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Usage of HbA1c as a marker to assess progression of COVID-19

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Abstract:

Background: Poor glycemic management has been linked to increased mortality from previous viral pandemics, including H1N1 flu and SARS. Incorporating diabetes status assessment into risk management for COVID-19 pneumonia patients is currently proposed by many investigations. **Objective:** Assessment of the impact of uncontrolled diabetes on the course of COVID-19 pneumonia in critically ill patients by measuring glycosylated hemoglobin (HbA1c) in the first 48 hours of admission. **Methods:** A retrospective cohort study was conducted on 40 critically ill patients from October 2021 to April 2022; recruiting patients admitted to the critical care department in Beni-Suef university hospital. HbA1c was measured in the first 48 hours from admission. **Results:** This study was conducted on 40 patients. Fifty per cent of the participants had diabetes, and 62.5% were hypertensive. There was a significant association between the higher HbA1c level (more than8.7%) and the need for mechanical ventilation (MV), higher length of stay in intensive care unit (ICU) and mortality in diabetic patients. The HbA1c had a statistically significant role in predicting the need for MV in diabetics. At a cut-off of 8.7%, HbA1c can predict the need for MV with 91% sensitivity and 63% specificity in diabetic patients. Likewise, the HbA1c had a statistically significant role in predicting mortality in the diabetic group. At a cut-off of 8.5%, HbA1c can predict mortality with 90.9% sensitivity and 89% specificity in diabetic

patients. **Conclusions:** High HbA1c led to increasing sepsis parameters , the need for mechanical ventilation , hospital stay and the mortality in diabetic patients with COVID-19 pneumonia.

Keywords: Adverse Outcomes; COVID-19; Diabetes.

1. Introduction:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused by coronavirus disease 2019 (COVID-19) resulted in significant impacts healthcare systems worldwide [(1–3)]. In order to direct physicians to carry out targeted treatment, it is vital to identify the risk factors linked with the progression of COVID-19. Recently, it has been shown that several of demographic and clinical factors might help with the risk stratification of the disease [(4–6)].

Poor glycemic management has been linked to increased mortality from previous viral pandemics, including H1N1 flu and SARS [(7,8)]. Incorporating diabetes status assessment into risk management for COVID-19 patients is currently proposed by many investigations. The glycosylated hemoglobin (HbA1c) test gives a reliable three-month average of glucose levels [(9)]. This test may be used to evaluate their current diabetes status to determine those at high risk for developing severe COVID-19 pneumonia [(10)]. Unlike other contributing factors for COVID-19-related mortality, such as older age, HbA1c may be modified by healthcare interventions and is widely accessible in routine practice [(11)]. Several studies have indicated that HbA1c is independently linked with hospital mortality [(12–14)].

Simple prognostic measures are required in the context of COVID-19 pneumonia which optimize the level of care and diagnostic as well as therapeutic interventions, so this study aimed to assess the impact of diabetes on the course of COVID-19 disease in critically ill patients by measuring HbA1c in the first 48 hours of admission and follow-up severity of the disease.

2. Patients and Methods:

The study gained ethical clearance from the responsible committee in the Faculty of Medicine, Beni-Suef University. Due to the study's retrospective nature, the need for informed consent was waived.

Subjects:

We performed a retrospective cohort study on 40 critically ill patients; 20 cases were diabetics and 20 were non-diabetics as control. The study was conducted from

October 2021 to April 2022 on patients admitted to the critical care department at Beni-Suef university hospital. We included moderate cases of COVID-19 pneumonia patients, defined as the local institutional protocol by a SpO2 reading of less than 94% percent on room air at sea level and evidence of lower respiratory involvement by clinical examination or imaging. We excluded cases with severe illness at presentation and cases at high risk of mortality as defined by acute physiology and chronic health evaluation score II (APACHE ll). APACHE II score is commonly used to describe multiple organ function for assessing disease severity and estimate hospital mortality. Also, patients with acute kidney injury, myocarditis, pulmonary embolism, and cytokine storm were excluded from the study.

Methods:

The following data were collected from every patient: age, gender, his gases, chronic diseases, renal and hepatic function tests, coagulation profile, arterial blood gases, SpO2, inflammatory markers (C-reactive protein [CRP], D-dimer, serum ferritin, and total leucocytic count [TLC]), APACHE II score, and COVID-19 Reporting and Data System (CO-RADS) from baseline to 10 days of admission. The HbA1c data was collected in the first 48 hours of ICU admission and measured by BECKMAN COULTER device version AU480. Outcomes of the patients were also collected, including the need for MV and in-hospital mortality.

Statistical Analysis

Retrieved data were summarized and processed with IBM SPSS statistical software (version 25). Frequencies were used to describe categories, and numeric were summarized into median (range). The hypothesis of significant associations between various parameters and HbA1c was tested by the Chi-square test for categorical variables and the Mann-Whitney test for continuous variables. The prediction utilities of HbA1c were investigated by receiver operator characteristic (ROC curve), and the outputs were presented with diagnostic accuracy measures. P-value <0.05 was regarded as statistically significant.

3. Results:

This study was conducted on 40 patients with confirmed COVID 19 to assess the impact of uncontrolled diabetes on course of COVID-19 pneumonia disease in critically ill patients by measuring of HbA1c in first 48 hours of admission and follow up severity of the disease. The mean age of the studied patients was 60.2±14.5 years and 47.5% were females. Overall, 50% of the participants were diabetic, and 62.5% were hypertensive.

Table (1): Demographic data of the included patients.

Items	Non-diabetic (no=20)	Diabetic (no=20)	P-value
Age (mean ±SD)	58.3±14.6	66.9±9.4	0.032
Sex **Males** **Females**	 9 (45.0%) 11 (55.0%)	 12 (60.0%) 8 (40.0%)	 0.342

SD: Standard deviation.

There was a significant increase of serum urea, creatinine, HbA1c, PCO2, APATCH-II and ferritin among diabetic than non-diabetic patients. Besides, there was no significant increase CORAD score from the first to the second assessment in the non-diabetic , but in the diabetic group there was a significant increase of the CORAD score. There was a significant decrease of the CRP in non-diabetic, but it didn't change significantly in the diabetic patients. Also, there was a significant difference between both groups regarding the CRP at day 10 (P-value<0.05), **Table 2**.

Table (2): Laboratory results of the included patients.

Items	Non-diabetic (no=20)	Diabetic (no=20)	P-value
Na	138.7±5.2	135.8±5.2	0.084
K	4.1±0.4	4.2±0.6	0.227
S. UREA	56.6±9.7	108.2±70.2	0.017*
S. Creatinine	0.9±0.5	1.6±1.1	0.023*
ALT	47.4±37.6	40.8±28	0.535
AST	40.6±31.7	45.5±28.9	0.606
HbA1C	5.9±0.8	9.5±1.2	<0.001*
PH	7.4±0.08	7.3±0.1	0.387
PCO2	39.5±6.4	47.2±14.1	0.034*
HCO3	24.1±4.9	27.4±6.6	0.080
PO2	80.8±18.4	80.1±13.5	0.892
FIO2	75±18.7	83.3±20.2	0.187

P/F RATIO	121.3±62	103.8±36.5	0.283
Sao2	87.7±7.2	87.9±5.2	0.960
APATCH II	13.2±4.5	20.6±6.3	<0.001*
IL-6	75.4±10.7	101.4±97.6	0.415
LDH	489.1±232	601.3±265.8	0.163
TLC	10.1±4.5	8.2±4.4	0.188
CRP	124.3±96.4	104.6±102.8	0.537
PCT	0.3±0.2	0.6±0.3	0.001*
D dimer	2.3±1.3	1.7±1.2	0.137
Ferritin	706.7±359.6	953.3±169.4	0.011*
CO-RADS (on admission)	4.6±0.8	4.5±0.6	0.999
CO-RADS after days	4.5±0.6	4.8±0.4	0.082
CRP on the 10th day	19.6±3.3	92.3±9.1	<0.001*

S: serum, ALT: Alanine transaminases, AST: Aspartate transaminases, HbA1C: glycosylated hemoglobin, APACH II: The Acute Physiology and Chronic Health Evaluation II, IL-6: Interleukin-6, LDH: Lactate dehydrogenase, TLC: Total leukocytic count, CRP: C-Reactive protein, PCT: Procalcitonin, CORADS: COVID-19 Reporting and Data System.

There was a significant difference between diabetics and non-diabetic groups regarding the need for MV (and the invasive MV) and length of stay but the mortality were significantly higher in diabetic patients (**Table 3**).

Table (3): Outcomes of the study (need to MV, ICU stay and death) among the studied groups.

Items	**Non-Diabetic (no=20)**	**Diabetic (no=20)**	**P-value**
Need to MV No Yes	 18(90.0%) 2(10.0%)	 8(40.0%) 12(60.0%)	0.001*
Invasiveness of MV	No=2	No=12	<0.001*

Invasive **Non invasive**	0(0%) 2(100%)	8(66.7%) 4(33.3%)	
Invasive MV PEEP 8 and fio2 80% PEEP 5 fio2 60% PEEP 6 fio2 80% **Non invasive MV** PEEP 7 fio2 80%	----- ---- 2(100%)	6(50%) 2(16.7%) 4(33.3%) -----	----------
Length of stay (days) (mean±SD)	13.4±7.2	25.4±13.8	0.001*
Mortality Alive Died	18(90.0%) 2(10.0%)	9(45.0%) 11(55.0%)	0.002*

MV: Mechanical ventilation, SD: Standard deviation.

There was a significant association between the higher HbA1c level (≥8.7) and the need to MV, higher length of stay in the ICU and the mortality in the diabetic patients(**Table4)**.

Table (4): Relation between the outcome (need to MV, ICU stay and death) and HbA1c (at a cut off 8.7 according to ROC curve analysis) in diabetic patients.

Items	**HbA1c <8.7 (no=6)**	**HbA1c ≥8.7 (no=14)**	**P-value**
Need to MV No Yes	5(83.3%) 1(16.7%)	3(21.4%) 11(78.6%)	0.018* (FET)
Length of stay (day) (mean ±SD)	16.3±4.8	21.3±12.1	0.022*
Mortality Alive Died	5(83.3%) 1(16.7%)	4(28.6%) 10(71.4%)	0.024*(FET)

MV: Mechanical ventilation, SD: Standard deviation.

The HbA1c had a statistically significant role in prediction of the need for MV in diabetic group. At a cut off 8.7, HbA1c can predict the need for MV with 91% sensitivity and 63% specificity in diabetic patients (**Figure 1**).

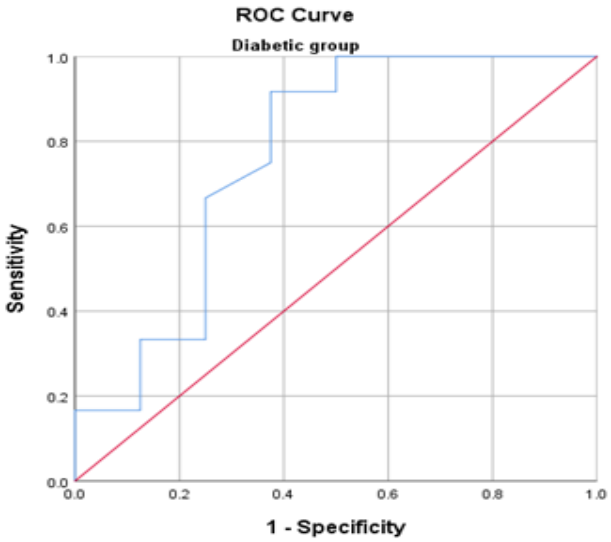

Figure (1): ROC curve analysis for prediction of need for MV using the HbA1c on admission in diabetic patients (sensitivity =91% and Specificity=63%)

Likewise, the HbA1c had a statistically significant role in the prediction of mortality in the diabetic group. At a cut-off 8.5%, HbA1c can predict the mortality with 90.9% sensitivity and 89% specificity in the diabetic patients (**Figure 2**).

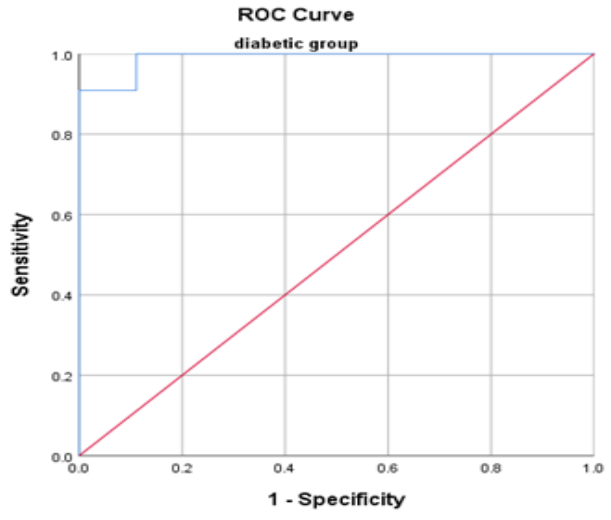

Figure 2: ROC curve analysis for prediction of mortality using the HbA1c on admission in diabetic patients (sensitivity =50% and Specificity=77%).

Regarding the correlation between APACHE II and CRP,, D dimer, ferritin, CORADs, HbA1c in diabetic patients, there was no statistically significant linear correlation between APACHE II and CRP, D dimer, ferritin, CORADs, HbA1c (P-value>0.05).

Table (5): Correlation between APACHE II and CRP, D dimer, ferritin, CORADs, HbA1c in diabetic patients:

Independent variables (no=20)		**APACHE**
CT CORADS	R	0.041
	P-value	0.864
D dimer	R	0.297
	P-value	0.204
Ferritin	R	0.359
	P-value	0.120
HbA1C	R	0.411
	P-value	0.072
CRP	r	0.401
	P-value	0.079

4. Discussion:

Diabetes worsens the outcome of virtually any acute or chronic medical condition, resulting in a shortened life expectancy. Mortality from infectious diseases is also increased in patients with diabetes, especially for sepsis and pneumonia. Since the very beginning of the SARS-CoV-2 pandemic, diabetes emerged as one of the most common comorbidities and a potential driver of poor outcomes. [15]

This study was conducted on 40 patients with confirmed COVID 19 to assess the impact of uncontrolled diabetes on course of COVID-19 pneumonia disease in critically ill patients by measuring of HbA1c in first 48 hours of admission and follow up severity of the disease.

Our study found that there was a significant difference between diabetics and non-diabetic groups regarding the need for

MV (60% Vs 10%), length of hospital stay (25.4±13.8 Vs 13.4±7.2 days) and the mortality were significantly higher in diabetic patients (55% Vs 10%). In addition, there was a significant association between the higher HbA1c level (>8.7) and the need to MV, higher length of stay in the ICU and the mortality in the diabetic patients.

Several reports agreed with our results like the meta-analysis performed by Zhu et al. about the predictive value of HbA1c for in-hospital adverse prognosis in COVID-19. They found that six studies referred HbA1c as a dichotomous variable, involving a sum of 1180 subjects and 301 deaths, and showed that higher HbA1c was significantly related to increased hospital mortality compared with groups with lower HbA1c (OR 2.300 [1.679–3.150]; p = 0.000, I2 = 48%; p = 0.087). [16]

Also, Fadini et al. in their study about diabetes and admission hyperglycemia as a predictor of COVID-19 severity revealed that admission glucose levels were closely related to most clinical and biochemical parameters of COVID-19 severity collected during hospitalization, including the PaO_2/FiO_2 ratio. Remarkably, for each 2 mmol/l (36 mg/dl) higher admission glucose, the probability of severe progression significantly increased by about 15% independently from any other clinical-biochemical variable. [17]

Lui et al. in their study about the impact of glycemic status on clinical outcomes among patients with COVID-19 showed that patients who developed clinical deterioration had worse glycemic status, and higher HbA1c and admission random blood glucose level. [18]

Pazoki et al. investigated the mortality risk and severity of COVID-19 patients with diabetes mellitus. The results were obtained from 574 patients treated with COVID-19; 135 of the 176 patients with diabetes mellitus had severe conditions with a higher mortality rate of 30.7% than the non-diabetic patients with a mortality rate of 12.6%. [19]

The study of Unluguzel Ustun et al. about the association between Hb A1c and severity of COVID-19 patients also found that the mortality rate in diabetic patients with high Hb A_{1c} levels (>6.0%) was 39.96% while non-diabetic patients had a lower mortality rate (7.58%). [20]

In a multivariable model of the study of Windham et al. it was found that patients with HbA1c $\geq$ 7% ($N = 123$), the odds of death and/or intubation within 7 days of admission increased 19% for every 1 unit increase in

HbA1c value [OR: 1.19 (1.01, 1.43); $p = 0.04$]. [21]

The HbA1c had a statistically significant role in prediction of the need for MV in diabetic group. At a cut off 8.7, HbA1c can predict the need for MV with 91% sensitivity and 63% specificity in diabetic patients. Likewise, the HbA1c had a statistically significant role in the prediction of mortality in the diabetic group. At a cut-off 8.5%, HbA1c can predict the mortality with 90.9% sensitivity and 89% specificity in the diabetic patients.

In line with our study, Liu et al. reported in their study that using disease worsening as the end point, ROC curve analysis was used to identify the optimal HbA1c cutoff value, which was 8.6% (70 mmol/mol). With this value, the area under the ROC curve was 0.90 (95% CI, 0.83–0.98, p < 0.001), and the sensitivity and specificity for predicting disease worsening in the patients with diabetes were 100.0% and 82.7%, respectively. [24]

Near results were found in the study of Yanagisawa et al. in their study about HbA1c level as a risk factor for oxygen therapy requirement in patients with coronavirus disease 2019. They reported that the ROC analysis based on the predicted probability obtained from the multivariate logistic regression for oxygen therapy requirement demonstrated that the area under the ROC curve (AUC) was 0.962 (95% CI: 0.927–0.997, P < 0.001). In addition, the optimal cut-off value of HbA1c level for oxygen therapy requirement was 5.9% (sensitivity, 0.682; specificity, 0.885). [25]

In the study of Jain et al. about the age and HbA1 role in predicting major adverse outcomes in Indian hospitalized patients with COVID-19 infection investigated the Receiver Operating characteristic (ROC) analysis, the cut off value of HbA1C was < 5.77 % with sensitivity of 89 %. They revealed that patients with HbA1C < 5.77 have lesser chance of suffering from major adverse outcome in comparison to those with HbA1C > 5.77. [26]

To test the ability of HbA1c levels to diagnose severe and critical diseases, Li et al. used the ROC curve to analyze the optimal prediction threshold of COVID-19 exacerbation. The AUC of HbA1c levels to distinguish between moderate and severe-critical diseases was 0.938 (95% CI 0.906–0.970), and the HbA1c level cut off of 6.0% (42 mmol/mol) had 80.2% sensitivity and 100% specificity. [27]

Some biological mechanisms have been raised to explain the potential causal relationship between prolonged uncontrolled hyperglycemia and poor outcomes in

COVID-19 patients. Impaired immune response to viral infections is the main cause. Particularly, hyperglycemia may inhibit intracellular destruction of microbes, neutrophil chemotaxis, and phagocytosis, thereby providing higher affinity for cellular binding and effective virus entry and reducing viral clearance. [28]

In addition, it can also cause direct glycosylation of proteins, thus changing the structure of complements. Chronic hyperglycemia downregulates the expression of ACE2 possessing anti-inflammatory property through glycosylation, making cells vulnerable to viral inflammation and destruction, which might interpret higher predisposition of COVID-19 with chronic hyperglycemia to ARDS. [15]

Furthermore, endotheliitis might be a possible mechanism leading to organ dysfunction causing critical illness in COVID-19, which might be exacerbated by endothelial dysfunction associated with chronic hyperglycemia. [29]

The laboratory results among our studied patients showed that there was a significant increase of serum urea, creatinine, HbA1c, PCO2, APATCH-II and ferritin among diabetic than non-diabetic patients. Besides, there was no significant increase CORAD score from the first to the second assessment in the non-diabetic but in diabetic group there was a significant increase of the CORAD score. There was a significant decrease of the CRP in non-diabetic, but it didn't change significantly in the diabetic patients. Also, there was a significant difference between both groups regarding the CRP at day 10.

Matching with our study, **Liu et al.** found that compared to the group without diabetes, patients with diabetes presented higher HbA1c level as expected (8.1% Vs 6.3%). Moreover, patients with diabetes demonstrated a significantly higher incidence of lymphopenia (53.1% versus 33.6%). As for the inflammatory markers, the CRP level was significantly higher in the group with diabetes (39.3 mg/L Vs 7.6 mg/L. The serum urea level showed a significant elevation in their study, however no significant difference was observed regarding creatinine level. [24]

Coppelli et al. reported that diabetic patients had worse inflammatory profiles and were associated with a higher D-dimer compared with non-diabetic patients. [30] Inflammatory markers such C-reactive protein, dimer-D, and ferritin are elevated in COVID-19, indicating a high-grade systemic inflammation, according to Zhou et al. [31] and Pititto and Ferreira [32], who also

emphasized that DM is a low-grade inflammatory condition.

Oxygen saturation did not differ significantly between both groups; however, it decreased in both groups and reached 87.9±5.2 for diabetic patients. On the other hand, the mean PCO2 was higher in diabetic patients compared to non-diabetic patients. Bezuidenhout et al. had the same results in their study about arterial blood gas and acid-base abnormalities in COVID-19 intensive care patients. They revealed that most patients had acidemia (pH < 7.35) and low oxygen saturation of 88%. [33]

Chest CT imaging is a more reliable, feasible, and rapid method to diagnose and assess COVID-19, especially in epidemic regions. According to our findings, there was no significant increase in CORADs score from the first to the second assessment in non-diabetic patients, but in the diabetic group, there was a significant increase in CORADs score. Similarly, Bhandari et al. revealed that the CT severity score was significantly higher in the uncontrolled diabetes group than in the controlled diabetes group. [34]

The APACHE II score is the most widely used and well-known effective prediction scoring approach for hospital outcomes. Statistical analysis revealed a substantial difference in APACH II scores between the two groups. Patients with diabetes had a higher score compared to non-diabetic patients. Likewise, Elibol et al. showed that diabetic patients were associated with a higher APACHE II score, which was associated with mortality. [35]

There were some limitations in our study. First, the interpretation of our results might be limited by the sample size. Second, owing to the retrospective design of the study, the lack of data didn't allow us to analyze the type of DM and disease course. Third, in the urgent conditions, medical history was not taken in detail and some laboratory examinations were not performed in all patients.

5. Conclusions:

COVID-19 patients with diabetes were associated with unfavorable outcomes, including prolonged hospitalization, the need for mechanical ventilation, and a high mortality rate. In this study, HbA1c has a high sensitivity in predicting the mortality in diabetic patients with COVID-19 pneumonia.

Recommendations:

Tight glycemic control in diabetic patients with COVID-19 pneumonia

Abbreviations:

APACHE II: Acute physiology and chronic health evaluation score II.

CO-RADS: COVID-19 Reporting and Data System.

CRP: C-reactive protein.

ICU: Intensive care unit.

MV: Mechanical ventilation.

TLC: Total leucocytic count.

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Author Contribution:

"All authors contributed equally in all stages of the study".

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Ethics Approval and Consent to Participate:

This study was approved by research committee in Beni-Suef University. Consent for Publication Not applicable as the study was a retrospective from the medical records.

Competing Interests: The authors declare no conflict of interest.

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