Original Article

Association of hyperglycaemia at admission with in-hospital mortality and severity of illness among patients with COVID-19

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Abstract

Objective: The association between hyperglycaemia at admission and COVID-19 severity and in-hospital mortality is an area of active medical research. Our study aims to explore this association across diabetics and hyperglycaemic patients while keeping normoglycemic patients as control.

Materials and Methods: This retrospective cohort study involved a total of 90 patients with confirmed diagnosis of COVID-19 infection. Patients were divided into three equal groups based on their history and BSR levels (diabetics, hyperglycaemic, normoglycemic). Various laboratory parameters and inflammatory markers were compared across the study groups using Kruskal Wallis test. Finally, chi-square test was use to assess the association of severity and mortality across the study groups.

Results: Out of 90 patients, 38 (42.2%) were males versus 52 (57.8%) females. The mean age of all patients was 57.1 ± 14.7 years. Serum ferritin, LDH and lymphocyte levels were significantly higher in diabetics and hyperglycaemic patients than in normoglycemic COVID-19 patients ($p<0.05$). hyperglycaemia at admission was significantly associated with disease severity ($p=0.03$) but not with in-hospital morality ($p=0.07$).

Conclusion: Patients with diabetes and isolated stress hyperglycaemia have increased levels of inflammatory markers than normoglycemic patients. Hyperglycaemia at admission is associated with severe COVID-19 infection. More studies a required to validate and further explore this relationship. It has multiple advantages although its not without side effect, if not used appropriately and with caution.

Keywords: Hyperglycaemia, COVID-19.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus COVID-19 that has caused havoc around the world.[1] The disease first emerged in Wuhan city of China that quickly escalated to a pandemic due to its rapid transmissibility via droplets and increasing infectivity.[2] Young healthy patients having no comorbidities usually develop mild symptoms of COVID-19 or may remain asymptomatic.[3] On the contrary cytokine storm in severe COVID- 19 infection leads to fatal disease complications especially in old age patients with multiple co-morbid conditions.[4] These complications include acute respiratory distress syndrome, septic shock, vascular thrombosis, and multi-organ failure due to cytokine storm.[5]

Diabetes mellitus (DM) is an extremely common comorbid condition found among COVID-19 patients which is present between 20-60% of the hospitalized patients.[6] Diabetes has been reported as an independent risk factor for hospital admissions and disease mortality in COVID-19.[7,8]. Moreover, chronic hyperglycemia in diabetics causes endothelial dysfunction by exerting oxidative stress that leads to detrimental disease outcomes especially in COVID-19.[9] It has been illustrated that SARS-CoV-2 not only causes hyperglycemia in a diabetic patient, but even non-diabetic patients suffer from stress-induced hyperglycemia during the acute phase of the COVID-19 illness[9]. SARS-CoV-2 is also involved in directly infecting pancreatic beta cells resulting in beta cell dysfunction and insulin deficiency which causes hyperglycemia in a non-diabetic patient as well[10]. This isolated stress hyperglycemia (in non-diabetic patients) at hospital admission has been reported as a poor marker of disease severity which leads to abysmal outcomes in acute respiratory distress causing diseases.[6,11] The possible explanation is the alteration of the immune response due to an acute increase in inflammatory cytokine production that leads to immunosuppression along with activation of renin-angiotensin-aldosterone system.[5]

Both diabetes mellitus and isolated stress hyperglycemia can be regarded as a predictors of severity among patients suffering from COVID-19; however, literature also illustrates pre-infection low glucose levels as a predictor of severe prognosis in COVID-19[3,12]. Thus, slightly conflicting literature prompted us to find out a potential link between the glucose levels at admission with disease severity, hospital stay, and in-hospital mortality among patients with acute COVID-19 illness.

Materials and Methods

This retrospective cohort study was conducted in Department of Medicine, Benazir Bhutto Hospital, Rawalpindi, Pakistan. The study was ethically approved from the institutional review board (IRB). The study involved a total of 90 patients with a reverse transcription polymerase chain reaction (RT-PCR)-confirmed COVID-19 infection on a background history of clinical symptoms and radiological findings suggestive of mild to severe COVID-19. Sample size was calculated using the WHO sample size calculator. The determination of extent of severity was based on National Institute of Health COVID 19 disease Severity Criteria.[13] The criteria for disease severity is shown in Table 1.

Table 1: Criteria for COVID-19 disease severity as proposed by National Institute of Health

Asymptomatic	*Positive COVID 19 test results with no symptoms*
Mild	Cold symptoms, flu like illness, no lower respiratory tract findings
Moderate	Lower respiratory tract illness (dyspnea, crackles, CXR infiltrates) with SpO2 more than 94 %
Severe	SpO2<94%, oxygen requirement, Respiratory Rate > 30/min, CXR > 50% infiltrates
Critical	Respiratory failure, need for mechanical ventilation or high flow nasal canula, MOD.

Based on the basal sugar levels (BSR) at admission, patients were divided into three equal groups i.e., diabetic group, isolated hyperglycemia group (with no history of diabetes and BSR ≥ 140), and normoglycemic group (BSR < 140). Assessment of diabetic patients were made based on their history and consistently high Hba1c levels. Patients of pediatric age group and with diabetes type 1 were excluded from the study. Moreover, patients on self-medication with steroids were also excluded as they cause hyperglycemia. Clinical and laboratory data of all patients were obtained with 36 hours after admission. Stratified random sampling was used in which equal number of diabetic, isolated stress hyperglycemics,

and normoglycemic patients were included in the study (30 patients in each group).

Categorical variables including gender, comorbidities, outcome, and disease severity were expressed as frequency and percentages. Continuous variables including age, duration of hospital stay, SpO_2 levels, along with various laboratory investigations including BSR levels, serum LDH, ALT, AST, leukocyte count, and ferritin levels were expressed as median and IQR. Median values of laboratory parameters were compared across the study groups using Kruskal-Wallis test. Thereafter, association between the hyperglycemia at admission (diabetics, hyperglycemic, normoglycemic), disease severity (mild, severe, critical), and outcomes (dead or expired) were assessed using chi-square test. A p-value of < 0.05 was considered as statistically significant.

Results

In the present study analyzing data from 90 patients, 38 (42.2%) were males. The mean age of the participants was 57.1 ± 14.7 years. The baseline characteristics of the study participants are shown in Table 2.

Table 2: Baseline characteristics of the study participants

Parameters		*Frequency*	*Percentages*
Gender	Males	38	42.2%
	Females	52	57.8%
Smoking Status	Smokers	37	41.1%
	Non-smokers	53	58.9%
Age Groups (years)	≤40	13	14.4%
	41-60	39	43.3%
	>60	38	42.2%
Comorbidities	Hypertension	32	35.6%
	Ischemic heart disease	17	18.9%
	COPD	14	15.5%
	CKD	11	12.2%
	Asthma	9	10%
	Tuberculosis	2	2.2%
	Stroke	4	4.4%
WHO Disease Severity	Mild	9	10%
	Severe	69	76.6%
	Critical	12	13.3%
Study group	Known Diabetics	30	33.3%
	Isolated hyperglycemia	30	33.3%
	Normoglycemic patients	30	33.3%
Outcome	Dead	29	32.2%
	Alive/Discharged	61	67.8%

There was a significant difference in median ferritin levels (p=0.001) and median time of hospital stay (p=0.015). Comparison of various other laboratory parameters is elucidated in Table 3.

Table 3: Comparison of various laboratory parameters and hospital stay across the study groups

Parameters	*Diabetic group*	*Isolated stress Hyperglycemia*	*Normal patients*	*p-value*
SpO2 at admission (%)	92.5 (72-98)	93 (70-98)	92 (75-97)	0.608
Serum Creatinine (mg/dl)	1.0 (0.5-7.3)	0.95 (0.5-2.90)	0.9 (0.4-12)	0.254
Alanine Transaminase levels (U/L)	37 (12-177)	44 (12-126)	29 (12-561)	0.328
Aspartate transaminase levels (U/L)	49 (13-230)	57 (15-120)	41 (23-580)	0.313
Total leukocyte count (cells/mm^3)	11.95 (6.6-38)	11 (4.8-22)	10.5 (5.6-28)	0.324
Neutrophil count (cells/mm^3)	83.5 (44-94)	80.5 (56-91)	81 (47-95)	0.456
Lymphocyte count (cells/mm^3)	7.2 (0.6-19.6)	11 (2.1-20)	9 (1.2-41)	**0.018**
Serum LDH levels (U/L)	706 (500-2486)	832 (277-1820)	620 (171-2088)	**0.04**
Serum Ferritin (ug/L)	729 (210-1500)	400 (35-1072)	369 (240-1500)	**0.001**
Hospital stay (days)	12.5 (2-53)	7 (2-28)	6 (1-42)	**0.015**

Chi-square test showed a significant association between the severity of COVID-19 and hyperglycemia at admission. This association is shown in Table 4.

Table 4: Chi-square test showing association between hyperglycemia at admission and severity of COVID-19

Parameters		*Severity at admission*			*P-value*
		Mild	Severe	Critical	
Group	Diabetics	1	22	7	
	Hyperglycemia	1	26	4	0.03
	Normal	8	21	1	

On the contrary, there was no significant association between in-hospital mortality and hyperglycemia at admission. This is delineated in Table 5.

Table 5: Chi-square test showing association between hyperglycemia at admission and in-hospital mortality

Parameters		*Outcome*		*P-value*
		Alive	Dead	
Group	Diabetics	18	12	
	Hyperglycemia	24	6	0.07
	Normal	19	11	

Discussion

The rapid spread of COVID-19 illness across the globe reaching pandemic proportion, caused it to be declared as a public health emergency of international concern by World Health Organization. The clinical spectrum of COVID-19 ranges between asymptomatic to a severely critical illness. Severe form of illness is commonly seen in patients who are elderly of suffering from comorbidities such as diabetes, hypertension and obesity.

Our study shows that most of the diabetic population who suffered from COVID-19 illness were elderly females. Considerable amount of these patients was suffering from other comorbidities such as hypertension, obesity, asthma, and ischemic heart disease. A study conducted in Hunan, China reported a similar finding where most of the diabetic patients were elderly and suffering from other medical illnesses[14].

Moreover, various other parameters were compared among patients who are diabetic or have isolated hyperglycemia to the patients with normoglycemic profile. No significant difference was observed among SpO_2 levels, serum creatinine, alanine transaminase levels (ALT), aspartate transaminase levels (AST) as well as among total leukocytes and neutrophil count. Another study reported a similar finding where no significant difference was observed in creatinine, ALT, and AST levels across diabetics and non-diabetics.[3] Contrarily, a meta-analysis reports significantly increased levels of above mentioned parameters and evidence of liver injury in COVID-19 patients with multiple comorbid conditions.[15]

On the other hand, inflammatory markers such as lymphocyte count, serum ferritin and serum Lactate dehydrogenase levels were found to be significantly raised among diabetic and isolated hyperglycemia group versus normoglycemic patients. Multiple studies also show similar results.[6,16] However, another study done in Saudi Arabia reported moderately different results, where only ferritin was found to be

significantly elevated among diabetic COVID-19 patients, other inflammatory markers showed non-significant change ($p>0.05$).[4]

The inflammatory markers play a significant role during the course of COVID-19 illness. The isolated stress hyperglycemia assists in viral proliferation in COVID-19 patients by production of mitochondrial reactive oxygen species and thereby, activation of hypoxia inducible factor.[17] Rapid proliferation of SARS-CoV-2 activates innate inflammatory response causing cell death which recruits macrophages and lymphocytes. These immune cells release cytokines and chemokines that further enhance the inflammatory response. This leads to cytokine storm and overexuberant systemic illness that leads to multiorgan failure[18]. All these factors delineate the pathogenesis behind the exaggerated disease severity among patients with hyperglycemia

Another parameter which we evaluated to assess morbidity and mortality was hospital stay of COVID-19 patients. The hospital stay was found to be longer in patients with diabetes and isolated hyperglycemia as opposed to normoglycemic group. Several studies come to terms with this finding[10,11,19]. Longer hospital stay is directly related to increased risk of nosocomial infection, deep venous thrombosis and psychiatric illnesses among patients[20]. Moreover, it consumes medical resources and results in scarcity of vacant beds for patients who requires medical care[21].

Finally, yet importantly, we evaluated the association of hyperglycemia to COVID-19 severity and mortality. Our study proved that hyperglycemia is significantly associated with poor disease severity in hyperglycemic and diabetic patients than normoglycemic patients. These results are also comparable to the studies previously done[2,14]. Conversely, it was found that in-hospital mortality was not significantly associated with hyperglycemia at admission. However, literature proves otherwise showing a high correlation of mortality to hyperglycemia among COVID-19 patients[11,14].

Our study has many limitations, such as being a retrospective study hindered us from inferring any causality associated with the results. Another potential limitation is being a single-centered study with limited study population. However, our study resolutely reinforces the notion of hyperglycemia at admission having a strong association with disease severity among COVID-19 patients.

Conclusion

Patients with diabetes and isolated stress hyperglycemia have increased levels of inflammatory markers (including LDH, ferritin, and lymphocyte levels) than normoglycemic patients. Hyperglycemia at admission is significantly associated with poor COVID-19 severity but has no significant association with disease mortality. Further prospective cohort studies with appropriate randomization will aid in yielding a more accurate association between the COVID-19 severity and diabetes.

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