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Original Research Article

Admission HbA1c value as a prognostic marker in patients admitted with COVID-19

Vaibhav Jain*, Suraj S. Hegde

Department of General Medicine, SIMS and RC, Mangalore, Karnataka, India

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***Correspondence:**
Dr. Vaibhav Jain,
E-mail: dragster.vaibz@gmail.com

ABSTRACT

Background: Diabetes mellitus has been firmly established as a risk factor for the prognosis of COVID-19. However, the impact of pre-COVID-19 glycemic control on prognosis is yet to be fully understood. Our study aimed to establish the effect of HbA1c at admission on the outcome of patients admitted with COVID-19.
Methods: It was a prospective observational study of admitted adult patients with confirmed SARS-CoV-2 infection in a tertiary care centre based on data collected from the medical record section using the patient data registry between April 2021 to June 2021. Information regarding demographic and clinical features, laboratory values, and hospital outcomes was collected and analysed.
Results: 182 patients admitted to the hospital with COVID-19 during the study period were included, their mean age was 48.75 years, the mean HbA1c was 6.1. Males accounted for 69.8% (127) of the sample population. 41.2% (75) were known diabetics. 44.8% (81) were known hypertensives. The mortality rate overall was 25.3% (46). 63.7% (116) had HbA1c values >6.5. High HbA1c values was associated with longer duration of hospital stay (p=0.032), higher levels of inflammatory markers, increased need for mechanical ventilation (p=0.001), higher mortality rate (p=0.001).
Conclusions: Patients with COVID-19 with poor glycemic control as evidenced by admission HbA1c levels were found to have more severe disease course with increased level of inflammatory markers, longer duration of hospital stay and higher risk of mortality.

Keywords: COVID-19, Diabetes mellitus, Glycated hemoglobin, HbA1c, Hypertension, Inflammation, Endothelial glycocalyx

INTRODUCTION

The pandemic of COVID-19, caused by the SARS-CoV-2, has caused significant and unprecedented toll on life, healthcare systems and economy. There have been an estimated 57.6 crore cases resulting in approximately 64 lakh deaths as of July 2022.[1] This pandemic also changed our understanding of viral pneumonias with cases presenting as a spectrum of respiratory illness ranging from mild influenza like symptoms to systemic inflammatory response syndrome, acute respiratory distress syndrome (ARDS), multi-organ involvement and shock. Many risk factors have been identified in the progression of COVID-19 into a severe disease, including old age, underlying comorbidities such as hypertension, diabetes, obesity, chronic lung diseases, immunodeficient conditions among many others.[2] New risk factors including local immunodeficiencies like early type I interferon secretion capacity continue to be identified with newer studies.[2]

Diabetes mellitus is a well-known risk factor for worse clinical outcomes in patients with COVID-19.[3] Several studies have shown that diabetes is a common comorbidity

in COVID-19 and more diabetics affected by COVID-19 progress to severe disease.[4,5,9] Many pathological mechanisms have been put forward for linking diabetes and worse outcomes in COVID-19.[6] Infection with SARS-CoV-2 virus triggers activation of several immunomodulatory mechanisms and increased levels of inflammatory mediators including lipopolysaccharides, inflammatory cytokines and toxic metabolites and IFN γ.[7] Infection with SARS-CoV-2 also leads to increased reactive oxygen species (ROS) production and vascular endothelial damage.[8] Hyperglycemia induces all the above mechanisms leading to acute lung damage, ARDS and lung fibrosis. Hyperglycemia also increases the rate of thromboembolic, cardiovascular events and DIC. Further, hyperglycemia was also shown to increase viral replication.[10]

While diabetes was shown to be an important comorbidity adversely affecting outcome in COVID-19, the effect of glycemic control prior to infection is not as well studied. Glycated hemoglobin (HbA1c) is a good measure of glycemic control as it measures mean plasma glucose of the preceding 3 months. Moreover, HbA1c is not affected by acute critical illness thus serving as a stable index of relatively long-term glycemic status in patients with COVID 19. With this study we aimed to ascertain the impact of high HbA1C levels on the outcome of COVID-19 infection.

Aims and objectives

The aims and objectives of this study were to determine glycemic control in patients admitted with COVID-19 using HbA1c levels measured at the time of admission and to analyze predictive value of HbA1c for adverse prognosis in the above patients.

METHODS

This prospective observational study was conducted at a tertiary care hospital, Srinivas Institute of Medical Sciences and Research Centre recognized as a dedicated COVID-19 hospital in Mangalore, India. This study included all the patients admitted to the COVID ICU in the period between April 2021 to June 2021, who met the pre decided inclusion criteria. The total sample size was 182 patients.

Inclusion criteria

All adults (>18 years of age) hospitalized in the COVID-19 ICU with confirmed diagnosis of COVID-19 (laboratory/radiological confirmed) during the study period whose HbA1c was measured at the time of admission were included.

Exclusion criteria

Patients whose HbA1c levels were not measured at admission and patients whose outcome was unclear (discharged against medical advice/discharged at request) were excluded.

Data collection

All patients who met the above criteria were included in the study. These patients were diagnosed with COVID-19 based on radiological-HRCT thorax findings consistent with COVID-19 or laboratory results-RT-PCR (reverse transcriptase polymerase chain reaction assay) or RAT (rapid antigen test) being positive for COVID-19. HbA1c levels were recorded at the time of admission along with other laboratory investigations such as complete blood count, renal and liver function parameters, serum electrolyte levels (sodium, potassium, chloride and calcium), inflammatory markers such as C-reactive protein (CRP), d-dimer, ferritin levels. The HbA1c measurement in our laboratory was standardized as calibrated with SRL.

Investigations were repeated regularly and as per clinical indication. Treatment for COVID-19 was as per prevalent national and WHO guidelines. High flow oxygen therapy, non-invasive ventilatory support and mechanical ventilation was given as per clinical indication. Glycemic control was achieved using regular insulin as per blood glucose in overwhelming majority of cases and OHAs in few. Ionotropic support was instituted in patients with shock.

Ethical approval

This was a prospective observational study. Ethical Committee clearance was obtained for the same.

RESULTS

A total of 182 patients admitted in COVID-19 ICU whose HbA1c levels were recorded at the time of admission were included in the study. The mean HbA1c of the sample population was 7.8% (±2.23 SD). 116 (63.7%) of these patients had HbA1c >6.5. Of these, 100 (54.9% of the total) had HbA1c >7.

Of the patients admitted, 75 were known diabetics.

Of the known diabetics, 73 had HbA1c levels >6.5.

The median age was 48.75 years. The majority (69.8%) of the patients were males (127).

Hypertension was the most common comorbidity (44.8%) closely followed by diabetes mellitus.

13.8% of the patients had ischemic heart disease.

37% of the patients had either leukocytosis or leukocytopenia (<4,000 cells/mm^3 or >11,000 cells/mm^3). High HbA1c (>6.5) was significantly associated with deranged total leucocyte counts (p=0.001).

An overwhelming large fraction of patients had high CRP levels (84.6%) as expected in acute infection. High HbA1c levels (6.5) was significantly associated with having high CRP levels (p=0.006). It follows that diabetes was significantly associated with high CRP levels too (p<0.001).

High HbA1c levels were also associated with high inflammatory markers. Patients with HbA1c >6.5 had raised D-dimer levels and this association was significant (p=0.008). High HbA1c was associated with raised ferritin levels but it was not significant (p=0.32).

Table 1: Overall outcomes.

Parameters	Categories	N	HbA1c (cut off 6.5)		Chi square	P value
			≤6.5 (N (%))	>6.5 (N (%))		
Sex	F	55	24 (36.4)	31 (26.7)	1.854	0.173
	M	127	42 (63.6)	85 (73.3)		
TC categories	<4000	14	10 (15.2)	4 (3.5)	10.724	0.005
	4000-11000	114	43 (65.2)	71 (61.7)		
	>11000	53	13 (19.7)	40 (34.8)		
CRP (cut off >25)	≤25	26	15 (25.9)	11 (9.9)	7.447	0.006
	>25	143	43 (74.1)	100 (90.1)		
D-dimer (cut off 900)	≤900	78	36 (59)	42 (37.8)	7.124	0.008
	>900	94	25 (41)	69 (62.2)		
Ferritin (cut off 336)	≤336	59	24 (38.7)	35 (31.2)	0.991	0.32
	>336	115	38 (61.3)	77 (68.8)		
DM	Absent	107	64 (97)	43 (37.1)	62.301	<0.001
	Present	75	2 (3)	73 (62.9)		
IHD	Absent	156	62 (93.9)	94 (81.7)	5.243	0.022
	Present	25	4 (6.1)	21 (18.3)		
HTN	Absent	100	43 (65.2)	57 (49.6)	4.12	0.042
	Present	81	23 (34.8)	58 (50.4)		
Fever	Absent	31	16 (24.2)	15 (12.9)	3.809	0.051
	Present	151	50 (75.8)	101 (87.1)		
SOB	Absent	72	33 (50)	39 (33.6)	4.72	0.03
	Present	110	33 (50)	77 (66.4)		
Cough	Absent	63	26 (39.4)	37 (31.9)	1.045	0.307
	Present	119	40 (60.6)	79 (68.1)		
Altd. sensorium	Absent	173	63 (96.9)	110 (95.7)	0.179	0.672
	Present	7	2 (3.1)	5 (4.3)		
Loosestool	Absent	176	63 (95.5)	113 (97.4)	0.507	0.477
	Present	6	3 (4.5)	3 (2.6)		
Vomiting	Absent	171	59 (89.4)	112 (96.6)	3.795	0.051
	Present	11	7 (10.6)	4 (3.4)		
Remdesivir	No	38	18 (27.3)	20 (17.2)	2.562	0.109
	Yes	144	48 (72.7)	96 (82.8)		
Steroids	No	11	7 (10.6)	4 (3.4)	3.795	0.051
	Yes	171	59 (89.4)	112 (96.6)		
Mech. ven	No	116	53 (80.3)	63 (54.3)	13.988	0.001
	NIV	4	2 (3)	2 (1.7)		
	Yes	62	11 (16.7)	51 (44)		
Mortality	No	136	59 (89.4)	77 (66.4)	11.797	0.001
	Yes	46	7 (10.6)	39 (33.6)		

Table 2: Hba1c distribution.

Parameters	Hba1c (cut offs 6.5, 7)	Valid percent
<6.5	64	35.2
6.5-7.0	18	9.9
>7	100	54.9
Total	182	100

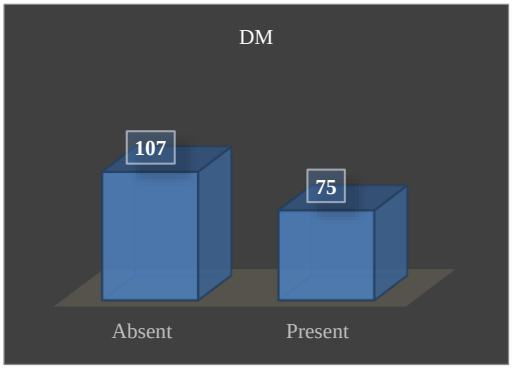

Figure 1: Diabetes mellitus.

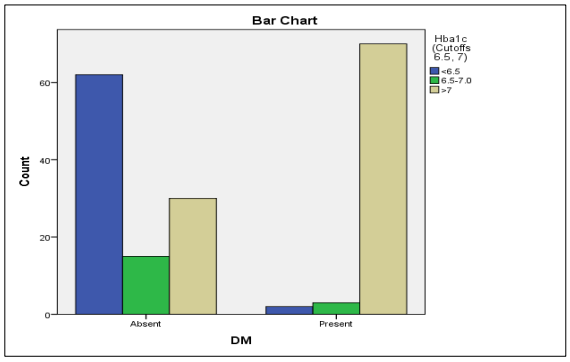

Figure 2: Hba1c distribution in diabetics and non-diabetics.

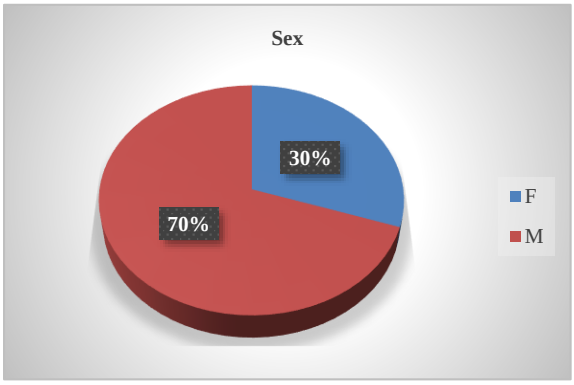

Figure 3: Sex.

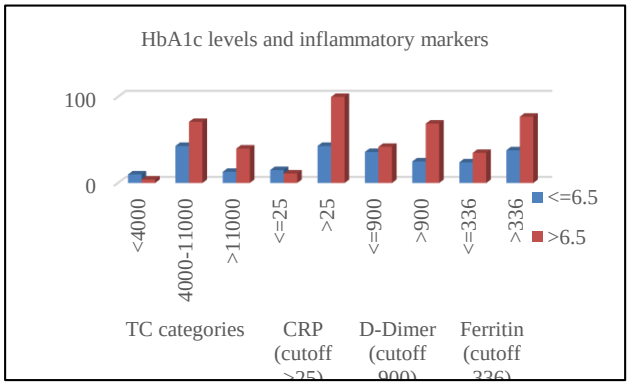

Figure 4: HbA1c levels and inflammatory markers.

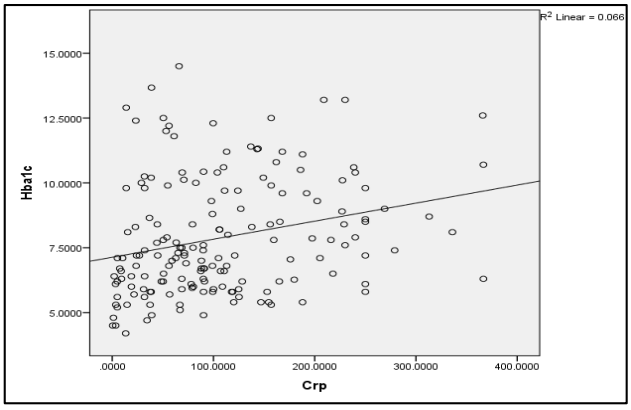

Figure 5: Hba1c and CRP.

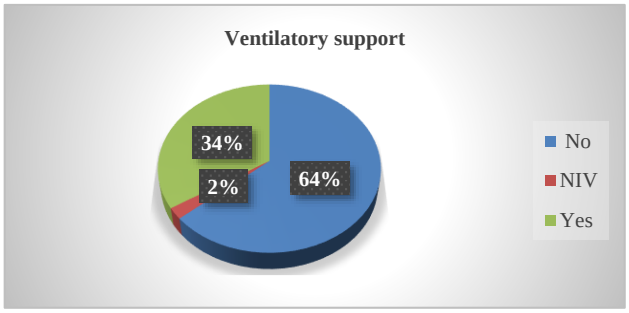

Figure 6: Ventilatory support.

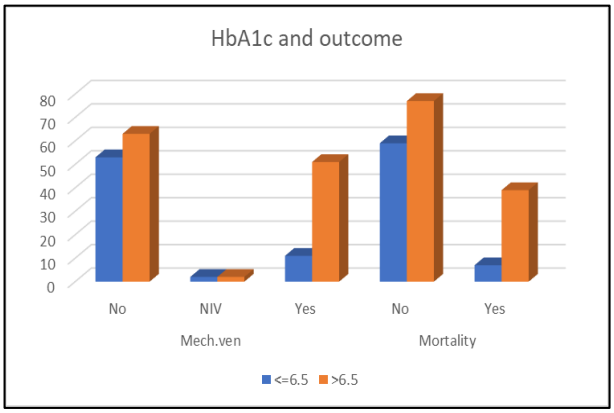

Figure 7: HbA1c and outcome.

There was also linear correlation between HbA1c levels and levels of CRP (p=0.001) and D-dimer (p=0.036) as evidenced by Pearson's correlation. Higher HbA1c levels were associated with higher levels of these inflammatory markers.

Remedesevir was used in a large majority of the patients (144) as per the guidelines prevalent at the time as were IV steroids (171) and low molecular weight heparin.

36% of the patients required ventilatory support during the course of their stay in the COVID-19 ICU with 34% requiring intubation and mechanical ventilation.

High HbA1c levels were associated with significantly higher rates of use of NIV and Intubation and mechanical ventilation (p=0.001).

The mean duration of hospital stay in our study was 7.89 (±4.72) days. There was linear association between HbA1c and duration of stay in the hospital. This association was significant (p=0.036) as per Pearson's correlation model.

High HbA1c (>6.5) was significantly associated with higher mortality rate (p=0.001).

Thus, high HbA1c (>6.5) was a good predictor of adverse predictor of severity of illness with COVID-19 and also outcomes in patients with COVID-19 admitted to the ICU showing significant association with increased levels of inflammatory markers, requirement of mechanical and non invasive ventilation. High HbA1c levels also showed a strong linear correlation with duration of hospital stay.

Patients with high HbA1c levels also had higher rates of mortality in the COVID-19 ICU.

DISCUSSION

A number of previous studies have well documented the effect of uncontrolled blood sugars and outcomes in critically ill patients with COVID-19. Hyperglycemia causes endothelial dysfunction, generates oxidative stress, induces inflammation and promotes viral replication. All of these processes are also observed in critical illness with COVID-19 and in conjunction they lead to increased severity of disease. Further, COVID 19 infection is a diabetogenic state.[11,12] Increased incidence of hyperglycemia in previously normoglycemic patients, increased insulin resistance and increased rates of ketoacidosis was observed in patients with COVID 19 patients.[13] Many mechanisms have been proposed for this, prominent among them are attributed to the involvement of ACE-2 receptors in the islet of Langerhans, abnormal cytokine response in viral infections, use of glucocorticoids in treatment of COVID-19 with ARDS. Diabetes and COVID-19 have a complex and mutually destructive relationship with each one accentuating the effects of the other.[14] Poor control of blood glucose causes chronic damage to the endothelial glucocalyx and vascular injury predisposing to thrombosis. Chronic hyperglycemia also causes abnormal cytokine responses, inhibition of leukocyte recruitment, and neutrophil dysfunction. Using glycated hemoglobin as an indicator of chronic hyperglycemia our study showed that poorly controlled blood sugars prior to COVID-19 infection has adverse effects on outcomes in critically ill patients with COVID-19.

Dysregulation of immune function has been observed in previous studies with critically ill patients with viral infections.[15,16] Similarly in our study patients with high HbA1c had significantly deranged leucocyte counts possibly due to secondary immune response. Patients with high HbA1c had increased levels of inflammatory markers-CRP, LDH, N/L ratio. Chronic hyperglycemia causes microvascular injury and endothelial dysfunction inducing a pro- thrombotic state.[17] In this setting, COVID-19 infection leads to higher rates of thrombotic and embolic phenomenon. Patients with high HbA1c in our study had significantly higher levels of D-dimer levels probably reflecting the above.

Prior studies have showed that uncontrolled blood sugars in admitted critically ill patients with COVID-19 negatively impact outcomes in these patients. In our study patients with poor pre-infection blood sugars as evidenced by high HbA1c levels also had poorer outcomes than patients with normal HbA1c levels. Patients with high HbA1c had increased oxygen demand, had higher rates of requiring ventilatory support. These patients had longer duration of hospital stay.

Patients with COVID-19 are more susceptible to vascular complications, 'cytokine storm', secondary infections (bacterial, fungal) and overwhelming sepsis. Chronic hyperglycemia predisposes to all the above potentially life-threatening events. Accordingly, patients with high HbA1c levels had significantly higher rates of mortality.

Diabetes mellitus has a mutually interdependent relationship with the severity of COVID-19 infection. Along with obesity, older age and male gender, the presence of diabetes mellitus has been recognised as an important comorbidity affecting prognosis in patients with COVID-19 patients. In our study we showed that pre infection glycemic control also has a prognostic bearing on outcomes with COVID-19 infection.

CONCLUSION

The COVID-19 pandemic has severely challenged healthcare delivery systems. It has also changed our understanding and knowledge about viral infections and the role of chronic diseases in their outcome. Using glycated hemoglobin levels we can better identify the population at risk for developing severe disease. HbA1c screening at the time of admission can also help us better predict for adverse events in critically ill patients with COVID-19 and take necessary measures to minimise the risks of such events. Measuring glycemic control can also help in allocating resources such as vaccines to the most needed sections of the population.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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