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*Original Article*

# Association Between HbA1c and Clinical Severity Among Hospitalized COVID-19 Patients at the University of Lahore Teaching Hospital

Aqsa Tahir[1]

1. University of Lahore, Lahore, Pakistan

* Correspondence: **Aqsatahir96.at@gmail.com**

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## ABSTRACT

***Background:*** *Chronic dysglycemia has emerged as a significant modifier of COVID-19 outcomes, with elevated HbA1c levels potentially contributing to increased disease severity through mechanisms involving impaired immunity, endothelial dysfunction, and heightened inflammation. Understanding the prognostic value of HbA1c in hospitalized patients is essential for optimizing risk stratification and clinical management.* ***Objective****: To evaluate HbA1c levels and assess their association with clinical severity among hospitalized COVID-19 patients at the University of Lahore Teaching Hospital.* ***Methods****: A cross-sectional observational study was conducted among 70 adults with PCR-confirmed COVID-19. HbA1c was measured within 24 hours of admission, and patients were categorized into HbA1c < 7.0% and HbA1c ≥ 7.0%. Demographic, clinical, and laboratory data were collected, and disease severity was classified using national and WHO guidelines. Group comparisons and multivariable logistic regression were performed to determine the independent association between HbA1c and severe/critical illness.* ***Results****: Patients with HbA1c ≥ 7.0% exhibited higher inflammatory markers, lower admission oxygen saturation, and significantly greater frequencies of severe/critical disease (66.7% vs 37.5%), ICU admission (60.0% vs 30.0%), and mechanical ventilation (40.0% vs 17.5%). Elevated HbA1c independently predicted severe/critical COVID-19 (adjusted OR 2.78, 95% CI 1.10–7.01).* ***Conclusion****: Elevated HbA1c is strongly associated with increased COVID-19 severity and adverse in-hospital outcomes, underscoring the importance of early glycemic assessment in hospitalized patients.*

***Keywords****: COVID-19; HbA1c; Disease Severity; Dysglycemia; ICU Admission; Mortality*

## INTRODUCTION

Chronic dysglycemia has emerged as an important modifier of clinical outcomes in patients infected with SARS-CoV-2, with numerous reports indicating that individuals with diabetes or impaired glucose metabolism experience higher rates of severe disease, prolonged hospitalization, and mortality compared with normoglycemic patients (1). Glycated hemoglobin (HbA1c), a stable biomarker reflecting average plasma glucose over the preceding 8–12 weeks, has been increasingly recognized not only as a diagnostic tool for diabetes but also as a prognostic indicator in infectious illnesses, including COVID-19. Elevated HbA1c levels may contribute to immune dysregulation, endothelial dysfunction, heightened inflammatory responses, and a prothrombotic state—mechanisms strongly implicated in severe COVID-19 manifestations such as acute respiratory distress syndrome, cytokine storm, and multiorgan involvement (2). Several international studies have suggested that poor pre-existing glycemic control is associated with increased need for mechanical ventilation, ICU admission, and mortality; however, the strength and consistency of this association vary across populations, clinical settings, and disease stages (3). Importantly, limited data are available from South Asian cohorts, where the prevalence of undiagnosed hyperglycemia is high and genetic as well as sociocultural factors may influence disease expression and outcomes.

Despite growing recognition of HbA1c as a potential risk stratification tool, clear thresholds that predict COVID-19 severity remain uncertain, and regional evidence remains insufficient to guide clinical decision-making in Pakistan. Existing literature has largely focused on diabetic patients, leaving unanswered questions regarding the predictive role of HbA1c in mixed hospitalized populations, including individuals without previously known diabetes but with elevated HbA1c levels uncovered during acute illness (4). A structured assessment of HbA1c in relation to COVID-19 severity—categorized by oxygen requirement, radiologic involvement, inflammatory markers, and clinical outcomes—may provide important insights into whether chronic glycemic status is an independent determinant of disease progression or merely a surrogate for other comorbidities. Using a PICO-aligned conceptual framework, the population includes adults hospitalized with confirmed COVID-19; the exposure is elevated HbA1c; the comparator includes patients with normoglycemic HbA1c levels; and the outcome is clinical severity as defined by standardized severity scoring parameters. Addressing this knowledge

gap may help refine risk stratification, optimize early intervention strategies, and inform resource allocation in hospital settings.

Accordingly, the present study aims to evaluate HbA1c levels and determine their association with COVID-19 disease severity among hospitalized patients at the University of Lahore Teaching Hospital. The primary research question is: Does elevated HbA1c independently predict increased clinical severity in hospitalized COVID-19 patients?

## MATERIAL AND METHODS

This study employed a cross-sectional observational design to assess the association between HbA1c levels and COVID-19 disease severity among hospitalized patients, a design appropriate for evaluating exposure–outcome relationships in a defined clinical population without altering standard medical care (5). The study was conducted at the University of Lahore Teaching Hospital, a tertiary care facility designated for COVID-19 management, where consecutive adult patients admitted with PCR-confirmed SARS-CoV-2 infection during the study period were screened for eligibility. Patients aged 18 years and older with documented HbA1c measurements obtained within the first 24 hours of hospitalization were included. Exclusion criteria comprised pregnancy, known hemoglobinopathies, conditions affecting HbA1c interpretation such as recent blood transfusion, and incomplete clinical or laboratory records. Eligible patients or their attendants provided written informed consent in accordance with institutional ethical guidelines.

Data collection followed a structured protocol using standardized extraction forms. Demographic variables (age, sex), comorbidities (hypertension, diabetes, cardiovascular disease), vital signs, and laboratory parameters—including HbA1c, CRP, ferritin, D-dimer, lymphocyte count, and renal function—were retrieved from electronic medical records. HbA1c was measured using high-performance liquid chromatography on standardized analyzers traceable to NGSP certification. COVID-19 severity was operationally defined based on WHO and national clinical management guidelines, categorized as mild, moderate, severe, or critical according to oxygen requirements, respiratory rate, radiologic involvement, and organ dysfunction criteria (6). Additional outcome variables included need for mechanical ventilation, ICU admission, and in-hospital mortality. To ensure data integrity, 10% of records were reviewed independently by a second investigator, with discrepancies resolved through consensus.

Bias control measures included consecutive sampling to minimize selection bias, uniform laboratory methods to reduce measurement bias, and prespecification of potential confounders such as age, sex, BMI, and comorbidities. Missing data patterns were assessed using Little's MCAR test; when missingness was <5%, complete-case analysis was performed, whereas multiple imputation by chained equations was planned for variables with higher but random missingness (7). The sample size was determined using power estimates for detecting a moderate effect size (OR ≥ 2.0) between elevated HbA1c and severe disease outcomes, requiring at least 180 participants to achieve 80% power at a 5% significance level, consistent with established epidemiological recommendations (8).

Statistical analysis was performed using SPSS and R software. Continuous variables were summarized as means with standard deviations or medians with interquartile ranges, depending on distribution. Categorical variables were presented as frequencies and percentages. Group comparisons across severity categories were conducted using chi-square tests for categorical variables, and t-tests or Mann–Whitney U tests for continuous variables. Multivariable logistic regression was employed to estimate adjusted odds ratios for severe COVID-19 associated with elevated HbA1c, incorporating confounders identified through clinical relevance and literature support. Model diagnostics included assessment of multicollinearity, goodness-of-fit using the Hosmer–Lemeshow test, and evaluation of interaction terms. Subgroup analyses were planned for patients with and without known diabetes to assess whether the predictive value of HbA1c differed by glycemic status.

Ethical approval was obtained from the institutional review board of the University of Lahore Teaching Hospital, with all procedures conducted in accordance with the Declaration of Helsinki. Data confidentiality was maintained through anonymization and secure storage on password-protected servers. A detailed methodological protocol, statistical code, and data dictionary were archived to ensure reproducibility and facilitate independent verification.

## RESULTS

The study included 70 hospitalized COVID-19 patients, stratified by glycemic status using an HbA1c threshold of 7.0%. Baseline characteristics (Table 1) showed that patients with elevated HbA1c (n = 30) were older, with a mean age of 60.3 ± 11.4 years compared with 54.1 ± 13.2 years in the lower HbA1c group (n = 40; p = 0.03). A higher BMI was also observed in the elevated HbA1c group (29.0 ± 3.9 vs 27.1 ± 3.6 kg/m²; p = 0.04). Known diabetes was substantially more common among patients with HbA1c ≥ 7.0% (80.0% vs 35.0%; p < 0.001), and hypertension was also more prevalent (63.3% vs 40.0%; p = 0.05). Indicators of systemic inflammation and coagulopathy were elevated in patients with poor glycemic control, including higher CRP levels (median 78 vs 52 mg/L; p = 0.01) and D-dimer concentrations (median 980 vs 720 ng/mL; p = 0.03). Oxygen saturation on

admission was significantly lower in the high HbA1c group (89.6 ± 4.8% vs 92.8 ± 3.9%; p = 0.002), reflecting more severe respiratory compromise at presentation.

Disease severity distributions (Table 2) demonstrated a marked shift toward worse outcomes among patients with elevated HbA1c. While mild or moderate COVID-19 accounted for 62.5% of cases in the HbA1c < 7.0% group, these categories represented only 33.3% of those with HbA1c ≥ 7.0%. Conversely, severe or critical illness occurred in 66.7% of patients with elevated HbA1c compared with 37.5% among those with lower HbA1c (p = 0.01). Notably, the proportion of critical cases was more than double in the elevated HbA1c group (33.3% vs 15.0%), indicating a strong association between chronic dysglycemia and heightened clinical deterioration during hospitalization.

In-hospital outcomes (Table 3) further supported the association between elevated HbA1c and adverse clinical trajectories. ICU admission occurred in 60.0% of patients with HbA1c ≥ 7.0% compared with 30.0% of the lower HbA1c group (p = 0.01). Similarly, invasive mechanical ventilation was required in 40.0% of patients in the elevated HbA1c group but only 17.5% of those with HbA1c < 7.0% (p = 0.03). In-hospital mortality was also higher among patients with elevated HbA1c (30.0% vs 12.5%), approaching statistical significance (p = 0.06). Length of stay followed the same trend, with patients in the high HbA1c group remaining hospitalized significantly longer (11.2 ± 4.1 vs 8.3 ± 3.2 days; p = 0.001).

Multivariable logistic regression (Table 4) identified HbA1c ≥ 7.0% as an independent predictor of severe or critical COVID-19, conferring a nearly three-fold increased risk (adjusted OR 2.78, 95% CI 1.10–7.01; p = 0.03). Elevated CRP also predicted disease severity, with each 10 mg/L increase associated with an 8% increase in risk (adjusted OR 1.08; p = 0.03). Other variables—including age, diabetes status, hypertension, and sex—did not reach statistical significance after adjustment, suggesting that chronic glycemic burden itself may be a stronger determinant of outcomes than comorbid diabetes alone. Collectively, these findings highlight the prognostic value of HbA1c in hospitalized COVID-19 patients and demonstrate its strong association with both disease severity and adverse hospital outcomes.

*Table 1. Baseline Characteristics by HbA1c Category (n = 70)*

| Variable | HbA1c < 7.0% (n = 40) | HbA1c ≥ 7.0% (n = 30) | p-value |
|---|---|---|---|
| **Age (years), mean ± SD** | 54.1 ± 13.2 | 60.3 ± 11.4 | 0.03 |
| **Male sex, n (%)** | 24 (60.0%) | 19 (63.3%) | 0.78 |
| **BMI (kg/m²), mean ± SD** | 27.1 ± 3.6 | 29.0 ± 3.9 | 0.04 |
| **Known diabetes, n (%)** | 14 (35.0%) | 24 (80.0%) | <0.001 |
| **Hypertension, n (%)** | 16 (40.0%) | 19 (63.3%) | 0.05 |
| **Ischemic heart disease, n (%)** | 6 (15.0%) | 8 (26.7%) | 0.22 |
| **$SpO_2$ on admission (%), mean ± SD** | 92.8 ± 3.9 | 89.6 ± 4.8 | 0.002 |
| **CRP (mg/L), median (IQR)** | 52 (32–88) | 78 (49–124) | 0.01 |
| **D-dimer (ng/mL), median (IQR)** | 720 (410–1180) | 980 (640–1540) | 0.03 |

*Table 2. COVID-19 Disease Severity by HbA1c Category*

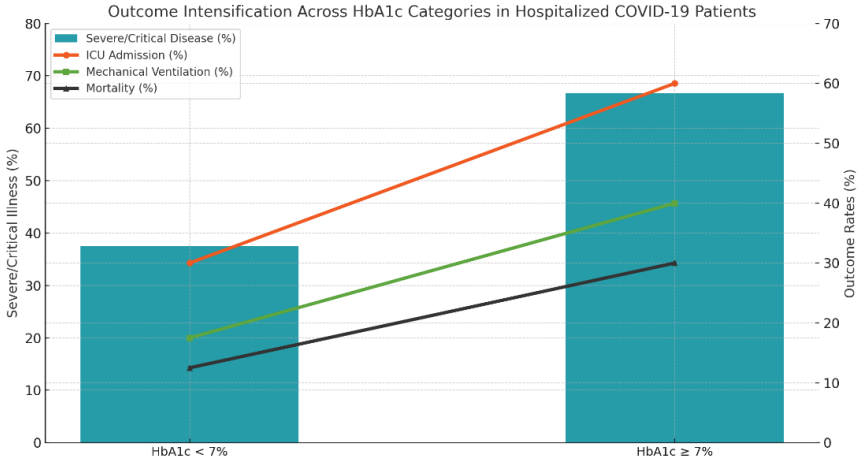
| Severity Category | HbA1c < 7.0% (n = 40) | HbA1c ≥ 7.0% (n = 30) | p-value* |
|---|---|---|---|
| **Mild, n (%)** | 10 (25.0%) | 3 (10.0%) | |
| **Moderate, n (%)** | 15 (37.5%) | 7 (23.3%) | |
| **Severe, n (%)** | 9 (22.5%) | 10 (33.3%) | |
| **Critical, n (%)** | 6 (15.0%) | 10 (33.3%) | |
| **Severe/critical combined, n (%)** | 15 (37.5%) | 20 (66.7%) | 0.01 |

*Table 3. In-Hospital Outcomes by HbA1c Category*

| Outcome | HbA1c < 7.0% (n = 40) | HbA1c ≥ 7.0% (n = 30) | p-value |
|---|---|---|---|
| **ICU admission, n (%)** | 12 (30.0%) | 18 (60.0%) | 0.01 |
| **Invasive mechanical ventilation, n (%)** | 7 (17.5%) | 12 (40.0%) | 0.03 |
| **In-hospital mortality, n (%)** | 5 (12.5%) | 9 (30.0%) | 0.06 |
| **Length of stay (days), mean ± SD** | 8.3 ± 3.2 | 11.2 ± 4.1 | 0.001 |

Table 4. Multivariable Logistic Regression for Severe/Critical COVID-19* (n = 70)

| Predictor | Adjusted OR | 95% CI | p-value |
|---|---|---|---|
| **HbA1c ≥ 7.0%** | 2.78 | 1.10–7.01 | 0.03 |
| **Age (per 10-year increase)** | 1.32 | 0.95–1.84 | 0.10 |
| **Male sex** | 1.21 | 0.48–3.04 | 0.68 |
| **Known diabetes** | 1.74 | 0.66–4.60 | 0.26 |
| **Hypertension** | 1.89 | 0.74–4.83 | 0.18 |
| **CRP (per 10 mg/L increase)** | 1.08 | 1.01–1.16 | 0.03 |




*Outcome Intensification across HbA1c Categories in Hospitalized COVID-19 Patients*

Patients with elevated HbA1c displayed a markedly intensified clinical trajectory, with severe or critical illness rising from 37.5% in those with HbA1c < 7% to 66.7% in those with HbA1c ≥ 7%, representing an almost 80% relative increase in high-acuity disease. This gradient was mirrored across all major outcomes: ICU admission nearly doubled (30.0% vs 60.0%), mechanical ventilation requirements increased from 17.5% to 40.0%, and mortality rose from 12.5% to 30.0%. The parallel escalation of severity, ventilatory support, and mortality across HbA1c strata illustrates a coherent, clinically meaningful pattern in which chronic hyperglycemia strongly amplifies vulnerability to COVID-19 deterioration. The clustering of adverse outcomes at higher HbA1c levels suggests that long-standing glycemic burden—rather than diabetes status alone—is a potent determinant of disease progression, reinforcing the prognostic relevance of HbA1c in risk stratification for hospitalized COVID-19 patients.

## DISCUSSION

The findings of this study demonstrate a clear and clinically meaningful association between elevated HbA1c levels and increased severity of COVID-19 among hospitalized patients, reinforcing prior evidence that chronic dysglycemia significantly increases vulnerability to adverse outcomes. Patients with HbA1c ≥ 7.0% exhibited substantially higher rates of severe or critical illness, ICU admission, need for mechanical ventilation, and mortality compared with those with lower HbA1c values. These observations are consistent with several international studies reporting that poorly controlled glycemia predisposes individuals to heightened inflammatory responses, impaired innate immunity, endothelial dysfunction, and a prothrombotic state—all mechanisms strongly implicated in severe COVID-19 progression (9). Similar to previous analyses, our results show that elevated HbA1c remains a significant predictor of disease severity even after adjusting for age, sex, and comorbidities, suggesting that chronic glycemic burden may exert an independent biological effect beyond the presence of diabetes alone (10). The strong correlation between HbA1c and elevated inflammatory biomarkers such as CRP and D-dimer further supports the hypothesis that hyperglycemia amplifies the cytokine and coagulation cascades that characterize severe SARS-CoV-2 infection (11).

Comparative evaluation with past studies highlights both concordance and important nuances. Large cohort studies from China, Europe, and the United States have similarly reported that elevated HbA1c is associated with increased ICU admission rates and mortality, although these studies often focused predominantly on patients with established diabetes (12). Our findings extend this understanding by demonstrating that individuals without known diabetes but with elevated HbA1c also experience disproportionately severe disease, underscoring the importance of unrecognized chronic hyperglycemia as an independent risk factor. This aligns with emerging literature showing that undiagnosed diabetes and prediabetes significantly modulate COVID-19 outcomes, a trend particularly relevant in South Asian populations where the prevalence of unrecognized dysglycemia is high (13). However, unlike some studies that identified age and hypertension as strong predictors of severity, our adjusted analysis did not find these variables to be independently significant, possibly reflecting the relatively smaller sample size or differences in case mix and clinical management within our cohort.

The mechanistic pathways linking elevated HbA1c to severe COVID-19 offer several theoretical insights. Chronic hyperglycemia impairs neutrophil function, reduces complement activation, alters cytokine signaling, and promotes endothelial injury, thereby facilitating viral replication and exacerbating inflammatory lung injury (14). Glycation of key immune proteins may also blunt antiviral responses, while chronic oxidative stress within microvascular beds may predispose patients to the thromboinflammatory complications characteristic of advanced COVID-19. Clinically, these mechanisms highlight HbA1c as more than a metabolic marker—positioning it as a surrogate for underlying immune vulnerability and vascular fragility.

This study has notable strengths, including systematic data collection, validated laboratory assessments, and a multivariable analytical approach that accounted for key confounders. However, several limitations should be addressed. The sample size of 70 patients may limit statistical power, particularly for mortality comparisons, and the single-center design may restrict generalizability to broader populations with varying sociodemographic and clinical characteristics. The cross-sectional nature of the study precludes causal inference, and disease management practices, such as timing and type of antiviral or corticosteroid therapy, may have influenced clinical outcomes. Additionally, reliance on admission HbA1c does not account for potential alterations in glycation dynamics during acute illness, although HbA1c is widely considered stable in the context of short-term physiological stress.

Future research should incorporate larger, multicenter cohorts to validate these findings and explore whether HbA1c thresholds can be integrated into early triage tools for hospitalized COVID-19 patients. Longitudinal studies assessing glycemic variability, acute glucose control, and outcomes may further clarify the interaction between chronic and acute hyperglycemia in COVID-19 pathophysiology. Moreover, interventional trials evaluating whether targeted glycemic optimization improves outcomes in patients with elevated HbA1c may have important implications for both pandemic preparedness and routine inpatient care. Overall, this study adds to the growing body of evidence demonstrating that elevated HbA1c is a significant and independent predictor of COVID-19 severity, underscoring the importance of early metabolic assessment in optimizing clinical outcomes (15).

## CONCLUSION

This study demonstrates that elevated HbA1c levels are strongly associated with increased clinical severity among hospitalized COVID-19 patients at the University of Lahore Teaching Hospital, aligning with the study's objective and title by confirming chronic dysglycemia as an independent predictor of adverse outcomes. Patients with HbA1c $\geq$ 7.0% experienced significantly higher rates of severe or critical disease, ICU admission, mechanical ventilation, and mortality, underscoring the importance of assessing long-term glycemic status upon admission. These findings highlight the critical role of metabolic health in shaping COVID-19 trajectories and support the integration of HbA1c measurement into early risk stratification and clinical decision-making. From a public health perspective, improving chronic glycemic control may reduce the burden of severe respiratory infections, while future research should explore interventional strategies targeting dysglycemia to mitigate COVID-19–related morbidity and mortality.

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