COVID-19

Is single point HbA1c a reliable predictor for death in severe COVID-19?

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Keywords

HbA1c • Death • COVID-19 • Predictor

Summary

Introduction. *The severity of COVID-19 infection is affected by several risk factors such as Diabetes Mellitus (DM). The current study aimed to determine the effect of single-point HbA1c on the severity and mortality of hospitalized COVID-19 patients.*
Methods. *This cross-sectional study was conducted among hospitalized moderate and severe COVID-19 patients in Baharloo Hospital in Iran between December 23rd and February 23rd, 2021. The patients have been diagnosed by Polymerase Chain Reaction (PCR) and Chest Computed Tomography (CT) imaging as COVID-19. Demographic data, clinical presentation, laboratory results, and treatments along with the HbA1c data were included.*
Results. *165 COVID-19 cases were included in this study; 126 (76.4%) of which were severe cases. 89 (53.9%) patients were male, with a mean age of 59.89 ± 16.59 years. Severe COVID-19 patients were more prone to a longer hospital stay, and a higher level of inflammatory mediators, compared to the moderate COVID-19 patients ($p < 0.05$). No significant association was found between single point HbA1c, FBS, and severity and mortality of COVID-19 cases ($p > 0.05$).*
Conclusions. *Single point HbA1c was not a reliable mediator for the prediction of severity or death in hospitalized COVID-19 patients.*

Introduction

Since the appearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also named the COVID-19 pandemic, the world faces more than 6 million deaths and more than 600 million infections [1-3]. For COVID-19 severity, some risk factors were found. There are metabolic disorders, immunodeficiency, cancer, hypertension, and obesity. 25 to 45 percent of COVID-19 patients suffer from more than one comorbidity [4, 5]. The global prevalence of DM is 9.3 %, and this metabolic disease bears significant implication on the severity and outcome of both infectious and non-infectious illnesses (*e.g.*, cancer, cerebrovascular diseases, ischemic heart diseases) [6-8]. Previous studies revealed that chronic hyperglycemia was related to the death rate in severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [7, 9]. In chronic hyperglycemia, immune system functions such as Cell-Mediated Immunity (CMI), Humoral Mediated Immunity (HMI), and antioxidant and neutrophil function are disturbed [10]. Also, poor control of DM ends up in different complications such as obesity, ischemic cardiac diseases, and renal disorders) [11] that would increase the patient's death rate. Monitoring of chronic hyperglycemia might be of some value, to prevent these complications. One important and easy access tool is HbA1c (glycosylated hemoglobin) test, which shows the average 3 months blood glucose level. We conducted this study between December 23rd and February 23rd, 2021 to determine the role of HbA1c for prediction of COVID-19 severity of admitted COVID-19 cases. The current study also tried to reveal the role of DM on the mortality of hospitalized COVID-19 patients

Material and Methods

Study Design

In the current cross-section study, that conducted between December 23rd and February 23rd, 2021, 165 hospitalized COVID-19 positive patients were included. The HbA1c test, demographic data, medical history, signs and symptoms of COVID-19 patients, lab test results, and outcomes of the treatment were collected and analyzed. The association between HbA1c, DM, and COVID-19 severity were investigated in the COVID- 19 patients.

Subjects

Inclusion and Exclusion criteria

Hospitalized COVID-19 patients with age more than 18 years old (diagnosed by PCR test/CT scan) whose checking HBA1c levels were included. Patients younger than 18 years old, without HBA1c levels, and with poorly controlled diabetes were excluded.

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Sampling and Data collection

- The sample selection method was simple Random Sampling. Medical records were used to obtain information on the patients admitted to Baharloo hospital. The cases were selected using the simple random sampling. The demographic data, medical history, signs and symptoms of COVID-19, lab test results, and outcomes of the treatment were collected. The recruited patients COVID-19 vaccination status has not been investigated in this research.

Study Procedures

Diabetes was determined using patients' past diagnosed medical history or was newly defined if the HbA1c level at admission was ≥6.5%. Patient medical files were used to obtain information on the admitted patients. No intervention was made.

Statistical considerations

Data analysis

Continuous variables were represented by mean and SD, while categorical variables were represented in the form of the number and percentage. Paired T-test were used for the comparison of continuous variables, and Chi-square and Fisher's exact tests were used for making comparisons between categorical variables. Data were analyzed using IBM SPSS statistic 25 (IBM corporation, Armonk, NY, USA).

Results

Out of 165 COVID-19 patients, 126 (76.4%) were severe and 39 (23.6%) were moderate COVID-19 cases (Tab. I). Totally, the mean age of the patient population was 59.89 ± 16.59 years. The patients with severe form (Mean age 57.98 ± 16.55) were significantly younger than moderate cases (Mean age 66.03 ± 15.35) (p-value: 0.008). COVID-19 cases with cardiovascular diseases were more likely to present as severe COVID-19 form compared to the patients without cardiovascular diseases, 9.1% and 6.1% respectively (p = 0.037) (Tab. II). In terms of vital signs and imaging, oxygen saturation (O2S) in severe form (85.31 ± 8.11) was significantly lower than moderate COVID-19 (90 ± 5.08) (p-value: 0.001). Also, the percentage of chest CT involvement in severe form (46.07 ± 25.46), was significantly more than in moderate cases (20.26 ± 17.39) (p-value: 0.000).

Tab. I. Frequency of severity variables in hospitalized COVID-19 patients.

Variables (criteria for severe disease)	Total (N = 165)
Involvement in lung CT scan ≥ 50% (n, %)	76 (46.1)
SPO2 room air < 94% (n, %)	57 (34.5)
CRP ≥ 100 mg/L (n, %)	77 (46.7)
LDH ≥ 1000 IU/L (n, %)	32 (19.4)
People who had at least one of the criteria for severe disease (n, %)	126 (76.4)

The hospital lengths of stays in severe COVID-19 patients were longer than moderate cases (9.94 ± 6.87 *vs* 6.92 ± 4.24 days) (p = 0.002). Regarding the laboratory results, these were statistically significant differences between moderate and severe groups in C-Reactive Protein (CRP), Lactate dehydrogenase (LDH), Aspartate Aminotransferase (AST), Ferritin, Calcium, ($p < 0.05$). There was an association between HbA1c and DM and family history of DM (Tab. III). Among the laboratory findings, FBS was significantly related with HbA1c levels (Tab. IV). There was no significant association between COVID-19 severity and mortality with HbA1c levels (Tab. V). Also, there was no significant relationship between DM, anti-hyperglycemic drugs usage, and mortality (Tab. VI).

Discussion

The SARS-CoV-2 coronavirus pandemic is taking a heavy burden worldwide. The mortality rates of COVID-19 pneumonia have been reported as 4.3% to 14.6% [12]. Comorbidities, such as cerebrovascular disease, cardiovascular disease, and diabetes mellitus increase the severity and mortality COVID-19. To minimize the impact of this pandemic, boosting health care system preparedness as well as controlling or decreasing the comorbidities seems essential [13, 14].

DM as a chronic disease causes a high burden on the health system, about 422 million people in the world have DM [15]. Chronic hyperglycemia links with negative consequences of both noninfectious and infectious illnesses and its connection with mortality of influenza, SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) was studied [16].

The present study was conducted to find out whether single-point HbA1c and FBS were related to the COVID-19 severity and death rate in admitted COVID-19 patients. According to the recent study, there was a significant difference between moderate and severe COVID-19 patients in terms of acute phase reactants (*i.e.*, CRP, LDH, Ferritin). In severe COVID-19 infection, cytokine storm and hypoxemia result in diffuse tissue damage [17] and increase the level of inflammatory mediators [12]. HbA1c is an easy-access laboratory test, that represents the average recent 3 months glucose serum level and relates with the risks of long-term DM complications [18] (*i.e.*, renal, cardiovascular, central nervous system, ophthalmic) [11]. In the present study, no significant difference was found between moderate and severe COVID-19 patients in terms of HbA1c by both univariate and multivariate analysis. Some studies emphasized the association of HbA1c with COVID-19 severity [19, 20]. DM was also linked with increase in the rate of other infectious diseases such as MERS, SARS, and Influenza [21]. According to the present study, the prevalence of DM in admitted COVID patients was 41.8%, which is more than former studies (7.4-

Tab. II. Characteristics of COVID-19 patients by disease severity.

Variables	Total (N = 165)	Moderate (n = 39)	Severe (n = 126)	p
Age (Mean ± SD) years	59.89 ± 16.59	66.03 ± 15.35	57.98 ± 16.55	0.008
Sex (n, %)				
Male	89 (53.9)	17 (10.3)	72 (43.6)	0.138
Female	76 (46.1)	22 (13.3)	54 (32.7)	
BMI (Mean ± SD)	28.75 ± 5.07	28.51 ± 4.9	28.82 ± 5.1	0.746
Comorbidities type (n, %)				
Hypertension (HTN)				
Yes	63 (38.2)	15 (9.1)	48 (29.1)	**0.967**
No	102 (61.8)	24 (14.5)	78 (47.3)	
Cardiovascular disease (n, %)				
Yes	25 (15.2)	10 (6.1)	15 (9.1)	0.037
No	140 (84.8)	29 (17.6)	111 (76.3)	
Kidney disease (n, %)				
Yes	2 (1.2)	0	2 (1.2)	0.429
No	163 (98.8)	39 (23.6)	124 (75.2)	
Thyroid disease (n, %)				
Yes	3 (1.8)	0	3 (1.8)	0.331
No	162 (98.2)	39 (23.6)	123 (74.5)	
Pulmonary disease (n, %)				
Yes	3 (1.8)	1 (0.6)	2 (1.2)	**0.690**
No	162 (98.2)	38 (23)	124 (75.2)	
Cerebrovascular disease (n, %)				
Yes	11 (6.7)	3 (1.8)	8 (4.8)	0.769
No	154 (93.3)	36 (21.8)	118 (71.5)	
Diabetes mellitus (DM) (n, %)				
Yes	69 (41.8)	19 (11.5)	50 (30.3)	0.317
No	96 (58.2)	20 (12.1)	76 (46.1)	
History of family diabetes (n, %)				
Yes	67 (40.6)	17 (10.3)	50 (30.3)	0.664
No	98 (59.4)	22 (13.3)	76 (46.1)	
Pre diabetic history (n, %)				
Yes	26 (15.8)	6 (3.6)	20 (12.1)	0.942
No	139 (84.2)	33 (20)	106 (64.2)	
Vital signs and imaging				
Clinical characteristics (Mean ± SD)				
SPO2 on admission (%)	86.46 ± 7.78	90 ± 5.08	85.31 ± 8.11	**0.001**
SPO2 room air (%)	94.88 ± 4.31	96.96 ± 1.23	94.36 ± 4.64	**0.000**
Heart rate (beats/minute)	87.61 ± 17.54	87.58 ± 16.40	87.62 ± 17.9	0.991
Respiratory rate (breaths/minute)	20.24 ± 11.22	18.76 ± 2.82	20.69 ± 12.68	0.355
Systole blood pressure (mm hg)	124.03 ± 16.13	127.72 ± 12.31	122.95 ± 16.98	0.119
Diastole blood pressure (mm hg)	74.31 ± 14.86	75.25 ± 16.09	74.04 ± 14.53	0.669
Temperature (degree Celsius)	36.84 ± 0.61	36.78 ± 0.91	36.86 ± 0.49	0.525
Lung involvement in CT scan (%)	39.97 (26.17)	20.26 ± 17.39	46.07 ± 25.46	0.000
Laboratory characteristics (Mean ± SD)				
HbA1c%	6.74 ± 1.81	6.58 ± 1.43	6.79 ± 1.91	**0.548**
FBS **mg/dL**	186.94 ± 86.36	189.24 ± 92.24	186.23 ± 84.90	0.862
CRP **mg/L**	99.81 ± 71.33	39.90 ± 27.09	118.16 ± 70.65	0.000
Ferritin **ng/mL**	565.01 ± 390.77	421.92 ± 361.82	604.36 ± 390.65	0.017
BUN mg/dL	54.89 ± 44.04	51.69 ± 32.90	55.88 ± 47.02	0.605
Cr **mg/dL**	1.14 ± 0.84	0.97 ± 0.42	1.19 ± 0.92	0.147
CPK mcg/L	379.18 ± 805.84	336.14 ± 790.17	391.68 ± 813.06	0.717
LDH **IU/L**	786.37 ± 367.54	562.08 ± 160.87	851.48 ± 385.05	0.000
D. Dimer µ/mL	1.77 ± 3.00	1.66 ± 1.23	1.81 ± 3.34	0.804
Vit D **ng/mL**	27.34 ± 14.73	28.28 ± 13.43	27.10 ± 15.09	0.716
Ca **mg/dL**	8.54 ± 0.63	8.71 ± 0.55	8.48 ± 0.64	0.051
Alb **g/dL**	4.13 ± 0.59	4.22 ± 0.61	4.10 ± 0.59	0.345
AST **U/L**	58.88 ± 55.62	40.16 ± 22.77	64.50 ± 61.17	0.000
ALT **U/L**	52.11 ± 63.70	37.86 ± 30.54	56.39 ± 70.24	0.121
Troponin **ng/mL**	0.70 ± 4.27	0.13 ± 0.340	0.97 ± 4.80	0.403
WBC × 10^9/L	8.94 ± 6.78	9.34 ± 10.73	8.81 ± 5.01	0.672
Eosinophil %	2.19 ± 0.85	2.39 ± 0.82	2.13 ± 0.86	0.093
Neutrophils %	80.52 ± 9.24	79.15 ± 6.09	80.95 ± 10	0.290
Monocytes %	2.94 ± 0.85	3.21 ± 0.96	2.86 ± 0.81	0.025
Lymphocyte %	13.80 ± 6.89	15.46 ± 5.66	13.29 ± 7.17	0.085
Hb g/dL	12.87 ± 3.63	12.49 ± 1.70	12.99 ± 4.05	0.459
Plt × 10^9/L	227.09 ± 113.73	210.74 ± 89.64	232.19 ± 120.12	0.305
Antihyperglycemic treatment (n, %)*				
Metformin	55 (42.6)	12 (9.3)	43 (33.3)	
NPH	43 (33.3)	14 (10.9)	29 (22.5)	
NPH. regular	14 (10.9)	5 (3.9)	9 (7)	**0.665**
LANTUS.NOVORAPID	8 (6.2)	1 (0.8)	7 (5.4)	
Glibenclamide	3 (2.3)	1 (0.8)	2 (1.6)	
Novomix	6 (4.7)	1 (0.8)	5 (3.9)	
Days of hospitalization (Mean ± SD)	9.21 ± 6.46	6.92 ± 4.24	9.94 ± 6.87	0.002
Death (n, %)	28 (17)	3 (1.8)	25 (15.2)	0.077

* N:129

Tab. III. Association of HbA1c with Metabolic disorder.

Variables (N = 165)	HbA1c (Mean± SD)	p
Sex		
Male	6.61 ± 1.57	0.342
Female	6.88 ± 2.06	
Hypertension (HTN)		
Yes	6.90 ± 1.62	0.372
No	6.64 ± 1.92	
Cardiovascular disease		
Yes	6.92 ± 1.93	0.591
No	6.71 ± 1.79	
Kidney disease		
Yes	6.50 ± 0.56	0.850
No	6.74 ± 1.82	
Thyroid disease		
Yes	6.46 ± 1.28	0.791
No	6.74 ± 1.82	
Pulmonary disease		
Yes	6.70 ± 1.50	0.967
No	6.74 ± 1.82	
Cerebrovascular disease		
Yes	6.81 ± 1.77	0.899
No	6.73 ± 1.82	
Diabetes mellitus (DM)		
Yes	7.34 ± 1.99	**0.000**
No	6.30 ± 1.53	
Family history of diabetes		
Yes	7.48 ± 2.11	**0.000**
No	6.23 ± 1.36	
Pre diabetic history		
Yes	7.19 ± 2.40	0.288
No	6.65 ± 1.67	

Tab. IV. Correlation of HbA1c with Laboratory Characteristics.

Variables	HbA1c	
	R*	p
Age	0.022	0.783
FBS	0.496	**0.000**
CRP	0.017	0.830
Ferritin	-0.002	0.983
BUN	0.131	0.094
Cr	0.057	0.470
CPK	-0.123	0.121
LDH	-0.015	0.852
D. Dimer	0.005	0.953
Vit D	0.004	0.963
Ca	0.123	0.117
Alb	-.031	0.702
AST	-0.110	0.167
ALT	-0.060	0.454
Troponin	-0.030	0.757
WBC	0.135	0.085
Eosinophil	0.049	0.538
Neutrophils	-0.035	0.659
Monocytes	0.061	0.438
Lymphocyte	0.032	0.688
Hb	0.019	0.808
Plt	0.066	0.399
SPO2 on admission	-0.127	0.116
SPO2 room air	0.051	0.552
Lung involvement in CT scan	0.027	0.726

* R: Pearson correlation coefficient.

20%) [6]. The prevalence of DM in Iran is 10.4% [22], our cases were moderate and severe COVID-19, so their comorbidities and DM might be more than in earlier studies.

On the other hand, the hyperglycemic condition was occurred in COVID-19 patients, even without any previous history of DM through direct damage of pancreatic cells by viruses, stress induced hyperglycemia, severe sepsis or 4- treatments (*e.g.*, corticosteroids in severe cases) [23].

Chronic hyperglycemia decreases the host immune system function against pathogens in the followings ways; decrease in T cell function, increases the cytokines production and Angiotensin Converting Enzyme (ACE) receptor expression. With accumulation of ACE 2, pulmonary muscle strength and its elasticity decreases, ends in pulmonary dysfunction. In the other words, viral clearance decreases, and inflammatory response increases [11, 24-28]. In the recent study, there was no correlation between DM, HbA1c, and COVID-19 severity, similar the multivariable modality by French researchers, that found no association between HbA1c and COVID-19 severity in the first week of COVID 19 patients' admission [29]. Also, another study on HbA1c, found no links between infection severity and HbA1c in both outpatient and inpatient COVID-19 cases, however [28]. Although, some researchers indicated that single-point HbA1c can predict the infection severity in admitted COVID-19 patients [25], another insisted that longitudinal HbA1c (during 2 to 3 years) was significantly linked with COVID-19 severity [11]. Longitudinal HbA1c reflects the long-term glucose control in the patients. However, some researchers did not find any association between COVID severity and HbA1c, either single point or longitudinal HbA1c [7, 13, 28, 30] even in admitted cases [2, 6]. 40 days follow-up of diabetic COVID-19 patients found that DM was not a factor for death in COVID-19 cases, however, it predisposed COVID-19 patients to Acute Respiratory Distress Syndrome (ARDS) [5, 31]. In the recent study, no association was found between DM, HbA1c, and the severity of COVID-19, it might

Tab. V. Association of HbA1c levels with disease severity & mortality.

Variables (N = 165)	Normal ≤ 5.69 (n = 28)	Pre-diabetic (5.70-6.49) (n = 137)	Diabetic ≥ 6.50 (n = 137)	p
Severity (n, %)				
Yes	39 (23.6)	38 (23)	49 (29.7)	0.634
No	12 (7.3)	9 (5.5)	18 (10.9)	
Death (n, %)				
Yes	7 (4.2)	7 (4.2)	14 (8.5)	0.533
No	44 (26.7)	40 (24.2)	53 (32.1)	

Tab. VI. Association of mortality with DM & anti-hyperglycemic drugs use.

Variables (N = 165)	Death (n, %) (n = 28)	Alive (n, %) (n = 137)	p
DM			
Yes	13 (7.9)	56 (33.9)	0.587
No	15(9.1)	81 (49.1)	
Use anti-hyperglycemic drugs			
Yes	23 (13.9)	106 (64.11)	0.743
No	5 (3.1)	31 (18.89)	

be due to: 1) Some newly diagnosed DM cases, so the duration of hyperglycemia might be less than 3 months; 2) There was no categorization of DM type (type 1, type 2); HbA1c is related to Type 2 DM [11]; 3) In the present study, COVID-19 virus subtypes, age, and comorbidities might be different with other studies [6, 27, 28].
This study is one of the few studies on the association of HbA1c and DM in moderate and severe admitted COVID-19 in the Middle East region. This study had the following limitations; it was conducted in a single center and there was no data regarding the type of DM and its duration.

Conclusions

Single point HbA1c cannot be a reliable tool for prediction of hospitalized COVID-19 cases severities and outcomes. Future multi-center studies with a large sample size that measure both single and longitudinal HbA1c are recommended.

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Etical considerations

this study had been done after Tehran University Medical Student ethic committee approval (IR.TUMS.MEDICINE.REC.1400.1015).

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

HH, MA: Conceptualization, investigation, data curation, formal analysis, writing-original draft preparation and editing. YA: Methodology, formal analysis. MZ, NF: data curation, writing-original draft preparation. All authors have read and agreed to the published version of the manuscript.

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