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Original Research Article.

Impact of Acute Glycemic Variability on Outcome of COVID-19 Associated Acute Respiratory Distress Syndrome

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ABSTRACT

Introduction: Diabetes mellitus has been associated with adverse outcomes in patients with novel coronavirus disease (COVID-19). Hyperglycemia worsens the outcome by the process of cytokine storm, endothelial dysfunction and multiple organ injuries. We aimed to assess the impact of admission hypoglycemia and glycemic variability in COVID related acute respiratory distress syndrome.

Methods: It was a retrospective study conducted from February 2021 to July 2021 at Guru Gobind Singh Medical College, Faridkot. All adult patients with SARS-Cov-2 infection and COVID-related ARDS were included.

Results: Non survivors were older and had more associated comorbidities like diabetes, hypertension, thyroid disease etc.

Conclusion: Patients with diabetes and COVID-19 have an increased risk of adverse outcomes with glucose levels <70 mg/dl and >200 mg/dl. Measures to curb glycemic fluctuations could be supported by continuous blood glucose monitoring.

Keywords: Blood Glucose, COVID-19, Hypoglycemia, Hyperglycemia, Mortality, Prognosis.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the single-stranded, enveloped RNA virus which led to the pandemic in recent times has evolved into various strains and manifested as fever, cough, respiratory difficulty, and a myriad of other symptoms.[1,2] Various studies have reported that approximately one-half of patients with coronavirus disease 2019 (COVID-19) had comorbidities, of which diabetes is the second most common.[3,4] This becomes significant as India hosts the second largest population of 73 million diabetic patients after China.[5] COVID-19 and diabetes, both associated with acute and chronic inflammation, can impact each other in terms of clinical progression and outcome.[6]

Glycemic variability has been recognized as a strong independent predictor of mortality among critically ill patients.[7,8] Hyperglycemia worsens the outcome by the process of cytokine storm, apart from the endothelial dysfunction and multiple organ injuries.[9] Interestingly hypoglycemia could also represent a trigger mechanism for cytokine storm during the COVID-19 illness. This study was planned to assess the prognostic role of hyperglycemia in COVID19 patients with or without previously known diabetes and various degrees of disease severity.

AIM

To study the blood glucose variability in COVID19 patients and its association with clinical outcomes.

METHODS

This retrospective study was conducted at the Department of Medicine, Guru Gobind Singh Medical College and Hospital, Faridkot, a tertiary care center. All adult patients (>18yrs) of covid19 admitted to our hospital over a period of 6 months from February 2021 to July 2021 were included in the study.

Inclusion Criteria

Adult patients aged >18 years admitted to the hospital.

All confirmed SARS-CoV-2 cases (RT-PCR) in swab or sputum with definite outcome discharge or death with associated acute respiratory distress syndrome.

Data collection: For each patient the following clinical variables were recorded in a dedicated database: age, gender, comorbidities like previously known diabetes, hypertension, coronary artery disease, chronic lung disease or chronic renal disease. Charlson comorbidity index (CCI) was calculated for each patient based on the history. On hospital admission C-

reactive protein (CRP mg/dl), lactate dehydrogenase (LDH, IU/L), serum creatinine(mg/dl), D-dimer (ng/dl) were measured.

Baseline blood sugar readings were recorded on admission, and glucose values were measured three times a day. The peak glucose was determined among all the values measured during hospital stay. Glucose values for the first 24hr, 48hr were recorded to calculate other parameters.

1. Mean blood glucose (Mean BG) level as arithmetic means of all recorded glucose values for each patient on consecutive 3 days (Mean BG 24, Mean BG 48)
2. Standard deviation (SD) of mean glucose levels for three consecutive days (SD 24, SD 48)
3. Coefficient of variation (CV) of glucose.

The primary endpoint for analysis was in -hospital mortality.

RESULTS

We studied a population of 111 adult patients with COVID-related acute respiratory distress syndrome. Out of this 68 were survivors (61%) and 43 succumbed to the illness (38.7%). The study population included male population of about 60.4% with various comorbidities with maximum being diabetes mellitus (38.7%), followed by hypertension (23.4%) and obesity (12.6%). Chronic kidney disease and coronary artery disease constituted 8.1% and 4.5% of the study population. Interestingly, we reported about 12 cases of Mucormycosis in the study (10.8%). In comparison between survivors and non survivors (table 1), non survivors were in older age groups (p value) with overall more comorbidities as indicated by Charlson Comorbidity Index (CCI) (2.2±1.7). Severe Covid illness was reported in 43 patients (38.73%). We also reported higher values of inflammatory markers in the non-survivor group, with C-reactive protein (mean-142+-88 mg/dl), lactic dehydrogenase LDH (740±627UI/L) and D-dimer (1429±1041). Higher values for serum creatinine (mean 1.6± 1.6mg/dl) were observed in the non-survivors group.

Glucose values and glucose variability was noted as depicted in table 2 and table 3 in the overall population and the comparison between survivors and non-survivors. Glycemia at admission was noted with 62 patients presenting with hypoglycemia (RBS <70 mg/dl), while 26 patients with normal glycemic control and rest with hyperglycemia (RBS >200 mg/dl).

However, admission glycemia (mg/dl) was more in survivors and mean blood glucose values, both at 24 hours and 48 hours were more in survivors. HbA1c could be investigated in about 40 patients with 30 patients (75%) having HbA1c > 6.5%. Out of the 111 patients, 13 had presented with diabetic ketoacidosis and 11 patients survived. About 16 patients (14.41%) with no previous history of diabetes mellitus reported with blood glucose >200 mg/dl.

Table 1: Comparison of clinical characteristics of survivor's vs non-survivors

		Survivors		Non-survivors		Total		P value
Number		68	61.3%	43	38.7%	111	100%	-
Age (Mean±SD)		52.32±12.62		54.74±13.69		53.26±13.03		0.176
Sex M/F		1.27	55.9%	2.07	67.4%	1.52	60.4%	-
Comorbidities	**All**	41	60.3%	32	74.4%	73	65.8%	-
	Diabetes Mellitus	23	33.8%	20	46.5%	43	38.7%	-
	Hypertension	15	22.1%	11	25.6%	26	23.4%	-
	Obesity	7	10.3%	7	16.3%	14	12.6%	-
	Hypothyroid	2	2.9%	3	7.0%	5	4.5%	-
	COPD	2	2.9%	1	2.3%	3	2.7%	-
	Chronic Kidney Ds	2	2.9%	7	16.3%	9	8.1%	-
	Coronary Artery Ds	2	2.9%	3	7.0%	5	4.5%	-
	Mucormycosis	8	11.8%	4	9.3%	12	10.8%	-
	Charlson index	1.6±1.4		2.2±1.7		1.8±1.5		0.035
Lab Indices	**C-RP**	112±78		142±88		123±83		0.035
		CV69.7		CV62.1		CV67.2		
	LDH	635±275		740±627		675±446		0.152
		CV43.3		CV84.4		CV66.0		
	D-Dimer	911±622		1429±1041		1112±845		0.002
		CV68.3		CV72.8		CV76.0		
	S. Creatinine	1.0±0.5		1.6±1.6		1.2±1.1		0.014
		CV50.2		CV100.1		CV89.6		
	RBS	212±117		192±102		204±112		0.476
		CV55.26		CV53.2		CV54.7		

Table 2: Glucose Values in Survivors and non- survivors

Glucose variability	Survivors	Non-survivors
<70	34	28
70-159	15	11
200-300	15	4
>300	4	0

Table 3: Glycemic variability in survivors vs non- survivors

	Survivors	Non-survivors	p
No. of patients	68	43	-
Hypoglycemia <70	34	28	-
Glycemia at admission	215±124	187±104	0.089
	CV64.3	CV60.8	
Mean 24mg/dl	220±142	187±114	0.103
	CV49.3	CV51.1	
Mean 48mg/dl	212±117	192±102	0.476
	CV50.1	CV48.4	
DKA	11	2	-
Mean variation	114	71	0.003

DISCUSSION

Our retrospective study among the COVID-19 patients and related ARDS revealed both episodes of hypoglycemia (<70 mg/dl) and hyperglycemia (>200 mg/dl). Episodes of hypoglycemia were documented in 28 non-survivors. Admission hyperglycemia, 220 and 187 mg/dl were seen in survivor and non-survivors' groups respectively. A significant association of admission mean glucose levels with adverse outcomes was not observed, possibly due to the fact that mean glucose levels do not provide information on the magnitude of hyperglycemia, hypoglycemia and glycemic variability.

In our survivor population, 22 patients had severe COVID-19, 33 had moderate COVID-19 and 3 developed mild COVID-19 illness. Hyperglycemia (>200 mg/dl) was evident in the survivor group with mean 24hrs glucose 220 mg/dl and hypoglycemia was detected in 34 patients. Eleven patients among survivors had presented with diabetic ketoacidosis. In a double center retrospective study, where 605 covid patients with no previous diabetes observed that admission hyperglycemia was an independent predictor for 28-day mortality.[10] Association between hyperglycemia and increased risk of death was confirmed in further studies performed in non-severe covid disease[11,12] and in non-diabetics.

Corticosteroids were used to treat the COVID-related ARDS as recommended by the various studies earlier and were reported to be associated with reduced mortality and lower need of mechanical ventilation.[14] Among our survivor population, about 55 patients had moderate and severe illness and responded well to treatment measures including dexamethasone, while 37 patients among non-survivors had moderate to severe disease. Apart from stress-induced rise in glucocorticoids[15], use of dexamethasone could explain the elevated mean 24 hours and 48 hours blood glucose in both the groups. Furthermore, SARS coronavirus 2 binds to the ACE2 receptors expressed on the surface of various tissues and cells, including pancreatic islets, causing pancreatic damage and inflammation leading to glycemic fluctuations.[16,17] This could well explain the patients with new onset diabetes in patients post inflammation secondary to COVID19 illness. Sixteen patients (14.4%) in our study population reported first ever episodes of hyperglycemia with blood glucose >200 mg/dl. Wang et al demonstrated 17% of patients in Wuhan developed pancreatic injury evidenced by abnormality in serum amylase or lipase levels.[18] Glycemic variability has been documented as a prognostic factor in diabetic patients with COVID-19 infection. Our survivor group had lesser variation in glucose as depicted by 64.3 CV in the first 24hrs, while the non survivors had greater glycemic variability (60.8) Hyperglycemia worsens the outcome by the process of cytokine storm, endothelial dysfunction, and multiorgan injuries.[9] In our study inflammatory markers like CRP (142±88), LDH (740±627) were elevated in non-survivor groups suggesting cytokine storm and poor prognosis. Endothelial dysfunction and prothrombotic state were evident by d-dimers (1429±1041) in the non-survivor group as compared to survivors (911±622). A study by Zhu et al showed that type 2 diabetic group had higher levels of inflammatory markers such as CRP and procalcitonin (57 and 33.3%) than the nondiabetic group (42 and 20.3%), respectively.[19] Similarly, D-dimer, which is a marker of coagulation status, was also elevated in the diabetic group compared to the nondiabetic group (50.5 vs 33.3%).[20] Our study revealed a significant number of patients in both survivor (n=34) and non-survivor (n=28) groups. Hypoglycemia induces upregulation of GLUT 3 glucose transporter in the plasma membrane of monocyte-macrophage and ensures adequate glucose supply to cells, further amplifying inflammation. Hypoglycemia also increases cardiovascular mortality by accentuating monocytes which are pro-inflammatory and enhancing platelet aggregation.[21] Besides representing a risk factor for cardiovascular mortality, it could represent a trigger mechanism for an impending cytokine storm.[22] Thus, both hypoglycemia and hyperglycemia could independently predict hospital mortality in critically sick individuals, irrespective of the severity of illness.

The drawback of our study was non availability of continuous blood glucose monitoring to document glycemic variability. Also, HbA1c could have helped in excluding previous hyperglycemia in patients presenting with first ever episodes of hyperglycemia. In conclusion, though higher glycemic variability is associated with poorer outcome of COVID-19, continuous glucose monitoring would help in better control of glycemic fluctuations and predicting prognosis.

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