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Comparison of clinical and laboratory parameters of COVID-19 in diabetic patients using different glucose-lowering drugs: a retrospective study

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ABSTRACT

Background and Objective: Diabetes is a common metabolic disease that increases the risk of mortality of COVID-19. This study was done to compare the clinical characteristics and laboratory parameters of COVID-19 in diabetic patients using different glucose-lowering drugs to find out the proper predictors of disease severity.

Methods: 157 diabetic patients with confirmed COVID-19 were enrolled in three groups according to the antidiabetic medications used before admission (metformin, insulin and sulfonylurea).

Findings: In 157 diabetic patients, the hospitalization length in the metformin group was lower than the no metformin group while duration of hospitalization and critical form of the disease in the insulin group were higher than the no insulin group. Furthermore, the levels of blood sugar, BUN, ALT and WBC were lower in the metformin group while ALP, ALT, BUN and creatinine levels were significantly higher in insulin group. In sulfonylurea group the levels of BUN and ALT were lower compared to the no sulfonylurea group. We also found that BUN and total bilirubin were the proper parameters to predict COVID-19 severity and mortality in metformin and insulin group respectively.

Conclusion: It seems that the outcomes of renal function test, bilirubin and O_2 saturation are important parameters to predict COVID-19 severity in diabetic patients using different antidiabetic medications.

Keywords: COVID-19, diabetes, glucose- lowering drugs, laboratory parameters.

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Introduction

In December 2019, the first report of patients with unknown acute respiratory failure in Wuhan province was provided by Zhu et al (1). They isolated a novel coronavirus named 2019-nCoV from the airway epithelial cells of patients with common respiratory symptoms. The Coronavirus disease 2019 (COVID-19) has spread rapidly over the entire world with a vast clinical representation from mild infection to multi-organ failure and rapid death[1]. Several risk factors, such as male gender, old age, obesity, and having one or more comorbidities, such as hypertension, cardiovascular disease, diabetes, etc. increase the life-threatening complications of COVID-19 (2).

Diabetes mellitus is a common metabolic disease that increases the risk of mortality and severity of COVID-19 (3). Initial studies have revealed that a large number of hospitalized patients with COVID-19 have been suffered from diabetes. Recently, it has been reported that approximately a quarter of patients admitted for COVID-19 in the United Kingdom (UK) had diabetes (3, 4). Another study revealed that the mortality rate of COVID-19 in diabetes patients is twice as high as in the general population (5). Indeed, hyperglycemia, inflammation, hypertension, and renal disorder in diabetic patients induce a critical form of COVID-19 and increase the risk of mortality (5). Furthermore, hyperglycemia even in non-diabetics individuals with COVID-19 enhances the severity of the disease. Hyperglycemia stimulates the secretion of proinflammatory cytokines and enhances oxidative stress that complicates COVID-19 (6).

Several studies have represented crucial information about the positive or negative effects of different glucose-lowering drugs on COVID-19 severity and mortality (7-9). In this regard, metformin was proposed as a suitable medication that reduces mortality of COVID-19 in diabetic patients due to its immune-regulatory and anti-inflammatory effects (10). Recent literature showed the lower rate of mortality in diabetics who consume metformin before admission (11), while taking insulin increases mortality rate by induction systemic inflammation and multi-organ injuries (9, 12). However, little is known about the impact of different anti-diabetic medications before hospitalization on the clinical characteristics, laboratory parameters, and severity of COVID-19 in patients with diabetes. Moreover, a study on laboratory parameters could provide valuable information about crucial predictors of the critical form of COVID-19 in diabetic patients and help clinicians to provide appropriate strategies for timely treatment. This study was done to compare the clinical characteristics, laboratory parameters, and severity of COVID-19 in diabetic patients using different glucose-lowering drugs to find out the proper predictors of disease severity and death in each group.

Methods

This For this retrospective study, the diabetic patients with confirmed COVID-19 were recruited from two university hospitals (Ayatollah Rouhani and Yahyanejad university hospital, Babol, Iran) between 20 April 2020 and 21 July 2020. The study was approved by the Ethics committee of Babol University of Medical Sciences (IR.MUBABOL.REC.1399.284).

COVID-19 infection was confirmed by positive nasopharyngeal swab reverse-transcription polymerase chain reaction (RT-PCR) assay regardless of clinical signs and symptoms or negative results from chest computed tomography (CT) images (7). The presence of diabetes was assessed based on the patients' medical history.

We extracted data from patients' medical files who had used one or more glucose-lowering drugs, including insulin, metformin and/or sulfonylurea, either discharged or dead. Their information, including age, gender, vital signs (pulse rates, respiratory rates, oxygen (O_2) saturation, body temperature, and blood pressure), medication, comorbidities (coronary heart disease, hypertension,

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chronic kidney disease, cancer, past surgical history, and chronic pulmonary disease), laboratory findings (blood sugar, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, albumin, sodium (Na), potassium (K), magnesium (Mg), calcium (Ca), C-reactive protein (CRP), complete blood count (CBC), erythrocyte sedimentation rate (ESR), prothrombin time (PT), partial thromboplastin time (PTT)) and CT images on admission was collected.

A total of 200 diabetic patients with confirmed COVID-19 were included, of whom patients younger than 18 years old, older than 85 years old, and those with hospitalization of fewer than 3 days and lack of complete information in medical files were excluded. Furthermore, patients who had been hospitalized more than once for COVID-19, data from only the first admission were included. Therefore, 157 patients were enrolled in this study. These patients were grouped according to antidiabetic medication used for at least seven days before admission. In the metformin group, 100 patients had used metformin alone or along with other antidiabetic medications (metformin-group) and 57 patients had used one or multiple antidiabetic drugs other than metformin (no-metformin-group). In the insulin group, 46 patients had used insulin alone or along with other antidiabetic medications (insulin-group) and 111 patients had used one or multiple antidiabetic drugs other than insulin (no-insulin-group). In the sulfonylurea group, 68 patients had used sulfonylurea alone or along with other antidiabetic medications (sulfonylurea-group) and 89 patients had used one or multiple antidiabetic drugs other than sulfonylurea (no-sulfonylurea-group).

The severity of the disease was graded as previously reported by Lou et al (7). Briefly, mild infection was defined as mild clinical symptoms without any signs of pneumonia on CT images. Moderate infection was defined as respiratory tract symptoms and CT images with signs of pneumonia. Severe clinical manifestations were defined as respiratory rates higher than 30 breath/minutes and O_2 saturation lower than 93%, and the critical type was defined as respiratory failure and the need for mechanical ventilation or intensive care.

Statistical analysis

Data were statistically analyzed by SPSS software version 22. Continuous data were presented as means ± standard deviation (SD), and categorical data as frequency and percentages. Statistical comparisons were made using Mann-Whitney U test for continuous data and Chi-square test for categorical data. Simple linear logistic regression was used for crud odds ratio (OR) with 95% confidence interval (95%CI) and multiple linear logistic regression was used for adjusted OR (95% CI) to identify appropriate predictors for mortality and critical form of COVID-19. $\alpha = 0.05$ was considered as the level of significance.

Results

Clinical outcomes of the whole population

In this retrospective study, 157 diabetes patients (65 male/92 female) with confirmed COVID-19 were included and analyzed from admission to discharge or death, of whom 19 patients (12.1%) died unfortunately and 138 patients (87.89%) were discharged. Furthermore, 39 individuals (24.84%) were mildly infected, 44 patients (28.02%) showed moderate symptoms of COVID-19, 34 patients (21.65%) had a severe clinical presentation, and 40 patients (25.47%) became critically ill (Figure 1).

Comparison of clinical outcomes and laboratory parameters between the metformin and no-metformin groups

Of 157 patients enrolled in the study, 100 patients were assigned to the metformin group and 57 patients into the no metformin group. Clinical characteristics and laboratory parameters on admission days are shown in Table 1**.** The mean age ±SD of patients in the metformin and no metformin groups

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were 58.7 ±10.98 and 60.77 ±12.10 years, respectively (P=0.92). Forty-six (56%) individuals in the metformin group and 36 (63.2%) participants in the no metformin group were females (P= 0.24). No significant differences were found in vital signs between the two groups on admission days. Besides, there was no difference in terms of ARBs and/or ACE inhibitors and statin use between the two groups.

The mean length of hospitalization in the no metformin group was 11 days (25th–75th percentile, 7-14 days), which was significantly higher than the metformin group (6 days (25th–75th percentile, 5-8 days) (P< 0.00). However, there were no significant differences in the rate of death (P= 0.49) and the severity of the disease (P= 0.15). However, analysis of laboratory parameters showed that the levels of blood sugar (191.3 ±89.67 vs. 235.21 ±118.53), BUN (23.87 ±13.7 vs. 31.6 ±19.20), ALT (32.76 ±24.14 vs. 53.26 ±38.12), and WBC (8606 ±4507 vs. 10445 ±6242) were significantly lower in the metformin group compared to the no metformin group. There were no significant differences in other laboratory variables (Table 1).

Comparison of clinical outcomes and laboratory parameters between the insulin and no insulin groups

Among the patients included in the study, 46 patients were in the insulin group and 111 patients were in the no insulin group. Clinical characteristics and laboratory parameters on admission days are shown in Table 1. The mean (±SD) age in the insulin group and no insulin group were 60.17 ±12.38 and 59.33 ±11.02 years (P= 0.63) and the number (%) of females in each group was 29 (63%) and 63 (56.8%), respectively (P= 0.29). No differences were observed in vital signs and use of ARBs and/or ACE inhibitors and statin (P= 0.33 and P= 0.47) between the two groups.

The duration of hospitalization in the insulin group (10 days (25th–75th percentile, 6-13.25 days)) was significantly longer than the no insulin group (7 days (25th–75th percentile 5- 10 days)) (P= 0.01). Also, the critical form of the disease was more observed in the insulin group compared to the no insulin group (19 (41%) vs. 21 (18.91%) (P= 0.07)). Furthermore, the comparison of laboratory outcomes showed that the levels of BUN (36.5±18.6 vs. 22.75±11.7), creatinine (1.67±0.71 vs. 1.4±0.69), ALT (64±26.13 vs. 30.34±17.41), ALP (254.89±110.08 vs. 201.71±86.60) were significantly higher in the insulin group compared to the no- insulin-group (P>0.00, P=0.01, P>0.00, and P>0.00, respectively).

Comparison of the clinical outcomes and laboratory parameters between the sulfonylurea and no sulfonylurea groups

Sixty-eight patients of 157 individuals enrolled in the study were in the sulfonylurea group and the remaining 89 patients were in the no sulfonylurea group. Clinical characteristics and laboratory parameters on admission days are shown in Table 1. The mean (±SD) age in the sulfonylurea group and no sulfonylurea group was 59.84±10.37 and 59.25±12.10 years, respectively (P= 0.74). Thirty-nine (57.40%) patients in the sulfonylurea group and 53 (59.6%) patients in the no sulfonylurea group were females (P= 0.45). No differences were observed in vital signs and the use of ARBs and/or ACE inhibitors and statin between the two groups. Furthermore, there was no difference in hospitalization length (P= 0.14), the rate of death (P= 0.27), and disease severity between the two groups (P=0.20).

Evaluation of the laboratory parameters on admission days showed the lower levels of BUN (22±4.17 vs. 30.25±21.79) and ALT (30.57±19.59 vs. 47.56±21.55) in the sulfonylurea group compared to the no sulfonylurea group (P<0.00 and P=0.01, respectively).

Comparison of the clinical outcomes and laboratory parameters between patients with critical and no critical manifestation

To find out the important variables related to critical form COVID-19 in diabetic patients who consume different anti-diabetic drugs, we compared the clinical and biological outcomes between patients with critical and no critical manifestation. In the metformin-group, we found that the LDH (P<0.00), BUN (P, 0.00), creatinine (P= 0.02), AST (P< 0.00), bilirubin (P= 0.02), and CRP (P<0.00) levels and WBC count (P< 0.00) were significantly higher and O_2 saturation (P< 0.00) was lower in patients with critical symptoms compared to no-critical patients. In the insulin group, the levels of respiratory rate, LDH, AST, ALT, and bilirubin were higher and O_2 saturation was lower in the critical

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patients compared to patients with no critical form of the disease (P< 0.00 for all comparisons). Comparison of critical and no-critical patients in the sulfonylurea group indicated that the LDH, BUN, and bilirubin levels and WBC count were higher and O_2 saturation was lower in the critical patients (P<0.00 for all comparisons) (Table 2).

To evaluation the ability of clinical and biological outcomes to predict the critical form of COVID-19, we analyzed them by Simple linear logistic regression and multiple linear logistic regression using cut-off, sensitivity, and specificity values (Table 3). Our data revealed that among clinical outcomes, O_2 saturation was the best predictor of critical condition for all groups. Regarding laboratory parameters, BUN levels on admission day were associated with the critical form of COVID-19 in the metformin group (adjusted OR: 1.52, AUC 0.80, cut-off: 30mg/dl, specificity: 82%, and sensitivity: 69). However, in the insulin group, the levels of serum total bilirubin were the best predictor of critical manifestation in COVID-19 (adjusted OR: 4.48, AUC: 0.92, cut-off: 1.3 mg/dl, specificity: 85%, and sensitivity: 100).

Comparison of the clinical outcomes and laboratory parameters between patients who died and discharged

To identify the main and most significant factors related to death in diabetic patients with COVID-19, we analyzed clinical outcomes and laboratory parameters between the patients who died and were discharged. The levels of LDH (P< 0.00), BUN (P< 0.00), creatinine (P= 0.01), AST (P=0.01), and CRP (P< 0.00) were higher and O_2 saturation was lower in dead patients compared to discharged patients in the metformin group. In the insulin group, the levels of LDH (P< 0.00), ALT (P=0.02), ALP (P=0.01), and total bilirubin (P< 0.00) were higher and O_2 saturation was lower significantly in patients who died. Comparison of dead and discharged patients in the sulfonylurea group indicated the higher levels of LDH (P< 0.00), BUN (P< 0.00), and CRP (P=0.01), and the lower level of O_2 saturation (P< 0.00) in patients who died (Table 4). Furthermore, analysis of clinical and paraclinical variables by simple linear logistic regression and multiple linear logistic regression indicated that O_2 saturation was the most important factor to predict the death of patients in all groups. Among laboratory parameters, BUN was the best predictor of death in the metformin group (adjusted OR: 1.56, AUC: 0.86, cut-off: 33mg/dl, specificity: 80%, and sensitivity: 73). In the insulin group, the level of total bilirubin significantly predicted death as well as critical symptoms (adjusted OR: 6.85, AUC: 0.90, cut-off: 1.4 mg/dl, specificity: 83%, and sensitivity: 100). No laboratory parameters predicted death in the sulfonylurea group (Table 5).

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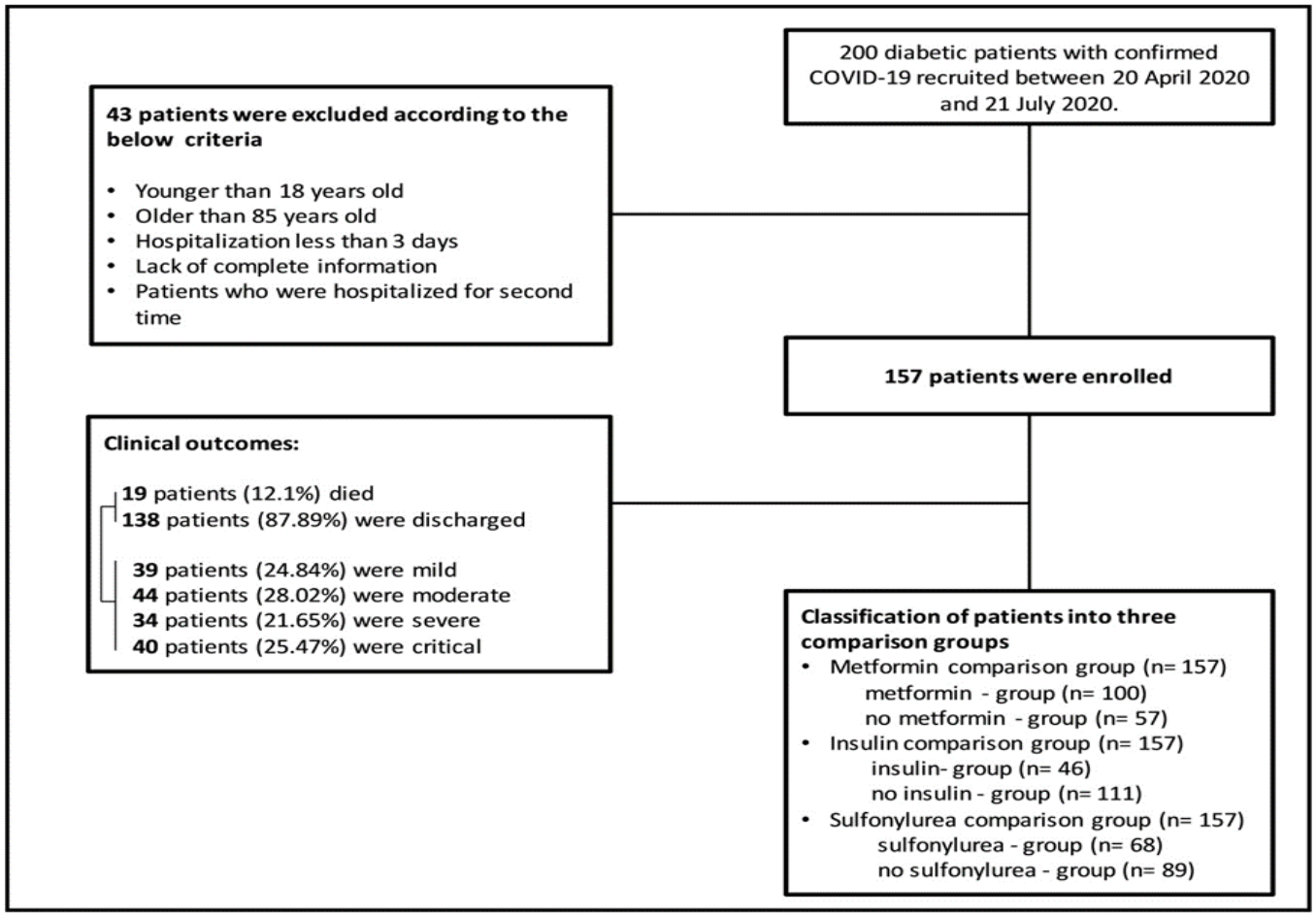

Figure 1. Study flowchart

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Table 1. Comparison of clinical characteristic and laboratory parameters between diabetic patients with COVID-19 in metformin group/no metformin group, insulin group/no insulin group and sulfonylurea group/no sulfonylurea group

Variable	Metformin group (n= 100)	No metformin group (n= 57)	P-value	Insulin group (n= 46)	No insulin group (n= 111)	P-value	Sulfonylurea group (n= 68)	No sulfonylurea group (n= 89)	P-value
Age (years)	58.7 ±10.98	60.77 ±12.10	0.29	60.17± 12.38	59.33 ±11.02	0.63	59.84 ±10.37	59.25± (12.1	0.74
Male (%)	44 (44%)	21 (36.8%)	0.24	17 (37%)	48 (43.2%)	0.29	29 (42.6%)	36 (40.4%)	0.45
Female (%)	56 (56%)	36 (63.2%)		29 (63%)	63 (56.8%)		39 (57.4%)	53 (59.6%)	
Hospitalization length (Days)	6 (5-8)	11 (7-14)	**>0.00**	10 (6- 13.25)	7 (5- 10)	**0.01**	7 (5-11.25)	8 (6- 12)	0.14
Death (%)	11 (13.92%)	8 (10.25%)	0.49	3 (7.1%)	16 (13.91%)	0.24	6 (9.6%)	13 (17.1%)	027
Clinical severity									
Mild (%)	29 (29%)	10 (17.5%)		7 (15.21%)	32 (28.82%)		17 (25%)	22 (24.7%)	
Moderate (%)	26 (26%)	18 (31.6%)		11 (23.91%)	33 (29.72%)		21 (30.9%)	23 (25.8%)	
Severe (%)	24 (24%)	10 (17.5%)	0. 15	9 (19.6%)	25 (22.5%)	0.07	18 (26.5%)	16 (18%)	0.2
Critical (%)	21 (21%)	19 (33.3%)		19 (41%)	21 (18.91%)		12 (17.6%)	28 (31.5%)	
Vital signs									
Body temperature (°C)	37 ±0.71	36.9 ±1.05	0.23	36.83 ±1.17	37.06 ±0.67	0.11	37.02 ±0.81	36.97 ±1.04	0.70
systolic blood pressure (×10 mmHg)	12.47 ±2.39	12.75 ±2.74	0.49	12.93 ±2.75	12.42 ±2.41	0.24	12.5 ±2.56	12.6 ±2.5	0.75
diastolic blood pressure (×10 mmHg)	7.34 ±0.23	7.66 ±0.36	0.12	7.67 ±1.6	7.36 ±1.09	0.17	7.41 ±1.16	7.49 ± 1.34	0.68
Pulse rate (BPM)	85.84 ±16.03	89.23 ±15.68	0.20	88.30 ±13.44	86.56 ±16.9	0.53	81 ±78- 93.5	82 ±78- 92.2	0.80
Respiratory rate (BPM)	19.47 ±2.39	19.42 ±2.74	0.95	19.5 ±2.59	19.43 ±2.84	0.89	19.74 ±3.07	19.24 ±2.5	0.46
O2 saturation (%)	93.3 ±7.27	92.84 ±6.22	0.63	92.57 ±5.13	93.43 ±7.09	0.45	93.49 ±5.04	92.94 ±7.55	0.61
Comorbidity									
Coronary heart disease (%)	33 (33%)	27 (47%)	0.09	13 (28%)	47 (42%)	0.14	25 (36%)	35 (39%)	0.8
Hypertension (%)	49 (49%)	33 (59.6%)	0.13	28 (60.9%)	55 (49.5)	0.80	32 (47.1%)	51 (57.3%)	0.13
Chronic kidney disease (%)	1 (1 %)	4 (7.1%)	0.06	3 (6.5 %)	2 (1.8 %)	0.10	2 (2.9%)	3 (3.4 %)	0.41
Cancer (%)	1 (1%)	3 (5.3%)	0.13	3 (6.5%)	1 (0.9 %)	0.08	1 (1.5%)	3 (3.4 %)	0.41
Past surgical history (%)	14 (14%)	11 (19.3%)	0.25	9 (19.6%)	16 (14.4%)	0.28	11 (16.26%)	14 (15.7%)	0.55
Chronic pulmonary disease (%)	0 (0%)	2 (3.5%)	0.13	2 (4.3%)	0 (0 %)	0.09	0 (0 %)	2 (2.24 %)	0.32

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ARBs and/or ACE inhibitors (%)	14 (14%)	15 (26.3)	0.08	11 (23.9%)	18 (16.22%)	0.26	9 (13.23%)	20 (22.47%)	0.15
Statin (%)	20 (20%)	12 (21.9%)	0.51	9 (19.6%)	23 (20%)	0.52	13 (19.1%)	19 (21.3%)	0.44
Laboratory findings									
Blood sugar (mg/dl)	191.03 ±89.67	235.21 ±118.53	**0.01**	225.85 ±120	199.29 ±98.38	0.16	210.44 ±99.6	204.49 ±95.81	0.73
LDH (Unit/l)	463.77 ±284	472.02 ±216	0.85	474 ±196.34	463 ±251.7	0.8	453.25 ±252.5	477 ±233.61	0.57
BUN (mg/dl)	23.87 ±13.7	31.6 ±19.20	**0.01**	36.5 ±18.6	22.75 ±11.7	**> 0.00**	22 ±4.17	30.25 ±21.79	**> 0.00**
Creatinine (mg/dl)	1.21 ±0.61	1.44 ±0.75	0.14	1.67 ±0.71	1.4 ±0.69	**0.01**	1.16 ±0.57	1.4 ±0.71	0.11
AST (Unit/l)	36.99 ±20.58	42.16 ±24.40	0.33	49.37 ±37.06	34.51 ±22.45	0.08	34.35 ±21.13	42.31 ±23.11	0.12
ALT (Unit/l)	32.76 ±24.14	53.26 ±38.12	**0.03**	64 ±26.13	30.34 ±17.41	**> 0.00**	30.57 ±19.29	47.56 ±21.55	**0.01**
ALP (Unit/l)	207.06 ±99.37	235 ±138.07	0.14	254.8 ±110.08	201.71 ±86.60	**> 0.00**	200.19 ±83.7	230.36 ±100.21	0.10
Bilirubin (mg/dl)	1.14 ±0.9	1.24 ±0.83	0.47	1.24 ±0.7	1.15 ±0.6	0.55	1.14 ±0.56	1.21 ±0.61	0.62
Na (meq/l)	134 ±4.3	134 ±5.1	0.91	134.3 ±5.08	134.2 ±4.5	0.98	133.76 ±4.65	134.39 ±4.68	0.40
K (meq/l)	4.2 ±0.55	4.2 ±0.41	0.95	4.23 ±0.46	4.2 ±0.52	0.73	4.15 ±0.45	4.25 ±0.54	0.18
Mg (mg/dl)	2.1 (0.43)	2.31 ±0.86	0.29	2.24 ±0.48	2.16 ±0.52	0.46	2.19 ±0.79	2.18 ±0.46	0.92
Ca (mg/dl)	8.66 ±0.93	8.5 ±0.87	0.25	8. 5 ±0.92	8.67 ±0.9	0.28	8.6 ±0.91	8.5 0.90	0.31
CRP (mg/dl)	95.2 ±69.9	102.3 ±85.6	0.07	103.23 ±80.77	95.58 ±60.60	0.56	102.32 ±75.35	94.39 ±76.42	0.51
WBC (/mm^3)	8606 ±4507	10445 ±6242	**0.03**	10752 ±5119	8661 ±4224	0.10	9192 ±5506	9389 ±51.3	0.75
RBC (/mm^3)	4.26 ±0.79	4.27 ±0.72	0.92	4.28 ±0.79	4.25 ±0.75	**0.02**	4.3 ±0.71	4.3 ±0.8	0.64
Platelets (× 10^9/L)	247 ±111	260.5 ±120	0.48	256.24 ±126	250.86 ±109	0.80	256 ±113.4	249.37 ±115.4	0.74
Hb (g/dl)	11.4 ±2.1	11.2 ±4.91	0.66	11.05 ±1.89	11.51±2	0.18	11.6±1.86	11.7±2.36	0.81
HCT (%)	34.7 ±5.82	35.1 ±4.98	0.66	35.31 ±4.96	35.110 ±5.73	0.38	35.43 ±5.55	35.12 ±5.47	0.23
MCV (fl)	82 ±8.08	81 ±8.87	0.72	82.39 ±8.03	81.59 ±8.5	0.59	81.81 ±9.7	81.83± 7.81	0.79
MCH (pg)	27 ±3.54	26.57 ±5.53	0.54	26.12 ±6.22	27.15 ±3.28	0.17	26.95 ±3.43	26.77 ±4.97	0.92
MCHC (g/dl)	32.44 ±1.72	32.35 ±2.53	0.80	32 ±31- 34	32 ±31- 34	0.99	32 ±1.97	32 ±1.14	0.91
ESR (mm)	52.9 ±30.1	57.23 ±29.47	0.40	66.07 ±34.85	49.67 ±28.28	**0.02**	52.29 ±30.54	56.13 ±31.67	0.39
PT (Second)	13.82 ±2.02	13.94 ±3.17	0.77	13.2 ±3.4	13.4 ±5.65	0.23	13 ±2.11	13 ±2.48	0.79
PTT (second)	30 ±5.64	34.28 ±7.24	0.33	30 ±5.5	31±4.66	0.20	30 ±2.43	30 ±2.27	0.21

Data are expressed as mean±SD or number (%). P<0.05 was considered as statistically significant.

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Table 2. Comparison of clinical characteristics and laboratory parameters between patients with critical and no-critical form of COVID-19 in metformin group/no metformin group, insulin group/no insulin group and sulfonylurea group/no sulfonylurea group

Variable	Metformin group (n=100)		P-value	Insulin group (n=46)		P-value	Sulfonylurea group (n=68)		P-value
	no-critical ((n=79	Critical (n=21)		no-critical (n=27)	Critical (n=19)		no-critical (n=56)	Critical (n=12)	
Age (years)	58.03± 1.2	61.66 ± 2.57	0.18	59.55 ± 1.92	61.24 ± 3.77	0.66	60.16 ± 1.29	58.33 ± 3.88	0.58
Body temperature (°C)	37.03 ± 0.08	37.16 ± 0.08	0.44	36.09 ± 0.08	36.7 ± 0.45	0.56	37 ± 0.60	37.04 ± 0.18	0.92
systolic blood pressure (×10 mmHg)	12.43 ± .02	12.61 ± 0.46	0.75	12.39 ± 0.48	12.94 ± 0.73	0.99	12.35 ± 0.33	12.16 ± 0.79	0.32
diastolic blood pressure(×10 mmHg)	7.31 ± 0.12	7.42 ± 0.21	0.67	7.65 ± 0.26	7.70 ± 0.46	0.91	7.35 ± 0.16	7.66 ± 0.28	0.40
pulse rate (BPM)	84.05 ± 1.54	92.57 ± 4.78	**0.05**	88.66 ± 2.37	87.71 ± 3.6	0.94	84.04 ± 1.77	99.17 ± 7.88	**> 0.00**
Respiratory rate (BPM)	19.34 ± 0.2	19.95 ± 0.85	0.30	18.55 ± 3.73	21.12 ± 6.64	**> 0.00**	19.48 ± 0.39	20.92 ± 0.98	0.14
O2 saturation (%)	95.14 ± 3.9	86.71 ± 13.29	**> 0.00**	96.48 ± 6.3	89.29 ± 1.47	**> 0.00**	94.96 ± 0.3	86.58 ± 2.25	**> 0.00**
Blood sugar (mg/dl)	191.97 ± 10.24	187.48 ± 18.380	0.83	230.48 ± 24.31	217.94 ± 25.11	0.73	208.27 ± 13.39	220.58 ± 28.99	0.70
LDH (Unit/l)	378.80 ± 19.45	783.43 ± 84.32	**> 0.00**	394.69 ± 30.33	611.24 ± 42.22	**> 0.00**	372.75 ± 21.79	828.91 ± 10.5	**> 0.00**
BUN (mg/dl)	19.03 ± 1.016	42.05 ± 6.15	>0.00	34.51 ± 3.97	38.94 ± 5.71	0.51	18.51 ± 0.98	38.28 ± 7.36	> 0.00
Creatinine (mg/dl)	1.13 ± 0.07	1.55 ± 0.2	**0.02**	1.56 ± 0.15	1.54 ± 0.15	0.92	1.10 ± 0.08	1.45 ± 0.24	0.10
AST (Unit/l)	33.71 ± 2.81	54.10 ± 9.37	> 0.00	35.45 ± 3.69	73.12 ± 11.72	> 0.00	31.59 ± 3.73	47.25 ± 4.31	0.06
ALT (Unit/l)	31.05 ± 2.47	39.19 ± 6.68	0.17	39.55 ± 6.325	105.71 ± 20.70	**> 0.00**	28.95 ± 3.36	38.17 ± 4.49	0.21
ALP (Unit/l)	103.25 ± 11.61	207.83 ± 18.65	0.98	245.38 ± 24.14	271.12 ± 49.73	0.60	198.52 ± 11.37	208± 23.17	0.72
Total bilirubin (mg/dl)	1.03 ± 0.08	1.53 ± 0.25	**0.02**	0.98 ± 0.08	1.69 ± 0.25	**> 0.00**	1.04 ± 0.08	1.60 ± 0.31	**0.02**
Na (meq/l)	134.19 ± 0.49	133.71 ± 0.99	0.66	134.31 ± 1.01	133.82 ± 1.10	0.75	133.68 ± 0.64	134.17 ± 1.18	0.74
K (meq/l)	4.17 ± 0.05	4.31 ± 0.14	0.17	4.18 ± 0.08	4.31 ± 0.10	0.34	4.14 ± 0.06	4.15± 0.14	0.94
Mg (mg/dl)	2.1 ± 0.04	2.15 ± 0.1	0.60	2.20 ± 0.08	2.31 ± 0.13	0.35	2.21 ± 0.11	2.06 ± 0.08	0.55
Ca (mg/dl)	8.68 ± 0.11	8.58 ± 0.12	0.68	8.25 ± 0.19	8.68 ± 0.14	0.13	8.74 ± 0.11	8.33 ± 0.20	0.12

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CRP (mg/dl)	85.34± 6.92	132.43 ± 19	> 0.00	95.03 ± 12.06	117.22 ± 29.16	0.41	86.17 ± 8.78	177.66 ± 21.32	> 0.00
WBC (/mm3)	7621 ± 414	12495 ± 1204	**> 0.00**	10603 ± 929	11005 ± 1323	0.80	8850 ± 741	10554 ± 1605	0.35
RBC (/mm3)	4.18 ± 0.08	4.55 ± 0.16	0.07	4.26 ± 0.15	4.34 ± 0.18	0.74	4.27 ± 0.10	4.43 ± 0.15	0.47
Platelets (× 109/L)	250.01 ± 12.29	238.68 ± 26.64	0.68	239.86 ± 19.98	284.18 ± 37.25	0.25	252.18 ± 14.66	276.14 ± 38.14	0.50
Hb (g/dl)	11.41 ± 0.23	11.63 ± 0.47	0.67	10.68 ± 0.38	11.38 ± 0.38	0.37	11.47 ± 0.25	12.38 ± 0.62	014
HCT (%)	34.75 ± 0.65	34.74 ± 1.29	0.99	34.30 ± 0.87	34.22 ± 1.33	0.94	35.77 ± 0.77	34.22 ± 1.26	0.38
MCV (fl)	82.42 ± 0.91	81.91 ± 1.78	0.56	83.80 ± 1.10	79.88 ± 2.53	0.12	83.06 ± 1.10	75.95 ± 3.10	0.10
MCH (pg)	27.03 ± 0.37	26.92 ± 0.95	0.90	27.69 ± 1.07	23.42 ± 1.48	0.09	26.83 ± 0.45	27.54 ± 1.06	0.51
MCHC (g/dl)	33.38 ± 0.2	32.28 ± 0.37	0.49	32.48 ± 0.44	33.04 ± 0.57	0.57	32.54 ± 0.26	31.91 ± 0.59	0.32
ESR (mm)	51.35 ± 7.44	58.71 ± 7.44	0.33	66.14 ± 7.40	65.94 ± 5.80	0.98	51.23 ± 4	57.25 ± 0.64	0.54
PT (Second)	13.74 ± 0.22	14.12 ± 0.39	0.44	13.66 ± 0.24	15.24 ± 1.27	0.10	13.69 ± 0.29	13.61 ± 0.64	0.92
PTT (second)	33.28 ± 0.65	33.29± 1.59	0.99	33.97 ± 1.19	36.12 ± 2.20	0.35	32.54 ± 0.61	32.25 ± 1.03	0.28

Data are expressed as mean±SD or number (%). P<0.05 was considered as statistically significant.

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Table 3. Simple linear logistic regression and multiple linear logistic regression analysis to predict critical form of COVID–19 diseases in metformin group, insulin group, sulfonylurea group and total patients

Variable	Crude OR	95% CI	Adjusted OR	95% CI	ACU (P value)	Cut off	Specificity (%)	Sensitivity (%)
Metformin group								
O2 saturation	0.81	0.68- 0.97	0.83	0.71- 0.95	0.76 (0.00)	91.5%	90	61
LDH	1	1-1.01	1	1-1.01	0.86 (0.00)	450 mg/dl	74	86
BUN	1.48	1.02-1.59	1.52	1.08-1.60	0.80 (0.00)	30 mg/dl	82	69
Creatinine	0.47	0.08 -2.54	-	-	-	-	-	-
Total bilirubin	1.32	0.66- 2.06	-	-	-	-	-	-
CRP	0.99	0.97- 1.01	-	-	-	-	-	-
Insulin group								
O2 saturation	0.45	0.38- 0.62	0.51	0.41- 0.60	0.89 (0.00)	91.5%	84	86
Respiratory rate	2.02	1- 4.79	1.58	1.04- 2.41	0.79 (0.00)	21	97	40
LDH	1.01	0.99- 1.02	1.01	1-1.01	0.82 (0.00)	461 mg/dl	70	89
AST	1.12	0.99- 1.26	1.05	1- 1.11	0.80 (0.00)	44.5 mg/dl	76	70
ALT	0.98	0.94 -1.01	-	-	-	-	-	-
Total bilirubin	2.85	1.21- 6.5	4.48	2.51 – 6.12	0.92 (0.00)	1.3 mg/dl	85	100
Sulfonylurea group								
O2 saturation	0.80	0.60- 1.07	0.75	0.59- 0.94	0.84 (0.00)	91.5%	93	75
LDH	1	0.99- 1.02	1	1- 1.01	93 (0.00)	493 mg/dl	84	79
BUN	1.02	0.93 -1.12	-	-	-	-	-	-
CRP	1.02	0.99 -1.04	-	-	-	-	-	-
Total bilirubin	0.6	0.1 -3.22	-	-	-	-	-	-
AST	0.98	0.87- 1.09	-	-	-	-	-	-
Total								
O2 saturation	0.88	0.78- 1	0.84	0.73- 0.97	0.78 (0.00)	91.5%	90	63
Respiratory rate	1.23	1.02- 1.5	1.22	1.02-1.46	0.66 (0.00)	20	70	60
LDH	1	1- 1.01	-	-	-	-	-	-
BUN	1.03	0.41- 1.56	-	-	-	-	-	-
Creatinine	0.62	0.45 -2.21	-	-	-	-	-	-
AST	1.01	0.98- 1.04	-	-	-	-	-	-
ALT	1.01	0.99- 1.03	-	-	-	-	-	-
CRP	1	0.99- 1.01	-	-	-	-	-	-
Total bilirubin	1.97	1.15- 2.26	2.00	1.2- 3.49	0.70 (0.00)	1 mg/dl	60	68

The adjusted OR, crude OR, 95% CI, AUC, cut off, specificity and sensitivity are shown. $P < 0.05$ was considered as statistically significant.

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Table 4. Comparison of clinical characteristics and laboratory parameters between death and discharged patients with COVID-19 in metformin group/no metformin group, insulin group/no insulin group and sulfonylurea group/no sulfonylurea group

Variable	Metformin group (n=100)		P-value	Insulin group (n=46)		P-value	Sulfonylurea group (n=68)		P-value
	Discharged (n=88)	Dead (n=12)		Discharged (n=40)	Dead (n=6)		Discharged (n=100)	Dead (n=4)	
Age (years)	58.40 ±1.14	61.58 ±3.75	0.34	60.43 ± 1.93	58.5 ± 5.85	0.72	59.7 ± 1.29	62 ± 5.9	0.67
Body temperature (°C)	37.04 ± 0.08	37.13 ±0.11	0.7	36.94 ± 0.08	36.05 ± 1.24	0.1	37.01 ± 0.06	37.25 ± 0.33	0.37
systolic blood pressure (×10 mmHg)	12.56 ±0.26	11.75 ± 0.41	0.26	12.92 ± 0.44	13 ± 1.12	0.95	12.59 ± 0.32	11.2 ± 0.4	0.23
diastolic blood pressure (×10 mmHg)	7.36 ±0.11	7.16 ± 0.27	0.1	7.75 ± 0.26	7 ± 0.26	0.27	7.45 ± 0.14	6.7 ± 0.47	0.24
pulse rate (BPM)	84.82 ± 1.54	91.33 ± 6.96	0.08	88.30 ± 2.18	88.33 ± 4.89	0.91	86.13 ± 1.98	94 ± 18.05	0.27
Respiratory rate (BPM)	19.47 ± 0.25	19.5 ± 0.66	0.96	19.30 ± 0.4	20.83 ± 1.16	0.18	19.67 ± 0.39	20.75 ± 1.1	0.5
O2 saturation (%)	94.5 ± 0.4	84.58 ± 4.7	**> 0.00**	93.58 ± 0.65	85.83 ± 2.56	**> 0.00**	94.02 ± 0.55	85 ± 3.48	**> 0.00**
Blood sugar (mg/dl)	187.7 ± 9.28	215.4 ± 34.5	0.31	22.54 ± 19.51	22.6 ± 24.44	0.95	210.95 ± 12.4	202.25 ± 60.1	0.86
LDH (Unit/l)	415.06 ± 21.93	821 ± 98.37	**> 0.00**	440.23 ± 26.75	704.67 ± 91.86	**> 0.00**	418 ± 26.27	968 ± 213	**> 0.00**
BUN (mg/dl)	20.96 ± 1.35	45.25 ± 9.01	> 0.00	34.5 ± 3.4	47.16 ± 9.5	0.19	20.42 ± 1.55	46.25 ± 10.4	> 0.00
Creatinine (mg/dl)	1.16 ± 0.29	1.63 ±0.29	**0.01**	1.54 ± 0.12	1.71 ± 0.25	0.7	1.15 ± 0.08	1.32 ± 0.27	0.1
AST (Unit/l)	34.1 ± 2.76	58.17 ± 10.2	0.01	49.98 ± 6.26	45.33 ± 8.62	0.78	33.41 ± 3.39	49.5 ± 5.8	0.24
ALT (Unit/l)	32.20 ± 2.61	36.83 ± 6.26	0.12	54.85 ± 7.4	125 ± 14.49	**0.02**	30.11 ± 2.97	38 ± 5.84	0.51
ALP (Unit/l)	208.25 ± 10.56	198.33 ± 30.41	0.74	234.35 ± 15.32	391.63 ± 153.26	0.01	200.98 ± 10.65	187.5 ± 31.48	0.70
Total bilirubin (mg/dl)	1.11 ± 0.1	1.34 ± 0.17	0.4	1.07± 0.09	2.36 ± 0.41	**> 0.00**	1.09 ± 0.09	1.88 ± 0.61	0.29
Na (meq/l)	133.78 ± 3.4	136.33 ± 1	0.09	133.88 ± 0.82	135.83 ± 1.68	0.51	133.59 ± 0.58	136.5 ± 1.9	0.22

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K (meq/l)	4.18 ± 0.5	4.37 ± 0.41	0.3	4.25 ± 0.07	4.17 ± 0.16	0.93	4.16 ± 0.05	3.97 ± 0.3	0.43
Mg (mg/dl)	2.08 ± 0.04	2.3 ± 0.13	0.11	2.24 ± 0.07	2.26 ± 0.21	0.33	2.2 ± 0.2	2 ± 0.13	0.62
Ca (mg/dl)	8.67 ± .01	8.52 ± 0.19	0.59	8.36 ± 0.24	8.76 ± 0.24	0.38	8.7 ± 0.1	8.17 ± 0.11	0.22
CRP (mg/dl)	86.88 ± 7.07	156.47 ± 19.04	> 0.00	107.47 ± 14.5	75 ± 25.6	0.41	96.57 ±28.99	190.1 ± 40.36	0.01
WBC (/mm3)	8356 ± 451	10600 ± 956	0.12	10485 ± 761	12533 ± 898	0.36	8959 ± 684	12766 ± 3484	0.24
RBC (/mm3)	4.25 ± 0.08	4.34 ± 0.2	0.7	4.35 ± 0.12	3.85 ± 0.3	0.15	4.30 ± 0.09	4.18 ± 0.34	0.74
Platelets ($\times 10^9$/L)	249.38 ± 0.61	234.83 ± 21.3	0.67	251.1 ± 20.11	290.83 ± 52.72	0.49	257.5 ± 14.5	239 ± 30.16	0.75
Hb (g/dl)	11.55 ± 0.21	10.81 ± 0.77	0.25	11.87 ± 0.3	12.28 ± 0.49	0.10	11.52 ± 0.23	12.42 ± 1.03	0.17
HCT (%)	34.65 ± 0.62	35.47 ± 1.72	0.64	34.54 ± 0.8	32.7 ± 1.53	0.42	35.63 ± 0.69	33.77 ± 3.03	0.43
MCV (fl)	81.66 ± 0.89	84.5 ± 1.53	0.25	82.01 ± 1.28	84.93 ± 3.03	0.41	82.06 ± 1.08	77.72	0.36
MCH (pg)	26.7 ± 0.38	28 ± 0.7	0.1	26.71 ± 0.9	22.16 ± 3.4	0.09	26.82 ± 0.43	29 ± 1.35	0.23
MCHC (g/dl)	32.39 ± 11.25	32.83 ± 0.61	0.41	32.62 ± 0.35	30.33 ± 1.4	0.11	32.39 ± 0.24	33 ± 1.22	0.55
ESR (mm)	50.51 ± 3.2	70.32 ± 9.32	**0.05**	63.6 ± 5.65	81.77 ± 11.08	0.26	51.27 ± 3.7	68.75 ± 21.15	0.27
PT (Second)	13.18 ± 0.22	13.9 ± 0.31	0.88	13.59 ± 0.22	17.1 ± 3.22	0.09	13.77 ± 0.14	13.07 ± 0.29	0.57
PTT (second)	34.91 ± 0.55	36 ± 2.34	0.12	35.07 ± 1.22	32.67 ± 2.21	0.37	32.53 ± 0.56	31.75 ± 1.75	0.73

Data are expressed as mean±SD or number (%). P<0.05 was considered as statistically significant.

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Table 5. Simple linear logistic regressions and multiple linear logistic regression to predict death in metformin group, insulin group, sulfonylurea group and total patients with COVID-19

Variable	Crude ratio	95% CI	Adjusted ratio	95% CI	ACU (P value)	Cut off	Specificity (%)	Sensitivity (%)
Metformin group								
O2 saturation	0.84	0.73- 0.96	0.84	0.75- 0.94	0.72 (0.01)	91.5%	85	67
LDH	1	0.99- 1	-	-	-	-	-	-
BUN	1.51	1.06-1.71	1.56	1.08-1.69	0.86 (0.02)	33 mg/dl	80	73
Creatinine	0.68	0.15 -3.4	-	-	-	-	-	-
AST	1.01	0.97- 1.04	-	-	-	-	-	-
CRP	1.01	1- 1.03	1.01	1-1.03	0.78 (0.00)	127.5 mg/dl	81	60
ESR	1.01	0.98	1.04	-	-	-	-	-
Insulin group								
O2 saturation	0.53	0.25- 1.13	0.74	0.57- 0.96	0.86 (0.00)	91.5%	75	83
LDH	0.99	0.98- 1.01	-	-	-	-	-	-
ALP	1.01	1.06-1.71	-	-	-	-	-	-
ALT	1	0.97 -1.02	-	-	-	-	-	-
Total bilirubin	10.01	1.51- 12.04	6.85	2.5 – 7.8	0.90 (0.00)	1.4 mg/dl	83	100
Sulfonylurea group								
O2 saturation	0.75	0.49- 1.15	0.82	0.68- 0.99	0.92 (0.00)	91.5%	85	100
LDH	1	0.99- 1.02	-	-	-	-	-	-
BUN	1.05	0.92 -1.20	-	-	-	-	-	-
CRP	10.3	0.97 -10.9	-	-	-	-	-	-
Total bilirubin	1.5	0.78 -8.61	-	-	-	-	-	-
Total								
O2 saturation	0.88	0.79- 0.98	0.88	0.80- 0.96	0.77 (0.00)	91.5%	84	73
LDH	1	1- 1.005	-	-	-	-	-	-
BUN	1.02	0.99- 1.06	-	-	-	-	-	-
Creatinine	0.75	0.45 -2.21	-	-	-	-	-	-
AST	0.97	0.94- 1.01	-	-	-	-	-	-
ALT	1.01	0.99- 1.03	-	-	-	-	-	-
CRP	1	0.99- 1.01	-	-	-	-	-	-
WBC	1	1- 1.01	-	-	-	-	-	-

The adjusted OR, crude OR, 95% CI, AUC, cut off, specificity and sensitivity are shown. P < 0.05 was considered as statistically significant.

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Discussion

There is a strong association between diabetes and the mortality rate of COVID-19 (13, 14). It seems that several disorders in diabetic patients, such as high expression of ACE2 receptors, chronic inflammation, hypertension, and nephropathy exacerbate the pathological processes of COVID-19 (15). In the present retrospective study, we suggested important predictors of death and critical form of COVID-19 in diabetes patients taking different glucose-lowering medications. Our results revealed that despite matching age, gender, comorbidities, and use of ARBs and/or ACE inhibitors, some baseline characteristics differed significantly between the groups. The hospitalization length and the severity of COVID-19 were higher in insulin-group compared to no insulin group. This result is consistent with the result previously reported by Chen et al (12). They reported that insulin usage was associated with a poor prognosis of COVID-19 in diabetic patients (12). Another study showed that insulin therapy of diabetic patients after COVID-19 infection increased the mortality rate, induced systemic inflammation, and aggravated injuries of vital organs (9). Therefore, they suggested that more attention is needed regarding diabetic patients with COVID-19 infection who have previously used insulin (9). In the present study, analysis of laboratory parameters in the insulin group showed high levels of BUN, creatinine, ALT, ALP, WBC and ESR compared to the no insulin group. Because insulin is often used as a last-line treatment for diabetic patients (16) and renal disorders, oxidative stress, and inflammation are more common among them (5, 16).

Besides, the multiple organ dysfunction following COVID-19 infection (17) exacerbated inflammation and increases the risk of renal disorders in patients using insulin. Furthermore, it has been reported that renal disorders on admission day can increase the mortality rate of COVID-19 patients (18). It also has been suggested that the high expression of ACE-2 receptors in urinary organs was responsible for renal impairment (18). The ACE-2 receptor appears to be essential for the SARS-COV-2 to enter the tissues [19]. Since diabetes leads to overexpression of ACE-2 receptor in renal tubules (20), it seems that these patients are at higher risk of renal impairment and acute kidney disease after being infected with COVID-19. Despite the higher levels of BUN and creatinine in the insulin group compared to the no insulin group, they are not proper predictors for death and critical form of COVID-19. Given that nephropathy is a common complication in diabetic patients using insulin (21), we did not find significant differences between patients with critical and no critical conditions. However, the level of serum total bilirubin was the best predictor for death and the critical form of COVID-19. A previous study on COVID-19 patients revealed that a higher level of bilirubin increased the rate of mortality and the severity of disease (22-24). We also indicated that total bilirubin is a proper predictor for death and a critical form of COVID-19 in diabetic patients.

Evaluation of the clinical severity and hospitalization length in the metformin group showed that these participants had a short hospital stay compared to the no metformin group. However, the severity of the disease and the mortality rate were not different between the two groups. It has been reported that in-hospital mortality was significantly lower in diabetic patients taking metformin compared to those who had not used metformin (7). Cariou et al. showed that taking metformin is associated with a lower risk of early death in diabetic patients with COVID-19 (11). It should be noted that metformin is the first-line treatment for diabetes and probably represents the low stage of the disease with fewer comorbidities, such as nephropathy (11). Therefore, we observed lower levels of BUN, creatinine, and blood sugar, and WBC count in patients taking metformin compared to the no metformin group. Nevertheless, we found that BUN and O_2 saturation were the main predictors for death and critical form of COVID-19 in the metformin group. Given that nephropathy is less common in patients taking metformin (11), renal injuries due to COVID-19 infection generate a significant difference between patients with critical and no critical conditions.

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In the sulfonylurea group, no significant difference was found in clinical severity, hospitalization length, and in-hospital death rate compared to the no sulfonylurea group. However, the levels of BUN and ALT were lower in the sulfonylurea group. Furthermore, O_2 saturation was the only predictor for death or critical form of COVID-19. Comparing patients with critical and no critical conditions, as well as dead and alive individuals in all groups, indicated that O_2 saturation was the best parameter to predict the severity of the disease. However, it must be acknowledged that the main limitation of the present study was the small sample size and consequent small statistical power. Furthermore, due to the focus on hospitalized patients, the less severe forms of the disease were not well considered. Another limitation was the lack of access to some laboratory parameters, such as eGFR, D-dimer, pro-brain Natriuretic Peptide (pro- BNP), and HbA1c that had not been measured in a large number of patients.

Conclusion

In conclusion, it seems that the outcomes of renal function test and serum total bilirubin along with O_2 saturation on admission day are important parameters to predict COVID-19 severity and the fate of the disease in diabetic patients using metformin and insulin. Therefore, our study suggested the essential factors to help choose appropriate procedures for COVID-19 treatment in diabetic patients.

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Authors' Contributions

Sahar Rostami-Mansoor: Conceptualization, Supervision, Writing – Original draft Soraya Khafri: Formal analysis, Validation, Editing Seyedeh Farzaneh Jalali: Investigation Faezeh Mohsenpoorc: Investigation Hadi Parsiand: Validation, Editing Masoumeh Bayanie: Investigation.

Competing Interests

The authors declare no conflict of interest.

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