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Original Research Article

IMPACT OF DIABETES ON INFLAMMATORY, COAGULATION AND RADIOLOGICAL MARKERS IN HOSPITALISED COVID-19 PNEUMONIA PATIENTS

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ABSTRACT

Background: Diabetes has been suggested as a risk factor for increased severity in COVID-19 pneumonia patients. Accumulating evidence has suggested that inflammatory responses play a critical role in the progression of COVID-19. **Objective:** This study intends to evaluate the impact of diabetes on various inflammatory and coagulataory markers in COVID-19 pneumonia**. Methods:** This is a single centre retrospective observational study. Seven hundred thirty-one patients diagnosed with COVID-19 with or without diabetes were included in this study. Data was collected on admission or during hospitalization by attending physicians and documented in the form of electronic medical records. **Results:** Of the 731 hospitalized patients with COVID-19, the median age was 60 years and 528 (72%) were male and 331(45 %) were diabetic. Hospitalised COVID-19 patients with diabetes had significantly higher N:L ratio, LDH, Ferritin, CRP and D-dimer compared with those without diabetes. **Conclusion:** We concluded that hospitalised Covid-19 pneumonia with diabetes mellitus are associated with increased inflammatory activity and greater coagulation abnormality compared to nondiabetic patients.

Keywords: Diabetes, COVID-19.

INTRODUCTION

COVID-19 has led to a global pandemic affecting over 71 million people and 1.6 million deaths world-wide. India has reported over 10 million cases and over 0.15 million deaths, currently occupies the second spot among the countries with the highest case burden worldwide**. (1)** Social restriction measures have been adopted worldwide and health-care systems reorganised to cope with a growing number of severely ill patients. Many previous studies have found high prevalence of comorbidities like diabetes, cardio-vascular diseases, obesity, hypertension, and chronic obstructive pulmonary disease in severe case.**(2)** The fatality rate has been found to be higher in older age groups, in whom comorbid health conditions are common. Diabetes has been found to be associated with disease progression of COVID-19 and worst outcome.**(3)** Diabetic patients due to low pulmonary function have been reported to be more susceptible to intensive care admissions, mechanical ventilation and deaths due to COVID-19 than those without diabetes.**(4,5)** Several studies have reported various inflammatory and coagulability marker such as serum ferritin, C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen and D-dimers in relationship to disease severity and progression.**(6,7)** However, it remains to be studied better the underlying

pathophysiologic link between diabetes and more aggressive course of Covid-19 pneumonia in them.

MATERIALS AND METHODS:

Study Design and Participants: This was a single-Centre retrospective observational study of 731 patients admitted to Mahatma Gandhi Hospital & Medical College, one of the major hospitals designated to provide medical care for COVID-19 patients in Rajasthan, with COVID-19 pneumonia during the month of October and November 2020. The positive finding of viral nucleic acid by RT PCR Test was considered essential for the enrolment in study. Study data about age, sex, comorbidities, levels of illness severity (mild, moderate, severe, and asymptomatic), signs and symptoms, laboratory parameters, and computed tomography (CT) severity score, treatment options, need for oxygen therapy, need for intensive care unit admission, need for ventilatory support (non-invasive and/or invasive) and outcome were collected from electronic medical records of hospital. Prior approval from institutional ethics committee was obtained with waiver of informed consent as only blinded review of retrospective records was done.

Statistical Analysis: Normally distributed continuous variables are expressed as mean ± Standard deviation and non-normally distributed continuous variables as medians and interquartile ranges. Meanwhile, categorical variables are described as numbers and percentages. The independent t-test was conducted to compare continuous variables between the group of patients with diabetes and that of patients without diabetes. Meanwhile, the $\chi 2$-test was used to analyse the associations between categorical variables. Two-sided $p < 0{\cdot}05$ were considered as statistically significant, and all statistical analyses were performed using SPSS.

RESULTS:

We studied 731 patients admitted in our hospital with Covid-19 pneumonia between October and November. Out of these patients, 331 were found to have diabetes based on the positive history of diabetes and/or HBA1C ≥ 6.5 % during current admission and 400 were labelled as non-diabetic due to negative history of diabetes and HBA1C < 6.5 % during current admission. The median age of our hospitalised cohort was 60 years (IQR 12–97). Out of them, 528 patients (72%) were male, and 303 patients (28 %) were female.

Diabetics Vs Non-Diabetics: As per expectations, patients with diabetes had higher levels of glycated hemoglobin (7.36 % vs 5.8%). Patients with diabetes had higher levels of median neutrophil: lymphocyte ratio (N:L ratio) (7 vs 6.3 P value <0.05), CRP (49.8 mg/L vs 40 mg/L, P value <0.05), ferritin (286 µg/L vs 257µg/L, P value <0.05), D-dimer (316 ng/mL vs 279 ng/ml, P value <0.05). Mean CT severity score was 14 and 13 in diabetic and non-diabetic COVID-19 pneumonia patients respectively (P value: NS). These results indicated that Covid-19 patients suffering from old or recently diagnosed diabetes had more severe inflammatory response and coagulation abnormalities as compared to those without diabetes. However, lung involvement was not significantly different radiologically in Covid-19 patient with diabetes and without diabetes radiologically. (Table 1)

Poorly controlled (HBA1C > 9 %) vs well controlled Diabetics (HBA1C < 7 %): Patients with poorly controlled diabetes had significantly higher ferritin (324 µg/L vs 273µg/L, P value <0.05) and D-dimer (340 ng/mL vs 319 ng/ml, P value <0.05) levels while median N:L ratio (6.04 vs 6.4 P value <NS), CRP (64 mg/L vs 55 mg/L, P value <NS), IL-6 (26 vs16 P value <NS) were insignificantly increased. Some of these values indicated Covid-19 patients with poorly controlled diabetes had greater degree of inflammatory response and coagulation abnormalities compared to those with well controlled diabetes. COVID-19 pneumonia patients with poorly controlled diabetes had significantly high mean CT severity score (15 vs12 (P value<0.05). This indicates more extensive involvement of lungs radiologically in COVID-19 patients with uncontrolled diabetes compared to those with well controlled diabetes. **(Table 2)**

Diabetics with comorbidities Vs Isolated Diabetics: Covid-19 patients with diabetes and comorbidities had insignificantly higher median N:L ratio (7.52 vs 6.48 P value NS), CRP (60 mg/L vs 38 mg/L, P value NS), LDH (314 U/L vs 283 µg/L, P value NS), IL-6 (19.2 vs11.2 P value NS) compared to those with isolated diabetics. Mean CT severity score was also not different in two groups (14 in each group). This indicates no significant difference in the inflammatory response and coagulation abnormalities as well as extent of lungs involvement radiologically in diabetic COVID-19 patients with comorbidities compared to those without comorbidities. **(Table 3)**

Table 1. Inflammatory and Coagulatory markers in Diabetics vs Non-Diabetics

Variable	Total (N=731)	DM (N=331)	Non-DM (N=400)	p-value
AGE (Median, IQR) yrs	60 (12-97)	63 (29-97)	57 (12-93)	
M:F ratio	528:203	231:100	297:103	
HBA1C %	6.425 (5-15.83)	7.36 (5.49-15.83)	5.8 (5-6.44)	0.000001
N: L Ratio	6.73 (0.48-237)	7 (0.48-237)	6.27 (0.5-194)	0.01
Creatinine (Median, IQR) mg/dl	0.8 (0.3-16.2)	0.8 (0.3-16.2)	0.8 (0.3-16)	0.0009
SGPT (Median, IQR) U/L	35 (8-2905)	34 (8-530)	37 (8.2-2905)	0.0003
CRP (Median, IQR) U/L	46 (5-77.4)	49.75 (5-774.5)	40.2 (5-509)	0.008
LDH (Median, IQR) U/L	309 (0.09-43984)	307.4 (140-8084.1)	311 (3-43984)	0.02
Ferritin(Median, IQR) µg /l	281.35 (1.1-94969.1)	285.5 (10.2-4565)	277.1 (1.1-94969.1)	0.00007
Procalcitonin (Median, IQR) ng/ml	0.116 (0.017-315)	0.12(0.039-315)	0.109 (0.017-74)	0.59
3.IL-6 (Median, IQR) pg/ml	13.7 (0.2-1214)	16.9 (0.2-1214)	12.3 (1.4-752.6)	0.41
D-dimer (Median, IQR) ng/ml	314 (1.4-100000)	316.5 (120- 74700)	279.5 (1.4-100000)	0.01
CT severity score	14 (0-25)	14 (0-25)	13 (0-25)	0.43

Table 2. Inflammatory and Coagulatory markers in uncontrolled Diabetes (HbA1c >=9) & well controlled diabetics (HBA1C <7 %)

Variable	HbA1c > 9 (n=50)	DMHbA1< 7 (n=93)	p-value
AGE (Median, IQR) yrs	60 (36-83)	62 (35-83)	
M:F ratio	35:15	63:30	
HBA1C %	10.54 (9-15.83)	6.2 (0.7-50)	0.01
N: L Ratio	6.05 (1.4-20.6)	6.4 (5.5-7)	0.88
Creatinine (Median, IQR) mg/dl	0.8 (0.4-3.6)	0.8 (0.3-16.2)	0.84
SGOT (Median, IQR) U/L	38 (19-92.8)	41 (23-274)	0.039
SGPT (Median, IQR) U/L	33 (11-217.7)	37.1 (11.9-200)	0.13
CRP (Median, IQR) U/L	64.55 (5-397.3)	55 (5-393)	0.1
LDH (Median, IQR) U/L	338.4 (140-943)	299.9 (0.1-1428)	0.28
Ferritin (Median, IQR) µg /l	324 (11.5-1947.5)	273 (10.2-2272)	0.5
Procalcitonin (Median, IQR) ng/ml	0.093 (0.05-0.45)	0.09 (0.04-55)	0.4
IL-6 (Median, IQR) pg/ml	26.05 (1.8-712)	16.1 (0.2-498)	0.24
D-dimer (Median, IQR) µg/ml	340 (140-59500.4)	319 (120-5000)	0.15
CT severity score	15 (7-24)	12 (0-21)	0.03

Table 3. Inflammatory and Coagulatory markers in Diabetics with other co-morbidities vs Diabetics without other co-morbidities

Variable	Total (n=331)	DM with comorbidities(N=221)	DM without comorbidities(N=110)	p-value
AGE (Median, IQR) yrs	63 (29-97)	65 (29-97)	59.5 (30-86)	
M:F ratio	231:100	152:69	75:27	
HBA1C %	7.36 (5.49-15.83)	7.5 (5.5-15.8)	7.2 (5.49- 12.3)	0.28
N: L Ratio	7 (0.48-237)	7.52 (0.48-237)	6.48 (1.1-76)	0.39
Creatinine (Median, IQR) µmol/l	0.8 (0.3-16.2)	0.9 (0.4-16.2)	0.8 (0.3-7.4)	0.02
SGOT (Median, IQR) U/L	39.85 (18-961)	39 (18-961)	40.5 (18.6-274)	0.85
SGPT (Median, IQR) U/L	34 (8-530)	32 (8-530)	44.5 (8.7-302)	0.03
CRP (Median, IQR) U/L	49.75 (5-774.5)	60 (5-774)	38.3 (5-436)	0.18
LDH (Median, IQR) U/L	307.4 (140-8084.1)	314.5 (140-8084)	283.5 (0.09-2377)	0.69
Ferritin(Median, IQR) µg /l	285.5 (10.2-4565)	269 (10.2-4565)	324 (26.8-2272)	0.89
Procalcitonin (Median, IQR) ng/ml	0.12 (0.039-315)	0.13 (0.04-315)	0.09 (0.04-51)	0.61
IL-6 (Median, IQR) pg/ml	16.9 (0.2-1214)	19.2 (0.2-1214)	11.2 (1.8-712)	0.51
D-dimer (Median, IQR) µg/ml	316.5 (120-74700)	321 (120-100000)	354 (120-9250)	0.08
CT severity score	14 (0-25)	14 (0-25)	14 (0-24)	0.99

Table 4. Inflammatory and Coagulatory markers in Diabetics with other co-morbidities & Non-diabetics

Variable	**DM with other comorbidities (N=221)**	**Non-DM (N=400)**	**p-value**
AGE (Median, IQR) yrs	65 (29-97)	57 (12-93)	
M:F ratio	152:69	297:103	
HBA1C %	7.5 (5.5-15.8)	5.8 (5-6.44)	<0.001
N: L Ratio	7.52 (0.48-237)	6.27 (0.5-194)	0.04
Creatinine (Median, IQR) mg/dl	0.9 (0.4-16.2)	0.8 (0.3-16)	0.02
SGOT (Median, IQR) U/L	39 (18-961)	143 (4.83-4438)	0.001
SGPT (Median, IQR) U/L	32 (8-530)	37 (8.2-2905)	0.002
CRP (Median, IQR) U/L	60 (5-774)	40.2 (5-509)	0.04
LDH (Median, IQR) U/L	314.5 (140-8084)	311 (3-43984)	0.06
Ferritin(Median, IQR) µg /l	269 (10.2-4565)	277.1 (1.1-94969.1)	0.0005
Procalcitonin (Median, IQR) ng/ml	0.13 (0.04-315)	0.109 (0.017-74)	0.76
IL-6 (Median, IQR) pg/ml	19.2 (0.2-1214)	12.3 (1.4-752.6)	0.56
D-dimer (Median, IQR) µg/ml	321 (120-100000)	279.5 (1.4-100000)	0.06
CT severity score	14 (0-25)	13 (0-25)	0.41

Diabetics with Comorbidities Vs Non-Diabetics: Patients with diabetes and other comorbidities had significantly higher median N:L ratio (7.52 vs 6.27 P value <0.05), CRP (60 mg/L vs 40 mg/L, P value <0.05), ferritin (269 µg/L vs 277 µg/L, P value <0.05), D-dimer (321 ng/mL vs 279 ng/ml, P value NS). Mean CT severity score was 14 and 13 in diabetics with comorbidities and non-diabetic COVID-19 pneumonia patients respectively (P value: NS). Diabetic Covid-19 patients with comorbidity had more severe inflammatory response compared to those without comorbidity. However, lung involvement was not significantly different in diabetic Covid-19 patient with comorbidity compared to nondiabetic patients radiologically. (Table 4)

Table 5. Inflammatory and Coagulatory markers in Isolated Diabetics & Non-Diabetics

Variable	DM without other comorbidities (N=110)	Non-DM (N=400)	p-value
AGE (Median, IQR) yrs	59.5 (30-86)	57 (12-93)	
M:F ratio	75:27	297:103	
HBA1C %	7.2 (5.49- 12.3)	5.8 (5-6.44)	<0.01
N: L Ratio	6.48 (1.1-76)	6.27 (0.5-194)	0.84
Creatinine (Median, IQR) mg/dl	0.8 (0.3-7.4)	0.8 (0.3-16)	0.06
SGOT (Median, IQR) U/L	40.5 (18.6-274)	143 (4.83-4438)	0.23
SGPT (Median, IQR) U/L	44.5 (8.7-302)	37 (8.2-2905)	0.39
CRP (Median, IQR) U/L	38.3 (5-436)	40.2 (5-509)	0.65
LDH (Median, IQR) U/L	283.5 (0.09-2377)	311 (3-43984)	0.58
Ferritin(Median, IQR) µg /l	324 (26.8-2272)	277.1 (1.1-94969.1)	0.47
Procalcitonin (Median, IQR) ng/ml	0.09 (0.04-51)	0.109 (0.017-74)	0.98
IL-6 (Median, IQR) pg/ml	11.2 (1.8-712)	12.3 (1.4-752.6)	0.29
D-dimer (Median, IQR) µg/ml	354 (120-9250)	279.5 (1.4-100000)	0.42
CT severity score	14 (0-25)	13 (0-25)	0.26

Isolated Diabetics Vs Non-Diabetics: There was no significant difference in median N:L ratio, CRP, ferritin, IL-6, D-dimer in Covid-19 patient with isolated diabetes and non-diabetic Covid-19 patients. Mean CT severity score was 14 and 13 in isolated diabetic and non-diabetic COVID-19 pneumonia patients respectively (P value: NS). These results indicated no significant difference in the inflammatory response as well as extent of lungs involvement in isolated diabetic COVID-19 patients compared to those without diabetes. **(Table 5)**

DISCUSSION:

These results show that the inflammatory and hypercoagulability markers significantly increase in diabetic group of COVID-19 patients when compared to their non-diabetic counterparts.

People with diabetes are more susceptible to certain infectious diseases, such as staphylococcus aureus and mycobacterium tuberculosis, possibly because of their dysregulated immune system.**(7)** Recently, COVID-19 has been a focal topic of research, and several investigators have focused on diabetes as a predictor of clinical course and prognosis of COVID-19 cases.**(8-11)** A systematic review by Huang et al. revealed that diabetes was associated with mortality, increased severity and acute respiratory distress syndrome in patients with COVID-19.**(11)** Certain other studies found that diabetes negatively affected medical complications, including mortality in COVID-19 cases.**(9,10)** Currently, the exact mechanisms behind worse outcome in diabetics with Covid-19 pneumonia is not known. SARS-CoV-2 virus infects cells of the upper respiratory tract, epithelial cells of the lung alveoli and immune cells (CD3, CD4, and CD8 T

cells) causing apoptosis of lymphocytes.**(12,13)** Predominant affection of T cells of adaptive immunity might lead to overstimulation of the innate immune system and increase the secretion of various cytokines.**(13,14,15)** The over-production of these pro-inflammatory cytokines (TNFα, IL-6, IL-1β, and CXC-chemokine ligand 10) might result in a state of cytokine storm, which may lead to vascular hyperpermeability, multiorgan dysfunction syndrome(MODS), and death.**(13,16)** High serum concentrations of inflammatory biomarkers like C-reactive protein, procalcitonin, ferritin as well as a high neutrophil-to-lymphocyte ratio has been found to be associated with both increased COVID-19 severity and death.**(13,17,18,19)** Patients with diabetes may have dysregulated inflammatory innate and adaptive immune. As diabetes is characterised by low-grade chronic inflammation, the possibility of cytokine storm is also more likely. Diabetes results in a proinflammatory homeostatic immune response skewed towards helper T cell 1 (Th1) and T17 cells and a decrease in regulatory T cells (Treg).**(13,20)** In patients with high viral load, the ability to raise an acute inflammatory immune response might also be compromised in diabetic patients, exposing them to worst outcome. One study reported that diabetic patients with COVID-19 had a higher concentration of inflammatory bio markers, such as C-reactive protein, IL-6, serum ferritin , and a higher erythrocyte sedimentation rate, as compared with patients with non- diabetic COVID-19 patients.**(13,21)** These results were supported by findings from a multicenter study of patients with COVID-19 (952 with diabetes and 6385 without diabetes)in China , showing that diabetic patients had more prevalence of lymphopenia (44·5% vs 32·6%), and raised inflammatory biomarkers (C-reactive protein 57·0% vs 42·4% and procalcitonin 33·3% vs 20·3%].13,22 Diabetic patients with Covid-19 are more susceptible to the harmful effects of the cytokine storm as compared to non-diabetics. COVID-19 has also been found to be associated with hypercoagulability. **(13,23)** The endothelial dysfunction associated with hypoxia can favor intra-vascular coagulation during COVID-19 infection. Post-mortem studies have found abnormal lung vasculature, massive pulmonary interstitial fibrosis, variable degrees of hemorrhagic pulmonary infarction, severe endothelial injury, wide-spread intra vascular thrombosis with occlusion of alveolar capillaries, damaged capillaries, and growth of abnormal vessels through a mechanism of intussusceptive angiogenesis. **(13,24)** Moreover, intravascular disseminated coagulation can be a life-threatening event in severe COVID-19, and anticoagulant therapy has been shown to improve the prognosis.**(13,25,26)** Diabetes leads to a prothrombotic state, with a dysregulation between clotting and fibrinolysis and a higher risk of thromboembolic events. **(13,27)** In a retrospective study from China, diabetic patients admitted to hospital with COVID-19, deceased patients had a longer prothrombin time and higher D-dimer concentration.**(4)** COVID-19 cases with diabetes may often have other risk factors such as high body weight, advance age, that could aggravate the pro-coagulant state and the risk of thrombotic events.**(13)**

Our study has several limitations that need to be addressed. Firstly, it was a retrospective study involving only hospitalised patients leading to a recruitment bias as asymptomatic patients and those with mild symptoms were less likely to be enrolled. Significant proportion of Covid-19 patients with diabetes had coexisting conditions in our studies. Therefore, further well controlled studies are needed in future to establish an independent role of diabetes in COVID-19.

CONCLUSION

In our study, we found that diabetes mellitus is associated with greater disease severity and poor outcomes including death. Stronger personal prophylactic strategies are advised for patients with diabetes, and more intensive surveillance and treatment should be considered when they are infected with COVID-19.

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