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New Onset Hyperglycemia in Patients of COVID-19 in India

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Abstract

Objectives: This study aimed to evaluate manifestations of COVID-19 infection in patients of raised fasting blood glucose (FBG) level without pre-existing diabetes mellitus.

Methods: This study comparatively evaluate the difference between patients of raised FBG level and normal FBG level for COVID-19 manifestations by enrolling 2750 admitted COVID-19 patients. Patients were categorized into two Groups, where Group 1 had patients with raised FBG level (=126 mg/dL) and Group 2 had patients with normal FBG level (<126 mg/dL). Information regarding clinical symptoms, past medical history, laboratory feature, treatment and outcome was extracted from medical records to compare among both the Groups.

Results: COVID-19 patients with raised FBG level were found to be have severe symptomatic presentation, raised inflammatory markers and hypercoagulable state. Total white cell count, NLR (Neutrophil to Lymphocyte ratio), serum level of IL-6 (Interleukin-6), FDP and D-dimer were found to be significantly higher ($p<0.05$) in case of raised FBG level as compared to normal FBG level. Radiological findings detected by chest radiograph and computed tomography chest suggested severe lung involvement in patients of raised FBG level. COVID-19 patients with raised FBG level required intensive supportive treatment as compared to patients of normal FBG level in terms of ICU care ($p=0.0033$), non-invasive ventilation ($p=0.0323$) and invasive ventilation ($p=0.0455$). Patients with raised FBG level had higher mortality ($p=0.0178$) and required prolonged hospitalization ($p=0.0008$) as compared to patients of normal FBG level.

Conclusion: FBG >126 mg/dL at admission without pre-existing diabetes mellitus, should be considered a risk factor for higher susceptibility of COVID-19 infection and severity by clinical presentation, inflammatory storm, pulmonary invasion, requirement of more intensive treatment and a poor outcome.

Keywords: COVID-19; Fasting blood glucose; Hyperglycemia; Management.

Introduction

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), was the pathogen behind Corona virus disease (COVID-19) that emerged from Wuhan in China and was rapidly spread across most of the nation's worldwide. The disease presentation may range from an asymptomatic state to a severe pneumonia associated with acute lung failure.[1] Patients of COVID-19 mostly presented with fever, cough, shortness of breath, fatigue, loss of appetite, sputum production, joint pain, nausea, vomiting and diarrhea. Although, a large number of patients may not exhibit noticeable symptoms. Number of patients also suffer from severe or critical disease with lethal complications such as pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, septic shock, disseminated intravascular coagulation and ultimately leading to death.[2,3] The total number of confirmed COVID-19 cases worldwide have risen to 85,509,194 with 1,868,622 deaths as of 6th June 2020. India, a nation already been the diabetes capital of world has reported 10,395,938 cases of COVID-19 with 150,372 deaths.[4] Diabetes mellitus is an established risk factor for significantly elevated morbidity and mortality rates in a wide array of acute or chronic diseases, such as

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cardiovascular diseases, cerebrovascular diseases, cancer and infections due to poor glycemic control.[5-8] Angiotensin-converting enzyme 2 (ACE2) has been identified as a surface receptor responsible for SARS coronavirus (SARS-CoV) invasion in human cells with direct interaction with its spike glycoprotein (S protein).[9] Consequently, a dysregulated immune system in diabetes mellitus responsible for various infections in diabetic patients.[10] Anti-inflammatory effect of ACE2 is well known and its expression is reduced in patients of DM or hyperglycemic patients possibly due to glycosylation. This might explain the occurrence of a severe acute lung injury and ARDS in diabetic patients. A study published in New England Journal of Medicine showed that fasting hyperglycemia was strongly correlated with mortality in patients with or without diabetes.[8]

It is well documented that chronic hyperglycemic state was associated with impaired immunity and also trigger lower respiratory tract infection and poor prognosis.[7,11-13] Recently, a descriptive study suggested that diabetes and/or acute uncontrolled hyperglycemia (defined as blood glucose measurements >180 mg/dL twice within any 24 h period) were associated with an increased mortality and length of hospital stay in COVID-19.[14]

Furthermore, well controlled blood glucose (glycemic variability within 72-180 mmol/l) was reportedly associated with markedly lower mortality compared with individuals with poorly controlled blood glucose (>180 mg/dL) in patients of diabetes mellitus for COVID-19.[15] However, direct correlation between new onset hyperglycemia at admission and clinical outcomes of COVID-19 patients without diagnosed diabetes has not been well established. The present study was designed in this context to evaluate the association between raised fasting blood glucose level with progression and prognosis of COVID-19 in patients admitted to S.M.S. Medical College and attached hospitals, Jaipur, India. The study was also aimed to compare the clinical presentation, severity of disease, management and outcome in hyperglycemic and normoglycemic patients without pre-existing diabetes mellitus.

Material and Method

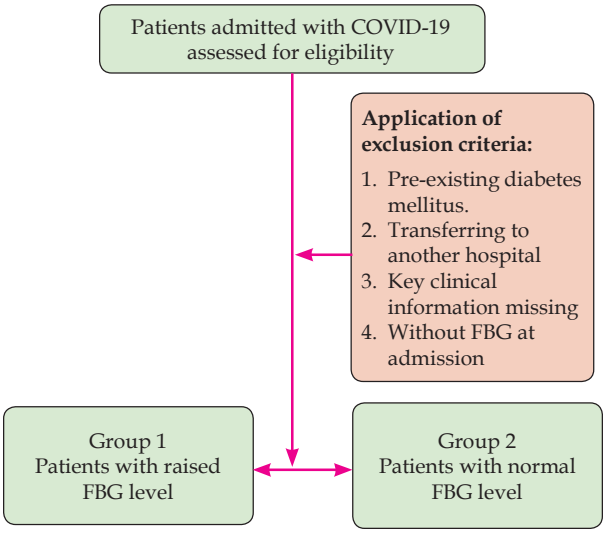
Study Design: This is retrospective observational study, conducted on 2750 COVID-19 positive patients, admitted at RUHS Hospital of S.M.S. Medical College, Jaipur, India from 1st October to 30th November 2020. This study was approved by the Institutional Ethics Committee. All COVID-19 positive patients screened for history of pre-existing diabetes mellitus. After exclusion of pre-existing diabetes mellitus, selected patients categorized into two Groups on the basis of fasting blood glucose level. Group 1 had patients with raised fasting blood sugar at hospitalization while Group 2 had normal fasting blood sugar level at hospitalization. Both of these Groups were matched for age, gender and absence of other comorbidities.

Data Collection: The diagnosis of COVID-19 was based on World Health Organization interim guidance; wherein confirmed cases were positive on reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swab specimens.[1] Patients admitted in given time period were segregated on the basis of previous history of diabetes mellitus. In this study, all non-diabetic patients having proper essential medical records, were selected for comparison. Selected patients tested for fasting blood glucose (FBG) after overnight fasting within 24 hours of hospitalization according to the WHO guidelines. Serum concentrations of FBG was measured by using an automatic biochemical analyzer (Beckman Coulter AU5800 Analyzer, USA). On the basis of fasting blood glucose level selected patients categorized into two Groups viz. patients had raised FBG level included in Group 1 while patients with normal FBG level were included in Group 2. Information regarding demographic data, chronic medical illness, clinical presentations, laboratory investigations, chest radiograph (CXR) findings, high-resolution computed tomography (HRCT) scans of chest, treatment and outcome was extracted from medical records of admitted patients. The laboratory findings were based upon hemogram, C-reactive protein (CRP), ferritin, fibrin degradation product (FDP), D-dimer and Interleukin-6 (IL-6). Radiological findings were inferred using average visual score from digital chest radiograph (CXR) (scored from 0 to 4 according to visual assessment of involved lung area) (16), CT severity score from HRCT chest (assigned out of 25 based upon percentage area involved in each of the 5 lobes) (17) and proportion of patients with CT severity scores >10/25. All patients received standard treatment, including antiviral therapy remdesivir in standard dose, respiratory support (nasal cannulation, mask oxygenation, high-flow nasal cannula oxygen therapy, non-invasive positive pressure ventilation or invasive mechanical ventilation), symptomatic and supportive treatment and antimicrobial therapy, as appropriate, to prevent or treat secondary infections, which was in accordance with the COVID-19 diagnosis and treatment

protocols released by the Indian council of medical research (ICMR). This retrospective project did not interfere with the course of medical management. Data regarding supportive treatment among both Groups by oxygen therapy, ICU care, non-invasive ventilation (NIV) and invasive ventilation was also collected. Outcome of COVID-19 infected patients was measured by the number of recovered patients; duration of hospital stays and number of deaths during the course of treatment. All collected data of study populations were compiled, interpreted and compared in both the Groups to establish differences in COVID-19 manifestations on the basis of FBG level. Most of COVID-19 patients were excluded because of following reason: (1) Patient's record of 28 days was not available; (2) At admission FBG not measured; (3) having previously diagnosed diabetes. The patient selection was mentioned in Fig. 1 by flow diagram.

Statistical analysis

The descriptive statistics for quantitative data was expressed as mean and standard deviation and qualitative data was expressed as proportions. The parameters were compared among different Groups using chi-square and z-score test for significant differences. The level of significance was assigned at a p-value less than 0.05.



Results

This study conducted on 2750 COVID-19 patients of without previous history of diabetes mellitus. In this study 910 patients (33.09%) had raised FBG level at admission whereas 1840 patients (66.91%) had normal FBG level during hospitalization. Hence, one third of COVID-19 patients presented with new onset hyperglycemia. The mean age of selected SARS-CoV-2 infected patients was 45.56 years (45.56 ± 14.74). Mean age of Group 1 with raised FBG was 46.32 years (46.32 ± 15.19), whereas mean age in Group 2 of normal FBG was 45.21 years (45.21 ± 14.23), and the difference was non-significant (p=0.060) (Table 1). This study includes1780 (64.72%) male patients and 970 (35.28%) female patients. There were no significant gender differences observed among both Groups (p=0.798).

Clinical presentation: Overall, 1550 patients (56.36%) had symptomatic presentation while remaining 43.64% patients have asymptomatic presentation. Patients who have raised FBG level exhibited a significantly greater (p<0.001)) symptomatic presentation as compared to patients who have normal FBG level (63.73% patients of Group 1 and 52.72% patients of Group 2). In our study selected patients of COVID-19 mostly presented with fever (27.78%), cough (27.20%), sore throat (22.69%), shortness of breath (21.53%), headache (20.36%), chest pain (5.387%) and other symptoms (10.18%) like pain abdomen, vomiting, diarrhea, altered sensorium, loss of taste, loss of smell. Fever (31.64% in Group 1 v/s 25.86 in Group 2), cough (29.46% in Group 1 v/s 26.08% in Group 2) and shortness of breath (26.38% in Group 1 v/s 19.14% in Group 2) were found more often (p<0.05) in patients of raised FBG level compared to Group of normal FBG level with p-value 0.001, 0.061 and <0.001 respectively.

Laboratory findings: The observed laboratory parameters were as follows: average total leukocyte count 6.62 x 109/L ± 2.91, platelet count 2.18 Lac/µl ± 0.84, neutrophil/lymphocyte (N/L) ratio 3.06 ± 1.47, C-reactive protein 6.10 mg/L ± 3.80, ferritin 361.94 ng/mL ± 202.18, fibrin degradation product 25.45 µg/L ± 22.88, D-dimer 4.05 µg/L ± 5.12 and interleukin-6 37.89pg/mL ± 63.08. The mean values of laboratory parameters among Group 1 and Group 2 were as follow: total leukocyte count 7.04 v/s 6.34x109 (p<0.001), N/L ratio 3.15 v/s 2.98 (p=0.0067), C-reactive protein 6.45 v/s 5.84 mg/L (p=0.0001), ferritin 381.56 v/s 350.43 ng/mL (p=0.0001), D-dimer 4.56µg/L v/s 3.72µg/L (p=0.0001), IL-6 levels 44.23pg/mL v/s 35.39pg/mL (p =0.0005). All the above parameters were significantly higher in patients with raised FBG level as compared to patients of normal FBG level, except the platelet counts and FDP.

Severity of disease: As per ICMR guidelines, COVID-19 patients categorized for the severity of disease into asymptomatic, mild, moderate,

Comparative Evaluation of Raised Fasting Blood Glucose (FBG) Level in COVID-19 (N=2750)

Table 1: Comparative Evaluation of Raised Fasting Blood Glucose (FBG) Level in COVID-19 without pre-existing diabetes mellitus.

Characteristic	Total Patients (N=2750)	Group 1 Patients with Raised FBG (N1=910)	Group 2 Patients with Normal FBG (N2=1840)	P-value
Age (Year)	45.56 year ± 14.74	46.32 year ± 15.19	45.21 year ± 14.23	P=0.0600
Gender				
Male	1780	586 (64.0)	1194 (64.89)	x^2 = 0.0655, P=0.798
Female	970	324 (35.6)	646 (35.11)	
Clinical features				
Symptomatic patients	1550	580 (63.73)	970 (52.72)	Z=5.482, P<0.001
Fever	764	288 (31.64)	476 (25.86)	Z=3.183, P=0.001
Cough	748	268 (29.46)	480 (26.08)	Z= 1.865, P=0.061
Shortness of breath	592	240 (26.38)	352 (19.14)	Z=4.348, P<0.001
Sore throat	624	208 (22.86)	416 (22.60)	Z=0.211, P=0.833
Headache	560	196 (21.54)	364 (19.88)	Z=1.076, P=0.280
Chest pain	148	50 (5.50)	98 (5.32)	Z=0.184, P=0.857
Other	280	106 (11.65)	174 (9.46)	Z=1.788, P=0.073
Laboratory Investigation				
Total leukocyte count (x109 /L)	6.62 ± 2.91	7.04 ± 3.96	6.34 ± 2.12)	P<0.001
Platelet (Lac/μL)	2.18 ± 0.84	2.12 ± 0.64	2.20 ± 0.92	P=0.468
Neutrophil/lymphocyte ratio	3.06 ± 1.47	3.15 ± 1.98	2.98 ± 1.28	P=0.0067
C-reactive protein (mg/L)	6.10 ± 3.80	6.45 ± 3.93	5.84 ± 3.72	P=0.0001
Ferritin (ng/mL)	361.94 ± 202.18	381.56 ± 214.5	350.43 ± 194.41	P=0.0001
FDP (μg/L)	25.45 ± 22.88	26.23 ± 25.12	24.87 ± 21.25	P=0.1378
IL-6 (pg/mL)	37.89 ± 63.08	44.23 ± 64.25	35.39 ± 62.45	P=0.0005
D-dimer (μg/L)	4.05 ± 5.12	4.56 ± 5.98	3.72 ± 4.67	P=0.0001
Severity of disease				
Asymptomatic	1200	330 (36.27)	870 (47.28)	Z= -5.482, P<0.001
Mild	701	243 (26.7)	458 (24.89)	Z=1.025, P=0.3030
Moderate	396	156 (17.14)	240 (13.04)	Z=2.881, P=0.0039
Severe	268	106 (11.65)	162 (8.80)	Z=2.366, P=0.0177
Critical	185	75 (8.24)	110 (5.98)	Z=2.229, P=0.025
Radiological imaging				
Chest radiograph				
Average visual score	0.69 ± 0.84	0.72 ± 0.9	0.67 ± 0.82	P=0.1455
Classic for COVID images	402	173 (19.01)	229 (12.45)	Z=4.585, P<0.001
HRCT chest	1062 (38.62)	354 (38.90)	708 (38.48)	Z=0.214, P=0.833
CT severity score	6.31 ± 5.89	9.4 ± 8.75	7.78 ± 8.28	P=0.003
CT severity score >10/25	358 (33.70)	138 (38.98)	220 (31.07)	Z=2.570, P=0.011
Management				
ICU care	306	124 (13.63)	182 (9.89)	Z=2.930, P=0.0033
Oxygen support	384	136 (14.95)	248 (13.48)	Z= 1.044, P=0.298
Non-invasive ventilation	116	49 (5.38)	67 (3.64)	Z=2.140, P=0.0323
Invasive ventilation	78	34 (3.74)	44 (2.39)	Z= 1.99, P=0.0455
Outcome				
Alive	2676	876 (96.26)	1800 (97.83)	x^2 = 5.675, P=0.0172
Death	74	34 (3.74)	40 (2.17)	x^2 = 5.675, P=0.0172
Mean Duration of hospital stay	13.91 ± 5.78	14.45 ± 6.12	13.69 ± 5.34	P=0.0008

severe and critical ill patients. In this study 46.64% patients are asymptomatic while 25.49% patients had mild, 14.40% patients had moderate, 9.75% patients had severe and 6.73% patients had critical disease. Proportion of asymptomatic patients were significantly higher (47.28%) in group of controlled FBG level as compared to group of raised FBG level (36.27%) (p<0.00). Proportions of moderate disease, severe disease and critical disease were significantly higher in patients of raised FBG level as compared to group of normal FBG level (p=0.0039, 0.0177 and 0.0254 respectively). No any significant difference observed in patients of mild disease.

Radiological findings: For assessment of lung involvement in sample population, digital chest radiograph (CXR) of all patients and HRCT chest of 1062 patients (38.62%) was available. CXR represented classic for COVID-19 images in 402 patients (14.61%) with average visual score of 0.69± 0.84 out of 4. The average CT severity score was 6.31 ± 5.89out of 25 with CT severity score >10/25 in 358 patients (33.71%). Number of patients with classic for COVID images in CXR were significantly (p<0.001) higher in group of raised FBG level (19.01%) as compared to group of normal FBG level (12.45%). CT severity score was significantly (p=0.003) higher in group of raised FBG level (9.4 ± 8.75) as compared to group of normal FBG level (7.78 ± 8.28) with a CT severity score >10/25 in 38.98% and 31.07% patients in respective Groups (p=0.011).

Management: In this study total 384 patients (13.96%) needed oxygen support, 116 patients (4.22%) needed non-invasive ventilation, 78 patients (2.84%) needed invasive ventilation and total 306 patients (11.13%) needed ICU care. A significant need (p=0.0323) of non-invasive ventilation arose in group of raised FBG level (5.38%) as compared to patients of normal FBG level (3.64%). Similarly, need of invasive ventilation also found to be significantly higher (p=0.0455) in group of raised FBG level 3.74% patients) as compared to group of normal FBG level (2.39% patients). The need of ICU care in patients of raised FBG level and normal FBG level was 13.63% and 9.89%, respectively (p=0.0033).

Outcome: A total of 2676 patients (97.31%) alive whereas, 74 patients (2.69%) succumbed to COVID-19 till 28 days of positivity. Total number of alive patients in group of raised FBG level was proportionally lower (96.26%) than that of normal FBG level (97.83%) (p=0.0172). COVID-19 related mortality in group of raised FBG level was significantly higher (3.74%) as compared to group of normal FBG level (2.17%) (p=0.0172). Average duration of hospital stays was significantly prolonged (p=0.0008) in patients with raised FBG level (14.45 days± 6.12) as compared to patients with normal FBG level (13.69 days± 5.34).

Discussion

The ongoing COVID-19 pandemic is taking a heavy toll worldwide and effective measures have to be taken to minimize its influences and to lower its mortality. Bhandari et al in their study suggest that uncontrolled diabetes mellitus associated with higher susceptibility for COVID-19 infection and severity in terms of clinical manifestations, inflammatory storm, rapid pulmonary invasion, requirement of more intensive treatment and a poor outcome.(18)Previous studies have shown that diabetes and acute uncontrolled hyperglycemia (defined as blood glucose >180 mg/dL twice within any 24 h period) are related to morbidity and/or mortality from COVID-19.[14,19,20] Hyperglycemia and/or diabetes were identified to be risk factors for morbidity and mortality caused by infection with community-acquired pneumonia (CAP), SARS and MERS.[12-13]

Previous studies showed that, patients of COVID-19 might suffer from stress hyperglycemia[13] may develop acute insulin resistance, manifested by hyperglycemia and hyperinsulinemia.[21] Certain non-diabetic conditions like systemic inflammatory response syndrome (SIRS), severe sepsis, and traumatic brain injury tend to have hyperglycemia.[21] Hyperglycemia at admission to the intensive care unit (ICU) is directly related to increased mortality or morbidity.[22] At the same time, drugs such as corticosteroids and antibiotics, could also increase serum level of glucose.[23,24] Corticosteroids used for treatment of COVID-19 patients, promotes gluconeogenesis in the liver, reduces glucose uptake and utilization in peripheral tissues and enhance the effects of other glycemic hormones.[24] This study shown about impact of new onset hyperglycemia on presentation and progression of COVID-19. In our study nearly one third of patients (33.09%) presented with new onset hyperglycemia during early hospitalization after matching with age and gender. 368More than half of patients (56.36%) have symptomatic presentation for COVID-19 and symptomatic presentation especially fever, cough and shortness of breath were found to be higher in patients having raised FBG level as compared to group of normal FBG level. Hence, hyperglycemia tends to precipitate various symptoms of

COVID-19 by increasing inflammatory response. Hyperglycemia reduces expression of ACE2 and its anti-inflammatory effect mostly due to glycosylation. This might explain the occurrence of a severe acute lung injury and ARDS in diabetic patients. This makes hyperglycemic population with or without other comorbidities susceptible to a higher morbidity and mortality due to COVID-19. A severe disease in such patients requires intensive approach to manage COVID-19.

Patients with raised FBG level have increased inflammatory markers especially total leukocyte count, neutrophil-to-lymphocyte ratio, ferritin, C-reactive protein, D-dimer and IL-6 as compared to patients with normal FBG level. The average white blood cell count was found to be higher in patients of raised FBG level mostly attributable to exaggerated secondary inflammatory response in these patients. Neutrophil to lymphocyte ratio was also raised in peripheral blood of patients of raised FBG level, possibly due to neutrophilia or a relative lymphocytopenia as a consequence of COVID-19 infection.

Furthermore, the serum levels of inflammatory biomarkers such as ferritin, IL-6, and CRP were also raised in group of raised FBG level. IL-6 is a predictor of disease severity and prognosis, and has longer expression time than other cytokines like TNF and IL-1.[25] Huang et al. confirmed the elevated IL-6 levels beside a significantly low lymphocyte count, in patients with SARS-CoV-2 infection, especially those presenting with severe pneumonia.[26] Elevated level of serum ferritin is an indicator of activation of the monocyte-macrophage system, that contributes significantly to the inflammatory storm associated with COVID-19.[27] In the present study enhanced ferritin levels were found to be in patients of raised FBG level, suggesting a higher susceptibility of such patients for an inflammatory storm, responsible for rapid deterioration of COVID-19. Inflammation in COVID-19 can cause hypoxia induced thrombin activation which significantly enhances serum level of D-dimer.[27] In this study D-dimer levels were observed to be significantly higher in patients with raised FBG level as compared to the patients of normal FBG level.

This finding is an indication of a hypercoagulable state and even disseminated intravascular coagulation in such patients. In our study, patients having raised FBG level are more prone for symptomatic presentation as compared to patients of normal FBG level. Higher proportion of patients presented with severe and critical illness in group of raised FBG level. Lung involvement in COVID-19 patients assessed by chest radiograph and high-resolution computed tomography (HRCT) of chest. Classic for COVID images on CXR with average visual score were found to be higher in patients of raised FBG level as compared to group of normal FBG level suggestive of higher probability of lung involvement in patients of raised FBG level. Average CT severity score also found to be higher in patients of raised FBG level as compared to patients of normal FBG level. Quantitative HRCT of lung can automatically detect nature of lung involvement and quantify the dynamic changes of lung lesions during COVID-19. Patients having active COVID-19 disease associated with ground glass opacity (GGO) in HRCT chest, while GGO with consolidation were the main appearances at recovery state.[28]

COVID-19 patients having moderate, severe or critical illness required supportive oxygen therapy by low flow mask, high flow mask, non-invasive ventilation or invasive ventilation. Patients having raised FBG level were needing more invasive and non-invasive ventilation with ICU care as compared to patients of normal FBG level. A low recovery rate, high mortality and prolonged hospitalization indicated a poor outcome in patients with raised FBG level as compared to the patients of normal FBG level. It is recommended that close attention be paid to hospitalized COVID-19 patients with raised FBG level, regardless of whether they have been previously diagnosed as having diabetes.

Insulin therapy is proved to be a milestone for control of hyperglycemia in patients of COVID-19. However, intense glucose control in patients of hyperglycemia during ICU care predispose for risk of hypoglycemia which further enhances morbidity and mortality in these patients. A recent review study showed that, to treat hyperglycemia, insulin therapy should be used to maintain the glucose level between 8 mmol/l and 10 mmol/l. Insulin therapy in patients of COVID-19 reduces the mortality and morbidity resulting from high FBG.[29] Limitations of this study includes that this was a retrospective study. This study did not cover HbA1c, a long-term glycemic control indicator that helps distinguish patients with poor long-term glycemic control from those with COVID related hyperglycemia. Simultaneously data related to effect of glucose lowering agents (e.g. insulin, metformin) on the outcome of our patients was not available. However, we believe that acute hyperglycemia has higher prognostic importance as compared to long-term glycemic control in hospitalized COVID-19 patients.

Conclusion

From the findings of the present study, it can be concluded that FBG >126 mg/dL during hospitalization is an independent predictor for severity and mortality in patients with COVID-19 without pre-existing diabetes mellitus. The severity of COVID-19 in patients of raised FBG level is a consequence of dysfunctional immune system, with higher susceptibility to viral infection and an enhanced immune response like cytokine storm. Such type of immune response provides a favorable environment for viral survival and a longer recovery duration in hyperglycemic patients. Higher attention required for management of COVID-19 patients with raised FBG level as compared to patients of normal FBG level. Sugar charting and management should be recommended for all COVID-19 patients even if they do not have previously diagnosed diabetes mellitus, as most of COVID-19 patients are prone to glucose metabolic disorders.

Hyperglycemia should be considered a risk factor for an overall higher susceptibility for COVID-19 infection and severity in terms of symptomatic presentation, inflammatory storm, rapid pulmonary invasion, requirement of more intensive treatment and a poor outcome. During a pandemic of COVID-19, FBG can facilitate the assessment of prognosis and early intervention of hyperglycemia to help improve the overall outcomes in treatment of COVID-19.

Ethical approval: This study was approved by ethical and research committee of SMS Medical College Hospital, Jaipur, India.

Author contributions: S. Bhandari and G. Rankawat formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript; G. Rankawat collected and analyzed data for study. G. Rankawat write the manuscript. S. Bhandari conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

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References

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.
2. Hui DS, Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2019. 91: 264–266. doi:10.1016/j.ijid.2020.01. 009. PMC 7128332. PMID 31953166.
3. Murthy S, Gomersall CD, Fowler RA. Care for Critically Ill Patients with COVID19. JAMA 2020. 323 (15):1499doi:10.1001/jama.2020.3633.PMID.
4. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int/
5. Bragg F, Holmes MV, Iona A et al (2017) Association between diabetes and cause-specific mortality in rural and urban areas of China. JAMA 317(3):280–289. https://doi.org/10.1001/jama. 2016.19720
6. Gregg EW, Cheng YJ, Srinivasan M et al (2018) Trends in causespecific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data. Lancet 391(10138):2430–2440. https://doi.org/10.1016/ s0140-6736(18)30314-3
7. Pearson-Stuttard J, Blundell S, Harris T, Cook DG, Critchley J (2016) Diabetes and infection: assessing the association with glycaemic control in population-based studies. Lancet Diabetes Endocrinol 4(2):148–158. https://doi.org/10.1016/ s2213-8587(15) 00379-4
8. Rao Kondapally Seshasai S, Kaptoge S, Thompson A et al (2011) Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 364(9):829–841. https://doi.org/10.1056/ NEJMoa1008862
9. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11(8):875-879.
10. Hodgson K, Morris J, Bridson T, Govan B, Rush C, Ketheesan N. Immunological mechanisms

contributing to the double burden of diabetes and intracellular bacterial infections. Immunology. 2015;144(2): 171-185.

11. Ehrlich SF, Quesenberry CP Jr, Van Den Eeden SK, Shan J, Ferrara A (2010) Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. Diabetes Care 33(1):55–60. https://doi.org/10.2337/dc09-0880
12. Lepper PM, Ott S, Nuesch E et al (2012) Serum glucose levels for predicting death in patients admitted to hospital for community acquired pneumonia: prospective cohort study. BMJ 344:e3397. https://doi.org/10.1136/bmj.e3397
13. McAlister FA, Majumdar SR, Blitz S, Rowe BH, Romney J, Marrie TJ (2005) The relation between hyperglycemia and outcomes in 2, 471 patients admitted to the hospital with community-acquired pneumonia. Diabetes Care 28(4):810–815. https://doi.org/10. 2337/diacare.28.4.810
14. Bode B, Garrett V, Messler J et al (2020) Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol:193229682092446. https:// doi.org/10.1177/1932296820924469
15. Zhu L, She ZG, Cheng X et al (2020) Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 31(6):1068–1077.e3. https://doi.org/10.1016/j.cmet.2020.04.021
16. Warren MA, Zhao Z, Koyama T, Bastarache JA, Shaver CM, Semler MW et al. Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. Thorax. 2018 Sep;73(9):840-846. doi: 10.1136/thoraxjnl-2017-211280. Epub 2018 Jun 14. PMID: 29903755; PMCID: PMC6410734.
17. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, Alvarado-Arnez LE, Bonilla-Aldana DK, Franco-Paredes C, Henao-Martinez AF, Paniz-Mondolfi A. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel medicine and infectious disease. 2020 Mar 13:101623.
18. Bhandari S, Rankawat G, Singh A, Gupta V, Kakkar S. Impact of glycemic control in diabetes mellitus on management of COVID-19 infection, J Diabetol 2021;12:22-7.
19. Zhou F, Yu T, Du R et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229):1054–1062. https:// doi.org/10.1016/s0140-6736(20)30566-3
20. Yang X, Yu Y, Xu J et al (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 8(5):475–481. https://doi.org/10.1016/s2213-2600(20)30079-5
21. Bar-Or D, Rael LT, Madayag RM et al (2019) Stress hyperglycemia in critically ill patients: insight into possible molecular pathways. Front Med (Lausanne) 6:54. https://doi.org/10.3389/fmed.2019. 00054.
22. Whitcomb BW, Pradhan EK, Pittas AG, Roghmann MC, Perencevich EN (2005) Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. Crit Care Med 33(12):2772–2777. https://doi.org/10.1097/01.ccm.0000189741.44071.25.
23. Burcelin R, Amar J (2015) Diabetes: antibiotics or prodiabetics? Nat Rev Endocrinol 11(7):385–386. https://doi.org/10.1038/ nrendo.2015.75.
24. Johns EC, Reynolds RM (2019) Topical glucocorticoids and risk of type 2 diabetes mellitus. Nat Rev Endocrinol 15(7):379–380. https://doi.org/10.1038/s41574-019-0212-8.
25. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016;8(8): 959-970.
26. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395 (10223):497-506.
27. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020;e3319. https://doi.org/10.1002/dmrr.3319.
28. Ma, C., Wang, XL., Xie, DM. et al. Dynamic evaluation of lung involvement during coronavirus disease-2019 (COVID-19) with quantitative lung CT. Emerg Radiol 27, 671–678 (2020). https://doi.org/10.1007/s10140-020-01856-4.
29. Stapleton RD, Heyland DK (2020) UpToDate: glycemic control and intensive insulin therapy in critical illness. Available from www.uptodate.com/contents/glycemic-control-and-intensiveinsulin-therapy-in-critical-illness. Accessed 30 Mar 2020.