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Predictors of adverse in-hospital outcome and recovery in patients with diabetes mellitus and COVID-19 pneumonia in Iraq

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ABSTRACT

Background and aims: There is limited data about the prognosis and impact of COVID-19 pneumonia on patients with diabetes mellitus (DM). We aimed to assess blood indices, ECG markers of sudden death and malignant arrhythmias on admission, and diabetes lowering drugs as possible predictors of adverse in-hospital outcome and COVID-19 pneumonia recovery status.

Methods: A retrospective study included patients with newly diagnosed COVID-19 pneumonia from August 20, to October 5, 2020.

Results: A total of 192 patients with COVID-19 pneumonia were included in the present study, of whom 67 patients had DM. Low lymphocytes % [0.4(0.1−0.9), P = .011] and QTc interval prolongation [0.4(0.1−0.8), P = .022] were associated with increased length of ICU stay. On the other hand, metformin use [0.3(0.2−4), P = .032] and DPP-4 inhibitors use [0.3(0.2−3), P = .040] were associated with decreased length of ICU stay. QTc interval prolongation [0.4(0.1−0.9), P = .017] was associated with increased length of hospital stay, while using metformin [0.4(0.2−3), P = .022] was associated with decreased length of hospital stay. Low lymphocytes % [0.5(0.4−1.6), P = .001], insulin use [0.4(0.3−5), P = .003], and old age [0.5(0.1−2.3), P = .025] were associated with extensive lung injury. The risk for in-hospital death was associated with high neutrophil% [1(1−1.4), P = .045], while metformin use was associated with decreased risk for in-hospital death [0.1(0.1−0.6), P = .025]. Insulin use [0.3(0.2−4), P = .013] was associated with partial recovery following acute COVID pneumonia.

Conclusions: Metformin and DPP-4 inhibitors use were associated with favorable in-hospital outcomes, while insulin use was associated with extensive lung injury and post-acute COVID-19 pneumonia partial recovery.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by infection from highly contagious coronavirus termed as severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) [1]. COVID-19 infection has a heterogeneous presentation and the clinical spectrum of infection ranges from asymptomatic infection to life-threatening and even death [2–4].

Patients with pre-existing chronic medical conditions, such as diabetes mellitus(DM), are considered as the high-risk group for adverse morbidity and death related to COVID-19 pneumonia [5]. DM has been identified as a risk factor for adverse outcomes from various types of infections, including those caused by respiratory viruses [6]. Increased susceptibility to respiratory infections may be related to inflammatory and immune imbalances associated with chronic hyperglycemia, which may aggravate viral infection, such as COVD-19 infection [7].

The initial studies from China reported a higher prevalence of diabetes among patients with severe COVID-19 disease requiring hospital or intensive care unit (ICU) admission. However, the mechanisms underlying adverse outcomes related to COVID-19

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infection remain undefined and there is limited data about the prognosis and impact of COVID-19 pneumonia on patients with DM in the literature [1,6].

The main aim of the present study was to assess baseline blood indices, ECG markers of sudden death and malignant arrhythmias on admission, and diabetes lowering drugs as possible predictors of adverse in-hospital outcome and post-acute COVID-19 pneumonia recovery status in patients with DM and COVID-19 pneumonia.

2. Methods

This was an observational retrospective study that included Iraqi patients with newly diagnosed COVID-19 infection who presented to the outpatient clinic or admitted to the Al-Sader teaching hospital in Al-Najaf governorate from August 20, to October 5, 2020. All patients were presented with features consistent with OCVID-19 pneumonia based on clinical symptoms (fever, cough, sputum, or shortness of breath) and radiological findings. Patients diagnosed with COVID-19 according to positive nasopharyngeal swab by real time polymerase chain reaction (PCR). At hospital admission, the baseline clinical characteristics, complete blood count, ECGs were recorded using medical records and collected by physicians at research site –level at the hospital. At outpatient clinic, the evaluation of patients was performed by physicians through the clinical interview with the patient during the outpatient clinic visit. The baseline clinical characteristics included age, sex, hypertension, DM, diabetes lowering drugs or insulin, smoking, body mass index (BMI), previous coronary artery disease, and in-hospital clinical outcome. DM type II was defined as glycated haemoglobin (HbA1c) 6.5% or any established diagnosis prior to admission. Complete blood indices included white blood cell count (WBC), lymphocyte count and %, neutrophil count and %, red blood cell count (RBC), hemoglobin (Hb), red blood cell mean volume (MCV), red blood cell width distribution (RDW), platelet count, platelet distribution width (PDW), and platelet mean volume (PMV). ECG markers of malignant arrhythmias and sudden cardiac death included QTc, T from peak to end interval (Tp-e), and QTc/Tp-e ratio which represents transmural dispersion of repolarization (TDR). The severity of lung injury by COVID-19 pneumonia was assessed by CT scan score at the time of hospital admission or outpatient clinic. According to pneumonia severity and radiological features of lung injury, patients with mild-moderate pneumonia were treated at home and patients with severe pneumonia were admitted to the hospital and followed up until discharge or death. All patients, whether admitted to the hospital or treated at home, must have a second visit to outpatient clinic after 14 day from the resolution of fever related to COVID-19 pneumonia or discharge from the hospital to assess recovery status and post-recovery persistent. Post-acute COVID-19 recovery status included complete recovery after 14 day from the resolution of the fever without persistent symptoms and partial recovery with persistent symptoms after 14 day from the resolution of fever, including persistent shortness of breath, cough, fatigue, smell, and taste loss. Patients with incomplete data or discharge on their responsibility before completion of treatment or not attended 14-day post-discharge or recovery visit were excluded. The main outcome was defined as the length of ICU stay, duration of hospital admission, degree of lung injury according to CT score, in-hospital death, complete recovery, and partial recovery with persistent symptoms. Approval of this study was provided by our medicine College Board.

2.1. ECG examination

The 12-lead ECGs were obtained for all patients at the time of outpatient clinic visit or within 24 h of hospital admission with a paper speed of 25 mm/s and voltage of 10 mm/mV by using a standard ECG system (Marquette Electronics, WI, USA) while the patient was resting in the supine position. ECG readings were measured manually by two cardiologists blinded to the patient's status, using calipers and a magnifying glass. Any disagreement in ECG interpretations between cardiologists was resolved by consensus. Tp-e interval was measured from the peak of the T wave to the end of the T wave in the precordial leads. The mean value of the measurements was used in the analysis. The QT interval was measured from the beginning of the QRS complex to the end of the T. Measured QT intervals were corrected by Bazett's formula (QT/(RR interval)1/2) and defined as corrected QT interval (QTc). The Tp-e/QTc ratio was calculated from these measurements [8].

2.2. Statistical analysis

Statistical analysis was performed using SPSS ver. 23.0 (SPSS Inc., Chicago, IL, USA). *P*-value of $< .05$ was chosen for statistical significance. Baseline clinical data of the patients and clinical outcomes were expressed as mean ± standard deviation for continuous variables or as numbers with percentages for categorical data. Blood indices and ECG markers were expressed as mean ± SD. Univariate and multivariate logistic regression analyses were used to calculate the odds ratio and confidence intervals [OR (CI)] and assess the association of complete blood indices, ECG markers, and baseline characteristics with in-hospital outcomes, including the length of hospital and ICU stay, degree of lung injury according to CT score, and in-hospital death and post-acute COVID-19 pneumonia recovery status. Baseline clinical characteristics, including age, sex, hypertension, diabetes lowering drugs, smoking, BMI, previous coronary artery disease, ECG markers, and complete blood indices underwent univariable logistic regression to the in-hospital outcomes and post-recovery status. Those with a P value of $< .05$ were candidates for inclusion in the final multivariable logistic regression analysis.

3. Results

A total of 192 patients with COVID-19 pneumonia were included in the present study. The patients were categorized into DM group [67 patients with age (years) 60 ± 10, 29(43%) were males] and without DM group [125 patients with age (years) 45 ± 15, 62(49%) were males). Fever (81%) was the most common clinical symptom among patients with DM followed by dry cough(76%), shortness of breath(63%), gastrointestinal tract (GIT) symptoms (46%), fatigue(45%), taste loss (27%), productive cough (25%), and smell loss(22%). Among patients with DM, metformin was the most commonly used diabetes lowering drug (52%) followed by sulfonylurea (36%), insulin (22%), and dipeptidyl peptidase-4(DPP-4) inhibitors (21%). Patients' characteristics are shown in Table 1.

Patients with DM were older (60 year versus 45 year, $P < .000$) and had a higher rate of hypertension (66% versus 33%, $P < .000$) and severe pneumonia requiring hospital admission (52% versus 14%, $P < .000$) than patients without DM. On the other hand, patients without DM had a higher rate of mild-moderate COVID-19 pneumonia treated at home and not requiring hospital admission(86% versus 48%,$P < .000$) compared to patients with DM. No significant difference in the distribution of BMI, previous coronary artery disease, and smoking pattern between DM and without DM groups. Regarding blood indices distribution, higher values of neutrophil % (78 vs 67, $P = .001$), PDW (14 versus 12, $P = .002$), PMV (9.5 versus 8.8, $P = .014$), neutrophil/lymphocyte ratio (10 versus 6, $P = .035$), and platelet/lymphocyte ratio(288 versus174, $P = .002$) were observed among patients with DM compared to patients without DM. On the other hand, higher values of lymphocyte % (24

Table 1
Patients' characteristics.

Variables	Diabetes **N=67** mean ± SD or n(%)	Without diabetes **N=125** mean ± SD or n(%)	P value
Age (years)	60 ± 10	45 ± 15	.000
Male, n(%)	29(43%)	62(49%)	.403
BMI	29.8 ± 5	28.8 ± 6	.267
Hypertension, n(%)	44(66%)	41(33%)	<.000
Coronary artery disease, n(%)	10(15%)	14(11%)	.457
Smoking, n(%)	9(13%)	23(18%)	.378
Mild-moderate pneumonia, n(%)	32(48%)	108(86%)	<.000
Severe pneumonia, n(%)	35(52%)	17(14%)	<.000
Diabetes medications			
Metformin, n(%)	35(52%)	–	–
Sulphonylurea, n(%)	24(36%)	–	–
DPP-4 inhibitors, n(%)	14(21%)	–	–
Insulin, n(%)	15(22%)	–	–
Clinical symptoms			
Fever, n(%)	54(81%)	108(86%)	.291
Dry cough, n(%)	51(76%)	97(77%)	.816
Productive cough, n(%)	17(25%)	36(29%)	.613
Smell loss, n(%)	15(22%)	48(38%)	.024
Taste loss, n(%)	18(27%)	51(41%)	.055
GIT symptoms, n(%)	31(46%)	65(52%)	.449
Shortness of breath, n(%)	42(63%)	67(54%)	.226
Fatigue, n(%)	30(45%)	55(44%)	.232
Blood indices			
WBC, × **10^9/L**	9.6 ± 4	9.8 ± 5	.852
Lymphocytes %	15 ± 11	24 ± 15	.001
Neutrophil %	78 ± 12	67 ± 20	.001
Lymphocyte count, × **10^9/L**	1.1 ± .8	2 ± 1.2	.001
Neutrophil count, × **10^9/L**	8 ± 4	7 ± 5	.342
RBC, **10^6/μL**	4.3 ± .7	4.6 ± .6	.019
Hb, g/dl	12 ± 2	12.8 ± 2	.061
MCV, fl	84 ± 7	87 ± 6	.083
RDW, %	45 ± 6	45 ± 4	.735
Platelet count, × **10^9/L**	250 ± 139	260 ± 104	.653
PDW, %	14 ± 2	12 ± 2	.002
PMV, fl	9.5 ± 1.4	8.8 ± 1.2	.014
Neutrophil/lymphocyte	10.6 ± 4	6 ± 3	.035
Platelet/lymphocyte	288 ± 121	174 ± 111	.002
ECG markers			
QTc interval, ms	438 ± 32	423 ± 29	.023
Tp-e interval, ms	68 ± 12	70 ± 13	.307
TDR	.15 ± .0	.16 ± .0	.462
In-hospital outcome			
Length of hospital stay, days	11 ± 10	3 ± 4	.001
Length of ICU stay, days	8 ± 9	3 ± 5	.003
Degree of lung injury	46 ± 25	25 ± 20	<.000
Death, n(%)	17(25%)	15(12%)	.018
Recovery status			
Complete recovery	29(58%)	70(64%)	.509
Partial recovery	21(42%)	40(36%)	.509

BMI = body mass index, DPP-4 = dipeptidyl peptidase-4, GIT = gastrointestinal tract, ICU = intensive care unit, MCV = mean cell volume, PDW = platelet distribution width, PMV = platelet mean volume, RBC = red blood cell count, RDW = red blood cell distribution width, SD = standard deviation, TDR = transmural dispersion or repolarization, Tp-e = T from peak to end interval, WBCs = white blood cells.

versus 15, P = .001), lymphocyte count (2.1 versus 1.1, P = .001), and RBC (4.6 versus 4.3, P = .019) were observed in patients without DM compared to patients with DM. Patients with DM had significant prolongation in QTc interval (438 versus 423, P = .023) compared to patients without DM while no significant differences in Tp-e interval and TDR were observed between groups. The prevalence of complete and partial recovery showed no significant difference between DM and without DM groups. The prevalence of adverse in-hospital outcomes, including increased length of hospital and ICU stay, extensive lung injury, and death was higher among patients with DM than patients without DM (P < .05). (Table 1).

3.1. Predictors of in-hospital outcome and recovery status among patients with DM

Baseline comorbidities, blood indices, and ECG markers on admission which showed significant association with in-hospital outcome and post-acute COVID-19 recovery status in univariate analysis were selected for final multivariate analysis.

Low lymphocytes % [0.4(0.1–0.9), P = .011] and QTc interval prolongation [0.4(0.1–0.8), P = .022] were associated with increased length of ICU stay. On the other hand, metformin use [0.3(0.2–4), P = .032] and DPP-4 inhibitors use [0.3(0.2–3), P = .040] were associated with decreased length of ICU stay. QTc interval prolongation [0.4(0.1–0.9), P = .017] was associated with increased length of hospital stay, while using metformin [0.4(0.2–3), P = .022] was associated with decreased length of hospital stay. Low lymphocytes % [0.5(0.4–1.6), P = .001], insulin use [0.4(0.3–5), P = .003], old age [0.5(0.1–2.3), P = .025], and high RDW [0.3(0.1–2.6), P = .044] were associated with extensive lung injury. Risk for in-hospital death was associated with high neutrophil% [1(1–1.4), P = .045], while metformin use was associated with decreased risk for in-hospital death [0.1(0.1–0.6), P = .025]. (Table 2).

3.2. Predictors of post-acute COVID-19 status

Female sex [0.2(0.1–0.4),P = .009] and high PMV [0.2(0.1–0.9),P = .045] were associated with complete recovery following acute COVID-19 pneumonia. On the other hand, insulin use [0.3(0.2–4), P = .013] was associated with partial recovery associated with persistent symptoms following acute COVID-19 pneumonia (Table 3).

4. Discussion

Previously described, coronaviruses, including middle east respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), epidemics were associated with severe course and adverse outcome including higher deaths among patients with DM [7]. It has been suggested that diabetes might adversely impact the course of the coronaviruses infection through its effects on receptors that mediate virus entry into the cells including DPP-4, which is involved in the regulation of several physiological processes and is modulated by chronic hyperglycemia and diabetes lowering drugs commonly used in diabetic patients [6].

In the setting of the COVID-19 pandemic, DM has been reported as frequent comorbidity of COVID-19 infection associated with a worse prognosis. The adverse outcome of patients with diabetes is the likely consequence of clustering of several comorbidities, including chronic hyperglycemia, older age, and hypertension, which all contribute to an increase in the risk of disease severity in these patients [9]. Also, DM can affect white blood cells function and response to viral infection via decreased mobilization of polymorphonuclear leukocytes, chemotaxis, phagocytic activity, and elevated pro-inflammatory cytokine levels which may exaggerate the cytokine storm seen in COVID-19 [5,6]. Furthermore, patients with DM were noted to have more pronounced inflammatory and coagulation abnormalities than in non-diabetic patients, independently of other comorbidities [7,10].

A comprehensive meta-analysis of 30 studies showed that DM was associated with adverse outcomes in patients with COVID-19. This adverse association was influenced by age and hypertension. All these comorbidities are characterized by systemic inflammation and hypercoagulability that contribute to COVID-19 progression and eventually to a poor outcome [11]. Besides immune, inflammatory, and coagulation disturbances noted in DM, it has been found that patients with diabetes have a higher prevalence of prolonged QT and decreased repolarization reserve with a significant increase in the risk of arrhythmic death, make patients with diabetes particularly vulnerable to the proarrhythmic effects of QT prolongation [12].

The relationship of anti-diabetes drugs with COVID-19 severity and prognosis is inconsistent among studies. Racial disparity, study design, number of enrolled patients, potential confounders inherently found in observational studies, and frequency of adverse events in some studies may be the possible causes for this inconsistency in the literature.

The available data from observational and retrospective studies showed controversial results regarding the association between metformin use and clinical adverse outcomes in patients with DM and COVID-19. Some studies showed no definite association between metformin use and clinical outcomes, including survival, and raised concerns about the possible risk of lactic acidosis in cases of multiple organ failure [13–15], while others reported that metformin use was associated with a higher risk of disease progression in patients with COVID-19 with DM during hospitalization [16]. However, five studies with a total of 6937 patients showed that metformin use was associated with reduction in mortality rate from COVID-19 infection [17]. The potential beneficial effect of metformin noted in COVID-19 infection might be attributed to its inherent anti-inflammatory properties beyond its glucose-lowering action and independent of glucose control, which could positively influence the prognosis and disease course of patients with DM and COVID-19 [18,19].

Regarding DPP-4 inhibitors and COVID-19 prognosis and severity, it has been reported that DPP-4 plays a role in various physiological processes, including the immune responses. DPP-4 inhibitors may exert immune regulatory functions, that are potentially beneficial in autoimmune and inflammatory diseases, such as rheumatoid arthritis.[5] An upregulation of DPP-4 in patients with DM remains a plausible explanation for the greater severity of COVID-19 in patients with DM [20]. A recent meta-analysis (n = 1607 patients with DM; 16 trials) found a significant reduction in inflammatory markers following DPP-4 inhibitors use

Table 2
Predictors of in-hospital outcome in patients with diabetes * **.

Length of ICU stay		
	OR(CI)	**P value**
Low lymphocytes %	0.4(0.1–0.9)	.011
QTc prolongation	0.4(0.1–0.8)	.022
Metformin	−0.3(0.2-4)	.032
DDP-4	−0.3(0.2-3)	.040
Length of hospital stay		
	OR(CI)	P value
QTc prolongation	0.4(0.1–0.9)	.017
metformin	−0.4(0.2-3)	.022
Lung injury		
	OR(CI)	P value
Low lymphocytes %	0.5(0.4–1.6)	.001
Insulin	0.4(0.3-5)	.003
Old age	0.5(0.1–2.3)	.025
RDW	0.3(0.1–2.6)	.044
In-hospital death		
	OR(CI)	P value
High neutrophil %	1(1–1.4)	.015
Metformin	−0.1(0.1–0.6)	.025

DPP-4 = dipeptidyl peptidase-4, OR(CI) = odd ratio(95% confidence interval), RDW = red blood cell distribution width.
* Significant variables, including baseline blood parameters, comorbidities and ECG markers, and diabetes lowering drugs with P value < .05 in the univariate logistic regression model were entered as predictors of in-hospital outcome in the final multivariate regression model.
** Only variables significant with P value < .05 are displayed in the table.

Table 3
Predictors of post-acute COVID-19 recovery status in patients with diabetes* **.

Complete recovery		
Predictor	OR(CI)	P value
Female sex	0.2(0.1–0.4)	.009
High PMV	0.2(0.1–0.9)	.045
Partial recovery with persistent symptoms		
Insulin	0.3(0.2-4)	.013

OR(CI) = odd ratio(95% confidence interval), PMV = platelet mean volume.
*Significant variables, including baseline blood parameters, comorbidities and ECG markers, and diabetes lowering drugs with P value < .05 in the univariate logistic regression model were entered as predictors of recovery status in the final multivariate regression model.
** Only variables significant with P value < .05 are displayed in the table.

compared with placebo [18,21].

In our study, insulin use was associated with extensive lung injury as evident on CT examination of the chest and partial recovery with persistent symptoms following acute COVID-19 infection. Insulin inhibit the action of A Disintegrin And Metalloprotease (ADAM)17 in an experimental study conducted on mice [22]. ADAM-17 is involved in the shedding of several transmembrane proteins, including angiotensin-converting enzyme 2(ACE2),which may suggest that insulin increases the activity of ACE2 and subsequently increases the infectivity of SARS-CoV-2 [23].According to Chen et al. study, patients with COVID-19 infection using insulin for treatment of DM were associated with poor prognosis compared to non-insulin users.[24] Consistent with our results, a recent study conducted in Lombardo found that treatment with insulin and lower lymphocyte count were associated with higher mortality, even after adjustment for sex and age, whereas the use of metformin or DPP-4 inhibitors were associated with a lower mortality rate [25].

4.1. Limitations

The present study has several limitations. This was a retrospective study including relatively a small number of patients with DM, and the data of patients were extracted from medical patient history or records. The specific rhythm type that occurred in those who died of COVID-19 was not reported in medical records because of a lack of telemetry information or serial ECGs. Therefore, we cannot verify the specific type of cardiac rhythm or arrhythmic events that occurred during ICU staying or prior to death. It is not possible to eliminate the potential effects of unmeasured confounders as with every observational study. A randomized controlled trial is required to confirm the potential favorable effects of metformin and DPP-4 inhibitors or the unfavorable effects of insulin use in the setting of COVID-19 infection.

5. Conclusions

Metformin and DPP-4 inhibitors use were associated with favorable in-hospital outcomes, while insulin use was associated with extensive lung injury and partial recovery following acute COVID-19 pneumonia. Low lymphocyte %, high neutrophil %, old age, prolongation of QTc interval, and high RDW were predictors for adverse outcomes in diabetic patients with COVID-19 pneumonia.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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