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Comparison of Inflammatory Markers and Lung Involvement Between Diabetic And Non Diabetic Covid-19 Patients

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ABSTRACT:
INTRODUCTION: *Diabetic patients who develop COVID-19 have been seen to have a worse prognosis and increased mortality in most studies. The reason for increased severity of COVID-19 infection in diabetes is unclear. Since the onset of the corona virus disease pandemic in 2019 (COVID-19), numerous studies have attempted to identify laboratory predictors of the course of this disease. Identification of laboratory biomarkers associated with COVID-19 has also shed light on pathological mechanisms of the disease.*
OJECTIVE: *The objective of this study is to compare the inflammatory markers (CRP, Ferritin, CK, LDH, D-dimer and NLR) in COVID- 19 patients with and without diabetes and to compare the association of diabetes with the severity of COVID- 19 based on lung involvement.*
MATERIALS AND METHODS:
We retrospectively collected laboratory data of 100 RT-PCR and radiologically confirmed covid 19 patients from Rajiv Gandhi Govt general Hospital in Chennai during the period May 2020 to July 2020 for whom the inflammatory markers such as CRP, Ferritin, CK, LDH, D-dimer, NLR were tested at admission. The participants were divided into 2 groups: as Group1- 50 type 2 diabetics with COVID-19 and Group2 : 50 non diabetes COVID-19 patients based on previous history of Diabetes mellitus. CT findings were evaluated at admission in both groups and categorised as those with less than 50 % and more than 50% lung involvement.
RESULTS:
The mean values of CRP (127.25 ± 38.17), Ferritin, (922.61 ± 186.78) and NLR (14.71 ± 4.41) in Diabetic COVID-19 patients showed 4 fold rise when compared to non diabetic COVID-19 patients CRP (27.86 ± 5.57), Ferritin (248.33 ± 49.66) and NLR (4.22 ± 0.84). The mean value of D-dimer (1.64 ± 0.49) in diabetics COVID-19 patients showed 3 fold rise when compared to non diabetic COVID-19 patients D-dimer (0.58 ± 0.12).The mean value of CK (176.93 ± 53.07) and LDH (423.04 ± 126.09) in diabetics COVID 19 patients showed 2 fold rise when compared to non diabetic COVID 19 patients CK (78.94 ± 15.78) and LDH (254.06 ± 50.81). The Bilateral lung involvement in diabetic group had a wider distribution (>50% lung involvement) than those with non diabetic COVID-19 patients (<50% lung involvement).
CONCLUSION:
Diabetic COVID 19 patients appears to be at higher risk of severe illness from COVID 19 than those without diabetes due to ongoing inflammation, impaired immune response, which entails them to have worse prognosis.
KEY WORDS: *Inflammatory markers, Covid-19, Diabetes, Ferritin.*

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I. Introduction

The high prevalence of diabetes globally makes it a frequent comorbidity in patients with coronavirus-associated disease 2019 (COVID-19). Diabetic patients who develop COVID-19 have been seen to have a worse prognosis and increased mortality in most studies [1,2]. Meta-analysis of nine studies from China (n = 1936) have shown a significant correlation between severity of COVID-19 and diabetes [3]. A study across 88 centres in USA including 1122 COVID-19 pateints, found diabetes to be associated with more than fourfold increase in mortality [4].

The reason for increased severity of COVID-19 infection in diabetes is unclear. Poor glycaemic control impairs several aspects of the innate and adaptive immune response to viral infections and also potentiating the secondary bacterial infection in the lungs is one of the reasons of increased severity [5,6]. Zhu et al. found that a well-controlled blood glucose level was associated with lower mortality as compared to individuals with poorly

controlled blood glucose level in patients with COVID-19 and those with pre-existing type 2 Diabetes [7]. Defective or inappropriateT-cell action, impaired natural killer cell activity and defects in complement action could reduce viral clearance in diabetes [8]. Since the onset of the coronavirus disease pandemic in 2019 (COVID-19), numerous studies have attempted to identify laboratory predictors of the course of this disease [9,10]. The laboratory tests includes increased levels of C-reactive protein, lactate dehydrogenase (LDH) , Ferritin, interleukin 6 (IL6), Creatine kinase, D-dimer and Neutrophil Lymphocyte ratio. These laboratory markers were shown to indicate patients with poor prognosis at an early stage of the disease [11]. Identification of laboratory biomarkers associated with COVID-19 has also shed light on pathological mechanisms of the disease. In this context, it is important to note that there are strong associations between type 2 diabetes, obesity, abnormal secretion of adipokines and cytokines like TNF-alfa and interferon, which would further impair immunity and predispose to severe infection [12].

The immune system has a strong sense of distinguishing self from non-self. It kills foreign pathogens or molecules that come in its way. Unfortunately, the immune system sometimes commences exaggerated response and become so hyperactive that instead of killing non-self, it starts to kill the self-antigens. Cytokine storm is an example of a hyperactive immune response. It's termed as "storm" since the immune system cells are being hyperactive, releasing large amounts of cytokines. When the system is continually challenged, as in case of SARS(Severe Acute Respiratory Syndrome) and MERS(Middle East Respiratory Syndrome) studies show evidence of increased circulating levels of pro-inflammatory cytokines (e.g., Interferon γ, Interleukin (IL-1B, IL-6, IL-12) and Chemokines (CXCL10, and CCL2) which were responsible for severe pulmonary inflammation.

Further, diabetes is associated with increased plasminogen levels which have been postulated to increase the virulence of SARS CoV-2 [13]. SARS CoV-2 enters the cell by binding to ACE2, a multistep process which involves several enzymes and proteins [14]. There is experimental evidence for downregulation of ACE2 in diabetes [15], which may predispose to more severe lung injury. Increased viral replication in diabetes may also due to an increase in furin, a type-1 membrane bound protease involved in the entry of corona viruses into the cell [16].

The objective of this study is to compare the inflammatory markers (CRP, Ferritin, CK, LDH, D-dimer and Neutrophil-Lymphocte ratio[NLR]) in COVID- 19 patients with and without diabetes and to compare the association of diabetes with the severity of COVID- 19 based on lung involvement.

II. Materials And Methods

We retrospectively collected laboratory data of 100 RT-PCR and radiologically confirmed covid 19 patients from Rajiv Gandhi Govt general Hospital in Chennai during the period May 2020 to July 2020 for whom the inflammatory markers such as CRP, Ferritin, CK, LDH, D-dimer, NLR were tested at admission. We also collected the clinical information of the patients, including age, sex, clinical history of hypertension, heart disease, and type 2 diabetes and CT findings of patients' lungs at admission. The participants were divided into 2 groups: as Group1- 50 type 2 diabetics with COVID-19 and Group2 : 50 non diabetes COVID-19 patients based on previous history of Diabetes mellitus. CT findings were evaluated at admission in both groups and categorised as those with less than 50 % and more than 50% lung involvement.

STATISTICAL ANALYSIS

Statistical analysis of data was performed using SPSS software version 23. Independent t-test and Chi-square test were used for statistical analysis. The minimum value of the level of statistical significance, p-value, in all statistical tests was set at 0.05.

III. Results

TABLE no 1 : Comparison of Variables between the Group 1 (Diabetic COVID-19) and Group 2 (Non Diabetic COVID-19)

	GROUP 1 (DIABETIC COVID-19)	GROUP 2 (NON DIABETIC COVID-19)	P-value
Age	56 ± 12.439	54.44 ± 12.04	56.60*
Gender	34 (68%)	25 (50%)	The Chi-square value is 3.34. (P-Value > 0.05)
	16 (32%)	25 (50%)	

TABLE- 1 shows Comparison of Variables like age and sex between the Groups. Group I: 50 diabetic patients diagnosed with COVID-19 had a mean age of 56 years, Out of which 34 (68%) were male patients and 16(32%) were female patients. Group 2 : 50 non diabetic patients diagnosed with COVID-19 had a mean age of 55 years, Out of which 25 (50%) were male patients and 25(50%) were female patients.

Table no 2: Comparison of the Inflammatory markers between the Group 1 (Diabetic COVID-19) and Group 2 (Non Diabetic COVID-19)

INFLAMMATORY MARKERS	GROUP 1 (DIABETIC COVID-19)	GROUP 2 (NON DIABETIC COVID-19)	P-value
NLR	14.71 ± 4.41	4.22 ± 0.84	<0.05
CRP	127.25 ± 38.17	27.86 ± 5.57	<0.05
FERRITIN	922.61 ± 186.78	248.33 ± 49.66	<0.05
D- DIMER	1.64 ± 0.49	0.58 ± 0.12	<0.05
LDH	423.04 ± 126.09	254.06 ± 130.37	<0.05
CK	176.93 ± 53.07	78.94 ± 67.38	<0.05

Table-2 shows comparison of Inflammatory markers like CRP, Ferritin, CK, LDH, D-dimer and NLR in Diabetic COVID-19 patients with non diabetic COVID-19 patients. Independent t-test showed statistically significant difference of mean ($p< 0.05$) between Diabetic COVID-19 patients with non diabetic COVID-19 patients irrespective of age and sex. The mean values of CRP (127.25 ± 38.17), Ferritin, (922.61 ± 186.78) and NLR (14.71 ± 4.41) in Diabetic COVID-19 patients showed 4 fold rise when compared to non diabetic COVID-19 patients CRP (27.86 ± 5.57), Ferritin (248.33 ± 49.66) and NLR (4.22 ± 0.84). The mean value of D-dimer (1.64 ± 0.49) in diabetics COVID-19 patients showed 3 fold rise when compared to non diabetic COVID-19 patients D-dimer (0.58 ± 0.12).The mean value of CK (176.93 ± 53.07) and LDH (423.04 ± 126.09) in diabetics COVID 19 patients showed 2 fold rise when compared to non diabetic COVID 19 patients CK (78.94 ± 15.78) and LDH (254.06 ± 50.81).

Table no 3: Comparison of the Severity of Lung Involvement by CT Chest between the Group 1 (Diabetic COVID-19) and Group 2 (Non Diabetic COVID-19)

CT Chest findings Grade (LUNG INVOLVEMENT)	GROUP 1 (DIABETIC COVID-19)	GROUP 2 (NON DIABETIC COVID-19)	P-value
Severity Score <50 %	21	45	The Chi-square value is 25.66. (P-Value is <0.05)
Severity Score >50 %	29	5	

Table-3 shows Comparison of the Severity of Lung Involvement by CT Chest between the Groups. The Bilateral lung involvement in diabetic group had a wider distribution (>50% lung involvement) than those with non diabetic COVID-19 patients (<50% lung involvement).

IV. Discussion

Type 2 diabetes is viewed as a chronic, low-grade inflammatory disease caused by metabolic syndrome, long term immune system imbalance, or nutrient excess associated with obesity [17,18]. Viral infection may cause sharp fluctuation of blood glucose level of diabetes patients, which may adversely affect the recovery of patients. It had been reported that a known history of diabetes was an independent predictor for morbidity and death in patients with SARS [19]. There is a reason to suspect that diabetes combined with SARS-CoV-2 pneumonia may form a vicious circle, which is detrimental to the prognosis of COVID-19.

Reports showed that ICU patients, non-ICU patients and recovering patients differ in CT imaging result which shows that CT results can be used as one of the indicator for determining the severity of the SARSCoV- 2 pneumonia [20]. According to the quantifiable score, we found that the diabetes group presented with a higher CT imaging score compared with non-diabetes group, which means pneumonia in diabetic patients is more severe compared to non-diabetic patients

In the present study we aimed to compare the inflammatory markers and severity of lung involvement in diabetic and non diabetic COVID 19 patients. In terms of laboratory results, our analysis revealed elevated CRP, ferritin and NLR in both the group of patients who were admitted to hospital, suggesting the close relation of SARS-CoV 2 infection and inflammation [21]. But there were obvious differences in the mean of inflammatory markers between diabetics and non diabetic COVID- 19 patients. It is important to note that the levels of these

enzymes were even higher in patients with diabetes when compared to patients without diabetes, which give us a clue that the injury of organs was much more serious in diabetes patients group than those without diabetes.

Yang et al. reported that lymphocytopenia occurred in more than 80% of critically ill patients with COVID-19 [22]. In our study, patients with diabetes and COVID-19 at admission had a higher Neutophil Lymphocyte ratio. The severity of lymphocytopenia may reflect the aggravation of the disease. Lymphocytopenia is a prominent feature of critically ill patients with COVID-19 because targeted invasion by SARS-CoV viral particles damages the cytoplasmic component of the lymphocyte and causes its destruction [23].

As one of the most distinctive acute phase reactants, CRP can increase rapidly after the onset of inflammation, cell damage or tissue injury. Pulmonary diseases with inflammatory features usually raise serum CRP level in response to inflammatory cytokines such as IL-6, IL-1 or TNF-α. CRP levels can activate the complement and enhance phagocytosis, thus clearing the pathogenic microorganisms invading the body. CRP levels can be used for early diagnosisof pneumonia, and patients with severe pneumonia had high CRP levels[24]. It is an important index for the diagnosis and assessment of severe pulmonary infectious diseases [25]. In our study, CRP levels at admission in Diabetic COVID 19 patients showed a four fold rise when compared to non diabetic COVID 19 patients. Zhou et al. study indicated that as one of the indices for assessing the severity of lung injury, the level of CRP was significantly higher in COVID-19 patients with diabetes than in the control group. Matsumoto's study also showed that CRP levels and the diameter of the largest lung lesion increased as the disease progressed [26]. Thus CRP levels were positively correlated with lung lesion and disease severity. This suggests that in the early stage of COVID-19, CRP levels could reflect lung lesions and disease severity.

Serum ferritin concentrations have been shown to reflect the status of iron stores in healthy Individuals. Ferritin being an acute-phase-protein is increased in both infectious and noninfectious inflammation. High concentrations referred to as hyperferritinemia are observed in septic shock, macrophage activation syndrome (MAS), Still's disease in adults and catastrophic antiphospholipid syndrome (CAPS) [27]. In several studies of the inflammatory biomarker, characteristic of patients with laboratory confirmed SARS-CoV-2 infection, serum ferritin seems to be relevant for assessing the disease severity and outcome of patients. The extreme elevation of serum ferritin in critically ill patients with COVID 19 in conjunction with additional clinical and laboratory features prompted the suggestion that COVID-19 may be the fifth member of hyperferritinemic syndromes [22]. In our study, patients with diabetes with COVID-19 at admission had a higher ferritin levels. But studies have suggested that serum ferritin composed of H -subunit expression is driven by inflammatory stimuli and H-ferritin may work as an immunomodulatory molecule, displaying both pro-inflammatory and immunosuppressive functions [27,28]. Moreover, analysis of the glycosylation of serum ferritin could contribute to a better understanding of the role of serum ferritin in COVID-19, since a decrease of the glycosylated fraction of serum ferritin has been proposed as a marker of excessive macrophage activation [29].

D-dimer is an activation marker of fibrinolysis. Some studies have shown that D-dimer is a significant prognostic factor in patients with pneumonia and sepsis [30,31]. In our study, D-dimer levels at admission were quite different between the diabetic and nondiabetic COVID 19 patients. Guozhen Li et al. found that patients with COVID-19 with higher level of D-dimer at admission, especially those with diabetes, are significantly associated with the risk of death[32]. Magro et al. reported that severe COVID-19 infection was associated with microvascular injury and thrombosis [33]. In patients with diabetes with signs of microangiopathy, the lung's diffusion capacity was significantly reduced[34].

Chest CT plays an important role in COVID-19 screening, primary diagnosis, and evaluation [35]. Chest computed tomography (CT) most commonly shows ground-glass opacifications with or without consolidative abnormalities. They are also more likely to be bilateral, have a peripheral distribution and involve the lower lobes [36]. While some confirmed cases may present normal CT images, abnormalities have also been identified prior to the development of symptoms in some patients. In all cases, a semi-quantitative CT severity scoring proposed by Pan et al was calculated considering the extent of anatomic involvement [36]. Type 2 Diabetes causes a micro-vascular damage in patients with lung disease[37]. Patients with Type 2 Diabetes patients present frequently with respiratory symptoms and are at increased risk of several pulmonary diseases [37]. Type 2 Diabetes lead to alveolar capillary micro-angiopathy and interstitial fibrosis via over-inflammation 37. Several molecular mechanisms induced by over-inflammation have been suggested to explain the micro-vascular disease, and the consequent endothelial dysfunction and damage in lungs of patients with Type 2 Diabetes. In our study, the bilateral pulmonary lesions of COVID-19 patients in the diabetes group had a wider distribution than those in the non diabetes group .

V. conclusion

The COVID-19 global pandemic poses considerable health hazards, especially for patients with diabetes mellitus. Diabetic COVID 19 patients appears to be at higher risk of severe illness from COVID 19 than those without diabetes due to ongoing inflammation, impaired immune response, which entails them to have worse prognosis. Meticulous attention should be paid to the management of blood glucose in COVID 19

with diabetes, and anti-inflammatory therapy combined with immunomodulation may be considered as one of the effective treatment methods.

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