Clinical characteristics and outcomes of COVID-19 diabetic versus non-diabetic patients: A retrospective comparative study

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Abstract.

BACKGROUND AND OBJECTIVE: Coronavirus disease-19 (COVID-19) has caused significant morbidity and mortality worldwide. Diabetes mellitus (DM) and related comorbidities have a significant impact on clinical presentation and outcomes. The aim is to compare clinical presentation and outcomes among COVID-19 patients with or without DM.

SUBJECTS AND METHODS: Data from 312 patients who tested positive for COVID-19 at a single hospital were collected respectively from January to April 2021. It included demographic data, clinical symptoms, underlying comorbidities, clinical chemistry, and hematological laboratory findings. Different inflammation indices were calculated. The findings of COVID-19 diabetic and non-diabetic patients were compared.

RESULTS: The percentage of COVID-19 patients with DM and hypertension or cardiovascular diseases was significantly higher compared to non-diabetic patients (78.6 % vs. 35%, and 46.4% vs. 23%, $p < 0.001$) respectively. The diabetic patients showed a significant increase in D-dimer and alkaline phosphatase levels (1922.2 vs.1154.5, $p = 0.007$ and 85.3 vs.75.5, $p = 0.01$) respectively. On the other hand, diabetic patients showed a significant decrease in serum albumin (3.5 vs.3.6, $p = 0.012$). The mean death probability indicator (ANDC), and ICU admission were higher in diabetic patients (72.2%, and 36.6%; respectively) versus the non-diabetic patients (60.7% and 26.1%; $p < 0.001$, 0.071; respectively). Also, the estimated glomerular filtration rate (eGFR) was significantly higher in diabetic patients as compared to non-diabetic patients.

CONCLUSION: The diabetic patients had more comorbidities, a higher rate of ICU admission.

Keywords: COVID-19, diabetes mellitus, inflammatory indices, blood glucose

1. Introduction

Coronavirus disease 2019 (COVID-19) has been declared a public health emergency of worldwide significance by the World Health Organization (WHO). Up until February 2022, the cumulative number of cases reported globally is now nearly 404 million including nearly 5.7 million deaths [1].

The COVID-19 virus has been shown to affect people of all ages but particularly affected older age groups especially those with chronic illnesses such as hypertension, DM, and cardiovascular diseases (CVD). Many studies reported that DM was common morbidity in patients with COVID-19. In China, the prevalence of DM in COVID-19 patients was 8.2% [2]; 21% in the United Kingdom [3]; 33.8% in the United States [4]; and 35.5% in Italy [5].

Diabetes mellitus and poor glycemic control have previously been identified as important indicators of viral pneumonia severity and mortality in Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [6, 7]. Male sex, older age, previously related comorbidities (primarily chronic lung diseases, hypertension, and DM), systematic inflam-

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mation, and malnutrition are the most significant risk factors associated with adverse outcomes such as mortality and increased COVID-19 severity [8–10]. Previous studies have linked respiratory diseases to malnutrition [11]. Similar investigations have revealed that roughly 50% of COVID-19 patients describe gustatory and olfactory impairment, which may cause them to consume fewer foods [12]. Li and colleagues revealed a high prevalence of under-nutrition (52.7%) among COVID-19 patients [13]. Malnutrition (under/over nutrition), on the other hand, alters the immune response, increasing the risk of infections including influenza, respiratory viruses, and COVID-19 [14–16].

The severity outcomes could be attributed to many factors including increased release of inflammatory cytokines such as interleukin-6 (IL-6), which promotes insulin resistance and raises the likelihood of severe disease development [17]; the presence of other comorbidities with DM such as hypertension as the virus [18].

Diabetic patients are at a higher risk of developing the severe form of COVID-19 despite other comorbidities, such as hypertension. Increased severity of COVID-19 in diabetic patients could be attributed to poor glycemic control; immune defects, and associated comorbidities [19]. Poor glycemic control encourages immunological dysfunction through decreased production of interleukins in response to an infection, impaired neutrophils' function, and increased secretion of cytokines including interleukin-1 (IL-1), IL-6, interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α). Excess cytokine in circulation keeps the immune system in a threat state [19, 20].

The prevalence of DM among the general Jordanian population was 16% in 2020 [21]. People with DM are one of the high-risk groups for COVID-19 because their immune system is debilitated. Therefore, this study aims to assess the clinical and biochemical data of diabetic and non-diabetic COVID-19 positive patients and to compare their outcomes including inflammatory biomarkers and indices.

2. Subjects and methods

This single-center retrospective study enrolled 312 adult patients aged 20–95 who were diagnosed with COVID-19 from 1st January to 30th April 2021. Preg-

nant or breastfeeding females were excluded from the study. The study was reviewed and approved by the Institutional Review Board (IRB) of The Hashemite University number (1/14/2020/2021) and by the Helsinki Declaration. Because the study was retrospective, no informed consent was required.

Data collected from the electronic and printed medical records at the time of admission included age, sex, presenting symptoms, comorbid conditions, admission to the intensive care unit (ICU), number of hospitalization days, and mortality.

Laboratory test results include blood glucose, neutrophil count, lymphocyte count, white blood cell count (WBC), ferritin, hemoglobin (Hb), and platelet count. Also, liver and kidney function tests were collected. Liver function tests included albumin level, alanine aminotransferase (ALT), aspartate aminotransaminase (AST), serum direct and total bilirubin, lactate dehydrogenase (LDH), and alkaline phosphatase level (ALP). The renal function tests included urea and creatinine levels as well as the estimated glomerular filtration rate (eGFR) that was calculated for all the patients using the modification of diet in renal disease (MDRD) equation [22], as well as levels of electrolytes. C-reactive protein (C-RP), D-dimer, and procalcitonin were also obtained.

The following inflammatory indices were calculated using neutrophil count, platelet count, lymphocyte count, C-RP, D-dimer, and albumin level: The prognostic nutritional index (PNI) score was determined with the following formula: $10 \times$ serum albumin (g/dL) + $0.005 \times$ peripheral lymphocyte count (/mm^3) [23]; the neutrophil to lymphocyte ratio (NLR) [24]; the platelet to lymphocyte (PLR) [25]; the systemic immune-inflammation index (SII) was calculated with the formula: platelet counts $\times$ neutrophil counts/lymphocyte counts [26]; the C-RP to albumin ratio (CAR) [27]. Another indicator for evaluating death probability depending on the summation of the scores from four predictors including age, NLR, D-dimer, and C-RP variables was named ANDC calculated using the following formula:

$(1.14 \times$ age $-20)$ (years) + $(1.63 * NLR)$ + $(5.00 \times D - dimer, mg/L)$ + $(0.14 \times C-RP, mg/L)$ [28].

2.1. Statistical analysis

Analyses were carried out using Statistical Package for Social Sciences (SPSS) software (IBM Corp.

Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). The values represent mean ± SD for the continuous variables, or percentage relative to the total number of patients in each group for the categorical variables. Independent samples t-test was used to assess the differences between diabetic and non-diabetic patients for the continuous variables, while the Chi-square test was used for the categorical variables. p-value < 0.05 was considered statistically significant.

3. Results

The study population consisted of 312 patients, of whom 40% were females and the mean age was 58.5 years (range 20–95 years). Among the entire study population, 112 (36%) self-reported preexisting DM. Those with preexisting DM were significantly older (mean age 63.8 vs 55.2 years). They also had a higher prevalence of hypertension (78.6% vs 35.0%) and CVD (46.4% vs 23.0%). COVID-19 outcomes were more severe in diabetic patients than in non-diabetic patients, as evidenced by a larger proportion of ICU admitted cases (severe), which was close to being statistically significant ($p = 0.071$) as shown in Table 1.

In Table 2, hemoglobin, white cell counts, absolute lymphocyte and neutrophils count, C-RP, bilirubin, lactate dehydrogenase, creatinine, ferritin, and procalcitonin tests were not significantly different. The mean estimated glomerular filtration rate (eGFR) was significantly lower in the diabetic group than in the non-diabetic group (78.9 ± 57.9 vs. 100.2 ± 63.6 mL/min/1.73 m^2, $p = 0.004$). Although creatinine levels were not significantly higher in the DM group than in the non-diabetic group, the other renal indicator, urea levels in the diabetic group were significantly higher than in the non-diabetic group ($p \leq 0.001$). The albumin level was significantly lower in the diabetic group ($p = 0.012$). ALT and AST showed a significant decrease in the diabetic group compared to the non-diabetic group. Alkaline phosphatase was significantly higher in the diabetic group compared to the non-diabetic group.

Table 3 showed the markers of the inflammatory response; D-dimer levels were significantly higher in diabetic patients (diabetic: 1922.2 ± 4883.6, non-diabetic: 1154.5 ± 4607.2, $p = 0.007$), whereas ANDC was significantly higher in diabetic patients ($p \leq 0.001$).

4. Discussion

The effect of preexisting chronic diseases such as DM has been studied in previous pandemics such as H1N1, MERS-CoV, and SARS-CoV. These pandemics result in an increase in hospitalization, ICU admissions, and mortality rates among diabetic patients when compared to those without DM [6, 29, 30].

DM is the most commonly reported comorbidity among COVID-19 patients. Diabetics who tested positive for COVID-19 made up 36% of the study's participants, which is much higher than the prevalence of DM among the general Jordanian population, which was 16% in 2020 [21]. The prevalence of COVID-19 positive diabetics in hospitalized patients varies across the Middle East. It was 19.5% in Qatar [31], 29.3% in Kuwait [32], 8.3% in Iran [33] and 31.2% in UAE [34].

Even though the difference was not statistically significant, we discovered that patients with DM had more severe COVID-19 outcomes than those without DM, which is linked to ICU admission and a greater rate of death. These results were in agreement with previous studies, in a study of 401 patients in India, the mortality rate in COVID-19 patients with or without DM was 6.3% and 1.4%, and ICU admission was 24.3 and 12.3% [35]. Also, results from different studies in UAE, Kuwait, and Qatar [31, 32, 34] were in line with the results of the current study. Previous studies had a sample size of 300–400 participants and were retrospective in nature.

Aside from the infectious nature of the disease, the presence of comorbidities such as hypertension and CVD may also contribute to the severity of the disease in diabetic patients. In the current study, more than three-fourths of the diabetic patients were hypertensive, 50% had CVD, and were significantly older than non-diabetic patients. These factors can increase the risk of poor disease prognosis [33–35]. COVID-19 is a multisystem infection rather than only a respiratory infection. The biomarkers are divided into eight groups based on the system or organ involved: hematological, inflammatory, coagulation, cardiac, hepatic, muscular, renal, and electrolytes (25). These biomarkers can be utilized for a variety of purposes, including ICU admission criteria and disease severity grading.

Among hepatic biomarkers, many studies have demonstrated that COVID-19 lowers serum albumin levels in diabetic and non-diabetic patients. The pathophysiology behind low serum albumin

Table 1

The characteristics of patients with COVID-19 with or without DM

Variable	Total (n = 312)	Diabetic group (n = 112)	Non-diabetic group (n = 200)	p- value
Age (years)[a]	58.5 ± 15.7	63.8 ± 12.7	55.2 ± 16.5	**<0.001**
Gender [b]				
Males	188 (60.3)	72 (38.3)	116 (61.7)	0.335
Females	124 (39.7)	40 (32.3)	84(67.7)	
Admitted to ICU [b]	93 (29.9)	41 (36.6)	52 (26.1)	**0.071**
Mortality [b]	45 (14.4)	21 (18.8)	24 (12.0)	0.130
Hospitalization days [a]	9.7 ± 6.9	10.2 ± 6.6	9.4 ± 6.7	0.395
Comorbidity [b]				
Hypertension	158 (50.6)	88 (78.6)	70 (35.0)	**<0.001**
Cardiovascular diseases (CVD)	98 (31.4)	52 (46.4)	46 (23.0)	**<0.001**
Chronic liver diseases	3 (1.0)	1 (0.9)	2 (1.0)	0.926
Chronic kidney diseases	29 (9.3)	12 (10.7)	17 (8.5)	0.518
Cancer	10 (3.2)	5 (4.5)	5 (2.5)	0.345
Symptoms [b]				
Fever	230 (74.0)	79 (71.2)	151 (75.5)	0.421
Cough	247 (79.7)	91 (82.7)	156 (78.0)	0.377
Dyspnea	266 (85.5)	96 (85.6)	170 (85.0)	0.867
Fatigue	285 (91.9)	102 (92.7)	183 (91.5)	0.829
Anorexia	140 (45.2)	45 (40.9)	95(47.5)	0.285
Diarrhea	53 (17.1)	15 (13.6)	38 (19.0)	0.271
Vomiting	24 (7.7)	6 (5.5)	18 (9.0)	0.375
Loss of taste and smell	20 (6.5)	5 (4.5)	15 (7.5)	0.347

[a]Data are presented as mean ± SD; [b]n (%).

Table 2

Biochemical findings of patients with COVID-19 with or without DM

Variable	Total (n = 312)	Diabetic group (n = 112)	Non-diabetic group (n = 200)	P-value
Blood sugar, (mg/dl)	193 ± 95.8	249.8 ± 92.8	159.6 ± 80.1	**<0.001**
White blood cells, (10^9/L)	8.6 ± 4.8	8.7 ± 4.9	8.6 ± 4.7	0.867
Absolute neutrophils, (10^9/L)	7.2 ± 4.6	7.1 ± 3.9	7.3 ± 4.9	0.757
Absolute lymphocyte, (10^9/L)	1.1 ± 1.8	1.22 ± 2.99	1.0 ± 0.64	0.229
Hemoglobin (g/dL)	13.2 ± 2.0	13.0 ± 2.1	13.3 ± 1.9	0.899
Platelets, (10^9/L)	242.4 ± 91.4	246.8 ± 105.5	239.9 ± 82.7	0.219
Albumin, g/dl	3.6 ± 0.55	3.5 ± 0.58	3.6 ± 0.53	**0.012**
Total protein, g/dl	6.59 ± 0.70	6.48 ± 0.72	6.67 ± 0.69	0.269
Direct bilirubin, mg/dl	0.25 ± 0.21	0.23 ± 0.15	0.25 ± 0.25	0.335
Total bilirubin, mg/dl	0.52 ± 0.41	0.49 ± 0.27	0.54 ± 0.27	0.234
ALT, U/L	37.4 ± 52.3	26.9 ± 18.2	43.2 ± 63.3	**0.027**
AST, U/L	46.6 ± 60.7	34.2 ± 18.9	53.6 ± 73.7	**0.006**
Alkaline phosphatase, U/L	79.0 ± 36.4	85.3 ± 38.1	75.5 ± 35.0	**0.010**
Magnesium, mg/dl	2.21 ± 0.38	2.19 ± 0.39	2.22 ± 0.37	0.432
Phosphorus, mg/dl	3.72 ± 1.6	3.82 ± 1.5	3.67 ± 1.6	0.424
Calcium, mg/dl	8.9 ± 0.64	8.92 ± 0.62	8.96 ± 0.66	0.601
Potassium, mg/dl	4.29 ± 0.21	4.24 ± 0.60	4.32 ± 0.66	0.764
Urea, mg/dl	57.1 ± 51.8	72.1 ± 62.2	48.7 ± 42.8	**<0.001**
Creatinine, mg/dl	1.36 ± 2.3	1.57 ± 2.4	1.2 ± 2.2	0.238
eGFR (mL/min/1.73 m^2)	92.4 ± 62.2	78.9 ± 57.9	100.2 ± 63.6	**0.004**

Data are presented as means ± SD; eGFR: Estimated glomerular filtration rate; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

Table 3
Comparison of coagulative, inflammatory markers and indices in COVID-19 patients with or without DM

Inflammatory markers and indices	Diabetic group ($n = 112$)	Non-diabetic group ($n = 200$)	P-value
C-RP, mg/L	112.9 ± 82.5	101.3 ± 80.9	0.204
D-dimer, ng/ml	1922.2 ± 4883.6	1154.5 ± 4607.2	**0.007**
Ferritin, ng/ml	600 ± 527	635 ± 647	0.657
Procalcitonin, ng/ml	1.32 ± 4.5	1.84 ± 5.3	0.447
Lactate dehydrogenase, U/L	364.2 ± 151.6	357.9 ± 168.2	0.596
PNI	41.3 ± 16.4	41.1 ± 7.0	0.883
NLR	11.4 ± 11.9	9.9 ± 9.1	0.229
PLR	363.9 ± 302.6	316.5 ± 211.8	0.111
SII	2808.1 ± 3362.7	2453.4 ± 2644.1	0.310
ANDC	74.2 ± 27.2	60.7 ± 27.4	**<0.001**
CAR	3.38 ± 2.54	2.99 ± 2.59	0.208

C-RP: C-reactive protein; PNI: prognostic nutritional index; NLR: neutrophil to lymphocytes ratio; PLR: platelet to lymphocyte; SII: systematic inflammation index; CAR: C-RP to albumin ratio; ANDC: mean death probability indicator. Data are presented as mean ± SD.

in COVID-19 infection is thought to be secondary to increased capillary permeability, decreased protein synthesis, decreased half-life of serum albumin, decreased serum albumin total mass, increased volume of distribution, and increase expression of vascular endothelial growth factor [36]. The result of this study is in accord with recent studies indicating that COVID-19 diabetic patients have low serum albumin [32, 34, 37]. In contrast to the present findings about liver function, Bertolini and colleagues observed that abnormal liver function tests were frequently observed in COVID-19 patients; not only the diabetics [38]. Hundt and colleagues (2020) observed abnormal liver tests in hospitalized patients with COVID-19, both at admission (AST 66.9%, ALT 41.6%) and peak hospitalization (AST 83.4%, ALT 61.6%), and this was associated with severe COVID-19 outcomes, such as ICU admission, mechanical ventilation, and death; associations with male sex, age, body mass index, and DM [39].

Some studies found that eGFR was significantly lower in diabetic patients [32, 34, 37, 40]. Due to a lack of information on the time of onset of DM and previous renal function results, it could be linked to the advent of late complications of DM affecting the kidneys. Another possibility is that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will target the kidney through an Angiotensin Converting Enzyme-2 (ACE2)-dependent pathway, causing renal injury [40]. Serum urea was shown to be increased in some studies [32, 34, 41], which was consistent with the results of the current study. The prevalence of chronic diseases such as hypertension, older age, and DM may increase the risk of renal dysfunction

in COVID-19 patients, including diabetics; diabetic patients in the current study had hypertension and were older than non-diabetic patients [42].

Many biomarkers, including inflammatory and coagulative biomarkers, have been tested in COVID-19 patients. In the current study, D-dimer was the only coagulative biomarker that showed a significant increase in diabetic patients compared to non-diabetic patients. Such results agree with the findings reported in a study conducted in UAE (4.612 and 4.449 ng/ml) [34] and another one conducted in Egypt (1.5 and 1.9 μg/mL) [43]. Also, it is linked to disease severity and in-hospital mortality. Increases in plasma D-dimer levels are also associated with inflammation, and intravascular coagulation [44]. A level of > 2.0 μg/ml on admission could predict mortality [45].

The uses of many inflammatory indices such as PNI, NLR, PLR, SII, ANDC, and CAR were highlighted in this study. Some were used to estimate the disease severity such as PNI, SII, and PLR [46–48]. ANDC was the only index that indicated a significant increase in diabetic compared to non-diabetic patients. It is a formula that includes four variables: age, NLR, D-dimer, and C-RP. It is elucidating that D-dimer level and mean age were significantly higher in diabetic patients, which increase the ANDC score. Our findings go in line with data reported by Farag et al. that increasing age, hypertension, and high levels of D-dimer were reported as important predictors of mortality among COVID-19 patients [43].

To the best of our knowledge, this is the first study to assess the outcomes of COVID-19 in diabetic compared to non-diabetic patients. The effect of

COVID-19 in diabetic patients should be investigated further and for longer periods with larger sample size.

5. Conclusion

Diabetic individuals were shown to have an increase in age, hypertension, CVD, high D-dimer levels, and ANDC score, as well as a decrease in serum albumin and eGFR. More studies with larger sample sizes are needed to compare data of COVID-19 patients admitted with and without DM.

5.1. Strengths and limitations

The study's key strength was that it was the first to investigate COVID-19's impact on diabetic patients. Due to the severity of the epidemic disease, our study was subject to a few limitations that should be mentioned. First, the study used a single-center, retrospective, and observational design. Second, the sample size was relatively small. Third, obesity has been demonstrated to play a significant influence on COVID-19 outcomes, although weight data were not available for all patients. Fourth, other blood glucose monitoring data, like glycosylated hemoglobin, which could have provided a more accurate picture of the link between blood glucose control and disease severity, was missing.

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Author contribution

Conceptualization: H.Al., and B.Al.; Methodology: I.Al.; Software: H. Al.; Validation: H.Al., B.Al, and I.Al.; Formal Analysis: H. Al.; Investigation: I.Al.; Resources: I.Al.; Data Curation: H. Al.; Writing – Original Draft Preparation: H.Al.; Writing – Review & Editing: B. Al.; Visualization: I. Al.; Supervision: H. Al.; Project Administration: H.Al. and B. Al.

Ethical Considerations

The study protocol was carried out following the principles of the Declaration of Helsinki, as revised in 2000. Ethical approval for this research was obtained from the Ethical Review Board at The Hashemite University (No. 1/14/2020/2021).

Informed consent

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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