore, there is also discussion on harmful effects of some oral hypoglycemic agents such as Sodium-Glucose-Transporter-2 inhibitors versus beneficial effects of metformin on COVID-19 infected individuals with diabetes [31, 32]. Therefore, further studies investigating impact of different glucose-lowering medications on infected diabetic patients are warranted.

We demonstrate a guide identifying predicting factors and their cutoff points for poor outcomes including need to ICU care and invasive mechanical ventilation and in-hospital death in admitted COVID-19 patients with diabetes. These risk factors could be considered by clinicians to pay special attention to high-risk patients.

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Authors' contributions HR, H-SE and MQ had the idea for and designed the study and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. HR, H-SE, AS and ESh drafted the paper. AZ, MN, SH-DM, FO, ShS, Zkh, and NShH collected the MM, and MQ did the analysis, and all authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published. All authors agree 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 are appropriately investigated and resolved.

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Compliance with ethical standards

Conflict of interest Not applicable.

Code availability Not applicable.

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Affiliations

Hadith Rastad[1] · Hanieh-Sadat Ejtahed[2,3] · Armita Mahdavi-Ghorabi[4] · Masoud Arzaghi[5] · Anis Safari[6] · Ehsan Shahrestanaki[6] · Mohammad Rezaei[7] · Mohammad Mahdi Niksima[7] · Akram Zakani[8] · Seyede Hanieh Dehghan Manshadi[7] · Fatemeh Ochi[7] · Shabnam Saedi[7] · Zeinab Khodaparast[9] · Neda Shafiabadi Hassani[10] · Mehdi Azimzadeh[11] · Mostafa Qorbani[11,12]

1 Social Determinants of Health Research Center, Alborz University of Medical Sciences, Karaj, Iran

2 Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

3 Obesity and Eating Habits Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

4 Department of Basic and Clinical Research, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran

5 Elderly Health Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

6 Dietary Supplements and Probiotic Research Center, Alborz University of Medical Sciences, Karaj, Iran

7 Student Research Committee, Alborz University of Medical Sciences, Karaj, Iran

8 Clinical Research Development Center of Rajaei, Alborz University of Medical Sciences, Karaj, Iran

9 Clinical Research Development Center of Kamali Hospital, Alborz University of Medical Sciences, Karaj, Iran

10 Cardiovascular Research Center, Alborz University of Medical Sciences, Karaj, Iran

11 Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

12 Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran