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Evaluating HbA1c as a Prognostic Indicator in COVID-19 Patients

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Abstract

Background: Diabetes mellitus has been widely recognized as a significant risk factor influencing the prognosis of COVID-19, with patients exhibiting poorer outcomes and higher mortality rates. However, the role of pre-COVID-19 glycemic control in determining the severity of the disease and clinical outcomes remains a subject of ongoing investigation.

Material and Methods: This prospective observational study included adult patients admitted with confirmed SARS-CoV-2 infection. Conducted at a tertiary care center, it relied on data retrieved from the patient data registry in the medical records section. The study period spanned from May 2021 to July 2021. Data on patient demographics, clinical characteristics, laboratory results, and hospital outcomes were collected and analyzed to explore factors affecting the prognosis of COVID-19. **Results:** A total of 155 patients hospitalized with COVID-19 during the

study period were included. The mean age of the patients was 46.77 years, and the average HbA1c level was 6.6%. Most male patients were known to have diabetes. Elevated HbA1c levels were significantly associated with a longer duration of hospital stay (p=0.032), higher levels of inflammatory markers, an increased need for mechanical ventilation (p=0.001), and a higher mortality rate (p=0.001).

Conclusions: Patients with COVID-19 and poor glycemic control, as indicated by elevated admission HbA1c levels, experienced a more severe disease progression. This was characterized by higher levels of inflammatory markers, prolonged hospital stays, and an increased risk of mortality.

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

Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has placed an immense burden on healthcare systems worldwide. Among the various risk factors associated with severe disease and poor outcomes in COVID-19, diabetes mellitus has emerged as a significant comorbidity.[1] Patients with diabetes are not only more susceptible to severe infections but also experience higher rates of hospitalization, complications, and mortality.[2]

Chronic hyperglycemia, as measured by glycated hemoglobin (HbA1c), provides an indication of long-term glycemic control over the preceding 2–3 months and is a well-established marker for diabetes management. Recent studies have suggested that HbA1c levels at the time of hospital admission may serve as an important prognostic indicator in patients with COVID-19, reflecting both pre-existing glycemic control and potential vulnerability to poor outcomes.[3,4]

Elevated HbA1c levels have been associated with heightened inflammatory responses, prolonged hospital stays, increased need for intensive care interventions, and higher mortality rates in patients with COVID-19.[4] This is due to the detrimental effects of chronic hyperglycemia on immune function and endothelial health, which exacerbate the hyperinflammatory state observed in severe COVID-19.[5]

Infection with the SARS-CoV-2 virus activates several immunomodulatory pathways, resulting in elevated levels of inflammatory mediators such as lipopolysaccharides, inflammatory cytokines, toxic metabolites, and interferon-gamma (IFN-γ). Additionally, SARS-CoV-2 infection promotes the production of reactive oxygen species (ROS) and causes vascular endothelial damage. Hyperglycemia exacerbates these processes, contributing to acute lung injury, acute respiratory distress syndrome (ARDS), and lung fibrosis. Furthermore, hyperglycemia has been linked to an increased risk of thromboembolic events, cardiovascular complications, and disseminated intravascular coagulation (DIC). Studies have also shown that hyperglycemia enhances viral replication, further worsening the disease severity.[6]

Thus, the aim of this study was to assess glycemic control in patients admitted with COVID-19 by measuring HbA1c levels at the time of admission and to evaluate the predictive value of HbA1c in determining adverse outcomes in these patients.

Material and Methods

This prospective observational study was conducted at Srinivas Institute of Medical Sciences and Research Centre, a designated COVID-19 hospital in Mangalore, India. The study included all patients admitted to the COVID ICU between May 2021 and July 2021 who met the predetermined inclusion criteria. A total of 155 patients were included in the study.

The study included all adults aged over 18 years who were hospitalized in the COVID-19 ICU with a confirmed diagnosis of COVID-19 (either laboratory or radiologically confirmed) during the study period, and whose HbA1c levels were measured at the time of admission. Patients were excluded if their HbA1c levels were not measured at the time of admission or if their outcomes were unclear, such as those discharged against medical advice or at their own request.

This study was conducted as a prospective observational study, and approval was granted by the Ethical Committee.

Patients who met the inclusion criteria were included in the study. The COVID-19 diagnosis was confirmed based on radiological findings from HRCT thorax, consistent with COVID-19, or through positive laboratory results from RT-PCR (reverse transcriptase polymerase chain reaction) or RAT (rapid antigen test). HbA1c levels were recorded at the time of admission, along with other laboratory tests such as complete blood count, renal and liver function tests, serum electrolytes (sodium, potassium, chloride, calcium), and inflammatory markers including C-reactive protein (CRP), d-dimer, and ferritin. HbA1c measurements were standardized and calibrated with SRL in our laboratory.

Investigations were repeated as needed, based on clinical indications. Treatment followed the latest national and WHO guidelines for COVID-19. High-flow oxygen therapy, non-invasive ventilatory support, and mechanical ventilation were provided as clinically required. Glycemic control was primarily managed with regular insulin according to blood glucose levels, with oral hypoglycemic agents (OHAs) used in select cases. Inotropic support was initiated in patients with shock.

Results

A total of 155 patients admitted to the COVID-19 ICU, with HbA1c levels recorded at the time of admission, were included in the study. The mean HbA1c level of the sample population was 7.2%

(±2.44 SD). Among these patients, 102 (65.8%) had an HbA1c greater than 6.5%. Of these, eighty-three patients (53.5% of the total) had an HbA1c greater than seven.

One hundred and fifteen individuals were known diabetics, with sixty-five having HbA1c levels greater than 6.5%. The median age was 46.77 years, and the majority (61.2%) were male (95 individuals). Hypertension was the most common comorbidity, affecting 49.5%, closely followed by diabetes mellitus. Ischemic heart disease was observed in 14.7%.

Table 1: A substantial proportion of patients (87.2%) exhibited elevated CRP levels, as expected in cases of acute infection. High HbA1c levels (>6.5) were significantly associated with elevated CRP levels ($p=0.007$), and diabetes was also strongly linked to elevated CRP levels ($p<0.001$). Additionally, high HbA1c levels were associated with increased inflammatory markers. Patients with HbA1c >6.5 showed significantly elevated D-dimer levels. Although high HbA1c levels were linked to increased ferritin levels, this association was not statistically significant ($p=0.47$).

Table 2: High HbA1c levels were associated with increased inflammatory markers. Patients with HbA1c >6.5 showed significantly elevated D-dimer levels. Although high HbA1c levels were linked to increased ferritin levels, this association was not statistically significant ($p=0.47$).

Figure 1: High HbA1c levels were associated with significantly higher rates of use of NIV and Intubation and mechanical ventilation ($p=0.001$). Thirty-nine percent of the patients required ventilatory support during their stay in the COVID-19 ICU with 32% requiring intubation and mechanical ventilation.

Table 1: Overall outcomes

Parameters	Categories	N	HbA1c (cut off 6.5)		Chi square	P value
			≤6.5 (N (%))	>6.5 (N (%))		

Sex	Male	95	27 (31.2)	28 (22.4)	1.38	0.12
	Female	60	31 (60.0)	76 (71.4)		
TC categories	<4000	10	8 (12.3)	5 (3.1)	8.32	0.005
	4000-11000	99	47 (61.7)	62 (58.2)		
	>11000	40	16 (19.2)	31 (30/1)		
CRP (cut off >25)	≤25	29	18 (25.1)	11 (9.9)	7.447	0.007
	>25	122	56 (78.0)	113 (91.2)		
D-dimer (cut off 900)	≤900	82	40 (61)	45 (39.2)	7.124	0.006
		105	31 (47)	77 (66.1)		
Ferritin (cut off 336)	≤336	65	30 (39.2)	33 (31.1)	0.962	0.30
	>336	121	41 (67.9)	78 (69.0)		
DM	Absent	101	68 (92)	45 (37.2)	60.213	<0.001
	Present	66	3 (2)	76 (61.3)		
IHD	Absent	132	73 (91.3)	98 (80.1)	7.382	0.051
	Present	31	3 (6.3)	25 (19.2)		
HTN	Absent	99	45 (52,2)	68 (50.1)	5.18	0.056
	Present	76	27 (32.4)	78 (2.1)		
Fever	Absent	21	13 (27.8)	18 (12.3)	3.124	0.050
	Present	132	87 (81.3)	111 (80.3)		
SOB	Absent	72	33 (50)	39 (33.6)	4.72	0.03

	Present	110	33 (50)	77 (66.4)		
Cough	Absent	70	22 (39.2)	32 (32.3)	1.123	0.621
	Present	112	43 (61.2)	72 (63.4)		
Altd.	Absent	143	76 (96.2)	121 (93.2)	0.291	0.780
sensorium	Present	12	2 (3.9)	3 (4.1)		
Loosestool	Absent	150	71 (91.2)	97 (90.3)	0.827	0.518
	Present	5	2 (3.1)	4 (3.1)		
Vomiting	Absent	131	72 (80.2)	109 (95.3)	3.990	0.180
	Present	28	9 (11.1)	3 (3.4)		
Remdesivir	No	49	21 (30.2)	19 (16.9)	2.123	0.222
	Yes	137	51 (70/4)	92 (89.0)		
Steroids	No	14	4 (8.1)	4 (3.5)	3.019	0.192
	Yes	121	52 (81.4)	101 (93.4)		
Mech. ven	No	118	43 (76.3)	51 (50.3)	8.901	0.001
	NIV	3	2 (2.3)	2 (1.1)		
	Yes	61	11 (12.1)	44 (39.0)		
Mortality	Absent	139	42 (81.2)	70 (61.2)	12.182	0.001
	Present	42	5 (9.0)	391(30.3)		

Table 2: Hba1c distribution.

Parameters	Hba1c (cut offs 6.5, 7)	Valid percent
<6.5	38	24.5

6.5-7.0	12	7.7
>7	105	67.7
Total	155	100

Figure 1: Ventilatory support.

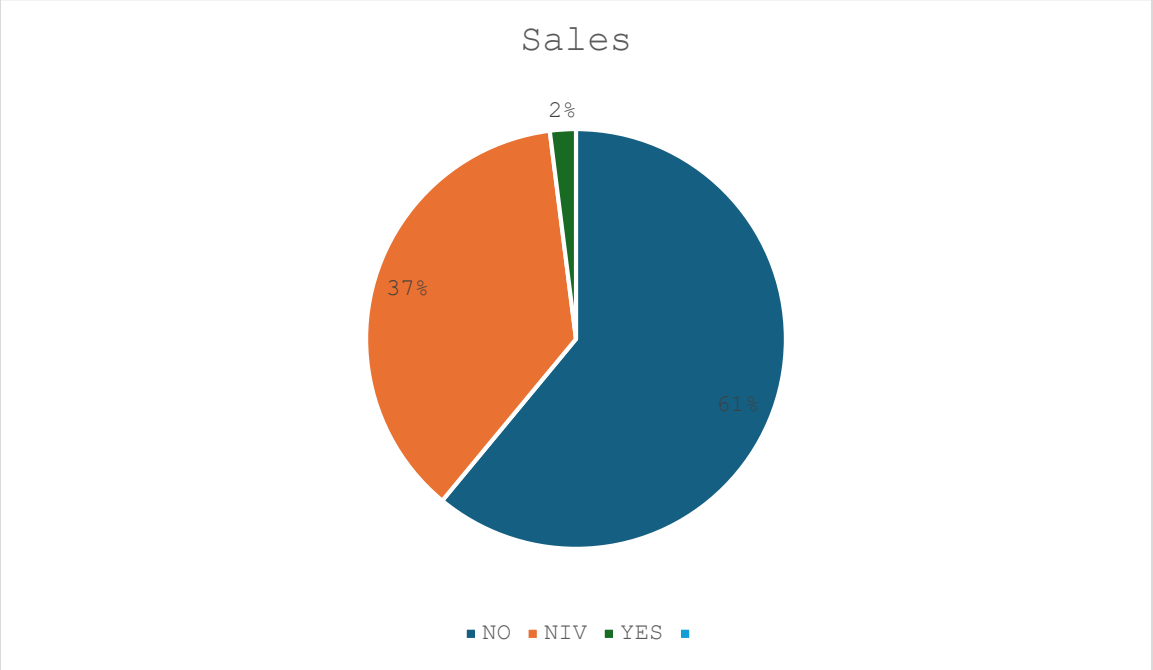
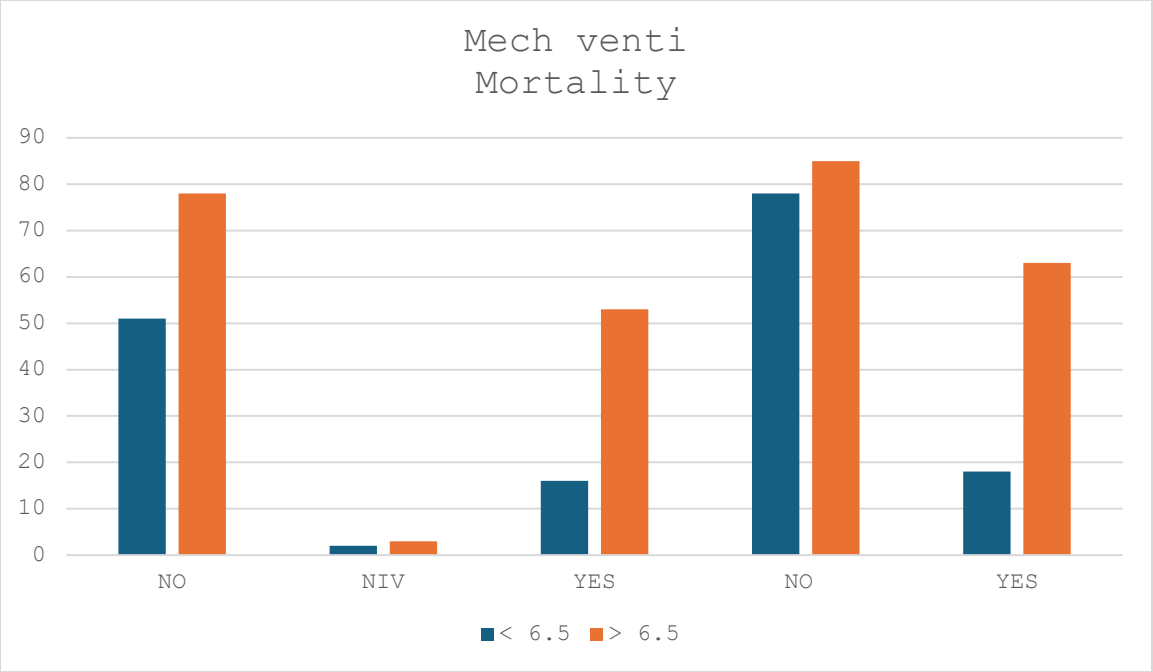


Figure 2: HbA1c and outcome.



Discussion:

The findings of this study suggest that admission HbA1c levels can serve as an important prognostic marker in patients hospitalized with COVID-19. Elevated HbA1c levels, reflecting poor pre-existing glycemic control, were associated with worse clinical outcomes, including prolonged hospital stays, higher levels of inflammatory markers, increased need for mechanical ventilation, and higher mortality rates. These results align with existing evidence linking chronic hyperglycemia to adverse outcomes in COVID-19 (7, 8).

Hyperglycemia is known to impair immune responses, increase oxidative stress, and exacerbate systemic inflammation, all of which contribute to the severe disease course observed in patients with uncontrolled diabetes (9). Elevated HbA1c levels were strongly associated with raised inflammatory markers such as CRP and D-dimer, consistent with prior studies demonstrating the role of hyperglycemia in amplifying the inflammatory cascade and coagulation abnormalities in COVID-19 patients (10).

Interestingly, while elevated HbA1c levels were linked to increased ferritin levels, this association was not statistically significant in our study. This may be attributable to the multifactorial nature of hyperferritinemia in COVID-19, which may not always correlate directly with glycemic control. However, the significant association of HbA1c with CRP and D-dimer reinforces its role as a marker of systemic inflammation and coagulopathy in COVID-19 (11).

Given these findings, HbA1c testing at the time of admission can provide valuable prognostic information for clinicians managing patients with COVID-19. Identifying patients with poor glycemic control enables targeted interventions to optimize glucose levels and mitigate complications. Further studies are warranted to explore the benefits of strict glycemic control and its impact on long-term outcomes in COVID-19 patients.

Previous studies have demonstrated that uncontrolled blood sugar levels in critically ill patients with COVID-19 are associated with worse outcomes. Similarly, our study found that patients with poor glycemic control prior to infection, as indicated by elevated HbA1c levels, experienced poorer clinical outcomes compared to those with normal HbA1c levels. Patients with elevated HbA1c had increased oxygen requirements and higher rates of ventilatory support. Additionally, these patients had a longer duration of hospitalization (3).

Individuals with COVID-19 are at an increased risk of vascular complications, cytokine storm, secondary bacterial or fungal infections, and severe sepsis. Chronic hyperglycemia predisposes patients to these life-threatening conditions. Consistent with this, our findings revealed that patients with elevated HbA1c levels had significantly higher mortality rates (3).

Conclusion

The COVID-19 pandemic has highlighted challenges in healthcare and reshaped our understanding of viral infections and chronic diseases. Glycated hemoglobin (HbA1c) levels can help identify

individuals at higher risk for severe disease. HbA1c screening upon admission can predict adverse outcomes in critically ill COVID-19 patients, allowing for targeted interventions. Monitoring glycemic control also aids in resource allocation, such as prioritizing vaccines for high-risk populations.

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