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Impact of inflammatory markers in diabetic SARS-CoV-2 critically ill patients

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Abstract: *Introduction:* Covid patients have elevated inflammatory markers especially in those with comorbid conditions like diabetes. The study aimed to compare the inflammatory response in critically ill SARS CoV-2 diabetic and non-diabetic subjects admitted in ICU. *Methodology:* A retrospective data collection study was conducted on113 critically ill SARS CoV-2 patients admitted in ICU. The data of C-reactive protein, ferritin, LDH, RBS and glycated hemoglobin were collected from laboratory. The duration of stay, diabetic and mortality status were collected from electronic repository of the hospital. Independent 't' test and Mann Whitney U test were used for parametric and non-parametric data respectively to compare the study groups. Chi-square analysis done for categorical variables. Spearmann correlation was used to correlate inflammatory markers with HbA1c. *Results:* Serum ferritin, LDH and CRP was elevated in diabetic population and was found to be statistically significant with CRP (p value 0.034). Duration of stay in hospital was reduced in diabetes (p value 0.033). Positive correlation of HbA1c was seen with CRP and LDH but found to be statistically significant only with CRP (r = 0.179, p = 0.040). *Conclusion:* **S**tudy concluded that inflammatory markers CRP, ferritin and LDH were comparatively elevated in diabetic versus non diabetic SARS CoV-2 patients.
Keywords: SARS CoV-2, Diabetes Mellitus, C-reactive protein, Ferritin, Lactate dehydrogenase.

Introduction

Highly pathogenic virus of coronavirus family labelled as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has a wide spectrum of hosts in nature. It affects different organ systems such as respiratory system, cardio-vascular system, renal system, hepatobiliary system, muscular and nervous system in, there by causing varied manifestations in patients [1-2].

The severe covid-19 infection is characterized by unrestricted secretion of cytokines, leading to cytokine release syndrome (CRS) [3]. People with co-morbid conditions like cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, hypertension, malignancy and elderly age group are more susceptible to develop cytokine storm, septic shock and other organ system involvement [3]. Diabetes is considered to influence the course and prognosis of COVID-19 illness, though the association of glycated hemoglobin (HbA1C) levels with inflammation and prognosis of COVID-19 cases has not yet been explored fully [4]. C-reactive protein (CRP) is produced from liver in response to IL-6 stimulation, which is found in higher levels in severe COVID-19 with CRS. Apart from this, fibrinogen, ferritin and lactate dehydrogenase (LDH) also tally with IL-6 levels in plasma. Accordingly, the current study was conducted to compare inflammamtory response in terms of serum ferritin, LDH and CRP in critically ill diabetics and nondiabetics SARS CoV-2 patients admitted in ICU (Intensive care unit).

Material and Methods

The current retrospective data collection study, spread over a period of six months from March 2020 to December 2020 was conducted

on one hundred and twenty-five consecutive covid positive patients who were admitted in ICU of tertiary care hospital for specialized care. Twelve patients were excluded from the study due to incomplete data. All covid cases were confirmed with Real Time Polymerase chain reaction (RT-PCR).

Patient data which includes age, gender, diabetic history, or mortality were captured from electronic repository. Laboratory inflammatory markers viz. Serum ferritin, LDH and CRP and HbA1c and RBS details were also collected. The captured data was spread on the excel sheet for further analysis. Patients were categorized in to two groups based on the HbA1c level as diabetes and non diabetes. All the patient details were collected after obtaining institutional ethical clearance.

Inclusion criteria: All patients who were positive for covid-19 by real-time polymerase chain reaction (RT-PCR) of both gender admitted to the intensive care unit were included in the study.

Exclusion criteria: Patients with incomplete laboratory data were excluded in the study. Patients with RT-PCR positive who were not admitted to ICU.

Statistical analysis: Normality distribution of the data was checked by Shapiro Wilk's test. Mean and SD for continuous data, and frequency (percentage) for categorical variables were calculated. Independent 't' test and Mann Whitney U test were used for parametric and non-parametric data respectively to compare the two study groups mean or median. Chi-square analysis was used for categorical variables. Spearmann correlation was used to assess the correlation of inflammatory markers with HbA1c and RBS. All p values < 0.05 were considered significant. SPSS version 23.0 was used for statistical analysis.

Results

Out of 125 screened patients only 113 patients with complete data were included in the study. Among them 77 were diabetic and 33 were non diabetic. Descriptive statistics of study variables is shown in Table 1. Comparison of inflammatory markers between the groups based on diabetic status is shown in Table 2.

Table-1: Descriptive statistics of study variables

Parameters	Whole study group (mean ±SD)
Age (yrs)	58.97 ± 15.5
Male: Female	79:33
Duration of stay (days)	10.90 ± 8.38
RBS (mg/dL)	214.7 ± 132.6
HbA1c (%)	8.4 ± 2.9
CRP (mg/L)	68.4 ± 28.3
Ferritin (µg/L)	577.4 ± 363.4
LDH (U/L)	521.2 ± 391.1
Diabetes : Non diabetic	64 : 29

RBS- random Blood sugar, HbA1c – Glycated hemoglobin, CRP – C-reactive protein, LDH – Lactate dehydrogenase

Table-2: Descriptive statistics between groups based on diabetes status

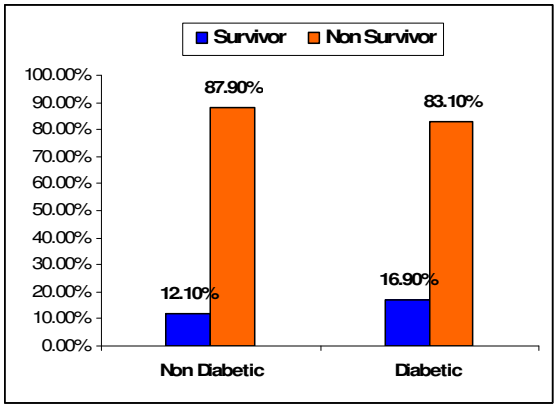
Parameters	Diabetic (n=77)	Non diabetic (n=33)	P value
Age (yrs)	61.8 ± 12.7	52.2 ± 19.4	0.008
Male : Female	50:29	29:4	0.006
Duration of stay (days)	10.65 ± 9.2	11.4 ± 6	0.033
RBS (mg/dL)	261.6 ± 13.4	102.6 ± 22.4	0.000
HbA1c (%)	9.6 ± 2.7	5.7 ± 0.6	0.000
CRP (mg/L)	70.1 ± 25.4	60.7 ± 33.5	0.004
Ferritin (µg/L)	594± 39.4	570.9±353.9	0.168
LDH (U/L)	535.5 ± 413	487.5 ± 33.9	0.238

RBS- random Blood sugar, HbA1c – Glycated hemoglobin, CRP – C-reactive protein, LDH – Lactate dehydrogenase. P value of < 0.05 is considered statistically significant.

Discussion

The present study was conducted to assess the inflammatory response in terms of serum ferritin, LDH and CRP in critically ill SARS CoV-2 diabetic and compare it with non-diabetics. The study found that the said inflammatory markers were elevated in diabetic covid patients. Elevated blood glucose levels and glycolysis support the replication of SARS-CoV-2 by way of activation of hypoxia-inducible factor 1α and synthesis of mitochondrial reactive oxygen species [5]. Higher the HbA1c level, more severe is the disease. Majority of critically ill covid patients were diabetic (Table 1).

Fig-1: Mortality status in diabetic and non diabetic



Average duration of stay for diabetics was less compared to nondiabetic because of increased mortality (Fig 1). With the upgrading of generations, of SARS-CoV-2, in turn reduces the time lapse between the admission and critical condition, resulting in added seriousness in the illness [6]. Although significant number of cases are asymptomatic or have mild symptoms, 15% develop severe pulmonary disease, compromised respiratory functions advancing towards coagulopathies, multiorgan failure and death. Despite of state of art care to critically ill patients, in the form of ventilatory support, oxygen supplementation, the mortality rate is high [7].

For clinical continuance of SARS CoV-2, a cross talk between innate and adaptive immunity is important [8]. The cytokine storm is a result of an aggravated dysfunctional immune response which is unable to tolerate viral load [9].

CRP is synthesized in liver in response to inflammation [10]. In present study, the chosen inflammatory markers, CRP, ferritin and LDH were elevated in diabetic subjects compared to nondiabetics. But only CRP elevation was found to be statistically significant (Table 2).

Similar results of elevated CRP in COVID 19 patients were found by Zhu N *et al.,*[11]. As per the study conducted by Wang G *et al.,* the CRP level was significantly higher in critical patients than the ones with less critical illness. This indicated that CRP can be a biomarker for the severity of COVID-19 disease. It can also be considered as a prime indicator of progression of disease in non-serious COVID-19 cases [12]. Ruan *et al*., 2020 also found significantly elevated CRP in non survivors compared to survivors [13].

Ferritin can indicate damage to cells in addition to inflammation process [14]. Ferritin and LDH are other surrogate markers of severe covid illness. Increased serum ferritin is as a result of CRS and secondary haemophagocytic lymphohistiocytosis (sHLH). sHLH is a hyperinflammtory syndrome accompanied by hypercytokinemia resulting in multiorgan failure, most often triggered by viral infections [15].

In a cross-sectional study conducted by Zhan y *et al*; [16] diabetic patients had significantly high serum ferritin. The elevated levels of ferritin was considered as a mortality predictor in a multicentric retrospective study in Wuhan [13]. As per meta analysis conducted by Zeng *et al*., ferritin levels can be used to categorize the severity in COVID-19 patients [17]. We found a significant positive correlation of CRP with HbA1c (Table 3).

Wang Z *et al*; also found a significant positive correlation of CRP and ferritin with HbA1c [4]. In their study, elevated serum ferritin levels were associated with higher risks of diabetes with an odds ratios (ORs) and 95 % confidence intervals (CIs) as 1.48 (1.31–1.69) in men and 1.43 (1.24–1.65) in women, higher levels of HbA1c with an ORs (95 % CIs) - 1.58 (1.21–2.05) and 1.37 (1.07–1.77) in men and women respectively, and HOMA-IR betas 0.07 (p value< 0.0001) and 0.06 (p value< 0.0001) in men and women respectively, independent of several confounders [16].

Table-3: Correlation of HbA1c with Inflammatory markers

Inflammatory Markers	Spearmann correlation	P value
CRP (mg/L)	0.179	0.040
LDH (U/L)	0.038	0.114
Ferritin (µg/L)	-0.049	0.639

CRP – C-reactive protein, LDH – Lactate dehydrogenase. P value of < 0.05 is considered statistically significant.

In patients with MERS (middle east respiratory syndrome) or SARS, diabetes was discovered to be a host-independent risk factor for mortality and morbidity [18]. According to Zhu L *et al*., type 2 diabetics had higher levels of inflammatory markers such as CRP and procalcitonin (57.0% and 33.3 %, respectively) than nondiabetics 42.4% and 20.3% respectively [19]. Phillips *et al*., discovered that in hyperglycemic conditions, the respiratory epithelium has an increased glucose concentration, which can impair its innate immune capability [20]. Hypoglycemia also accentuate cardiovascular mortality by stimulating pro-inflammatory monocytes and increasing platelet aggregation [21]. Since diabetic-COVID patients have higher levels of inflammation and coagulation, they need more integrated and comprehensive management than the control group [22].

Conclusion

Our study concluded that inflammatory markers CRP, ferritin and LDH were comparatively elevated in diabetic versus nondiabetic covid patients. This elevation of CRP level was statistically significant. The positive correlation between HbA1c and CRP was also found to be statistically significant.

Limitation: The sample size was small and it was a single centre study. Most of the critically ill patients were diabetic, we didn't have equal number of diabetic and non-diabetic group. The type of diabetes mellitus could not be identified in this retrospective data collection study, as the duration of diabetes mellitus could not be collected.

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