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Research Article

DIABETES MELLITUS IN COVID-19; A HOSPITAL-BASED LONGITUDINAL ANALYTICAL STUDY

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ABSTRACT

Objectives: The aim of the study was (1) to assess and compare the profile of COVID-19 patients with diabetes and without diabetes and (2) to determine the outcome of COVID-19 patients with diabetes mellitus.

Methods: A hospital-based longitudinal analytical study was conducted on a total of 2000 patients in Bengaluru during the study period from August 2020 to July 2021. The patients fulfilling the inclusion criteria were enrolled for the study after obtaining informed consent. Patients were divided into diabetic and non-diabetic groups and inflammatory markers were compared between these two groups and outcome of these patients was noted.

Results: Of the 2000 COVID-19 patients included, 358 were diabetics in this study. Mean age of non-diabetic patients was 41.71 (±15.37) years and diabetic patients were 54.37 (±11.95) years. The inflammatory markers such as Lactate Dehydrogenase (LDH), Ferritin, C-Reactive Protein (CRP), and Neutrophil-Lymphocyte ratio (NLR) were significantly high in patients with diabetes compared to the non-diabetic patients with COVID-19 ($p<0.05$).

Conclusion: This study shows that diabetes is a major risk factor and contributes to the severity and mortality of patients with COVID-19. Our recommendations are for the strict glycemic control in patients affected by COVID-19 during treatment for the same.

Keywords: Co-morbidities, Outcome, LDH, CRP.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus that causes the Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China in December 2019 and has since then spread worldwide and hence was declared a pandemic by the World Health Organization (WHO). As of August 2021, 214 million globally confirmed cases of COVID-19 have been reported on the WHO COVID-19 dashboard including 4.47 million deaths [1].

SARS-CoV-2 is a positive-stranded RNA virus that is enclosed by a protein-decorated lipid bilayer containing a single-stranded RNA genome; SARS-CoV-2 has 82% homology with human SARS-CoV, which causes severe acute respiratory syndrome (SARS) [2]. The main entry receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2) [3], which is expressed highly in the lung alveolar cells. These receptors have also been found in the cardiac myocytes, vascular endothelial cells, and Islet cells of the pancreas [4]. In human beings, the portal of entry of SARS-CoV-2 transmission is through the respiratory droplets and secretions [5]. SARS-CoV-2 infection is capable of inducing mild flu-like symptoms or being completely asymptomatic. It also has the potential to develop into a severe illness including a systemic inflammatory response syndrome leading to acute respiratory distress syndrome (ARDS) and multi-organ involvement (MODS) causing shock [6]. Patients suffering from severe COVID-19 or having succumbed to death had several similarities between them including advanced age and underlying co-morbidities such as cardiovascular disease (CVD), Type 1 Diabetes Mellitus (T1DM) or Type 2 Diabetes Mellitus (T2DM), Hypertension (HTN), and Chronic Obstructive Lung Disease (COPD) [7-9]. A few early studies have shown that underlying CVD and diabetes mellitus are common among patients with COVID-19 admitted to ICUs. [10,11] In this, we study the outcome of COVID-19 patients with diabetes mellitus.

Aims and objectives

The objectives are as follows:

1. To assess and compare the profile of COVID-19 patients with diabetes and without Diabetes.
2. To determine the outcome of COVID-19 patients with diabetes mellitus.

METHODS

A hospital-based longitudinal analytical study was conducted in a tertiary care center in Bengaluru, Karnataka, India. Ethical clearance for the study was obtained from the Institutional Ethics Committee (reference: BMCRI/PS/02/2020-21) as per ICMR guidelines.

Data were collected from a total of 2000 patients presenting to the Department of General Medicine Triage and/or admitted in the COVID wards/ICU from December 2020 to June 2021, out of which 358 patients were diabetic fulfilling the inclusion criteria.

After obtaining approval and clearance from the institutional ethics committee, the patients fulfilling the inclusion criteria were enrolled for the study after obtaining informed consent. Case record form with follow-up chart was used to record the duration of disease, history of treatment, and complications. COVID-19 infection was be diagnosed by either RT-PCR or Rapid Antigen Test (RAT) technique. Patients underwent biochemical investigations which included complete blood count, liver function test, renal function test, serum electrolytes, serology, CRP, LDH, D-dimer and serum Ferritin, ABG, Chest X-ray, Fasting Blood Sugar, and Post Prandial Blood Sugars. Patients are divided into diabetic and non-diabetic groups and inflammatory markers were compared between these two groups. The patients in both the groups were monitored; the clinical profile and laboratory investigations were measured either as

improvement (clinical improvement, decreasing trend of inflammatory markers and discharge) or deterioration (clinically worsening, increasing trend of inflammatory markers and death) of the patient.

Inclusion criteria

The following criteria were included in the study:

1. Patients willing to give informed written consent.
2. Adult patients (18 years and above) with either RT-PCR or Rapid Antigen Test positive for COVID-19.

Method of statistical analysis

The data were collected and entered in the MS excel spreadsheet and analyzed using STATA statistical software version 14 (StataCorp LCC, Lakeway Drive College Station, Texas, USA). The categorical variables were summarized using frequencies and proportions. The continuous variables were summarized using mean with standard deviation or median with interquartile range based on the data distribution. Age was categorized based on 10 year intervals. Chi-square test and Fischer's exact test were used to test the statistical significance of categorical data. T-test and Mann–Whitney U test were used to test the statistical significance of continuous variables. $p<0.05$ was considered to be significant.

RESULTS

A total of 2000 patients were included in the present study, of which 358 patients were found to be diabetic.

As shown in Table 1, of the 2000 patients 358 were diabetic. The mean age of non-diabetic patients was 41.71 (±15.37) years and diabetic patients were 54.37 (±11.95) years. Among the diabetic patients who died, the mean age was 58.9±13.4 years and among those who were discharged, the mean age was 53.5±11.4 years. This difference was statistically significant with a $p=0.008$ (Table 2).

Median lymphocytes in non-diabetic patients were IQR 27% (19–34) when compared to diabetic patients which was 21% (13–29). Median NLR in non-diabetic patients was 2 (1.5–3) when compared to diabetic patients which were 2.6 (1.8–4.1). Median LDH in non-diabetic patients was 238.5 U/L (195–323) when compared to diabetic patients which was 308U/L (225–435). Median CRP in non-diabetic patients was 3.45 mcg/ml (0.85–18.2) when compared to diabetic patients which was 21.4 mcg/ml (5.1–75.5). Median Ferritin in non-diabetic patients was 144.6 ng/mL (51.5–325.1) when compared to diabetic patients which was 285.8 ng/mL (119.4–610.8). All of these differences in the above mentioned parameters were statistically significant with $p<0.001$ as shown in Table 3.

Table 1: Demographic data comparing the diabetic with the non-diabetic population

Level	Diabetes absent (%)	Diabetes present (%)	p-value
Number	**1642**	**358**	
Age (in years)			
0–30	482 (29.6)	9 (2.5)	<0.001
31–40	403 (24.8)	38 (10.7)	
41–50	285 (17.5)	93 (26.3)	
51–60	241 (14.8)	113 (31.9)	
61–70	149 (9.2)	71 (20.1)	
71–100	66 (4.1)	30 (8.5)	
Sex			
Male	1002 (61.0)	230 (64.2)	0.26
Female	640 (39.0)	128 (35.8)	

Table 2: Demographic data in diabetic group

Diabetic patients	Discharged (%)	Death (%)
Number	**306**	**52**
Age (in years)		
0–30	8 (2.6)	1 (1.9)
31–40	34 (11.1)	4 (7.7)
41–50	85 (27.8)	10 (19.2)
51–60	100 (32.7)	15 (28.8)
61–70	57 (18.6)	14 (26.9)
71–100	22 (7.2)	8 (15.4)
Sex		
Female	112 (36.6)	16 (30.8)
Male	194 (63.4)	36 (69.2)

In our study, median value of TLC in the diabetic population was 7600 cells/cu mm (6200–10000). Among those who were discharged, TLC was 7450 cells/cu mm of blood (6150–9500) and among those who died TLC was 9500 cells/cu mm of blood (7000–12000). Neutrophil-lymphocyte ratio was 2.6 among those discharged to 6.5 to those who died. Lactate dehydrogenase was 297 U/L among the discharged patients and 528.5 U/L among the patients who succumbed to death.

Median value of D-Dimer between the two groups was 0.6 mg/L, among discharged 0.6 mg/L and among those who died was 1.2 mg/L. Median value of ferritin was 285.8 ng/mL and that among the discharged patients was 258.65 ng/mL and among those who died was 493.6 ng/mL. C-Reactive protein - Median was 21.4 mcg/ml, among the discharged was 17.9 mcg/ml and among those who died 88 mcg/ml.

The differences seen in the above-mentioned inflammatory markers comparing the diabetic patients who were discharged to those who succumbed to death were statistically significant with a $p<0.05$ as shown in Table 4.

DISCUSSION

After infection, the SARS-CoV-2 enters the target cells via the ACE2 receptors. Therefore, the expression of ACE2 receptors in any organ may provide a pathway for SARS-CoV-2 infection resulting in tissue injury. The expression of ACE2 receptors in the islet cells of the pancreas has been reported [12]. The role of these ACE2 receptors has been widely studied for the onset of diabetes, as ACE2 receptor deficiency has been associated with impairment of first-phase insulin secretion [13-15]. In our study, the inflammatory markers such as Lymphocytes, NLR, LDH, CRP, and Ferritin were significantly high in COVID-19 patients with diabetes when compared to the non-diabetic COVID-19 population. This difference was statistically significant. In a study conducted in September 2020, it was found that COVID-19 patients who also had diabetes had significantly higher levels of inflammatory markers when compared to the non-diabetic COVID-19 cases [16].

Furthermore, in the 358 diabetic patients in the study, 52 succumbed to death and the inflammatory markers such as TLC, NLR, CRP, LDH, D-dimer, and Ferritin were significantly elevated among those who died when compared to the diabetics who were discharged and this was statistically significant. In the study conducted by Alireza Abdi *et al*., the conclusion was that diabetes was a risk factor for COVID-19 and also contributed to the severity and mortality of the COVID-19 patients [17]. Matteo Apicella *et al*. studied diabetes in COVID -19 and also arrived at the conclusion that diabetic patients with COVID-19 had a worse outcome and higher mortality than the COVID-19 patients without diabetes [18]. The International Diabetes Federation (IDF) reported that the symptoms in diabetic patients were not different from the other COVID-19 patients [19]. However, the symptoms were more developed among the diabetic patients [20,21].

Thus, based on our findings, we can safely conclude that the COVID-19 patients with diabetes need strict glycemic control for a better outcome and prognosis. Emphasis has to be laid on the higher risk of contracting the COVID-19 virus by the diabetic population and strict COVID appropriate behavior has to be enforced to not contract the virus as precaution is always better than the usage of evidence-based treatment. Hence, a physician has to account for not only the

Table 3: Comparing inflammatory markers in diabetic and non-diabetic groups

Lab parameters	Diabetes absent	Diabetes present	p-value
Number	1642	358	
Hb (g/dl) mean (SD)	13.1279 (4.53644)	12.3467 (2.04848)	0.012
TLC (cells/cu mm) median (IQR)	7400 (5800, 9400)	7600 (6200, 10000)	0.21
N (%) mean (SD)	64.6153 (31.7084)	68.8467 (13.722)	0.050
L (%) median (IQR)	27 (19, 34)	21 (13, 29)	<0.001
NLR, median (IQR)	2 (1.5, 3)	2.6 (1.8, 4.1)	<0.001
LDH (U/L) median (IQR)	238.5 (195, 323)	308 (225, 435)	<0.001
D-DIMER (mg/L) median (IQR)	0.5 (.2, 0.9)	0.6 (.2, 1)	0.060
CRP (mcg/ml) median (IQR)	3.45 (.85, 18.2)	21.4 (5.1, 75.5)	<0.001
FERRITIN (ng/mL) median (IQR)	144.6 (51.5, 325.1)	285.8 (119.4, 610.8)	<0.001

*Hb: Hemoglobin, TLC: Total leucocyte count, N: Neutrophil, L: Lymphocyte, NLR: Neutrophil lymphocyte ratio, LDH: Lactate dehydrogenase, CRP: C reactive protein, IQR: Inter quartile range

Table 4: Comparing inflammatory parameters in diabetic group

Laboratory parameter	Total (n=358)	Survived (n=306)	Succumbed to death (n=52)	p-value
Hemoglobin (g/dl)	12.3±2.0	12.5±1.9	10.8±2.2	0.0002
Total leucocyte count (cells/cu mm)	7600 (6200–10000)	7450 (6150–9500)	9500 (7000–12000)	0.0170
Neutrophil (%)	68.8±13.7	66.9±13.0	80.0±12.1	<0.001
Lymphocytes (%)	21 (13–21)	23 (16–30)	10 (8–16)	<0.001
Neutrophils lymphocytes ratio	2.6 (1.8–4.1)	2.6 (1.6–3.3)	6.5 (4.7–14.8)	<0.001
Lactate Dehydrogenase (U/L)	308 (225–435)	297 (218–386)	528.5 (387–748)	<0.001
D-dimer (mg/L)	0.6 (0.2–1)	0.6 (0.2–0.9)	1.2 (0.5–2.5)	0.0003
C-Reactive protein (mcg/ml)	21.4 (5.1–75.5)	17.9 (4.4–56.75)	88 (48.7–168.2)	<0.001
Ferritin (ng/mL)	285.8 (119.4–119.4)	258.65 (115.7–592.8)	493.6 (199–1104)	<0.001

health status of the COVID-19 patient with diabetes but also to balance the glucose-lowering treatments carefully with specific treatments for the viral infection. Once again, the management of DM in patients with COVID-19 poses a tremendous clinical challenge and it definitely merits a team approach to reduce the risk of morbidity and mortality as much as possible.

Limitations

The study is a single center study.

CONCLUSION

Our study determined that the parameters such as hemoglobin, lymphocyte count, NLR, LDH, CRP, and ferritin were significantly different among the COVID-19 patients with and without diabetes. Fourteen percent of COVID-19 patients with diabetes succumbed to death and they showed significantly higher levels of NLR, LDH, CRP, d-dimer, and ferritin. This study shows that diabetes is a major risk factor and contributes to the severity and mortality of patients with COVID-19. Our recommendations are for the strict glycemic control in patients affected by COVID-19 during treatment for the same. The feasibility of using these parameters to predict the prognosis of COVID-19 patients with diabetes needs to be explored.

CONTRIBUTORS' LIST

Avinash H Rajanna = Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation.

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