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Well-controlled vs poorly-controlled diabetes in patients with COVID-19: Are there any differences in outcomes and imaging findings?

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ABSTRACT

Aims: We aimed to compare the clinical outcomes and imaging findings between COVID-19 patients with well-controlled diabetes and those with poorly-controlled diabetes.
Methods: In this retrospective single-center study, 117 patients with coexistent COVID-19 and type 2 diabetes mellitus were included. Patients were divided into two groups based on HbA1c values. Clinical data and laboratory parameters were collected from patients' medical records. Also, the chest computed tomography (CT) score was defined by the summation of individual scores from 5 lung lobes: scores of 0, 1, 2, 3, 4 and 5 were respectively assigned for each lobe if pulmonary involvement was 0%, less than 5%, 5%-25%, 26%-49%, 50%-75%, or more than 75% of each region.
Results: Among all patients with diabetes, 93 (79.5%) patients had poorly-controlled diabetes and 24 (20.5%) had well-controlled diabetes; 66 (56.4%) patients were male and the median age was 66 years (IQR, 55–75 years). The chest CT severity scores were not significantly different between patients with well-controlled diabetes and those with poorly-controlled diabetes ($p = 0.33$). Also, the mortality and recovery rates were similar between the two groups ($p = 0.54$ and $p = 0.85$, respectively).
Conclusion: Based on the results, clinical outcomes and chest CT severity scores are similar between patients with well-controlled and poorly-controlled diabetes among the Iranian population with COVID-19.

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1. Introduction

In December 2019, many cases with an unknown pneumonia were reported in Wuhan, China [1]. Subsequently, a beta-coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was isolated from the lower respiratory tract samples of infected patients and the disease, later declared by the World Health Organization as a

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pandemic, was termed the novel coronavirus disease-2019 (COVID-19). The clinical spectrum of COVID-19 varies widely; while the majority of patients present with a mild form of the disease, severe cases may develop acute respiratory distress syndrome (ARDS), multiple organ failure, and even death [2–4].

Currently, the diagnosis of COVID-19 is confirmed by real-time reverse transcriptase polymerase chain reaction (RT-PCR); however, chest computed tomography (CT) imaging has played a major role in the diagnosis and management of suspected or confirmed cases of COVID-19 [5,6]. In addition, various CT scores have been designed to assess the severity of disease [7–9]. Studies reporting the chest CT findings of COVID-19 have indicated that the most common findings are ground-glass opacities (GGO) and consolidation, which mainly have a peripheral distribution [10,11]. Moreover, chest CT severity scores are higher among severe cases of COVID-19 compared with patients with mild disease [8,9,12].

According to the literature, patients with comorbidities such as diabetes, hypertension, and cardiovascular disease, as well as older patients are prone to worse clinical outcomes and higher rates of complications associated with COVID-19 [3,13,14]. Studies from the previous pandemics including the influenza A (H1N1), SARS-CoV, and MERS-CoV pandemics indicated that diabetes and uncontrolled glycemia were significantly associated with disease severity and mortality in infected patients [15–17]. For example, a study evaluating the 2009 pandemic influenza A (H1N1) virus found that the fasting plasma glucose (FPG) level of H1N1 patients on admission was significantly associated with disease severity [18]. To this point, the role of glycemic control in the prognosis of patients with coexistent diabetes and COVID-19 is not clear. In this study, we aimed to compare the clinical outcomes and imaging findings between COVID-19 patients with well-controlled diabetes and those with poorly-controlled diabetes.

2. Methods

2.1. Study design and participants

We conducted a retrospective single-center study on patients who were admitted to a tertiary care hospital in Tehran, Iran with a suspicion of COVID-19 infection. From a total of 1357 patients with COVID-19, admitted between February 2020 and April 2020, 117 (8.6%) patients had type 2 diabetes mellitus (DM) and were included in our study. Diabetes mellitus was confirmed by reviewing patients' medical records. No exclusion criteria were considered for this study. The included patients were classified as patients with well-controlled or poorly-controlled DM according to hemoglobin A1c (HbA1c) levels recommended by the American Diabetes Association [19]. Patients with an HbA1c level of more than 7% were regarded as patients with poorly-controlled DM, while those with an HbA1c level of equal to or less than 7% were considered as patients with well-controlled DM.

Due to the unavailability of RT-PCR kits for detection of SARS-CoV-2 early in the outbreak in Iran, patients who had clinical features and chest CT findings highly suggestive of COVID-19 were considered as positive cases and thus, were included in this study. This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences.

2.2. Demographics and laboratory tests

Baseline demographics of patients were retrieved by collecting data from patients' electronic medical records. In this study, we assessed the underlying comorbidities (hypertension and cardiovascular disease), duration of diabetes, smoking history and medications [insulin, oral hypoglycemic agents (OHAs), angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers (ACEI/ARBs), statin and diuretics] of all participants. Individuals who had ceased smoking more than 10 years earlier were considered as non-smokers. Laboratory tests included the total count of leukocytes and lymphocytes, HbA1c, lactate dehydrogenase (LDH), C-reactive protein (CRP), magnesium (Mg), phosphorus (P), calcium (Ca), cardiac troponin I, procalcitonin (PCT), D-dimer, 25-OH-VitD, and zinc. In addition, RT-PCR assay was performed on nasopharyngeal specimens for SARS-CoV-2 detection in all patients with Taqman® Premix TAKARA (TaKaRa, Dalian, China) considering the protocols provided by the manufacturer.

2.3. Chest CT interpretation

All patients underwent chest CT examinations after admission and all CT scans were reported by the same radiologist (with years of experience in CT imaging) to reduce potential bias. The chest CT severity score was defined by the summation of individual scores from 5 lung lobes: scores of 0, 1, 2, 3, 4 and 5 were respectively assigned for each lobe if pulmonary involvement was 0%, less than 5%, 5%-25%, 26%-49%, 50%-75%, or more than 75% of each region. The range of total severity score was from 0 (no involvement) to 25 (maximum involvement).

The predominant patterns on chest CT imaging were classified into five groups: GGO, consolidation, GGO/consolidation (mixed), reverse halo sign and crazy-paving. Other secondary CT findings such as cavity, nodule, pleural effusion, pericardial effusion and lymphadenopathy (LAP) >10 mm were also recorded. Distribution of lung lesions was grouped into three categories: peripheral, peribronchovascular and perihilar. Also, lung opacifications fell into three different categories in terms of morphology: round, linear, or non-specific opacities.

2.4. Statistical analysis

Non-normally distributed continuous data were expressed as median [interquartile range (IQR)] and categorical data were presented as number (percentage). Normal distribution was evaluated by using the Shapiro-Wilk test. Chi-square test was used for comparison of proportions between groups. The differences of parametric and non-parametric continuous data were compared between groups by using the independent samples *T*-test and Mann-Whitney *U* test, respectively. All statistical analyses were performed by using the SPSS software version 23 (SPSS Inc., Chicago IL, USA). P-values less than 0.05 were considered statistically significant.

3. Results

3.1. Demographics, clinical and laboratory data

This study included 117 patients with COVID-19 who had pre-existing type 2 DM. The prevalence of diabetes among all patients with COVID-19 was 8.6%. Totally, 66 (56.4%) patients were male and the median age was 66 years (IQR, 55–75 years). Among the total population of patients with diabetes, 93 (79.5%) patients had poorly-controlled diabetes and 24 (20.5%) patients had well-controlled diabetes. Approximately 79% of the included patients tested positive for SARS-CoV-2 by RT-PCR. The clinical and laboratory findings of patients are demonstrated in Table 1. As shown, patients with well-controlled DM were significantly older than those with poorly-controlled DM ($p < 0.001$). Also, the distribution of male and female patients differed significantly between the two groups ($p = 0.04$). While the majority of patients in the well-controlled DM group were females, male patients constituted a higher percentage among patients with poorly-controlled DM. The median HbA1c value among all patients with diabetes was 8.6% (IQR, 7.5%–11%). When comparing comorbidities between the two groups, no significant difference was observed. Among all patients with coexistent diabetes and COVID-19, 62 (53%) patients had hypertension. Duration of diabetes was not statistically different between patients with well-controlled and poorly-controlled DM ($p = 0.77$). Approximately half of the patients recovered from COVID-19, but 22.2% of the patients died during hospitalization. In addition, about 18% experienced ARDS during the course of disease. Clinical outcomes, however, were not significantly different between patients with well-controlled and poorly-controlled DM ($p > 0.05$). Considering the medications used by patients for their underlying diabetes, the use of ACEI/ARBs or insulin did not differ between the two groups ($p = 0.25$ and $p = 0.18$, respectively). Among laboratory parameters, 56 (61.5%) patients of the total population had lymphocytopenia on admission. Only calcium and 25-OH-VitD levels differed significantly between the two groups ($p = 0.04$ for both).

3.2. Imaging findings

The imaging findings of patients on chest CT are presented in Table 2. The median total CT severity score was 11 and 10.5 among patients with well-controlled and poorly-controlled DM, respectively ($p = 0.33$). The highest CT scores were observed in the right lower lobes of patients in both groups. The most common chest CT pattern was GGO (51.3%) followed by consolidation (35%). In addition, 85.5% of the cases had lesions with a peripheral distribution on CT imaging; whereas no perihilar distribution was detected in any patient. In terms of morphology, linear opacities were more frequently seen in patients with poorly-controlled DM; however, this finding had borderline significance ($p = 0.08$). Among 117 patients with COVID-19 and diabetes, 10 (8.5%) and 43 (36.8%) patients had pleural effusion and hyperinflation on CT imaging, respectively.

3.3. Association between ACEI/ARB use and clinical outcome

After comparing the proportion of patients who had a fatal outcome between those receiving ACEI/ARBs and those who did not receive these medications, we found that patients who were using ACEI/ARBs had significantly higher rates of death and lower rates of recovery ($p = 0.03$ for both). ARDS was also more common among patients using ACEI/ARBs, although with borderline significance ($p = 0.08$).

4. Discussion

In this study, we investigated the clinical outcomes, laboratory parameters and imaging findings of patients with coexistent diabetes and COVID-19 who were admitted to our hospital between February 2020 and April 2020. Previous studies have reported that comorbidities such as diabetes are associated with an increased risk of death among patients with COVID-19 [3,13,14]. In addition, some have argued that glycemic control may be of great value in the prognosis of patients with coexistent diabetes and COVID-19 [20–22]. The mortality rate of hospitalized patients with coexistent COVID-19 and diabetes was about 22% in this study. Likewise, in a study in the United States, the mortality rate among patients with diabetes and/or uncontrolled hyperglycemia was approximately 29% [23]. These mortality rates are higher than those observed among the general population with COVID-19 [24].

Several hypotheses exist for the role of hyperglycemia in the progression of viral respiratory infections. Elevated blood glucose levels may negatively impact pulmonary function, as well as suppressing the immune system and increasing the production of inflammatory cytokines [25–28]. In addition, angiotensin-converting enzyme 2 (ACE2), one of the main receptors for SARS-CoV-2, is expressed within the pancreas, suggesting that this novel coronavirus can directly damage pancreatic islets [29]. Nevertheless, the impact of hyperglycemia on COVID-19 progression requires further investigation.

Recently, Zhu et al. investigated the association of blood glucose control with clinical outcomes in a large-scale study on 7337 patients with confirmed COVID-19, 952 of who had diabetes [30]. They found that 53.6% of patients with diabetes were male, which is similar to the results of our study (56.4%). Also, they reported a prevalence of 13% for diabetes among the total population of patients with COVID-19, whereas our study found a slightly lower prevalence of 8.6%. In Iran, diabetes has an estimated prevalence of 11.4% among 25–70-year-olds [31]. In another study in Italy, the prevalence of diabetes among patients with COVID-19 was 8.9% [32]. A recent meta-analysis also reported a pooled prevalence of 9% for diabetes among patients with COVID-19 [33]. In the study by Zhu et al, patients with diabetes had a relatively lower median age

Table 1 – Demographics and clinical characteristics of patients.

Variables	Total (n = 117)	Well-controlled (n = 24)	Poorly-controlled (n = 93)	P-value
Age, yrs	66 (55–75)	75.3 (67–86)	62.2 (54.5–72.5)	<0.001
Sex				
Male	66 (56.4)	9 (37.5)	57 (61.3)	0.04
Female	51 (43.6)	15 (62.5)	36 (38.7)	–
Comorbidities				
Hypertension	62 (53.0)	13 (54.2)	49 (52.7)	0.89
Cardiovascular disease	39 (33.3)	11 (45.8)	28 (30.1)	0.14
Smoking history				
Smoker	7 (6.0)	1 (4.2)	6 (6.5)	1.0
Non-smoker	110 (94.0)	23 (95.8)	87 (93.5)	–
Duration of diabetes, yrs	8 (5.5–15)	10 (4.3–15)	8 (6–15)	0.77
PCR assay				
Positive	72/91 (79.1)	14/20 (70.0)	58/71 (81.7)	0.35
Clinical Outcome				
Recovery	91 (77.8)	19 (79.2)	72 (77.4)	0.54
Death	26 (22.2)	5 (20.8)	21 (22.6)	0.85
ARDS	21 (17.9)	3 (12.5)	18 (19.4)	0.56
Medications				
Insulin	32 (27.4)	4 (16.7)	28 (30.1)	0.18
OHA	52 (44.4)	10 (41.7)	42 (45.2)	0.75
ACEI/ARB	42 (35.9)	11 (45.8)	31 (33.3)	0.25
Diuretics	16 (13.7)	4 (16.7)	12 (12.9)	0.73
Statin	32 (27.4)	6 (25.0)	26 (28.0)	0.77
Laboratory tests				
HbA1c, %	8.6 (7.5–11)	6.6 (6.5–7.0)	9.0 (8.0–11.2)	<0.001
Leukocyte, $\times 10^3/\mu L$				
<4	5 (5.2)	1 (5)	4 (5.2)	1.0
4–10	68 (70.1)	16 (80)	52 (67.5)	0.34
>10	24 (24.7)	3 (15)	21 (27.3)	0.39
Lymphocyte,/μL				
≤1500	56 (61.5)	13 (68.4)	43 (59.7)	0.43
>1500	35 (38.5)	6 (31.6)	29 (40.3)	0.55
Troponin, ng/mL	0.02 (0.01–0.07)	0.04 (0.02–0.2)	0.02 (0.01–0.05)	0.07
Procalcitonin, ng/mL	0.39 (0.16–1.19)	0.27 (0.17–0.53)	0.47 (0.15–1.56)	0.46
D-dimer, ng/mL	243 (18–549)	428 (92–1687)	112 (18–542)	0.53
LDH, U/L	478 (379–693)	456 (360–507)	481 (389–733)	0.41
CRP, mg/L	49 (21–70)	50 (18–74)	49 (22–70)	0.92
25-OH-VitD, ng/mL	24 (13–39)	14 (5–32)	27 (16–41)	0.04
Zinc, μg/dL	60 (47–71)	60 (21–60)	60 (48–71)	1.0
Mg, mEq/L	1.9 (1.7–2.1)	2.0 (1.7–2.4)	1.9 (1.7–2.1)	0.19
P, mg/dL	3.1 (2.5–4.2)	3.6 (2.5–6.0)	3.1 (2.4–4.0)	0.23
Ca, mg/dL	8.6 (8.2–8.9)	8.9 (8.4–9.9)	8.5 (8.1–8.8)	0.04

Data are presented as n (%) and median (IQR).
DM, diabetes mellitus; ARDS, acute respiratory distress syndrome; OHA, oral hypoglycemic agent; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; HbA1c, hemoglobin A1c; LDH, lactate dehydrogenase; CRP, C-reactive protein; Mg, magnesium; P, phosphorus; Ca, calcium.

compared with our study (62 versus 66 years, respectively). This could be due to the exclusion of patients older than 75 years in the mentioned study. In line with our study, a higher percentage of patients with well-controlled DM were female, while in patients with poorly-controlled DM male patients constituted a higher percentage. Besides, in parallel with our study, they showed that findings on chest CT imaging were similar between the two groups. However, chest CT imaging evaluations were only limited to bilateral/unilateral lesions in that study. About 18% of the patients with diabetes developed ARDS in our study; similarly, Zhu et al. reported that ARDS occurred in 17% of patients with diabetes. A major difference between these two studies, however, remains in the definition of well-controlled and poorly-controlled DM. Zhu and colleagues divided patients with diabetes into two groups based on the glycemic variability range; while, in our study, patients with diabetes were classified by long-term glycemic control (HbA1c values). This varying definition might explain the differences in the outcomes found between the study by Zhu et al. and this study. Zhu et al. indicated that patients with well-controlled blood glucose had a markedly lower in-hospital death rate compared with those with poorly-controlled blood glucose. However, our study failed to demonstrate a significant difference in clinical outcomes (recovery and death) between the two groups. Another possible reason for the paradoxical findings between the two studies might be the ethnical and geographical variations between the Chinese and the Iranian population. Our findings

Table 2 – Chest computed tomography findings of patients.

	Total	Well-controlled	Poorly-controlled	P-value
Total CT severity score	11 (8–14)	10.5 (7.25–12.75)	11 (8–15)	0.33
CT score according to lobe				
Right upper lobe	2 (2.0–3.0)	2 (1.25–3.0)	2 (2.0–3.0)	0.52
Right middle lobe	2 (1.0–2.0)	2 (1.0–2.0)	2 (1.0–2.0)	0.61
Right lower lobe	3 (2.0–3.0)	3 (2.0–3.75)	3 (2.0–3.0)	0.69
Left upper lobe	2 (1.0–3.0)	2 (1.0–3.0)	2 (1.0–3.0)	0.11
Left lower lobe	3 (2.0–3.0)	2.5 (2.0–3.0)	3 (2.0–3.0)	0.90
Predominant CT pattern				
GGO	60 (51.3)	12 (50)	48 (51.6)	0.88
Consolidation	41 (35)	10 (41.7)	31 (33.3)	0.44
GGO/Consolidation (mixed)	10 (8.5)	2 (8.3)	8 (8.6)	0.96
Crazy-paving	3 (2.6)	–	3 (3.2)	1.0
Reverse halo sign	1 (0.9)	–	1 (1.1)	1.0
Distribution of lung lesions				
Peripheral	100 (85.5)	18 (75)	82 (88.2)	0.11
Peribronchovascular	52 (44.4)	10 (41.7)	42 (45.2)	0.75
Perihilar	–	–	–	–
Morphology of lung opacifications				
Round	31 (26.5)	4 (16.7)	27 (29)	0.22
Linear	25 (21.4)	2 (8.3)	23 (24.7)	0.08
Non-specific	60 (51.3)	18 (75)	42 (45.2)	0.009
Other specific findings				
Nodule	2 (1.7)	1 (4.2)	1 (1.1)	0.37
Cavity	–	–	–	–
Pleural effusion	10 (8.5)	4 (16.7)	6 (6.5)	0.21
Pericardial effusion	3 (2.6)	–	3 (3.2)	1.0
Lymphadenopathy >10 mm	–	–	–	–
Emphysema	–	–	–	–
Fibrosis	2 (1.7)	–	2 (2.2)	1.0
Hyperinflation	43 (36.8)	9 (37.5)	34 (36.6)	0.93

CT, computed tomography; GGO, ground-glass opacity.

are supported by the most recent study on inpatients with COVID-19 and diabetes; in the CORONADO study, HbA1c values were not associated with death or the primary outcome (mechanical ventilation and/or death) in patients with COVID-19 [34].

Although HbA1c serves as a reliable test for measuring blood glucose values over a period of about three months, and HbA1c values greater than 6.4% indicate impaired glycemic control, it is unknown whether HbA1c values or FPG levels have a more dominant role in determining the prognosis of patients with COVID-19. Acute viral respiratory tract infections are associated with diminished insulin sensitivity [35,36]. Therefore, FPG levels may probably increase during hospitalization even in patients with diabetes who have HbA1c values lower than 7%, which could possibly explain the insignificant differences in clinical outcomes between patients with well-controlled and poorly-controlled DM.

Since the emergence of SARS-CoV-2 in December 2019, chest CT imaging has played a major role in the evaluation of patients with COVID-19. CT severity scores were soon developed to assess disease severity on imaging [10,37]. Studies showed that CT scores were significantly higher in severe cases compared with those in mild cases of COVID-19 [8,9,12]. To date, only one study has investigated the difference in CT scores between the general population and those with diabetes. This study found that chest CT scores were significantly higher among patients with diabetes compared with patients without diabetes [38]. Nevertheless, no study has evaluated CT scores among patients with well-controlled and poorly-controlled DM yet. We observed no significant difference in chest CT scores of patients with well-controlled and poorly-controlled DM. In addition, linear opacities were more frequently observed among patients with poorly-controlled DM than those with well-controlled DM. Linear opacities are also seen more commonly among patients with severe disease [12]. In more than 85% of the cases, pulmonary lesions with a peripheral distribution were observed, which is consistent with findings from previously published studies [39,40].

Currently, there is considerable uncertainty with the use of antihypertensive medications in patients with COVID-19 and underlying comorbidities. While some researches have recommended the continued use of ACEI/ARBs in patients with COVID-19 [41,42], others have turned against the use of these medications [43–45]. Our results demonstrated that patients with diabetes who were receiving ACEI/ARBs had markedly higher rates of death and lower rates of recovery compared with those who did not take these medications. Although these finding are intriguing, caution should be used in the interpretation of these results and more comprehensive studies on larger populations are needed.

4.1. Limitation

This study has several limitations. First, the number of cases in each group was markedly different, which necessitates a careful interpretation of the results. Larger prospective studies among different populations are needed to explore the association between diabetes, either well-controlled or poorly-controlled, and imaging findings and clinical outcomes. Also, as mentioned earlier, we did not evaluate patients' blood glucose tests during hospitalization and so, our assumption of glycemic control in patients with diabetes was solely based on HbA1c values.

5. Conclusion

This retrospective single-center study showed that patients with well-controlled or poorly-controlled diabetes did not significantly differ in terms of clinical outcomes and chest CT severity scores.

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Declarations of interest

None.

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