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Effect of COVID-19 on preexistent diabetes mellitus and its role as an unmasking effect on the new onset diabetes mellitus in recovered cases: A single center experience

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ABSTRACT

Introduction: Although blood sugar abnormalities have been reported during COVID-19 pandemic due to ongoing virus-related effects on insulin secretary effects on pancreases and stress and steroids used during management, its long-term effect remains unknown. Real world data on blood sugar abnormalities in follow-up with special emphasis on new onset diabetes mellitus (DM) or unmasking ongoing DM is an issue of concern which remains underestimated and under evaluated in clinical settings.

Methods: Prospective, observational, cohort study conducted between January 2021 to December 2022, included 1,500 COVID-19 patients above 18 years of age irrespective of their disease severity and comorbidity after a valid written consent. All the study cases were followed for six months of discharge from hospital. Protocolled recording of covariates such as blood sugar as fasting, post prandial, and random, HbA1C, blood pressure, anthropometric indices, ECG, blood sugar, lipid profile and uric acid were done at entry point. Documentation of indoor records such as CT Severity scores into mild (score < 8), moderate (score 9-15) and severe (score > 15); inflammatory markers such as IL-6, ferritin, CRP, LDH and D-dimer, and interventions used during hospitalization such as oxygen supplementation and oxygen plus BIPAP/NIV were done as a protocol. Statistical analysis was done by using chi test.

Results: In study of 1,500 post-COVID-19 cases, preexisting DM with aggravation in 10.6% (159/1,500), post-COVID-19 transient hyperglycemia in 42.86% (643/1,500), post-COVID-19 new onset DM in transient group in 21.15% (136/643), post-COVID-19 new onset DM in 10.14% (136/1,341), and no DM or hyperglycemia in 46.53% (698/1,500) cases ($p < -0.00001$). Significant association was observed between interventions used such as oxygen and oxygen plus BIPAP/NIV requirement, and cases without interventions with blood sugar profile such as new onset DM, preexistent DM with aggravation, post-COVID-19 transient hyperglycemia and no DM or hyperglycemia ($p < 0.00001$). Significant association was observed in blood sugar level switch from normoglycemic to transient hyperglycemic to DM range during pre- to post-COVID-19 state in follow up ($p < 0.00001$). Covariates analysis such as age, gender, body mass index observed significant association with cases with new onset DM, preexistent DM with aggravation, post-COVID-19 transient hyperglycemia and no DM ($p < 0.00001$). Comorbidities such as hypertension and IHD observed significant association with blood sugar profile in study cases in post-COVID-19 setting ($p < 0.00001$). Inflammatory markers during hospitalization, HRCT severity score and uric acid analysis during follow-up documented significant association with new onset DM, preexistent DM with aggravation, post-COVID-19 transient hyperglycemia and no DM or hyperglycemia during post-COVID-19 follow-up ($p < 0.00001$).

Conclusion: COVID-19 has been associated with blood sugar abnormalities such as transient hyperglycemia, aggravation of underlying DM as a result of ongoing disease process and treatment options used during management indoor settings. Inflammatory markers during hospitalization, interventions used during indoor period and severity of COVID-19 chest imaging has a positive association with blood sugar abnormalities. Proportionate number of transient hyperglycemia cases have evolved towards new onset DM cases in follow up of post-COVID-19 settings. COVID-19 illness has played a role in unmasking effect on new onset DM.

Keywords: COVID-19, diabetes mellitus, new onset DM, post-COVID-19, inflammatory makers, uric acid

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has presented a major threat to public health worldwide [1]. COVID-19 infections include symptoms like cough, fatigue, anosmia, and fever; which may progress to respiratory failure. Most patients recover completely but some may continue experiencing symptoms even after infection

recovery or may even present with new symptoms. This symptomatology occurring after the acute infection is called post-COVID-19 syndrome [2]. Diabetes mellitus (DM) is one such disease which reported significantly higher rates in the post-COVID-19 period [3].

DM is the seventh leading cause of mortality in the world [4]. As of now, 463 million adults are living with diabetes, and this number is expected to increase to 700 million by the end of the year 2045. Developing countries like India have seen an increase in prevalence of diabetes as compared to the rest of the world [5]. This might be due to greater adiposity of abdomen and greater waist circumference which are the characteristics of the "Asian Indian phenotype" [6]. India has gained the infamous title of "the diabetes capital of the world", as it has the highest number of diabetic subjects [7]. According to the study in [8], over 19% of the world's diabetic population lives in India. The American Diabetes Association (ADA) has primarily classified diabetes into two types–type 1 and type 2 [9]. Although various studies have been conducted regarding the pathophysiology of both the types of DM, the exact genetic and etiological basis of the disorders are still not known. Deficiency of insulin secretion [10], and impairment of insulin action [11] are the two main pathophysiologic processes which can lead to the development of DM. Transient hyperglycemia can be defined as temporary elevation of blood glucose levels beyond the normal range, without fulfilling the ADA criteria for diagnosing DM [12, 13].

SARS-CoV-2 utilizes the ACE-2 receptors for entry into the cells [14]. ACE-2 is primarily expressed on alveolar epithelial cells, but also at multiple other locations like heart, endothelium, renal tubular epithelium, intestinal epithelium, and pancreas [15]. Diabetes is known to predispose infections in general but there are some specific factors responsible for increased risk of infection with SARS-CoV-2. Increased ACE-2 expression in diabetics is one such postulated factor [16]. Studies have also reported the increased prevalence of diabetes in individuals who have experienced SARS-CoV-2 infection [17]. Although this association is poorly understood, it is plausible that the direct attack of pancreatic β-cells by the virus may lead to altered glucose metabolism [17]. The relationship between COVID-19 and diabetes can be therefore considered as bidirectional. DM has been independently associated with poor outcome in COVID-19 illness associated with inflammatory markers such as IL-6 [18-22], CRP [23-26], LDH [27-30], ferritin [31-34], and D-dimer [35-38]. Authors have also reported various CT severity assessment phenotypes [39-42] and their correlation with DM in recovered COVID-19 cases. The present study was conducted to further clarify the relationship between diabetes and COVID-19 especially in post-COVID-19 setting.

METHODS

Prospective observational study conducted January 2021 to December 2022 in pulmonary and critical care medicine in Venkatesh Chest Hospital and Critical Care Center, Latur and included 1,500 COVID-19 reverse transcription-polymerase chain reaction (RT PCR) confirmed cases with primary objective to find out the effect of COVID-19 in aggravating known DM. Primary objectives were to find the unmasking effect of COVID-19 in new onset DM; and secondary objectives were its role in aggravating known DM and covariates associated with new onset DM and aggravation of DM in accordance with anthropometry.

Ethics

This study was approved by the Institutional Review Board/Ethics Committee at Venkatesh Chest Hospital, Latur India (approval number: VCC/156-2021 and pproval date 16/01/2021).

Criteria

Inclusion criteria

1. Post-COVID-19 patients over the age of 18 attending post-COVID-19 outdoor care unit, willing to participate in study with for regular follow-up till six months of discharge were included.
2. All cases hospitalized in indoor units irrespective of disease severity and comorbidity were included in study.

Exclusion criteria

1. Patients not willing to participate or not willing to follow up in post-COVID-19 care outdoor unit at six months of discharge from hospital were excluded from study.

All study cases were undergone following assessment before enrolling in study: All post-COVID-19 patients (tested positive COVID-19 RT PCR), who have recovered from COVID-19 and were attending the outdoors for six months were included. Retrospective assessment of hospital records such as inflammatory markers assessment CRP, ferritin, LDH, IL-6 and D-dimer were recorded. HRCT Thorax findings were recorded as a protocol to assess severity of lung involvement as per COVID-19 reporting and data system, and categorized as mild if score < 7, moderated if score 8-15, and severe if score > 15 or 15-25. Clinical parameters such as oxygenation status and anthropometry parameters such as height, weight and body mass index (BMI) were recorded. Electrocardiogram and echocardiography was done as a protocol. Routine biochemistry measurements were also recorded to assess underlying comorbidity such as hypertension, DM, COPD, IHD, and obesity were recorded as covariates. Lastly, interventions required during hospitalization such as requirement of oxygen, oxygen plus ventilatory support were also recorded as protocol.

Case Definitions

1. Transient hyperglycemia: Recovered COVID-19 patients with random blood sugar levels more than 200 mg and HbA1C less than 6.5 gm% during hospitalization with or without use of medications causing abnormal sugar level, and; random blood sugar level at six-month follow-up is less than 200 with HbA1C less than 6.5gm%. These cases are termed as 'transient hyperglycemia' as they are not meeting the criteria for DM.
2. New onset DM: Recovered COVID-19 patients with random blood sugar levels more than 200 mg and HbA1C less than 6.5 gm% during hospitalization with or without use of medications casing abnormal sugar level, and; during follow up at six months of discharge form hospital random blood level is more than 200 with HbA1C more than 6.5 gm%. These cases are termed as

'new onset DM' as they are meeting the criteria for diagnosing the DM.

3. Preexistent DM: COVID-19 patients with known cases of DM with fasting blood sugar of more than 126 mg, post-prandial blood sugar of more than 200 mg and random blood sugar more than 200 mg with HbA1C more than 6.5% were categorized as preexistent DM. These patients were diagnosed in accordance with ADA criteria for DM.
4. Preexistent DM with aggravation: COVID-19 patient with known cases of DM fasting with abnormally raised blood sugars irrespective of their regular medications and treatments in previously well controlled cases. Fasting, postprandial and random sugar more than two-fold of their baseline sugars before COVID-19 illness with HbA1C more than 10.0 gm% during hospitalization were termed as aggravation of DM. Importantly, HbA1c returned to less than 10% recorded during six months follow-up discharge from hospital was essential criteria in aggravation of DM definition.
5. No DM: COVID-19 patients with fasting blood sugar of more than 100 mg, post prandial blood sugar less than 160 and random blood sugar of more than 160 mg with HbA1C less than 6.5% were categorized as no DM. These patients were diagnosed in accordance with ADA criteria for abnormal blood sugar levels.

Rational for follow up at six months in hospitalized cases: The present study has included hospitalized COVID-19 cases and followed for six months of discharge. To prevent confounding effect of abnormal sugar in hospitalized patients due to disease related stress, ongoing infection and treatment options used during hospitalization causing abnormal sugar such as steroids six-month follow up interval is selected. By this time transient effects causing falsely high blood sugar levels will be weaned off and actual sugar levels with HbA1C will guide the presence or absence of DM in recovered cases.

Inflammatory Markers Analysis

Analysis of inflammatory markers were done in Rosch automated biochemistry analyzer. Values of these inflammatory markers were considered significant in presence of four-fold raised titters. We have correlated inflammatory markers titers with cut off of four-fold rise with radiological phenotypes and interventions required during hospitalization.

1. CRP titter: Normal values up to 6 mg/L (0-6 mg/L)
2. LDH titter: Normal value up to 470 mg/L (90-470 mg/L)
3. Ferritin titer: Normal value up to 14-250 ng/ml in males, and female in age < 45 years old 6-160 ng/ml and age ≥ 45 years old 5-200 ng/ml
4. D-dimer titter: Normal value up to value up to 470 mg/L (70-470 mg/dL)
5. IL-6 titer: Normal value up to < 7 pg/mL (0-7 pg/ml)
6. Uric acid: normal range 3.5 to 6.5 mg
7. Lipid profile-serum cholesterol and triglycerides
8. Blood sugar estimation and criteria for DM
    a. Fasting: more than 126 mg
    b. Postprandial: more than 200 mg
    c. Random: more than 200 mg
    d. HbA1C: more than 6.5 gm%

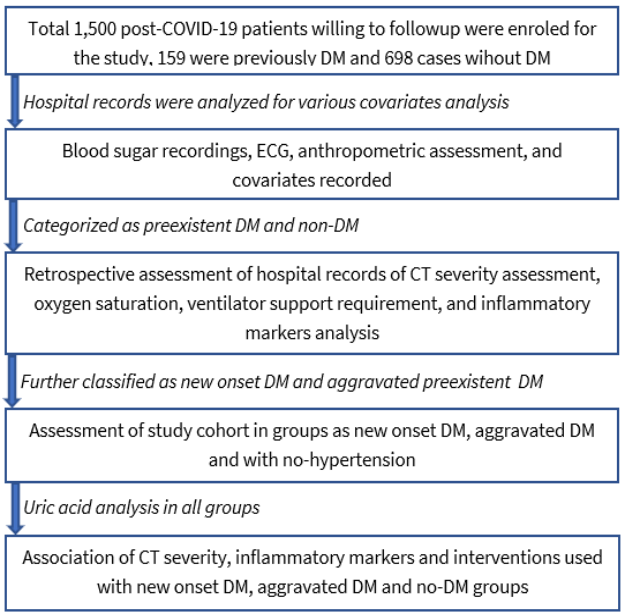

Figure 1. Flow of the study (Source: Authors' own elaboration)

Statistical Analysis

The statistical analysis was done by using chi-square test in R-3.4 software. Significant values of χ^2 were seen from probability table for different degree of freedom required. p-value was considered significant if it was below 0.05 and highly significant in case it was less than 0.001.

Study Design

Figure 1 shows the flow of the study.

RESULTS

In study of 1,500 post-COVID-19 cases, preexisting DM with aggravation in 10.6% (159/1,500), post-COVID-19 transient hyperglycemia in 42.86% (643/1,500), post-COVID-19 new onset DM in transient group in 21.15% (136/643), post-COVID-19 new onset DM in 10.14% (136/1,341) and no DM or hyperglycemia in 46.53% (698/1,500) cases (**Table 1**).

Interventions required during hospitalizations such as such as oxygen in 401/1,500 (26.7%), oxygen plus BIAPAP/NIV in 561/1,500 (37.4%), no interventions such as oxygen or oxygen plus BIPAP/NIV in 538/1,500 (35.8%) cases. Significant association was observed between interventions used and blood sugar profile such as cases with oxygen requirement in new onset DM 43/401 (10.7%), preexistent DM with aggravation in 67/401 (16.7%), post-COVID-19 transient hyperglycemia in 173/401 (43.1%) and no DM or hyperglycemia in 118/401 (29.4%) and oxygen plus BIPAP/NIV requirement in new onset DM 73/561 (13.0%), preexistent DM with aggravation in 66/561 (11.7%), post-COVID-19 transient hyperglycemia in 229/561 (40.8%) and no DM or hyperglycemia in 193/561 (34.4%) ($p < 0.00001$) (**Table 2**).

Significant association was observed in blood sugar switch during pre- to post-COVID-19 state in follow up from normoglycemic to transient hyperglycemic to DM range ($p < 0.00001$). Normoglycemic, transient hyperglycemic, and confirmed DM cases in pre-COVID-19 analysis were 698/1,500 (46.5%), 643/1,500 (42.8%) and 159/1,500 (10.6%), and in post-

Table 1. Profile of blood sugar status in post-COVID-19 setting with aggravation of previous DM

Blood sugar profile	Total post covid cases (n = 1,500)	Percentage (%)
No DM or hyperglycemia (n = 698/1,500)	698	46.53
Preexisting DM with aggravation (n = 159/1,500)	159	10.60
Post-COVID-19 transient hyperglycemia (n = 643/1,500)	643	42.86
Post-COVID-19 new onset DM in transient group (n = 136/643)	136	21.15
Post-COVID-19 new onset DM (n = 136/1,341)	136	10.14

Table 2. Interventions done and new onset DM in post-COVID-19 cases

Interventions	Post-COVID-19 new onset DM (n = 136)	Post-COVID-19 transient hyperglycemia (n = 507)	Preexisting DM with aggravation (n = 159)	No DM or hyperglycemia (n = 698)
No oxygen or BIPAP (n = 538)	20	105	26	387
Oxygen (n = 401)	43	173	67	118
Oxygen plus BIPAP/NIV (n = 561)	73	229	66	193

Note. $\chi^2 = 228.09$ & $p < 0.00001$

Table 3. New onset DM

	Normal blood sugar	Hyperglycemia	DM confirmed
Pre-COVID-19 (n = 1,500)	698	643	159
Post-COVID-19 (n = 1,500)	1,069	136	295

Note. $\chi^2 = 448.60$ & $p < 0.00001$

Table 4. Covariates analysis in post-COVID-19 cases

Variables	Post-COVID-19 new onset DM (n = 136)	Post-COVID-19 transient hyperglycemia (n = 507)	Preexisting DM with aggravation (n = 159)	No DM or hyperglycemia (n = 698)	p-value
Age < 65 (n = 836)	49	368	116	303	$\chi^2 = 141.83$
Age > 65 (n = 664)	87	139	43	395	$p < 0.00001$
Males (n = 972)	84	273	122	493	$\chi^2 = 47.54$
Females (n = 528)	52	234	37	205	$p < 0.00001$
BMI < 25 (n = 704)	85	278	111	230	$\chi^2 = 114.13$
BMI > 25 (n = 796)	51	229	48	468	$p < 0.00001$
HTN (n = 387)	43	167	98	79	$\chi^2 = 199.02$
No HTN (n = 1,113)	93	340	61	619	$p < 0.00001$
Hyperlipidemia (n = 533)	61	292	91	89	$\chi^2 = 303.70$
No hyperlipidemia (n = 967)	75	215	68	609	$p < 0.00001$
IHD present (n = 230)	56	78	77	19	$\chi^2 = 279.61$
IHD absent(n = 1,270)	80	429	82	679	$p < 0.00001$
More than fourfold inflammatory marker (n = 919)	90	393	102	334	$\chi^2 = 111.28$
Less than fourfold inflammatory marker (n = 581)	46	114	57	364	$p < 0.00001$
Uric acid normal (n = 587)	17	128	30	412	
Uric acid raised (n = 602)	77	312	91	122	$\chi^2 = 328.75$ $p < 0.00001$
Uric acid decreased (n = 311)	42	67	38	164	
HRCT severity score < 8 (n = 454)	16	78	21	339	
HRCT severity score 9-15 (n = 482)	51	198	61	172	$\chi^2 = 209.32$ $p < 0.00001$
HRCT severity score > 15 (n = 564)	69	231	77	187	

COVID-19 setting were 1,069/1,500 (71.2%), 136/1,500 (9.0%) and 295/1,500 (19.6%), respectively (**Table 3**).

Covariates analysis such as age < 65 (836/1,500) and > 65 (664/1,500), gender males (972/1,500) and females (528/1,500), BMI < 25 (704/1,500) and > 25 (796/1,500) observed significant association with cases with new onset DM 136/1,500 (9.0%), preexistent DM with aggravation in 159/1,500 (10.6%), post-COVID-19 transient hyperglycemia in 643/1,500 (42.86%) and no DM or hyperglycemia in 698/1,500 (46.53%) ($p < 0.00001$). Comorbidities such as hypertension (present in 387/1,500 and absent in 1,113/1,500 cases), hyperlipidemia (present in 533/1,500 and absent in 967/1,500 cases), and IHD (present in 230/1,500 and absent in 1,270/1,500 cases) observed significant association with blood sugar profile in study cases in post-COVID-19 setting ($p < 0.00001$). Inflammatory markers during hospitalization (less than fourfold and more than fourfold), HRCT severity score (mild, moderate and severe) and uric acid analysis during follow-up (increased, decreased and normal) documented significant association with new onset DM, preexistent DM with aggravation, post-COVID-19 transient hyperglycemia and no DM or hyperglycemia during post-COVID-19 follow-up ($p < 0.00001$) (**Table 4**).

DISCUSSION

1. **Profile of blood sugar in study cases:** In study of 1,500 post-COVID-19 cases, preexisting DM with aggravation in 10.6% (159/1,500), post-COVID-19 transient hyperglycemia in 42.86% (643/1,500), post-COVID-19 New onset DM in transient group in 21.15% (136/643), post-COVID-19 new onset DM in 10.14% (136/1,341) and no DM or

hyperglycemia in 46.53% (698/1,500) cases. Similar results have been observed in various other studies [18-38, 43-49]. The meta-analysis study in [50] reported a 59% higher risk of developing incident diabetes in post-acute COVID-19 phase versus healthy controls. It was also reported that there was a significantly increased risk and excess burden of incident diabetes in the post-acute phase of COVID-19 [51]. It was reported contradictory to our findings as no significant change in the incidence of pediatric type 1 diabetes across 216 centers in Germany, during the pandemic [52]. Similarly, it was also shown no association between new-onset Diabetes after the resolution of the acute infection [53].

2. Correlation of CT severity scores with blood sugar profile (n = 1,500): In present study, CT severity scores and new onset DM have a significant correlation. Scores < 8, 8-15, and > 15 documented new onset DM 16/136, 51/136 and 69/136, respectively, preexistent DM with aggravation in 21/159, 61/159 and 77/159, respectively, post-COVID-19 transient hyperglycemia in 78/507, 198/507 and 231/507, respectively, and; no DM or hyperglycemia in in 339/698, 172/698 and 187/698 cases, and respectively ($p < 0.00001$). Similar results have been observed in various other studies [18-38]. It has published data proving higher risk of new onset diabetes amongst patients who had moderate/severe COVID-19 infections [54]. The study in [55] also reported similar findings.

3. Correlation of BMI with blood sugar profile (n = 1,500): In present study, BMI > 25 had a significant correlation with new onset DM. BMI > 25 and BMI < 25 documented new onset DM in 51 versus 85 cases of total 136 cases, preexistent DM with aggravation in 48 versus 111 of total 159 cases and transient hyperglycemia in 229 versus 278 of total 507 cases ($p < 0.00001$). Similar results have been observed in various other studies [18-38]. A strong correlation ($p < 0.001$) between higher BMI and new onset DM in the 3-month post-COVID-19 period has been published [55]. The study in [56] also reported similar findings.

4. Correlation of age with blood sugar profile (n = 1,500): In present study, age > 65 years and new onset DM have a significant correlation. Ages < 65 and > 65 years documented new onset DM in 49 versus 87 cases of total 136, preexistent DM with aggravation in 116 versus 43 of total 159 cases and transient hyperglycemia in 368 versus 139 of total 507 cases ($p < 0.0043$). Similar results have been observed in various other studies [18-38]. The study in [51] also noted a higher risk and burden of new- onset DM 4 weeks after acute COVID-19 infection in patients older than 65 years. Another study in Ethiopia also reported similar findings [57]. On the contrary, the study in [55] observed no significant association between age and new-onset diabetes.

5. Correlation of Gender with blood sugar profile (n = 1,500): In present study, incidence of new onset DM was proportionately higher in females 9.8% (52/528) in comparison to males 8.6% (84/972). Gender difference as males versus females documented new onset DM in 84 versus 52 cases of total 136, preexistent DM with aggravation in 122 versus 37 of total 159 cases and transient hyperglycemia in 273 versus 234 of total 507 cases ($p < 0.00001$). Similar results have been observed in various other studies [18-38]. The study in [58] also noted a more evident association between new-onset diabetes 1-year post-discharge after COVID-19 in males. The findings in [57] revealed that male patients were 2.9 times more likely to develop new onset DM. However, other studies have shown no significant correlation between gender and blood sugar profile [55, 59].

6. Correlation of hypercholesterolemia with blood sugar profile (n = 1,500): In present study, hypercholesteremia and new onset DM have significant correlation. Cases with and without hypercholesterolemia and new onset DM in 61 versus 75 cases of total 136, preexistent DM with aggravation in 91 versus 68 of total 159 cases and transient hyperglycemia in 292 versus 215 of total 507 cases ($p < 0.00001$). The studies in [56, 60] reported triglyceride variables to be significant risk factors for new onset diabetes. Contrary to this, the study in [57] found no significant association between hypercholesterolemia and new-onset diabetes.

7. Correlation of BIPAP/NIV use with blood sugar profile (n = 1,500): Significant association was observed between interventions used and blood sugar profile and new onset DM. Cases without oxygen or BIPAP, oxygen supplementation and oxygen plus BIPAP/NIV use and new onset DM in 20/136, 43/136 and 73/136, respectively, preexistent DM with aggravation in 26/159, 67/159 and 66/159, respectively, and; transient hyperglycemia in 105/507, 173/507 and 229/507, respectively ($p < 0.00001$). Similar results have been observed in various other studies [18-38]. The study in [61] also noted that higher proportion of new onset- diabetes patients required oxygen support and ventilation as compared to patients with normoglycemia. The study in [55] also found a significant difference between duration of oxygen requirement in patients who developed new onset diabetes and those who did not.

8. Correlation of inflammatory markers during hospitalization and follow-up and blood sugar profile (n = 1,500): Significant association was observed between fourfold increase in titer of the inflammatory markers with blood sugar profile. Cases with and without fourfold raised inflammatory markers new onset DM in 90 versus 46 cases of total 136, preexistent DM with aggravation in 102 versus 57 of total 159 cases and transient hyperglycemia in 393 versus 114 of total 507 cases ($p < 0.00001$). Similar results have been observed in various other studies [18-38]. The study in [62] concluded from their analytical cross-sectional study that there was a consistent association between post-COVID-19 syndrome and upper ranges of inflammatory markers. On the contrary The study in [55] reported no significant association between inflammatory markers and new onset diabetes post-COVID-19.

9. Unmasking effect of COVID-19 on new onset DM: We have observed the propionate number of transient hyperglycemia cases were turned into new onset DM at six months follow-up. Post-COVID-19 New onset DM was documented in 136 cases of total 643 cases with transient hyperglycemia. Thus, a total of 21.1% of transient hyperglycemia cases which were not diagnosed to have DM were turned up into new onset DM group at six month follow up. A total of 136 cases with new onset DM in 1341 recovered COVID-19 cases without hyperglycemia, i.e., 10.14% incidence general cases were observed in present study. In recent metanalysis from six studies reported that

the new-onset diabetes among COVID-19 cases using a random effect model showed that 19.70% of COVID-19 cases were associated with DM [63].

Other Important observations in present study with plausible rationales or mechanisms:

a. Severity of illness: Proportionate number of cases with mild COVID-19 illness were transient hyperglycemia, new onset DM and aggravation of preexistent DM. Thus, CT severity showing mild disease was just a one-point assessment to disease severity and was not a temporal assessment or predictor of disease outcome as reported in one study [39-41]. Hence, we recommend to follow all post-COVID-19 cases for possible new onset DM irrespective of disease severity. Similar results have been observed in various other studies [18-38].

b. Gender: Although new onset DM in 84/136 and aggravation of DM in 122/159 is more frequently reported in male gender, proportionate number of transient hyperglycemia cases have been reported in female gender. Plausible explanation would be less severe illness with a smaller number of cases required aggressive interventions during hospitalization in females. Another possible reason would be lesser sympathetic activation is the reason for transient hyperglycemia in these cases. Similar results have been observed in various other studies [18-38].

c. Inflammatory markers: Although inflammatory makers have direct correlation with blood sugar abnormality as it indicates disease related burden and systemic inflammatory response, significant number cases with less than fourfold increase in titer of the inflammatory markers were having exaggeration of preexistent DM in 64.15% (102/159), in comparison with more than fourfold increase in titers. Plausible mechanisms would be ongoing disease related systemic burden and sympathetic override resulting in blood sugar abnormalities correlated with inflammatory markers titers, although less than fourfold which is manifested and evolved during COVID-19 illness over a period of time.

d. Uric acid as an important marker: This is simple, reliable and cost-effective marker of systemic inflammation and very good predictor of ongoing inflammation which is very correlated with inflammatory makers used for analysis of disease severity in COVID-19 illness in acute setting as well. Although raised uric acid titers are positively associated with abnormalities in blood sugar profile such as new onset DM in 56.61% (77/136) cases and transient hyperglycemia in 61.53% (312/507) cases, proportionate number of cases with low uric acid titer in new onset DM in 30.88% (42/136); and normal uric acid was observed in transient hyperglycemia in 25.24% (128/507) and 18.86% (30/159) cases with aggravation of preexistent DM ($p < 0.00001$). Thus, uric acid titer analysis can be used in two ways and can be used as predictor maker for blood sugar abnormality due to its association with systemic inflammation.

e. Comorbidities and confounding factors aggravated during recovery phase and possible cause for new onset DM and aggravate of preexistent DM: comorbidities such as HTN, IHD, abnormally high BMI and Hyperlipidemia were observed as risk factors for new onset DM, transient hyperglycemia and an aggravation of preexistent DM in post-COVID-19 patients and played a role as confounding factor due its association with blood sugar abnormalities irrespective of COVID-19 illness. Transient hyperglycemia was predominant in cases with BMI > 25, cases with hyperlipidemia and cases without IHD and HTN. New onset DM was documented in cases with hyperlipidemia, cases with IHD and cases with BMI < 25 and cases without HTN. Aggravation of DM was observed in cases with HTN, hyperlipidemia and BMI < 25 and those without IHD. Hence, we are labelling these comorbidities as 'confounding factors' because propaganda in the propionate number of cases without these abnormalities were also mentioned blood sugar abnormalities.

10. Post-COVID-19 Increased Incidence of New-Onset DM: Recent research has demonstrated a notable increase in the incidence of new-onset DM following SARS-CoV-2 infection. In a large retrospective cohort study of over 180,000 US veterans, COVID-19 survivors exhibited a 40% higher risk of developing diabetes compared to non-infected controls, with an excess burden of 13.46 cases per 1,000 people at 12 months [51]. This association is attributed to multiple mechanisms including direct pancreatic β-cell damage via ACE2 receptors, systemic inflammation, and treatment-related factors like corticosteroids [64]. A CDC analysis involving individuals under 18 years found that those with prior COVID-19 were 2.5 times more likely to be diagnosed with diabetes more than 30 days after infection, compared to their non-infected peers [65]. Additionally, a systematic review and meta-analysis of 3,711 patients across multiple countries revealed that 14.4% of hospitalized COVID-19 patients developed newly diagnosed diabetes during or after infection [66]. Although some cases may be due to transient stress hyperglycemia, persistent hyperglycemia in many patients indicates a chronic condition requiring long-term management. These findings highlight the importance of post-COVID-19 metabolic screening and early intervention to mitigate the long-term burden of diabetes globally.

Limitations of the Study

Our study has enough sample size and analyzing long term of effect of COVID-19 on blood sugar abnormalities including new onset DM and its aggravating effect on preexistent DM with its correlation with laboratory and clinical markers in assessment and management in indoor units. The first limitation is that COVID-19 cases expired during hospitalization with or without hyperglycemia were not included in present study, hence; its association with the worst COVID-19 outcome is not available. Second limitation is multivariate analysis of individual inflammatory marker with transient hyperglycemia, new onset DM and aggravation of preexistent DM is not done. Inflammatory makers were analyzed as a group in a present study. Third limitation is that the recovered COVID-19 cases with blood sugar abnormalities during indoor period and unwilling to follow-up till six months of discharge form hospital were not evaluated as proportionate number in these cases may have new onset DM.

CONCLUSIONS

COVID-19 has been associated with various blood sugar abnormalities during early illness and its evolution during hospitalization such as 'transient hyperglycemia' and 'aggravation of preexistent DM'. Inflammatory markers (IL-6, CRP, LDH, D-dimer, ferritin) during hospitalization, disease severity in chest imaging, interventions required during hospitalization have been positively associated with blood sugar abnormalities. Covariates such as age, gender, BMI, abnormal lipid profile, blood pressure abnormalities have been associated with abnormal blood sugar patterns in recovered COVID-19 cases.

Although, 'aggravation of DM' is common during evolution of COVID-19 illness due to rampant use of steroids during treatment of illness in indoor units in all the cases irrespective of disease severity and oxygenation status, its persistence is a real concern and a worrisome issue globally. Persistence of aggravation of DM in recovered cases in follow-up settings would be related to COVID-19 disease related immune dysregulation resulting in persistence of pancreatic dysfunction and disease related stress and prolonged use of steroids in proportionate number of cases those having severe illness and revived long course of steroid treatment with or without oxygen supplementation at home with residual lung abnormalities as a post-COVID-19 sequel.

Hyperglycemia during hospitalization can be underestimated and less efficiently evaluated for possibility of ongoing DM due to its occurrence with disease related stress, sympathetic overactivity and virus-related pancreatic beta cell dysfunction. Proportionate number of 'transient hyperglycemia' cases during hospitalization have been evolved to new onset DM in recovered cases during follow-up over six months without exposure to treatment with drugs causing blood sugar abnormalities. We recommend protocolized follow up of all recovered COVID-19 cases with history of transient hyperglycemia during hospitalization for ruling out ongoing new onset DM.

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Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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