

Unmasking of Pre-Existent Hyperglycemia and its Association with Ventilation in COVID-19 Patients: Experience at a Tertiary Care Hospital

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ABSTRACT

Objective: To determine the relationship between pre-existent hyperglycemia among patients with COVID-19 pneumonia requiring oxygen supplementation.

Study Design: Cross-sectional study

Place and Duration of Study: COVID-19 isolation wards, High Dependency Units, and Intensive Care Units of Mayo Hospital Lahore Pakistan, from Apr to May 2021.

Methodology: Eighty-one patients with hyperglycemia but without a prior diagnosis of diabetes mellitus were selected for this study. The data was collected from COVID PCR positive patients admitted to the isolation ward and intensive care unit at Mayo Hospital, Lahore. All the patients admitted during a 2-month duration from April to May 2021.

Results: A Total of 81 patients were included, of which 54(66.7%) were males. On the basis of HbA1c, 68(84%), 12(14.8%) and 1 (1.2%) patient(s) were diagnosed diabetic, pre-diabetic and non-diabetic respectively. Of the four patients requiring mechanical ventilation, 3(75%) were diabetic, and 1(25%) was pre-diabetic. Of patients who required non-invasive ventilation, 68(84.4%), 12(14.2%) and 1(1.3%) were diabetic, pre-diabetic and non-diabetic, respectively.

Conclusion: There is a significant burden of undiagnosed diabetes mellitus and pre-diabetes among patients with severe COVID-19 who require oxygen supplementation or admission to high-dependency units. Therefore, all patients should undergo thorough testing to exclude underlying diabetes mellitus.

Keywords: COVID-19, Diabetes, HbA1c, Hyperglycemia, Oxygen, Ventilation.

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INTRODUCTION

Diabetes mellitus is a major comorbidity in COVID-19 patients. Hyperglycemia in COVID-19, a global pandemic with 89 million cases worldwide, is associated with increased risk of intensive care unit (ICU) admissions and mortality.^{1,2} High blood glucose level at admission has been associated with increased risk of oxygen requirement, ARDS, invasive ventilation and poor outcome.³ In a study conducted in China, hyperglycemia associated with COVID-19 infection is significantly higher than stress-induced hyperglycemia in other critical illnesses.⁴ Severe metabolic complications, ketosis and hyperosmolar state associated with new-onset diabetes may further contribute to poor prognosis in COVID-19 patients.^{5,6}

In resource-limited countries with over-whelmed health care systems such as Pakistan, lack of effective screening programs and general social and public health neglect for non-communicable diseases like diabetes mellitus may lead to under-estimation of the actual burden of the disease.⁷ In the context of COVID-19,

this may lead to increased hospitalizations, thus overburdening the already fragile infrastructure of critical care. On the other hand, immediate screening for hyperglycemia and diabetes in patients admitted for other clinical conditions like COVID-19 may unmask already existing diabetes and pre-diabetes and help improve management and prognosis.^{8,9}

The rationale of this study was to find the frequency of pre-existent hyperglycemia in COVID-19 patients and its association with the severity of the disease in terms of oxygen requirement and different ventilation modes. By ascertaining this frequency, the study would help physicians adopt the clinical practice of immediate screening for diabetes mellitus, if not already diagnosed, in patients with COVID-19 to devise timely management and assessment for admission and critical care.

METHODOLOGY

The cross-sectional study was conducted at the COVID-19 Isolation Wards, High-Dependency Units, and Intensive Care Units of Mayo Hospital, Lahore Pakistan, from April to May 2021. All the patients admitted during the 2-month duration were taken as a population of the study. The approval for the study

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was obtained from the Institutional Review Board of King Edward Medical University / Mayo Hospital, Lahore (No 206 /RC/KEMU, dated 01st March 2021). The sample size was calculated taking, prevalence of diabetic patients who need to be taken to the ICU, as 4.1%.⁴

Inclusion Criteria: Patients of gender, above 18 years of age, presented with hyperglycemia (fasting blood sugar level more than 126 mg/dl or 2-hour post-prandial blood sugar more than 200 mg/dl on venous blood samples) and infected with COVID 19 as detected by Polymerase Chain Reaction on a nasopharyngeal swab.

Exclusion Criteria: Patients with previously diagnosed diabetes were excluded from the study.

A total of 81 patients fulfilling the inclusion criteria were included. Informed consent was taken before enrollment. Blood samples were taken from patients for blood sugar levels starting at the presentation time to fulfil one of the two diagnostic criteria stated above. Similarly, blood sampling for HbA1c was done within 48 hours of admission. Data was collected in a proforma containing name, age, gender, COVID category, blood sugar levels, HbA1c level, family history of diabetes, oxygen requirement, and required ventilation mode.

All results were analyzed using the Statistical Package for Social Sciences (SPSS) version 20. Quantitative variables like age were calculated as mean and standard deviation. Qualitative variables like gender were presented as frequency and percentages. The Chi-square test was applied by taking a *p*-value ≤ 0.05 as significant.

RESULTS

A total of eighty-one (81) patients were selected for this study. The mean age of patients was 54.64±12 years. The proportion of male participants was two-thirds. The remaining one-third were female patients. The glyceamic status using HbA1c is given in Table-I.

Table-I: Demographic and Diabetes Status of the patients (n=81)

Variables	n (%)
Gender	
Male	54(66.7%)
Female	27(33.3%)
Glycemic Status	
Diabetics (HbA1c≥ 6.5 %)	68(83.9%)
Pre-diabetics (HbA1c 5.7-6.4%)	12(14.8%)
Non- diabetic (HbA1c <5.7%)	01(1.2)

About 13(16.1%) patients were either pre-diabetic or non-diabetic. Family history of diabetes was positive in 39(48.1%) patients whereas 42(51.9%) patients do not have any past family history of diabetes (*p*-value=0.25). Diabetes in COVID-19 patients did not show any significant association with a specific mode of ventilation (*p*-value=0.82). However, all needed high dependency and ICU admissions requiring oxygen and non-invasive or invasive ventilation (Table-II).

Table II: Association of Various Demographic Factors with Diabetes Status (n=81)

Variables	Glycemic Status			p-value
	Diabetic	Pre diabetic	Non diabetic	
Family History				
Positive	31(45.4%)	08(67%)	0(0%)	0.25
Negative	37(54.5%)	04(33%)	01(100%)	
Ventilation				
Non-invasive	65(95.6%)	11(91.7%)	01(100%)	0.82
Invasive	03(4.4%)	01(8.3%)	0(0%)	

DISCUSSION

Diabetes mellitus is one of the leading causes of morbidity and mortality worldwide and negatively impacts infectious disease outcomes and mortality. However, direct evidence in settings of COVID-19 infection has only been reported in case reports.^{10,11} Therefore, it is still unknown whether diabetes can increase the risk of COVID-19 infection or vice versa. Further studies need to be elucidated. Liu et al. in their study noted that hyperglycemia and a history of diabetes at presentation predicted poor clinical outcomes.¹² The current study also observed similar findings related to hyperglycemia. However, the previous diabetic status was unknown, probably due to a lack of knowledge and prior screening of blood sugar levels in these patients.

Wang *et al.* interpreted that blood sugar testing and control are important for all COVID-19 patients even if there is no history of pre-existing diabetes, as most COVID-19 patients are prone to have impaired glucose levels.¹³ In addition, our study revealed a significant burden of undiagnosed diabetes and pre-diabetes in patients with severe COVID-19 disease who required oxygen supplementation or ICU admission. The authors thus concur with the previous studies that timely screening for diabetes in patients with COVID-19 should be prioritized.

Impaired fasting glucose at admission is also associated with adverse outcomes, as Zhang et al. stated in their multicenter retrospective cohort study.¹⁴

In our study, 14.8% of patients were diagnosed with pre-diabetes and of the total patients who required NIV and mechanical ventilation, 14.3% and 25% had pre-diabetes, respectively. This further highlights the need for establishing the glycemic status of the patient at the very outset of the diagnosis.

Sathish *et al.* stated in their study that the COVID-19 virus may cause new-onset diabetes mellitus or unmask pre-existing undiagnosed diabetes mellitus by injuring β -cells of the pancreas directly or interfering with the signalling pathways of insulin or by activating the renin-angiotensin system in the body. Newly diagnosed diabetes mellitus may also result from increased counter regulatory hormones (e.g., cortisol) and cytokines in response to the stress associated with severe illness or treatment with steroids.¹⁵ While 84% of patients in our study were found to have pre-existent diabetes, as per the results of HbA1c, only one had new onset hyperglycemia without prior history of diabetes. The study is thus inconclusive in determining the association of COVID-19 with new-onset diabetes due to a higher percentage of patients with pre-existing diabetes.

Several previous studies have determined that COVID-19 patients with newly diagnosed diabetes tend to develop a complicated clinical course; diabetes was associated with an increased risk of all-cause mortality.¹⁶⁻¹⁸ Our study provides insight into the severity of disease in terms of oxygenation and ventilation requirements of such patients. All patients with newly diagnosed diabetes required ventilation, of which 95.6% required NIV and 4.4% required mechanical ventilation. Similarly, 91.7% and 8.3% of patients with pre-diabetes required NIV and mechanical ventilation, respectively. While there was no significant association between modes of ventilation and glycaemic status, 84.4% and 75% of patients requiring NIV and mechanical ventilation were diagnosed with underlying diabetes mellitus.

LIMITATIONS OF STUDY

The limitations of this study were the small sample size, unknown prior diabetes status and lack of control groups. As a result, the study could not ascertain the association of undiagnosed diabetes with overall mortality or establish a correlation between COVID-19 infections with new-onset diabetes.

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CONCLUSION

This study concludes that there is a significant burden of undiagnosed and “hidden” diabetes mellitus and pre-diabetes among patients with severe COVID-19 who require oxygen supplementation or admission to high-dependency units. Given that impaired glycemic control is associated with increased mortality, all such patients should undergo thorough testing to exclude underlying diabetes mellitus at the very outset of diagnosis and admission. The unmasking of diabetes in such patients may eventually help improve management and outcomes, but further studies should be conducted to elucidate the outcome benefits of this practice. We also recommend that, in general, screening programs for diabetes be formulated for early recognition in patients of COVID-19, even with non-critical illnesses.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

WA & UM: Conception, study design, drafting the manuscript, approval of the final version to be published.

KW & UK: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

WA & AF: Critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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