The Association between Poor Glycemic Control in Diabetes Mellitus and Progression of COVID-19

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Research article

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a newly recognized disease whose rapid spread has resulted in a global pandemic. In this resepct, there are several comorbidities presumed to be associated with presentation of complications in COVID-19 such as diabetes mellitus (DM), hypertension (HTN), and cardiovascular diseases (CVDs). Therefore, this study aimed to explore whether DM was a risk factor influencing presentation, progression, and prognosis of COVID-19 or not.

Methods: A total number of 447 patients with confirmed COVID-19 were selected from two centers for COVID-19 in the city of Shiraz, south-central Iran, from February 20 to April 29, 2020. Then, demographic data, medical history, signs and symptoms, laboratory test results, as well as chest computed tomography (CT) scan reports were collected and analyzed.

Results: This study revealed that older age, HTN, and CVDs could be mostly seen in diabetic patients with COVID-19. In addition, such patients had prolonged hospital stay, lower oxygen (O_2) saturation, and abnormal laboratory test results such as higher white blood cell (WBC) count, lower lymphocyte count, elevated serum tumor markers such as aspartate aminotransferase (AST), and abnormal kidney function.

Conclusion: DM is an important risk factor for adverse endpoints in patients with COVID-19. In diabetic patients, proper consideration of clinical characteristics is thus of utmost importance. In addition, special clinical insight for disease prevention, good glycemic control during hospitalization, and efforts to develop a vaccine can help improve disease outcomes in this population.

Introduction

A novel coronavirus (nCoV) was identified, at the end of 2019, as the cause of a cluster of pneumonia cases in Wuhan, a city in Hubei Province of China. It then rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries across the world. In February 2020, the World Health Organization (WHO) also designated coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

On February 19, the first official report of the cases with COVID-19 in the city of Qom, Iran, was correspondingly released. As of September 25, 2020, the COVID-19 outbreak has infected at least 32 million people worldwide. Concurrently, according to the WHO statistics, over 435,000 cases and the death toll exceeding 25,000 people has been so far reported in Iran. Based on the report by Shiraz University of Medical Sciences, Shiraz, Iran, COVID-19 cases in Fars Province, Iran, had surpassed 50,000 people as of September 20, 2020, while the mortality rate from this fast-spreading disease had crossed 940 patients.

To this point, the disease manifestations have varied from asymptomatic infection to severe fulminant pneumonia, respiratory failure, and death; however, the proportion of severe or fatal infections may also show a discrepancy by location. Such estimates are rapidly changing as more data are becoming

available. With reference to the most recent WHO COVID-19 Situation Report, the global mortality rate is 5.3% [1].

The incubation period for COVID-19 is generally within 14 days following exposure, with most cases occurring approximately four to five days after being infected [2–4]. The proportions of asymptomatic infections have not been thus far investigated in a systematic and prospective manner. As estimated in the literature review, it is as high as 30–40% [5, 6].

The spectrum of symptomatic infections range from mild to critical and most infections are not severe [2, 7, 8]. Pneumonia seems to be the most frequent serious manifestation of this infection, primarily characterized by fever, cough, dyspnea, and bilateral infiltrates on chest imaging tests [8–10]. However, other features including upper respiratory tract infection (URTI) symptoms, myalgia, diarrhea, and loss of smell or taste are common. There are no specific clinical characteristics that can reliably distinguish COVID-19 from other viral respiratory infections, although development of dyspnea several days after the onset of initial symptoms is suggestive [4, 11]. Reviewing the complications, acute respiratory distress syndrome (ARDS) is assumed as the major complication in patients with the severe type of the disease and can manifest shortly after the onset of dyspnea. Furthermore, other side effects can be arrhythmias, acute cardiac injury, thromboembolic complications, and shock [3, 10, 12–14].

Comorbidities and other conditions, introduced to be associated with the severe cases of the disease and mortality are various. The severe condition can accordingly occur in healthy individuals of any age, but it is predominantly observed in older adults or those with underlying medical comorbidities such as cardiovascular diseases (CVDs), diabetes mellitus (DM), hypertension (HTN), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), types of cancer, obesity, and smoking [11, 15–19].

As well, DM and poor glycemic control are regarded as major risk factors of infections especially influenza and pneumonia. In addition, studies on patients with DM have found that viral respiratory infections possibly cause a more severe type of the disease compared with non-diabetic cases [20]. Indeed, DM has been widely investigated in previous epidemics and pandemics such as influenza A virus subtype H1N1 (A/H1N1), SARS, and Middle East respiratory syndrome-related coronavirus (MER-SCoV), and it has been further identified as an important risk factor for mortality and morbidity [21–23].

There are some data regarding the association between DM and COVID-19, supporting that DM should be taken into account as a major risk factor for rapid progression and poor prognosis of COVID-19 [20, 24]. They also demonstrate a significant association between DM status and higher mortality rate in diabetic patients with COVID-19 [17] and indicate that glycemia is associated with markedly improved outcomes in patients with COVID-19 and pre-existing DM if it is well-controlled [25], but there is still considerable ambiguity with regard to diabetic patients with COVID-19 (29, 30)

This study aimed to explore whether DM was a risk factor influencing presentation, progression, and prognosis of COVID-19 or not. Accordingly, a total number of 447 COVID-19 patients admitted to

Aliasghar Hospital and Chamran Hospital, and dedicated to COVID management and affiliated to Shiraz University of Medical Sciences, in the city of Shiraz, south-central Iran, from February 20 to April 29, 2020, was included to evaluate risk factors, comorbidities, and probable associated factors with this disease.

Materials And Methods

Design and Settings

This study was a retrospective evaluation of 447 patients with COVID-19, admitted from February 20 to April 29, 2020, to two hospitals for COVID-19, affiliated to Shiraz University of Medical Sciences, Shiraz, as the provincial center of Fars Province, in south-central Iran, with an area of 122842 km2 and a population of about 4,851,274 people, of whom 50.7% of the population are male and 49.3% are female [26].

Data Collection

COVID-19 diagnosis in these patients was validated either with positive reverse-transcription polymerase chain reaction (RT-PCR) from the upper respiratory tract or confirmation made by an expert team based on clinical symptoms and high-resolution computed tomography (HRCT) scan reports. Moreover, throat-swab specimens obtained from the upper respiratory tract of the patients upon their admission were stored in a viral-transport medium (VTM). Total ribonucleic acid (RNA) was further extracted using QIAamp™ viral RNA mini kit from Qiagen™ according to the manufacturer's instructions. With E-gene and Rdrp-gene probe/primer and superscript™ III platinum, one-step qRT-PCR kit of Invitrogen company mixtures was prepared. The mixtures transferred to Roche Light cycler™ 96 and Applied Biosystem ABI step one plus™ real time thermal cyclers with positive control and no template control (NTC) as well as an internal control. After 45 cycles the produced graphs were observed, any rise after the noise and before cycle 32 was considered as positive for SARS-COV 2 [27, 28]. SARS-CoV-2 was also examined by RT-PCR.

These individuals were selected by the convenience sampling method. For each patient, one questionnaire including demographic data, medical history, DM history and its medications, exposure history, and signs and symptoms of COVID-19 at presentation time was completed.

Laboratory test results, chest CT scan reports, and theraputic measures were additionally extracted from electronic medical records. Hospital course and clinical outcomes followed for each patient, ward or intensive care unit (ICU) admission, any comorbidity such as CKD, CVDs, or respiratory failure, and death were additionally recorded.

Ethical Considerations

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (No. IR.SUMS.REC.1399.076), Shiraz, Iran. Written informed consent was also completed for each patient.

Statistical Analysis

The qualitative and quantitative data were respectively described by frequency (percentage) and mean ± standard deviation (SD). Independent-samples t-test was also practiced for compression of mean of quantitative laboratory data (such as white blood cell [WBC] count, platelets, hemoglobin (Hb), polymorphonuclear leukocytes [PMNs], etc.) in non-diabetic, no-comorbidity, and diabetic groups. Chi-square test was further employed for compression of DM prevalence and no-comorbidity with categorical data (such as age group, gender, comorbidities, etc.). All statistical analyses were performed using the SPSS Statistics software (version 19) for windows. A p-value less than 0.05 was also considered statistically significant.

Results

Of the 406 patients, 241 (59.4%) cases were male, 107 (26.4%) individuals had preexisting DM, and 79 (19.5%) cases had a history of HTN. The most common symptoms were dyspnea (63.8%), dry cough (57.4%), and fever (28.8%). Besides, the prevalence of DM was highest among older patients (49.5% in those aged over 65 years old, $p < 0.001$). Moreover, the study results revealed that comorbidities like HTN (35.5% vs. 13.7%, $p < 0.001$) and CVDs (26.2% vs. 13.4%, $p = 0.002$) were significantly more prevalent among the diabetic patients in comparison with the non-diabetic individuals. Gender, respiratory failure, hypothyroidism, CKD, history of malignancy, and signs and symptoms, and chest CT scan reports did not show differences between the diabetic and non-diabetic patients (Table 1).

Table 1
Demographic data and comorbidities in COVID patients

Variables		Non-diabetic patients (n = 299)	Diabetic patients (n = 107)	P-value
Age (years old)	< 30	37 (12.4)	2 (1.9)	< 0.001
	30–49	122 (40.9)	10 (9.5)	
	50–64	62 (20.8)	41 (39.0)	
	> 65	77(25.8)	52 (49.5)	
Gender	Male	178 (59.5)	63 (58.9)	0.906
	Female	121 (40.5)	44 (41.1)	
Comorbidities	HTN	41 (13.7)	38 (35.5)	< 0.001
	CVDs	40 (13.4)	28 (26.2)	0.002
	Respiratory failure	18 (6.0)	11 (10.3)	0.142
	Hypothyroidism	19 (6.4)	11 (10.3)	0.183
	CKD	14 (4.7)	11 (10.3)	0.390
	Malignancy	5 (1.7)	4 (3.7)	0.251
Signs and symptoms	Fever	90 (30.1)	27 (25.2)	0.340
	dyspnea	191 (63.9)	68 (63.3)	0.952
	Cough	168 (56.2)	65 (60.7)	0.413
	Diarrhea	11 (3.7)	2 (1.9)	0.361
	Vomiting	28 (9.4)	5 (4.7)	0.127
CT scan results	Ground-glass opacity (GGO)	101 (77.7)	29 (22.3)	0.866
	Local patchy shadowing	10 (71.4)	4 (28.6)	
	Bilateral patchy shadowing	42 (73.7)	15 (26.3)	
	Interstitial abnormalities	1 (50.0)	1 (50.0)	
Death		18 (6.3)	11 (11.5)	0.094

Mean duration of hospital stay was also 7.64 ± 4.53 days for the diabetic patients and 6.06 ± 4.53 days for the non-diabetic ones (p = 0.006). Correspondingly, mean duration of ICU admission was 1.71 ± 4.69 and 1.00 ± 3.68 days for the diabetic and non-diabetic cases (p = 0.160). Although in-hospital death rate

was higher in patients with pre-existing DM relative to the non-diabetic individuals (10.2% vs. 6.7%), this difference was not statistically significant (p = 0.27).

Comparing laboratory test results for the patients on the admission day between the diabetic and non-diabetic individuals, serum sodium (Na) level was lower among the diabetic cases (136.74 ± 4.48 vs. 138.46 ± 4.52, p = 0.003). In addition, the diabetic individuals had lower oxygen (O_2) saturation than non-diabetic ones on the admission day (88.01 ± 12.96 vs. 91.71 ± 6.88, p = 0.001). Although lymphocyte count was lower, and PMN, C-reactive protein (CRP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine were higher in the diabetic group, these differences were not statistically significant (Table 2).

Table 2
Laboratory test results for diabetic and non-diabetic patients with COVID-19

	Mean ± SD		P-value
	Non-diabetic patients	Diabetic patients	
WBC	6.91 ± 3.21	7.22 ± 3.20	0.414
Hb	13.16 ± 2.26	14.12 ± 12.33	0.283
Platelet	233.45 ± 103.41	210.11 ± 87.12	0.062
PMN	67.71 ± 18.83	70.93 ± 14.46	0.195
Lymphocyte	21.71 ± 11.23	19.27 ± 12.31	0.120
CRP	32.33 ± 35.39	40.08 ± 33.92	0.125
Blood urea nitrogen (BUN)	16.83 ± 16.69	19.37 ± 13.46	0.200
Creatinine	1.39 ± 1.70	1.61 ± 1.39	0.239
Na	138.46 ± 4.52	136.74 ± 4.48	0.003
Potassium (K)	4.68 ± 8.27	4.15 ± 0.75	0.564
LDH	605.19 ± 545.89	984.4 ± 2170.28	0.252
ALT	47.91 ± 59.40	94.73 ± 464.06	0.192
AST	43.06 ± 50.01	52.34 ± 64.75	0.234
Alkaline phosphatase (ALP)	230.34 ± 104.78	234.14 ± 138.59	0.829
D-dimer	2018.15 ± 2662.72	1367.92 ± 1979.79	0.444
Troponin	7.9 ± 35.9	0.06 ± 0.25	0.389
Creatine phosphokinase (CPK)	212.12 ± 272.73	183.82 ± 151.52	0.565
O_2 saturation	91.71 ± 6.88	88.01 ± 12.96	0.001

Since the main purpose of this study was to explore whether DM was a risk factor for progression and prognosis of COVID-19, patients with comorbidities other than DM were excluded to avoid the impact of other comorbidities on the results. Laboratory test results also established that blood glucose level was much higher in the diabetic group compared with the one without any comorbidities, as expected (167.37 ± 59.12 mg/dl vs. 113.12 ± 34.04 mg/dl, $p < 0.001$). At the same time, elevated serum markers, indicating LDH (966.56 ± 2065.12 vs. 537.5 ± 377.59, $p = 0.094$), AST (53.25 ± 68.35 vs. 38.03 ± 24.69, $p = 0.037$), and decreased kidney function (creatinine: 1.2 ± 1.02 vs. 1.60 ± 1.34 $p = 0.005$) were found more frequently in the diabetic patients than in the ones without any comorbidities. Beyond that, patients with

DM had significantly reduced lymphocyte count (19.00 ± 11.83 vs. 22.73 ± 11.78, P = 0.029) and significantly increased WBC count (167.37 ± 59.12 vs. 6.47 ± 3.11, p = 0.025) (Table 3).

Table 3
Demographic data and laboratory test results for diabetic patients compared with non-diabetic ones without any other comorbidity

Variables		No comorbidity	Diabetic patients	P-value
Age (years old)	< 30	33(16.2)	2 (1.9)	< 0.001
	30–49	94(46.1)	10 (9.5)	
	50–64	44(21.6)	41 (39.0)	
	> 65	33(16.2)	52 (49.5)	
Gender	Male	132 (64.4)	63 (58.9)	0.340
	Female	73 (35.6)	44 (41.1)	
Laboratory findings	Fasting blood sugar (FBS)	113.12 ± 34.04	167.37 ± 59.12	< 0.001
	WBC	6.47 ± 3.11	7.34 ± 3.30	0.025
	Hb	13.4 ± 2.03	13.99 ± 11.93	0.552
	Platelet	232.52 ± 96.11	217.28 ± 108.93	0.224
	PMN	67.24 ± 20.94	70.98 ± 14.21	0.175
	Lymphocyte	22.73 ± 11.78	19.00 ± 11.83	0.029
	CRP	33.33 ± 39.37	40.66 ± 33.40	0.187
	BUN	13.45 ± 8.75	19.11 ± 13.15	< 0.001
	Creatinine	1.2 ± 1.02	1.60 ± 1.34	0.005
	Na	138.46 ± 4.03	136.88 ± 4.27	0.003
	K	4.76 ± 9.79	4.13 ± 0.75	0.546
	LDH	537.5 ± 377.59	966.56 ± 2065.12	0.094
	ALT	45.14 ± 40.95	90.11 ± 438.47	0.304
	AST	38.03 ± 24.69	53.25 ± 68.35	0.037
	ALP	221.4 ± 92.27	234.14 ± 138.59	0.200
	D-dimer	2169 ± 2396.87	1383.85 ± 1896.37	0.351
	Troponin	1.74 ± 8.57	0.063 ± 0.25	0.440
	CPK	164.35 ± 153.73	187.66 ± 153.72	0.466
	O_2 saturation	92.40 ± 60.07	88.01 ± 12.96	< 0.001
Status	Alive	189 (94.0)	85 (88.5)	0.098

Variables		No comorbidity	Diabetic patients	P-value
	Dead	12 (6.0)	11 (11.5)	

Discussion

It has been acknowledged that diabetic patients, compared with non-diabetic population, are more vulnerable to infection as well as development of poor prognosis once affected. In this resepct, DM with its high prevalence is an important comorbidity in patients with COVID-19 as some data have confirmed increased incidence and severity of COVID-19 in diabetic cases [29].

The United States Centers for Disease Control and Prevention (CDC) has further created a list of certain comorbidities associated with severe COVID-19 (defined as infection resulting in hospitalization, admission in ICUs, intubation or mechanical ventilation, or death). Among these comorbidities, DM has been introduced as an established risk factor for progression of COVID-19 [25, 30, 31]. The CDC has also declared increased mortality in individuals with DM (2.3% overall and 7.3% patients with DM) [32].

The main findings of this study were in line with this statement. In this report, diabetic patients had prolonged hospital stay with more organ dysfunctions, presented by drastic alterations in laboratory test results such as elevated serum markers (namely, LDH and AST), uremia (viz. rise of BUN and creatinine), and lower O_2 saturation, which were consistent with the results of previous reports [24–26, 33–36].

It should be noted that patients with DM have impairments in their immune system. They also suffer from poor innate immunity, dysregulated immune response, and dysfunctional exaggerated pro-inflammatory cytokine activation [37].

In addition, type 2 DM is associated with activation of the renin-angiotensin system in different tissues that may contribute to higher adverse risks in these patients with COVID-19 [38].

By binding to angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 enters into the cells and reduces the expression of ACE2 [39]. The wide distribution of ACE2 level in the lungs, vascular endothelium, heart, kidney, and intestines can thus partially explain the underlying mechanism of multi-organ failure (MOF), especially myocardial, kidney, and liver injury in COVID-19 patients [24, 31].

Moreover, in diabetic patients treated with ACE inhibitors and angiotensin II receptor blockers (ARBs), the ACE2 expression is considerably augmented, which is presumed to contribute to COVID severity [40].

There is also a bidirectional relationship between COVID-19 and DM [41]. Not only COVID-19 can have an effect on the pathophysiology of DM but also blood glucose control is very important for COVID-19 patients. Besides, DM is associated with an increased risk of severe COVID-19 and transient insulin resistance along with worsening of blood glucose control, which have been reported in previous CoV infection outbreaks as well as COVID-19 [21, 37]. This could be due to cytokine storm, direct virus-

mediated beta-cell damage, and special medications prescribed in the treatment course of viral infections such as anti-viral drugs or corticosteroids [31, 42].

Poor glycemic control has been generally specified as a factor affecting poor recovery of hospitalized patients in various studies [25, 43, 44]. This process is explained by a wide variety of immune response alterations associated with hyperglycemia. It has been further explained that even transient stress hyperglycemia can cause innate immune response dysfunction such as impairments in polymorphonuclear and monocytic cell chemotaxis and phagocytosis, complement function, and cytokine dysregulation [25, 44].

It has been well established that other comorbidities mainly CVDs, HTN, and age influence the association between DM and poor outcomes in patients with COVID-19 [45, 46]. Reviewing the related literature, the most combined comorbidities with DM are HTN and CVDs [33]. Based on the most recent meta-analysis conducted by Weiliang Tang et al. [26], older age and conditions such as HTN, DM, and CVDs could greatly affect the prognosis of COVID-19.

Aging and chronic diseases such as DM and HTN can thus predispose patients to long-term stress and subsequent immune dysfunction. These basic impairments in addition to the long-term deterioration of vascular structures and inflammation can consequently make the organs vulnerable to severe infection with worse prognosis [36].

There is still some controversies surrounding the effect of DM on mortality rate in COVID-19 patients, however, the bulk of studies have reported this association [24–26, 35]. In the present study, in-hospital death rate was higher in patients with pre-existing DM relative to the non-diabetic individuals. In spite of this, the difference was not statistically significant. It seems that respiratory failure involving lung volumes, pulmonary diffusing capacity, control of ventilation, bronchomotor tone, and bronchial neuroadrenergic innervation in diabetic patients with COVID-19 contribute to mortality [47].

Conclusion

In conclusion, DM can be assumed an important risk factor for adverse endpoints in COVID-19 patients. In diabetic cases, proper consideration of clinical characteristics can be of utmost importance. In addition, special clinical insight for disease prevention, good glycemic control during hospitalization, and efforts to develop a vaccine can help improve disease outcomes in this population.

Limitations

This study had several limitations. First, the data came from admitted diabetic patients with COVID-19, and the ones in outpatient settings were not included. Second, the glycemic data of pre-hospital status of these individuals was not accessible, which could be significantly associated with numerous clinical parameters. As well, evaluation of changes in blood glucose level was not possible because of COVID-19 progression. Third, given the retrospective nature of this study, determination of the effect of good blood

sugar management on prognosis of the infection was not feasible. Therefore, large-scale prospective cohort studies are required to understand the association and the importance of glycemic control in progression of COVID-19.

Abbreviations

ACE2: Angiotensin-Converting Enzyme 2

ALT: Alanine Aminotransferase

ARDS: Acute Respiratory Distress Syndrome

AST: Aspartate Aminotransferase

BUN: Blood Urea Nitrogen

CDC: Centers for Disease Control and Prevention

CKD: Chronic Kidney Disease

COPD: Chronic Obstructive Pulmonary Disease

COVID-19: Coronavirus Disease 2019

CRP: C-Reactive Protein

CT: Computed Tomography

CVDs: Cardiovascular Diseases

DM: Diabetes Mellitus

Hb: Hemoglobin

A/H1N1: influenza A virus subtype H1N1

HRCT: High-Resolution Computed Tomography

HTN: Hypertension

ICU: Intensive Care Unit

LDH: Lactate Dehydrogenase

MERS-CoV: Middle East Respiratory Syndrome-related Coronavirus

NTC: No Template Control

PMN: Polymorphonuclear

RNA: Ribonucleic Acid

RT-PCR: Reverse-Transcription Polymerase Chain Reaction

SARS: Severe Acute Respiratory Syndrome

VTM: Viral-Transport Medium

WBC: White Blood Cell

WHO: World Health Organization

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Shiraz University of Medical Sciences.

Consent to publish

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

MHD, STH and MJ contributed in designed the study, analyzed the data, and interpreted the results, wrote the manuscript drafting. **ARE** contributed in analysis of data and interpretation the results. **ARE, STH and MJ** contributed in interpretation the results wrote the manuscript drafting. The final version was confirmed by all authors for submission

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