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Impact of Diabetes Mellitus on patients with COVID-19

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Abstract

Background: Diabetic mellitus patients are more susceptible to SARS-CoV-2. The primary aim of the study was to analyze the demographical and routine laboratory parameters in COVID-19 patients having diabetes and to observe the impact of diabetes on the COVID-19 disease severity and outcome. The secondary aim was to compare the findings of the COVID-19 positive diabetic patients with COVID-19 positive non-diabetic having no other comorbidity.

Methods: In this retrospective study, consecutive COVID-19 patients of all age groups were enrolled. Demographical, clinical and laboratory details were collected and analysed. Patients were classified into two groups: group I (diabetic patients, n=38), group II (non-diabetic with no other comorbidity, n=37). Death was the primary outcome.

Results: Age was significantly higher in group I than group II ($p<0.001$). The mortality rate was 15/38 (39.47%) in group I and was significantly higher than group II ($p<0.001$). The frequency of patients with severe COVID-19 disease and those requiring ventilator support were significantly higher in group I than in group II ($p<0.05$ for both).

Significantly higher values of total leucocyte counts ($p<0.05$), neutrophil to lymphocyte ratio ($p<0.01$), urea ($p<0.01$), creatinine ($p<0.05$) and uric acid ($p<0.05$) were observed in group I than II. Serum calcium ($p<0.05$), albumin ($p<0.05$) and albumin to globulin ratio ($p<0.01$) were significantly lower in group I than II.

Conclusion: The severity, ventilator requirement and mortality were considerably higher in COVID-19 patients having diabetes.

Keywords: Hypoalbuminemia, Hypocalcaemia, Mortality, Neutrophil to lymphocyte ratio, SARS-CoV-2

Introduction

Diabetes mellitus (DM) is one of the most prevalent chronic conditions with devastating multi-systemic complications. It is estimated that currently 463 million people are affected by diabetes globally [1]. A study shows that a person having DM is more susceptible to SARS-CoV-2 infection [2]. Though, the majority of corona virus illnesses does not affect the patients severely, but previous outbreaks of two corona viruses by severe acute respiratory syndrome corona virus (SARS-CoV) in 2002–2003 and Middle East respiratory syndrome corona virus (MERS-CoV) in 2012 caused severe pneumonia having a mortality rate of 10% and 36% respectively [3]. Data suggests diabetes to bean independent risk factor for prediction of severity and death in both the outbreaks [2].

Thus, there are perceptions that COVID-19 patients with diabetes might have higher disease severity and poor outcome. However, the available information concerning COVID-19 patients with diabetes is not enough at present. Therefore, the primary aim of the present study was to analyze the demographical features and routine laboratory parameters in COVID-19 patients having diabetes mellitus and to observe the impact of diabetes mellitus on the COVID-19 disease severity and outcome. The secondary aim was to compare the findings of the COVID-19 positive

diabetic patients with the COVID-19 positive non-diabetic having no other comorbidity.

Materials and methods

This is a retrospective descriptive observational study, conducted at Jai Prakash Narayan Apex Trauma Centre, New Delhi which is now a dedicated COVID-19 care centre during the pandemic. The patients were admitted here after being diagnosed COVID-19 by real-time polymerase chain reaction (RT-PCR) and classified into mild, moderate and severe COVID-19 disease according to the World Health Organization and Ministry of Health and Family Welfare, Government of India, guidelines [4, 5]. Consecutive patients of all age groups admitted during the 23March to 30April, 2020 were enrolled in the study. The demographical, clinical and laboratory details on the day of admission were collected from hospital data base and analysed thoroughly. Patients were classified into two groups namely: Group I (diabetic patients, n=38), Group II (non-diabetic with no other comorbidity, n=37) based on their clinical history. Death was the primary outcome. The secondary outcomes were severity of disease and requirement for ventilator support. The study was conducted after obtaining the approval from the ethical committee of the institute. Patients having comorbidity other than diabetes mellitus and with incomplete information were excluded from the study.

Statistical Analysis

All statistical analyses were performed by GraphPad Prism 5.0 Software. Data are presented as count (percentages) for categorical variables. Results for continuous variables are expressed as mean ± SD or median ± IQR (Inter Quartile Range) as indicated. Categorical variables between groups are compared using the $\chi 2$ test or Fisher exact test, and continuous variables are analysed using Student's t test or Mann-Whitney U test as appropriate. A value of $p < 0.05$ is considered statistically significant.

Results

Demographical, Clinical Characteristics and Laboratory Findings in Diabetic Patients (group I)

Out of total 75 patients enrolled, 38 (50.67%) patients were diabetic. The mean age of the diabetic patient was 57±12.41 years. Of all the diabetics, 26/38 (68.42%) patients were males and 15/38 (39.47%) patients were above 60 years of age. The mortality rate was 15/38(39.47%) in the diabetic COVID-19 patients. Also, 36/38 (94.73%) patients had severe COVID-19 disease and 16/38 (42.10%) of patients required ventilator support during the treatment. Amongst the non-surviving diabetic patients, 13/15 (86.7%) patients were male and 5/15 one third were >60 years of age.

The haemoglobin level in diabetic patients was 10.88±2.76 gm/dl. Of all, 23/38 (60.52%) patients were anaemic. The median platelet count was 170 (106-221) $x10^3$ cells/cumm. Thrombocytopeina was seen in 13/38 (34.21%) patient. The median total leucocytes count was 10.3 (6.1-17.3) $x10^3$cells/cumm. Leucopenia was found in 2/38 (5.26%) patients and leucocytosis was observed in 16/38 (42.11%) patients. The prothrombin time and activated partial thromboplastin time were increased in 3/38 (7.89%) and 4/38 (10.53%) of patients respectively. Blood urea and creatinine levels were increased in 13/38 (34.21%) and 12/38 (31.58%) of patients respectively. Hypocalcemia was observed in 19/38 (50%) of the patients. Uric acid was altered in 11/38 (28.95%) of patients. Deranged in sodium level was also found in 18/38 (47.37%) of diabetic patients. We observed that 33/38 (86.84%) of patients were hypokalemic. Total bilirubin level was increased in 13/38 (34.21%) of patients. Hypoproteinemia was observed in 23/38(60.53%) and hypoalbuminemia was

present in all diabetic patients. The levels of aspartate transaminase, alanine transaminase and alkaline phosphatase were increased in 22/38 (57.90%), 13/38 (34.21%) and 10/38 (26.32%) of diabetic patients respectively.

Comparison of Group I (diabetic patient) with Group II (non-diabetic with no other comorbidity)

The details are given in table 1 and 2. The mean age of group I was significantly higher than group II (57±12.41yearsv/s 39 ± 15.81 years, $p<0.001$). Significantly higher number of patients in group I were affected with severe disease compared to group II (36/38, 94.73% v/s 29/37, 78.38%; $p<0.05$). 16/38 (42.10%) of diabetic patients required ventilator support during the illness ($p<0.05$). Mortality rate was significantly higher in group I than group II (15/38, 39.47% v/s 2/37, 5.4%; $p<0.001$).

Significantly higher values of total leucocyte counts ($p=0.043$) and neutrophil to lymphocyte ratio ($p=0.005$) were observed in group I than in group II. Significantly higher levels of blood urea ($p<0.01$), creatinine ($p<0.05$) and uric acid ($p<0.05$) were observed in group I than group II. Level of serum calcium also significantly lower in diabetic group ($p<0.05$).Serum calcium ($p=0.034$), albumin ($p=0.046$) and albumin to globulin ratio ($p=0.009$) were significantly lower in group I than group II.

Discussion

This study represents the first description of diabetic patients with COVID-19 disease from an apex COVID-19 care centre in north India. Overall, the mortality in COVID-19 disease varies from 0.7% to 10% but a study from Italy reported a mortality rate of 20.3% in COVID-19 patient with diabetes mellitus [6]. We found the mortality rate was 39.47% in patients with diabetes. Data suggests that diabetes is responsible for approximately one-third of deaths in hospitals in COVID-19 patients [7].

Diabetes has been shown to be an independent risk factor for mortality in previous pandemics including H1N1, SARS and MERS [8]. Studies show that diabetics have two fold higher risk of disease severity as well as higher mortality compared to non-diabetics [9]. Mortality rate is higher in those diabetic patients having poor glycemic control, higher HbA1c and higher body mass index (BMI) [10, 11]. Different factors lead to poor prognosis in patients with diabetes like age, gender, civilization, obesity, pro-inflammatory and pro-coagulative state in patients [12, 13]. Various studies like CORONADO reported that black, Asian and minority ethnic (BAME) may have a higher rate corona infection and may also have poor outcome [14]. COVID-19 related mortality in the diabetic population is more in males, elderly and in patient having severe inflammatory response, altered hepatic, renal, coagulation markers and cardiovascular complications [10, 15]. As seen in the present study. Of all the diabetic non-survivors in our study, one-third were elderly patients and more than four-fifth were males. In SARS and MERS pandemic also, increasing age has been postulated as chief predictor of mortality [16, 17]. The case fatality rate was twice in males in comparison to females, and 12- times higher in patients more than 80 years of age [12]. However, we found the case fatality rate was 6.5 times in males compared to females and two times in patients of less than 60 years of age compared to those more than 60 years of age.

The trends in the study show that most of the diabetic patients were severely affected by COVID -19 disease and more patients required ventilator support during the hospital stay. The admission rate in intensive care unit is higher for COVID-19 patients having diabetes [12,

18]. Considerably higher requirement of oxygen inhalation, non-invasive and invasive ventilation are found in the diabetic patients compared to the non-diabetic COVID-19 patients [19]. Diabetic ketoacidosis may occur in diabetes patients due to COVID-19 infection which may further increase the duration of hospital stay [20].

High frequency of neutrophilia and lymphocytopenia has been observed in the COVID-19 positive diabetic patients compared to the non-diabetics [12, 19]. In our study less than half of the diabetic patients had abnormal total leucocytes count. We also found significantly higher NLR in diabetic patients, indicating severe infection. Higher NLR is associated with higher mortality in COVID-19 disease [21]. Hyperglycemic state is responsible for severe infections which further increases the chances of hospital admission and higher mortality rates in poorly controlled diabetic patients [22]. Elevated level of angiotensin-converting enzyme 2 (ACE2) expressions observed in hyperglycaemia and diabetes, make the patients vulnerable to COVID-19 infections [23]. Dipeptidyl peptidase-4 (DPP-4) receptors expressed in various tissues may have a role in the inflammatory processes and respiratory infections [24]. Diabetic patients are more vulnerable to an inflammatory storm with increased levels of inflammatory biomarkers like C-reactive protein, D-dimer, Interkeukin-6, lactate dehydrogenase and serum ferritin [9,12].

In the present study 100% of diabetic patients had hypoalbuminemia. Hypoalbuminemia, high level of alanine aminotransferase, aspartate aminotransferase and γ-glutamyl transferase levels have been reported in the COVID-19 patients having diabetes compared to the non-diabetics [12, 19, 25,26].

The initial information on SARS-CoV-2 also shows an increased level of serum creatinine in 14.4% and elevated blood urea nitrogen (BUN) in 13.1% of COVID-19 patients [27]. Our study also shows a significantly higher level of serum creatinine, blood urea and uric acid levels in the diabetic patient compared to the non-diabetics. Hypercreatinemia, hyperuremia, hyperuricemia were found in 31.58%, 34.21% and 21.05%of COVID-19 patient having diabetes respectively. Previous data shows the presence of acute kidney injury in 6.7% of SARS patients resulting in 91.7% mortality [27].Reports from China, Italy and USA show more than 20% of the COVID-19 patients are affected by acute kidney injury [28]. The adverse outcomes may be a result of low serum calcium level in COVID-19 disease [29]. The current study demonstrates that significant difference was found in serum calcium level of the diabetics compared to the non-diabetic group. In our study 50% of the diabetes patients had hypocalcaemia which was associated with poor outcome of the disease.

Considering the disease burden, proper monitoring of blood glucose is very essential in diabetic patients [30]. Pneumococcal and annual influenza vaccinations are recommended for a person having diabetes (above 2 years of age) [8]. Also the stress, change in routine care, diet habit and effect on physical activity after pandemic also contribute to the adverse outcome of the disease [11]. There is a need to further study the natural course of COVID-19 in patients with diabetes and to understand the individual, regional and ethnic variations. Finally, with the huge population burden of diabetes we need to develop novel ways to deliver care to our patients with DM using remote patient monitoring, teleconsultation and telemedicine.

Limitations

Due to limited resources and unavailability of data of all patients for special parameters like CRP, D-dimer, IL-6, LDH and ferritin, the current study was primarily focused on routine laboratory parameters. But the data on routine blood parameters may have great support to predict the outcome for low-income countries where the budget for health care is very limited. The second limitation of this study is that we have not been able to comment on the role of glycemic control and HbA1c level on the severity or mortality of COVID-19. The next limitation is that the study lacks the information on effect of type1 and type2 diabetes mellitus individually on COVID-19 disease, the sample size was the main concern. However, the data does provide abundant scope for upcoming research.

Conclusion

The severity and mortality are considerably higher in COVID-19 patients having diabetes. The requirement of ventilator was also higher in diabetic patients. The current study indicates age, male gender, leucocytosis, neutrophil-lymphocyte ratio, altered renal function and hypoalbuminemia are associated with the poor outcome.

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Legend Tables

Table 1: Comparisons of Demographical and Clinical details of Group I and Group II

Parameter	Diabetic Patients (Group-I, n=38)	Non-diabetic with no other comorbidity (Group-II ,n=37)	P Value
Age(years)	57±12.41	39±15.81	<0.001
Proportion of elderly (>60 years of age)	15 (39.47%)	1 (2.70%)	<0.001
Male	26 (68.42%)	28 (75.68%)	0.4842
Outcomes			
Severe disease	36(94.73%)	29(78.38%)	<0.05
Required Ventilator Support	16(42.10%)	6(16.22%)	<0.05
Non-survivors	15(39 .47%)	2(5.40%)	<0.001

Note: Continuous data are presented as mean ± standard deviation or median ± IQR (Inter Quartile Range). Categorical data are presented as frequency (%).

Table 2: Comparisons of Laboratory Parameters among Group I and Group II

Parameter	Diabetic Patients (Group-I, n=38)	Non-diabetic with no other comorbidity (Group-II ,n=37)	P Value
Hematological Parameters			
Hemoglobin (gm%)	10.88±2.76	11.77±2.002	0.1155
Total leucocyte count (cells/µl)	10300(6100-17300)	7600(5050-9400)	<0.05
Neutrophil to lymphocyte ratio	2.85 (1.90-5.06)	1.61(1.13-2.65)	<0.01
Platelets ($X10^3$ cells/µl)	170 (106-221)	169 (112-264)	0.9662

Coagulation Profile			
Prothrombin Time (sec)	15.7(13-17.2)	14.70 (12-17.28)	0.4924
Activated partial thromboplastin time (Sec)	29.95(23-39.5)	30.6(28.5-36.30)	0.8407
Internatinal normalized ratio	1.17(0.95-1.28)	1.09(0.88-1.28)	0.4955
Liver Function Test			
Bilirubin Total(mg/dl)	0.8 (.6-1.3)	0.8(0.6-1.05)	0.6357
Total Protein (gm/dl)	6.23±0.97	6.35±1.1	0.6503
Albumin (gm/dl)	2.64±0.63	2.99±0.85	<0.05
Globulin (gm/dl)	3.5±0.70	3.35±0.71	0.1419
Albumin to globulin ratio	0.75±0.21	0.93±0.34	<0.01
Aspartate Transaminase (IU/L)	45.5 (28-77)	42(29-65)	0.6486
Alanine Transaminase (IU/L)	29 (20-46)	35(21-69)	0.2867
Alkaline Phosphatase (IU/L)	77.50(60.50-123)	85 (59.5-137)	0.9282
Renal Function Test			
Urea (mg/dl)	43(28-94)	26(21-38)	<0.01
Creatinine (mg/dl)	0.9(.7-1.3)	0.8(0.6-0.9)	<0.05
Uric Acid (mg/dl)	4.9 (3.7-7.3)	4.00(3.5-4.7)	<0.05
Calcium (mg/dl)	7.91±1.21	8.4±0.67	<0.05
Phosphate (mg/dl)	4 .0 (2.4-5.9)	3.6(2.7-4.85)	0.3704
Electrolytes			
Sodium (mEq/L)	134.71±6.08	135.5±134.7	0.5162
Potassium (mEq/L)	4.46±0.94	4.39±0.66	0.6442

Note: Data are presented as mean ± standard deviation or median ± inter quartile range.