Original Research Article

Coagulation Dysfunction and Inflammatory Storm in Post Covid -19, An Observational Cross Sectional Study

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Abstract

Background: The world was struggling in lockdown for months since December of 2019 due to novel coronavirus disease (COVID-19) outbreak, a pandemic declared by the World Health Organization. Research evidence is growing on the role of several symptoms, comorbidities, inflammation and hypercoagulability markers in relation to disease progression and deaths in COVID-19 patients. The incidence of diabetes, one of the leading causes of morbidity has been shown to be high and is associated with disease progression in COVID-19. More than 425 million individuals have diabetes worldwide and projections show this number rising to 629 million by 2045. This Study was done with fallowing objectives-To compare markers of coagulation dysfunction and markers of inflammation in Diabetic and Non-Diabetic Post COVID-19 patients.

Material and method: This is an observational cross -sectional study assessing Post COVID-19 . In this study among 214 patients participated, in which 129 patients were diabetic and 85 patients were non- diabetic.

Result: The following variables were significantly associated ($p<0.05$) with the diabetic Post COVID-19 patients: Age (Years), TLC (/cu.mm), S.Ferritin (ng/mL), S.Procalcitonin (ng/mL), D-Dimer (µg/mL), S.LDH (U/L), SpO2 (%), FBS (mg/dL), PPBS (mg/dL), A1c (%), PT (Sec), aPTT (Sec), INR

Conclusion: The presence of diabetes could further influence the magnitude of inflammatory and coagulation dysfunction in Post COVID-19. Strikingly, a recent study showed a significant increase in these markers in diabetic group as compared to non-diabetic group of Post-COVID-19 patients without other comorbidities, indicating the independent impact of diabetes.

Keyword-Post-COVID-19, Comorbidities, Inflammatory and coagulation dysfunction, Diabetes

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Introduction

The world was struggling in lockdown for months since December of 2019 due to novel coronavirus disease (COVID-19) outbreak, a pandemic declared by the World Health Organization[1]. Research evidence is growing on the role of several symptoms, comorbidities, inflammation and hypercoagulability markers in relation to disease progression and deaths in COVID-19 patients. The incidence of diabetes, one of the leading causes of morbidity has been shown to be high and is associated with disease progression in COVID-19 [2]. More than 425 million individuals have diabetes worldwide and projections show this number rising to 629 million by 2045 [3]. A research study with more than 1.3 million participants showed that 98% of adults with type 2 diabetes have at least one comorbid chronic disease and almost 90% have at least two. [4,5]Various reports suggest that diabetes activate several pathways leading to T-cell differentiation, immune system imbalance, pro- and anti-inflammation imbalance. Diabetes has been reported to be associated with infection and disease progression. According to recent research, virus invasion results in induction of coagulation activation, inflammatory responses, hypercoagulability induction and cytokine storms which may eventually cause disease progression in COVID-19 patients. The significant rise in ferritin, CRP and IL-6 levels reflect monocyte-macrophage activation resulting in inflammatory storm and cytokine storm.It is known that during inflammatory storm, as a result of plasmin activation, the significant rise in D-dimer level indicates hypercoagulability. The significant rise in fibrinogen and D-dimer indicate diabetic Post-COVID-19 patients are more susceptible to hypercoagulable state/intravascular coagulation. It is noteworthy that the association of diabetes and hyperglycemia with disease progression has been linked to increased inflammation, hypercoagulability and lung dysfunction in Post-COVID-19.This Study was done with fallowing objectives.

To compare markers of coagulation dysfunction and markers of inflammation in Diabetic and Non-Diabetic Post COVID-19 patients.

Material and Method

STUDY DESIGN: This is an observational cross -sectional study assessing Post COVID-19 Patients to determine markers of Coagulation Dysfunction and Inflammation in Diabetic and Non-Diabetic Post COVID-19.

SUBJECTS

The present study was carried out in a teaching hospital during the year 2020-21 at the Department of Pulmonary Medicine, SRN Hospital, MLN Medical College, Prayagraj(Allahabad). The patients who were diagnosed COVID-19 through RT-PCR and admitted in COVID-19 ICU in SRN hospital, then tested negative through RT-PCR and admitted in department of Pulmonary medicine, SRN Hospital, MLN medical College Prayagraj (Allahabad) were classified into Diabetic and Non- Diabetic and markers of coagulation dysfunction and inflammation were studied.

For inflammation markers venous serum samples were obtained and Total leucocyte count (TLC), Differential leucocyte count (DLC), N/L Ratio (neutrophil/lymphocyte) ratio, erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), Serum Ferritin (S. Ferritin), Serum Procalcitonin (S. PCT), Serum LDH (S. LDH) were analysed.

N/L Ratio is obtained by dividing neutrophils and lymphocytes obtained from DLC.

For coagulation dysfunction venous serum samples were obtained and Prothrombin time (PT), Activated partial thromboplastin time (APTT), International Nationalised Ratio (INR), were analysed.

For classifying diabetic and non-diabetic patient's venous serum samples were obtained and Fasting Plasma Sugar (FPS), Two Hour Post Prandial Plasma Sugar (2h PPPS), Glycosylated haemoglobin (HbA1C) were analysed.

CASE SELECTION:

- Patient were enrolled in this study as per inclusion and exclusion criteria
- Diagnosis of Diabetes in American Diabetes Association Standards of Medical Care in Diabetes2020.

- Patients were divided into the diabetes and non-diabetes group according to their medical history and blood investigations.
- Patients who were diagnosed COVID-19 through RT-PCR and then tested negative through subsequent RT-PCR and admitted in department of Pulmonary medicine, SRN Hospital, MLN medical College Prayagraj(Allahabad).

INCLUSION CRITERIA

Patients presenting with following-

- Confirmed COVID-19 patients tested negative through subsequent RT-PCR.
- Age ≥18 years, either sex.

EXCLUSION CRITERIA

- Patients with comorbidities other than Diabetes.
- Non COVID-19 Respiratory illnesses.
- Patients receiving glucocorticoids for kidney transplantation and chronic systemic lupus erythematosus, haemolytic anaemia patient and patient with myelosuppression after leukaemia chemotherapy.
- Patient not giving consent for participation in the study.

STUDY PROCEDURE

After obtaining written informed consent, patients qualifying inclusion criteria will be assessed as follows-

- Recording of demographic data
- All patients will be subjected to a set of questions.
- All patients are divided into two groups diabetic and non-diabetic according to American heart association criteria.
- Markers of coagulation dysfunction and inflammation are compared between two groups.

Investigations:

Battery of investigation were done to all these patients which was following:

- Haematological investigation- Hb, TLC, DLC, ESR, C-Reactive Protein, S. Ferritin, S. Procalcitonin, D-Dimer, S. LDH, FPS, 2h PPPS, HBA1C, PT, aPTT, INR.
- Radiological investigation- X-ray chest (PA) view.
- Other relevant investigations.

STATISTICAL ANALYSIS OF DATA: Data were coded and recorded in MS Excel spread sheet program. SPSS v23 (IBM Corp.) was used for data analysis. Descriptive statistics were elaborated in the form of means/standard deviations and medians/IQRs for continuous variables, and frequencies and percentages for categorical variables. If data were found to be non-normally distributed, appropriate non-parametric tests in the form of Wilcoxon Test were used. Chi-squared test was used for group comparisons for categorical data. In case the expected frequency in the contingency tables was found to be <5 for >25% of the cells, Fisher's Exact test was used instead. Statistical significance was kept at $p < 0.05$.

Result

In this study among 214 patients participated, in which 129 patients were diabetic and 85 patients were non- diabetic.

Participants in the group Diabetes had the larger proportion of Age: 60-69 Years and 70-79 Years.

The following variables were significantly associated ($p<0.05$) with the diabetic Post COVID-19 patients: Age (Years), TLC (/cu.mm), S.Ferritin (ng/mL), S.Procalcitonin (ng/mL), D-Dimer (µg/mL), S.LDH (U/L), SpO2 (%), FBS (mg/dL), PPBS (mg/dL), A1c (%), PT (Sec), aPTT (Sec), INR (Table-1) (figure-1,2,3,4)

Table 1: Association between Diabetes and Parameters

Parameters	Diabetic		p value
	Yes (n = 129)	No (n = 85)	
Age (Years)***	57.71 ± 12.24	52.26 ± 14.84	0.005[1]
Age* **			0.037[2]
20-29 Years	2 (1.6%)	7 (8.2%)	
30-39 Years	4 (3.1%)	7 (8.2%)	
40-49 Years	27 (20.9%)	19 (22.4%)	
50-59 Years	34 (26.4%)	26 (30.6%)	
60-69 Years	35 (27.1%)	16 (18.8%)	
70-79 Years	21 (16.3%)	6 (7.1%)	
80-89 Years	6 (4.7%)	4 (4.7%)	
Gender			0.500[2]
Male	95 (73.6%)	59 (69.4%)	
Female	34 (26.4%)	26 (30.6%)	
Weight (Kg)	68.09 ± 9.67	65.78 ± 9.16	0.204[3]
Height (cm)	162.83 ± 6.34	162.99 ± 6.59	0.945[3]
BMI (Kg/m²)	25.75 ± 4.00	24.79 ± 3.54	0.112[3]
BMI			0.560[4]
<18.5 Kg/m2	0 (0.0%)	1 (1.2%)	
18.5-22.9 Kg/m2	31 (24.0%)	21 (24.7%)	
23.0-24.9 Kg/m2	33 (25.6%)	28 (32.9%)	
25.0-29.9 Kg/m2	45 (34.9%)	28 (32.9%)	
30.0-34.9 Kg/m2	16 (12.4%)	6 (7.1%)	
35.0-39.9 Kg/m2	2 (1.6%)	1 (1.2%)	
40.0-44.9 Kg/m2	2 (1.6%)	0 (0.0%)	
Smoking (Yes)	45 (34.9%)	19 (22.4%)	0.050[2]
Hemoglobin (g/dL)	12.33 ± 1.94	12.57 ± 1.85	0.374[1]
TLC (/cu.mm)***	13420.93 ± 5625.65	11605.06 ± 4807.17	0.008[3]
Neutrophils (%)	84.32 ± 6.71	82.64 ± 8.43	0.110[3]
Lymphocytes (%)	10.93 ± 5.71	12.87 ± 8.05	0.124[3]
Monocytes (%)	2.66 ± 2.79	2.42 ± 2.09	0.290[3]
Eosinophils (%)	1.91 ± 0.63	1.92 ± 0.54	0.768[3]
Basophils (%)	0.00 ± 0.00	0.00 ± 0.00	-
N/L Ratio	9.91 ± 4.92	9.44 ± 6.88	0.119[3]
ESR (mm/Hr)	16.47 ± 6.20	16.02 ± 7.69	0.169[3]
CRP			0.077[2]
Non Reactive	48 (37.2%)	42 (49.4%)	
Reactive	81 (62.8%)	43 (50.6%)	
S.Ferritin (ng/mL)***	920.24 ± 565.82	598.85 ± 494.66	<0.001[3]
S.Procalcitonin (ng/mL)***	0.38 ± 0.46	0.35 ± 1.34	<0.001[3]
D-Dimer (µg/mL)***	3.27 ± 2.90	1.35 ± 1.74	<0.001[3]
S.LDH (U/L)***	829.34 ± 418.97	625.29 ± 339.75	<0.001[3]

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SpO2 (%)***	88.99 ± 11.23	93.76 ± 7.34	<0.001[3]
FBS (mg/dL)***	184.13 ± 72.70	100.58 ± 25.36	<0.001[3]
PPBS (mg/dL)***	240.43 ± 87.48	131.50 ± 28.00	<0.001[3]
A1c (%)***	8.43 ± 2.12	5.82 ± 0.48	<0.001[3]
PT (Sec)***	17.40 ± 3.08	14.65 ± 2.65	<0.001[3]
aPTT (Sec)***	31.10 ± 6.01	28.65 ± 4.61	<0.001[3]
INR***	1.56 ± 2.14	1.56 ± 3.82	<0.001[3]

***Significant at p<0.05, 1: t-test, 2: Chi-Squared Test, 3: Wilcoxon-Mann-Whitney U Test, 4: Fisher's Exact Test

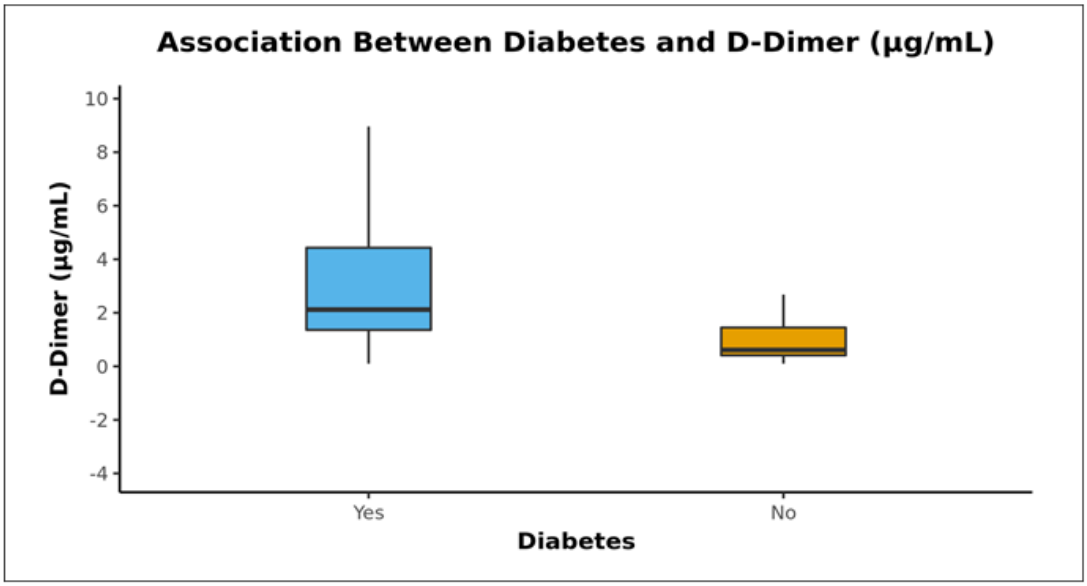

Figure 1

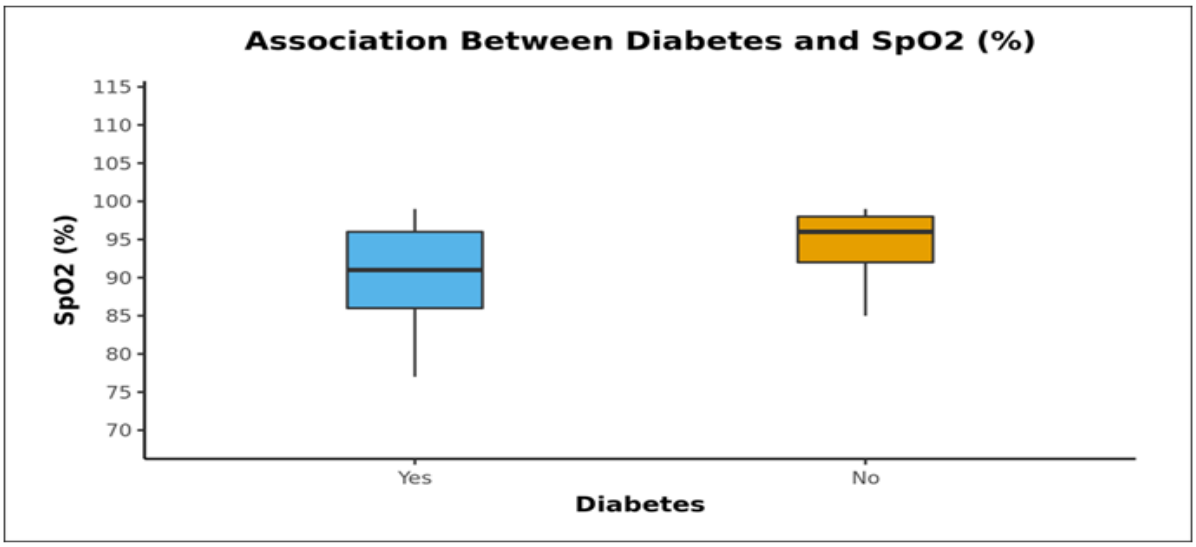

Figure-2

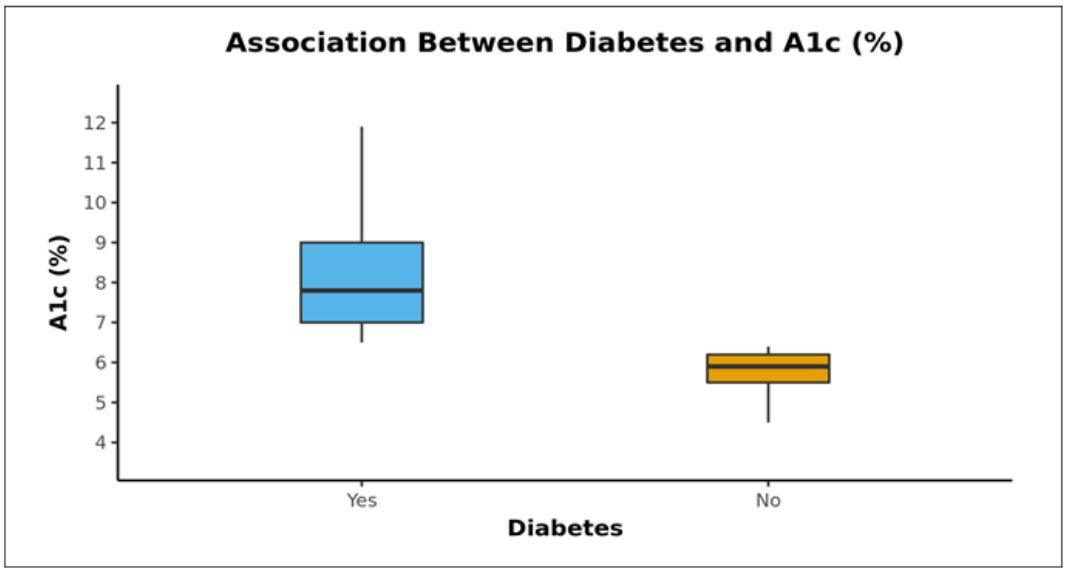

Figure-3

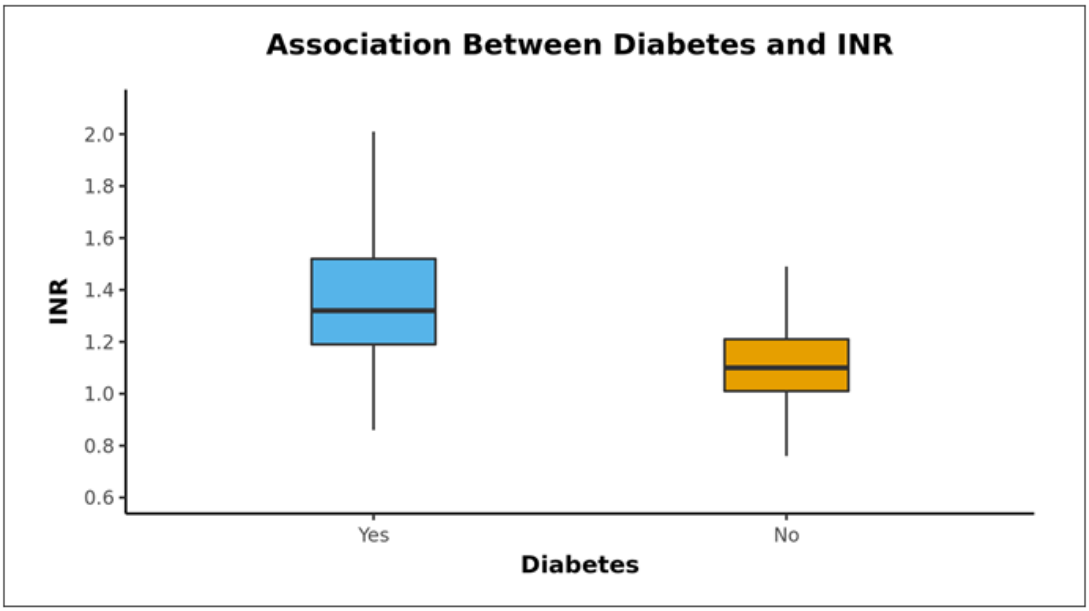

Figure 4

High HbA1c level is associated with inflammation, hypercoagulability, and low SaO2 in Post COVID-19 patients, and the mortality rate is higher in patients with diabetes.

Discussion

Varikasuvu S R et al.[6] have similar findings in patients of COVID-19. She found the levels of serum ferritin (standardized mean difference-SMD: 0.47, CI 0.17–0.77, p = 0.002), C-reactive protein (SMD = 0.53, CI 0.20–0.86, p = 0.002), interleukin-6 (SMD = 0.31, CI 0.09–0.52, p = 0.005), fibrinogen (SMD = 0.31, CI 0.09–0.54, p = 0.007) and D-dimers (SMD = 0.54, CI 0.16–0.91, p = 0.005) were significantly higher in diabetic COVID-19 cases as compared to non-diabetic COVID-19 patients, suggesting more susceptibility of diabetic COVID-19 patients to coagulation dysfunction and inflammatory storm. Similarly **Zhang Y, Li H, Zhang J et al.** [7] divided patients in three groups based on their blood glucose status .and compared with group 1, groups 2 and 3 had higher rates of leukocytosis, neutrophilia, lymphocytopenia,

eosinopenia and levels of hypersensitive C-reactive protein, ferritin and d-dimer (P < .05 for all). Group 2 patients had higher levels of lactate dehydrogenase, prevalence of liver dysfunction and increased interleukin-8 (IL-8) than those in group 1, and a higher prevalence of increased IL-8 was found in group 2 than in group 3 (P < .05 for all). The proportions of critical patients in groups 2 and 3 were significantly higher compared with group 1 (38.1%, 32.8% vs. 9.5%, P < .05 for both). Groups 2 and 3 had significantly longer hospital stays than group 1, which was nearly 1 week longer. The composite outcomes risks were 5.47 (1.56-19.82) and 2.61 (0.86-7.88) times greater in groups 2 and 3 than in group 1.

There was a significant difference between the 2 groups in terms of TLC (/cu.mm) (W = 6649.500, p = 0.008), with the median TLC (/cu.mm) being highest in the patients with Diabetes. The mean (SD) of TLC (/cu.mm) in the Diabetes: Yes group was 13420.93 (5625.65). The mean (SD) of TLC (/cu.mm) in the Diabetes: No group was 11605.06 (4807.17). The median (IQR) of TLC (/cu.mm) in the Diabetes: Yes group was 13300 (10000-16000). The median (IQR) of TLC (/cu.mm) in the Diabetes: No group was 10400 (8200-14700). The TLC (/cu.mm) in the Diabetes: Yes ranged from 2800 - 42800. The TLC (/cu.mm) in the Diabetes: No ranged from 2000 - 24500

Vaseghi G et al[8] studied Inflammatory markers in Covid-19 Patients and in that Twelve studies were included in the analysis that all of which were conducted in China in the year 2020. The result of combining 12 articles with 772 participants showed that the pooled estimate of the mean of lymphocyte with 95% CI was (Mean: 1.01; 95% CI (0.76- 1.26); p-value<0.001). About WBC the pooled result of 9 studies with 402 participants was (Mean: 5.11; 95% CI (3.90-6.32); p-value<0.001)

Inflammatory Markers increase in patients with Covid-19, which can be a good indicator to check patients.

There was a significant difference between the 2 groups in terms of D-Dimer (µg/mL) (W = 8523.000, p = <0.001), with the median D-Dimer (µg/mL) being highest in the Diabetes: Yes group.

Li Y, Zhaok et al[9] divided patients into three groups according to their clinical courses: an ordinary group (disease was mild or subsided, n = 136), an improved group (disease worsened first and improved gradually after treatment, n = 23)m and a poor group (disease worsened and deaths, n = 120) and tested the coagulation profile for 10 consecutive days after admission. median age of the 279 enrolled patients was 55·0 [interquartile range (IQR) 39·0–68·0]; it was highest in the poor group, followed by the improved group. Cardiovascular disease [n = 77 (27·6%)], respiratory disease [n = 29 (10·4%)], and endocrine disease [n = 35 (12·5%)] were the most common co-morbidities. On admission, D-dimer level was higher in the improved and poor groups than that in the ordinary group. The level decreased gradually in the improved group, but remained high in the poor group as the disease deteriorated.

Infection-induced coagulopathy and secondary hyper-fibrinolysis has been identified in severe cases of COVID-19. In addition, a higher D-dimer level on admission was related to a worse prognosis of COVID-19.

There was a significant difference between the 2 groups in terms of SpO2 (%) (W = 3484.000, p = <0.001), with the median SpO2 (%) being highest in the Diabetics. **Holman, N. et al.**[10] studied Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England and shows that increased COVID-19-related mortality is associated with glycaemic control and cardiovascular and renal complications of diabetes mellitus which were implicated in terms of severity by the levels of oxygen saturation in patients.

There was a significant difference between the 2 groups in terms of FBS (mg/dL) (W = 10172.500, p = <0.001), with the median FBS (mg/dL) being highest in the Diabetes: Yes group. PPBS (mg/dL) (W = 10309.500, p = <0.001), with the median PPBS (mg/dL) being highest in the Diabetes: Yes group and A1c (%) (W = 10965.000, p = <0.001), with the median A1c (%) being highest in the Diabetes: Yes group.

Thirunavukkarasu et al. studied New-onset diabetes in long COVID and Findings from these studies are supported by a recent Mendelian randomization analysis establishing a causal link between SARS-CoV-2 infection and NOD. Emerging evidence shows that NOD is also observed in the post-

acute COVID-19 phase, the so-called long COVID. In a retrospective cohort study of 47780 discharged COVID-19 patients (mean age 65 years) in England, the rate of NOD was 29 (95% CI, 26-32) per 1000 person-years over a mean follow-up of 4.6 months. In another retrospective cohort study of three data sources from a large United States health plan, among 193113 COVID-19 patients aged ≤65 years, NOD was the sixth most common post-acute clinical sequelae over a median follow-up of 2.9 months. Further, recent reports show an increase in new-onset type 1 diabetes, possibly linked to COVID-19, firstly in a US-based population and subsequently, in a cohort of children living in North West London. These clinical observations provide new evidence for new-onset diabetes in COVID-19 patients.[11]

There was a significant difference between the 2 groups in terms of PT (Sec) (W = 8275.000, p = <0.001), with the median PT (Sec) being highest in the Diabetes: Yes group. aPTT (Sec) (W = 7092.500, p = <0.001), with the median aPTT (Sec) being highest in the Diabetes: Yes group. INR (W = 8316.500, p = <0.001), with the median INR being highest in the Diabetes: Yes group.

Varikasuvu S.R.et al. [12] found that inCOVID-19 patients with diabetes have a significantly higher levels of coagulation dysfunction markers such as Fibrinogen (SMD = 0.31, CI 0.09–0.54, p = 0.007) and D-dimers (SMD = 0.54, CI 0.16–0.91, p = 0.005) than the non-diabetic COVID-19 cases.

Guoetal. [13] found that COVID-19 patients without other comorbidities but with diabetes (n = 24) were at higher risk of severe pneumonia, release of tissue injury related enzymes, excessive uncontrolled inflammation responses and hypercoagulable state associated with dysregulation of glucose metabolism. Furthermore, serum levels of inflammation-related biomarkers such as IL-6, C-reactive protein, serum ferritin and coagulation index, D-dimer, were significantly higher (P < .01) in diabetic patients compared with those without, suggesting that patients with diabetes are more susceptible to an inflammatory storm eventually leading to rapid deterioration of COVID-19.

YanY, YangY et al[14] studied 193 patients with severe covid-19, 48 (24.9%) had diabetes. Compared with patients with severe covid-19 without diabetes, patients with diabetes were older, susceptible to receiving mechanical ventilation and admission to ICU, and had higher mortality. In addition, patients with severe covid-19 with diabetes had higher levels of leukocyte count, neutrophil count, high-sensitivity C reaction protein, procalcitonin, ferritin, interleukin (IL) 2 receptor, IL-6, IL-8, tumor necrosis factor α, D-dimer, fibrinogen, lactic dehydrogenase and N-terminal pro-brain natriuretic peptide.

Conclusion and Recommendation

- Determining HbA1c level after hospital admission is thus helpful assessing inflammation, hypercoagulability, and prognosis of Post COVID-19 patients.
- Inflammatory Markers increase in patients with Covid-19, which can be a good indicator to find patients.
- The presence of diabetes could further influence the magnitude of inflammatory and coagulation dysfunction in Post COVID-19. Strikingly, a recent study showed a significant increase in these markers in diabetic group as compared to non-diabetic group of Post-COVID-19 patients without other comorbidities, indicating the independent impact of diabetes.
- However, little is known about the mechanism concerning the increase in the levels of inflammation markers and HbA1c level in case of post COVID-19 patients and more further studies are also required.
- Our data support the notion that diabetes should be considered as a risk factor for a rapid progression and bad prognosis of Post COVID-19. More intensive attention should be paid to patients with diabetes, in case of rapid deterioration.
- The mortality rate in patients with severe Post covid-19 with diabetes is considerable. Diabetes may lead to an increase in the risk of death.
- Hyperglycaemia in both diabetes and secondary hyperglycaemia patients with COVID-19 and Post COVID-19 may indicate poor prognosis. There were differences between patients with secondary hyperglycaemia and those with diabetes.

We recommend that clinicians pay more attention to the blood glucose status of Post COVID-19 patients, even those not diagnosed with diabetes before admission.

Once again, diabetes management in patients with Post COVID-19 poses a great clinical challenge, one that requires a much-integrated team approach, as this is an indispensable strategy to reduce the risk of medical complications and death as much as possible.

Conflicts of interest: No conflict of interest

Source of funding: There was no financial support concerning this work.

Ethical Clearance: A written informed consent was obtained from subjects prior to their inclusion in the study. The privacy of subjects and confidentiality of responses were assured. The study was approved by the Institute Ethical Committee of M.L.N. Medical College, Prayagraj, Uttarpradesh, India

References

1. Cucinotta D, Vanelli M .WHO declares COVID-19 a pandemic.Acta Biomed 2020; 91:157–160
2. Li J, Wang X, Chen J et al . COVID-19 infection may cause ketosis and ketoacidosis. Diabetes Obes Metab 2020. https ://doi.org/10.1111/dom.14057
3. International Diabetes Federation . 8th ed. 2017. IDF Diabetes Atlas.
4. Iglay K., Hannachi H., Joseph Howie P., Xu J., Li X., Engel S.S. Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus. Current Medical Research and Opinion. 2016;32(7):1243–1252.
5. Long A.N., Dagogo-Jack S. Comorbidities of diabetes and hypertension: mechanisms and approach to target organ protection. Journal of Clinical Hypertension. 2011;13(4):244–251.
6. Varikasuvu S R et al. Markers of coagulation dysfunction and inflammation in diabetic and non-diabetic COVID-19. Journal of Thrombosis and Thrombolysis https://doi.org/10.1007/s11239-020-02270-w
7. Zhang Y, Li H, Zhang J et al . The clinical characteristics and outcomes of diabetes mellitus and secondary hyperglycaemia patients with coronavirus disease 2019: a single-center, retrospective, observational study in Wuhan. Diabetes Obes Metab 22:1443–1454. https ://doi.org/10.1111/dom.14086
8. Vaseghi G et al. Inflammatory markers in Covid-19 Patients: a systematic R and meta-analysis. https:// doi.org/10.1101/2020.04.29.20084863
9. Yongli Yan, Yan Yang et al BMJ Open Diab Res Care 2020;8:e001343. doi:10.1136/bmjdrc-2020-001343.
10. Holman, N. et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population- based cohort study. Lancet Diabetes Endocrinol 2020;8, 823–833 .
11. Wang Z et al. Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients. https://doi. org/10.1016/j.diabres.2020.108214 0168-8227/_ 2020 Elsevier B.V
12. Varikasuvu SR et al. Markers of coagulation dysfunction and inflammation in diabetic and non-diabetic COVID-19. Journal of Thrombosis and Thrombolysis 2020;https://doi.org/10.1007/s11239-020-02270-w
13. Diabetes Metabolism Res Rev. 2020;e3319. wileyonlinelibrary.com/journal/https://doi. org/10.1002/dmrr.331.
14. Yongli Yan, Yan Yang et al BMJ Open Diab Res Care 2020;8:e001343. doi:10.1136/bmjdrc-2020-001343.