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Research Article

Impact of Diabetes Mellitus on Management and Outcome of COVID-19 Infection -

Govind Rankawat[1]*, Sudhir Bhandari[1], Ajeet Singh[1], Vishal Gupta[1] and Bhupendra Patel[2]

[1]Department of General Medicine, SMS Medical College and Attached Group of Hospitals, Jaipur, India

[2]Department of Physiology SMS Medical College and attached group of Hospital, Jaipur, Rajasthan, India

***Address for Correspondence:** Govind rankawat, Department of General Medicine, SMS Medical College and Attached Group of Hospitals, Jaipur, India, ORCID ID: orcid.org/0000-0003-3708-3068; E-mail: govindrankawat@gmail.com

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ABSTRACT

Purpose: The present study was designed to compare treatment strategy and outcome for COVID-19 infection among patients of diabetes mellitus and non-diabetics. This study also aimed to assess the impact of other comorbidities on each group.

Methods: A total of 1,048 admitted COVID-19 patients were enrolled for the present study to evaluate the differences in management and outcome among diabetics and non-diabetics. COVID-19 patients were categorized into four groups namely: group 1 of all diabetic patients, group 2 of all non-diabetic patients, group 3 had patients with isolated DM after exclusion of other comorbidities and group 4 included non-diabetic patients without other comorbidities. The pharmacological and supportive treatment data along with outcome of COVID-19 infection was acquired from the available medical records, for evaluation, interpretation and comparison among the different groups.

Results: In the present study, it was observed that COVID-19 patients with diabetes often required more intensive treatments like lopinavir-ritonavir combination (p = 0.0142), convalescent plasma (p = 0.0394), tocilizumab therapy (p = 0.0238) and other supportive treatment like oxygen therapy (p = 0.0182) and non-invasive ventilation (p = 0.0394). As compared to the non-diabetic group. Diabetic patients exhibited significantly lower recovery but higher mortality rates as compared to the non-diabetic group (< 0.001). COVID-19 infected diabetics required more time for discharge from hospital than the non-diabetic group (p = 0.007). Although the duration of seroconversion might be influenced by the impact of other comorbidities.

Conclusion: COVID-19 patients with diabetes mellitus required greater attention regarding pharmacological and supportive treatment as compared to the non-diabetic COVID-19 patients. Diabetic patients showed poor prognosis with development of lethal complications. Diabetics required more time for discharge from hospital as compared to the non-diabetic patients.

Keywords: COVID-19; Diabetes mellitus; Management; Outcome

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been identified as the causative agent of COVID-19 with an incubation period in the range of 2 to 14 days. The usual presentation of COVID-19 patients has been symptoms of fever, cough, dyspnea, headache, loss of appetite, fatigue, sputum production, and muscle and joint pains, nausea, vomiting and diarrhea [1,2]. The associated complications may vary from pneumonia, Acute Respiratory Distress Syndrome (ARDS), multi-organ failure, septic shock, disseminated intravascular coagulation to ultimate mortality [3,4].

Angiotensin-Converting Enzyme 2 (ACE2) has been identified as a surface receptor responsible for SARS coronavirus (SARS-CoV) invasion in human cells with direct interaction with its spike glycoprotein (S protein) [5]. Moreover, a ten to twenty-fold higher affinity of ACE2 towards Receptor-Binding Domain (RBD) of SARS-CoV-2 as compared to the RBD of SARS-CoV has been suggested. This might be the plausible explanation of ACE2 serving as a receptor for SARS-CoV-2 invasion [6]. Diabetes mellitus has already been a leading cause of morbidity worldwide that is capable of affecting almost each and every system of body [7]. Consequently, a deregulated immune system might develop, predisposing to various infections in diabetic patients [8]. ACE2 has anti-inflammatory effects and its expression is found reduced in patients of DM possibly due to glycosylation. This might explain the occurrence of a severe acute lung injury and ARDS in diabetic patients. This makes diabetic population with or without other comorbidities susceptible to a higher morbidity and mortality due to COVID-19. A severe disease in such patients requires intensive approach to manage COVID-19 (Figure 1). The purpose of this study was to assess whether diabetes mellitus influences the natural course, progression and prognosis of COVID-19 patients who were admitted to SMS Medical College Hospital, Jaipur, India. This study also aimed to assess whether diabetics required special considerations regarding management of COVID-19 with final outcome of illness as compared to non-diabetic COVID-19 patients.

METHOD

Study design

The present descriptive, observational study was conducted on 1,048 COVID-19 patients. All the patients with a positive reverse transcriptase- polymerase chain reaction (RT-PCR) for SARS-CoV-2 were categorized into four groups. In first part, all patients were divided into two groups based on whether they had diabetes namely: (I) Group 1 had all patients of DM and (II) Group 2 had all patients without DM. In the second part, patients with comorbidities other than diabetes were excluded to avoid the impact of other comorbidities, and then separated into two groups (I) Group 3 was inclusive of patients with isolated DM without any other comorbidities and (II) Group 4 had non-diabetic patients with without any other comorbid condition. This study was approved by the Institutional Ethics Committee.

Data collection

The diagnosis of COVID-19 was made based on World Health Organization interim guidance, wherein confirmed cases were positive on RT-PCR assay of nasal and pharyngeal swab specimens [9]. All patients were segregated and categorized in four groups. For assessment of management of COVID-19 patients, data concerning pharmacological treatment using hydroxychloroquine, lopinavir-ritonavir combination therapy (LPV/r), tocilizumab therapy, convalescent plasma and supportive treatment like oxygen therapy, ICU care and non-invasive ventilation was acquired for analysis from the available medical records. Outcome of COVID-19 infected patients was assessed by the number of recovered patients, duration of seroconversion (duration of first positive to first negative RT-PCR for COVID-19), duration of hospital stays and mortalities during treatment.

Statistical analysis

The descriptive statistics for quantitative data was expressed as mean and standard deviation and qualitative data was expressed as proportions. The parameters were compared among different groups

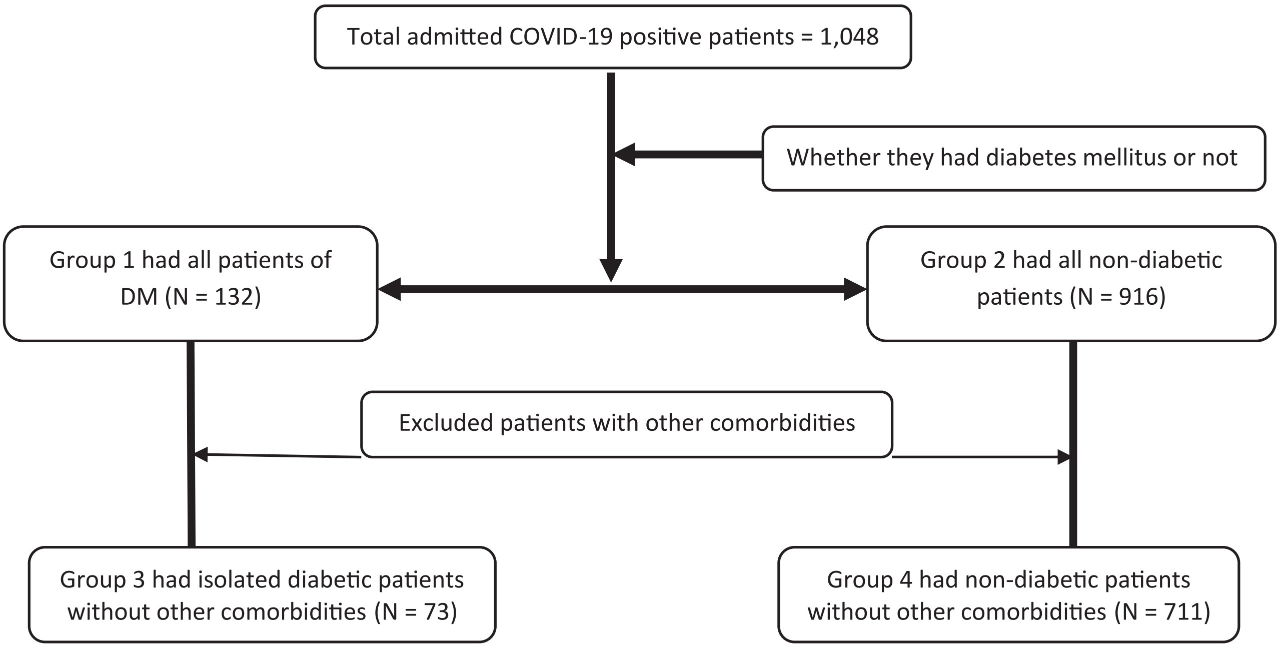

Figure 1:

using chi-square test and z-score for significant differences. The level of significance was assigned at a *p*-value less than 0.05.

RESULTS

A total of 1,048 laboratory confirmed COVID-19 patients (confirmed using RT-PCR) admitted at SMS Medical College Hospital, Jaipur, India were assessed and data from these patients was collected, evaluated, interpreted and compared within different groups to assess the differences in COVID-19 management and outcome in DM patients. All the patients were categorized into four groups as shown below:

Management and outcome differences among Group 1 and 2:

Every patient in each of the groups received hydroxychloroquine in standard dose without any difference in the diabetes and non-diabetes group. The diabetes group (15.15%) required lopinavir-ritonavir combination therapy more often as compared to non-diabetes group (8.51%) ($p = 0.0142$) (Table 1). Convalescent plasma was needed in 3.03% patients of diabetes group and 1.20% patients of non-diabetes group. There was a significant need ($p = 0.0155$) of tocilizumab therapy in diabetes group (2.27%) as compared to the non-diabetes group (0.43%). Oxygen therapy required in 15.90% patients of diabetes group and 7.96% patients of non-diabetes group ($p = 0.0028$). Need of ICU care was felt in 3.78% patients of diabetes group as compared to 2.98% patients of non-diabetes group ($p = 0.6030$). Non-invasive ventilation was required in 3.03% and 1.96% patients of diabetes and non-diabetes group, respectively ($p = 0.423$). A total of 708 patients (67.55%) patients recovered, while 42 patients (4.00%) succumbed and the remaining patients were undergoing treatment. Proportionally, recovered patients in diabetes group were lesser (56.81%) than the non-diabetes group (69.01%) and difference was statistically significant ($p = 0.0048$). COVID-19 related mortality in diabetes group (14.39%) was significantly higher ($p < 0.001$) as compared to non-diabetes group (2.51%). Mean duration required for seroconversion in diabetes group (7.38 days) was significantly prolonged ($p = 0.0217$) as compared to the non-diabetes group (6.00 days) with. Diabetes group (14.18 days) required a significantly longer ($p = 0.005$) duration of hospital stay as compared to non-diabetes group (12.27 days).

Management and outcome differences among Group 3 and 4

As a next step to evaluate whether diabetes was a risk factor for the disease progression and poor prognosis of COVID-19, patients with other comorbidities were excluded from the earlier groups to constitute Group 3 and 4. Every patient in Groups 3 and 4 received hydroxychloroquine in standard dose without any difference (Table 2). Requirement of LPV/r combination therapy in standard doses did not differ significantly ($p = 0.0601$) among isolated diabetes group (15.06%) and non-diabetes group without comorbidities (8.43%). The need of the convalescent plasma was significantly higher ($p = 0.0394$) in Group 3 (4.10%) as compared to Group 4 (1.12%) patients. Tocilizumab therapy was required in 2.73% of isolated diabetes group and only 0.28% patients of non-diabetes group without comorbidities with a significant difference ($p = 0.0238$). The need of oxygen therapy was significantly higher ($p = 0.0182$) in Group 3 (16.43%) as compared to Group 4 (8.15%). Non-invasive ventilation requirement was significantly higher ($p = 0.0394$) in isolated diabetes group (4.10%) as compared to the patients of non-diabetes group without comorbidities (1.12%). Isolated diabetes (5.47%) patient required ICU care more often as compared to the non-diabetes group without comorbidities (2.81%). A total of 556 patients (70.91%) patients recovered while 31 patients (3.95%) succumbed to COVID-19 and remaining patients were undergoing treatment. Proportionally,

Table 1: Management and outcome of patients infected with SARS-CoV-2 among diabetes and non-diabetes group.

	Patients infected with SARS-CoV-2			
Characteristics	**Total No./Mean value (N = 1048)**	**Group 1 (Diabetes) (N = 132)**	**Group 2 (Non-diabetes) (N = 916)**	***p* - value#**
Treatment				
Hydroxychloroquine	1048	132	916	
Lopinavir-ritonavir	98 (9.35%)	20 (15.15%)	78 (8.51%)	z = 2.44, *p* = 0.0142
Convalescent plasma	15 (1.43%)	4 (3.03%)	11 (1.20%)	z = 1.65, *p* = 0.0989
Tocilizumab therapy	7 (0.66%)	3 (2.27%)	4 (0.43%)	z = 2.42, *p* = 0.0155
ICU care	32 (3.05%)	5 (3.78%)	27 (2.94%)	z = 0524, *p* = 0.6030
Oxygen therapy	94 (8.96%)	21 (15.90%)	73 (7.96%)	z = 2.98, *p* = 0.0028
Non-invasive ventilation	22 (2.09%)	4 (3.03%	18 (1.96%)	z = 0.798, *p* = 0.423
Outcome				
Recovered patients	708 (67.55%)	75 (56.81%)	633 (69.10%)	z = 2.81, *p* = 0.0048
Death	42 (4.00%)	19 (14.39%)	23 (2.51%)	z = 6.50, *p* < 0.001
Duration of seroconversion	6.18 days, (95% CI: 6.18 ± 0.32, SD = 5.02)	7.38 days (95% CI: 7.38 ± 1.36, SD = 6.38)	6.00 days (95% CI: 6.00 ± 0.37, SD = 4.71)	*p* = 0.0217
Duration of hospital stay	12.47 days (95% CI: 12.47 ± 0.39, SD = 5.58)	14.18 days (95% CI: 14.18 ± 1.23, SD = 5.64)	12.27 days (95% CI: 12.27 ± 0.41, SD = 5.54)	*p* = 0.005

#*p* values indicate differences between diabetes and non-diabetes patients. *p* < .05 was considered statistically significant; z value is standardized score which measure distance between the mean and an observation.

Table 2: Management and outcome of COVID-19 infected patients in isolated diabetes group and non-diabetes group after excluding other comorbidities.

	Patients without other co-morbidities			
Characteristics	**Total No./ Mean value (N = 784)**	**Group 3 (Diabetes) (N = 73)**	**Group 4 (Non-diabetes) (N = 711)**	***p* -value#**
Treatment				
Hydroxychloroquine	784	73	711	
Lopinavir-ritonavir	71 (9.05%)	11 (15.06)	60 (8.43%)	z = 1.869, *p* = 0.0601
Convalescent plasma	11 (1.40%)	3 (4.10%)	8 (1.12%)	z = 2.064, *p* = 0.0394
Tocilizumab therapy	4 (0.51%)	2 (2.73%)	2 (0.28%)	z = 2.259, *p* = 0.0238
ICU care	24 (3.06%)	4 (5.47%)	20 (2.81%)	z = 1.259, *p* = 0.207
Oxygen therapy	70 (8.92%)	12 (16.43%)	58 (8.15%)	z = 2.362, *p* = 0.0182
Non-invasive ventilation	11 (1.40%)	3 (4.10%)	8 (1.12%)	z = 2.064, *p* = 0.0394
Outcome				
Recovered patients	556 (70.91%)	40 (54.79%)	516 (72.57%)	z = 3.18, *p* = 0.0014
Death	31 (3.95%)	14 (19.17%)	17 (2.39%)	z = 7.08, *p* < 0.001
Duration of seroconversion	6.19 days (95% CI: 6.19 ± 0.39, SD = 4.89)	7.38 days (95% CI: 7.38 ± 2.01, SD = 6.42)	6.11 days (95% CI: 6.11 ± 0.39, SD = 4.77)	*p* = 0.1152
Duration of hospital stay	12.44 days (95% CI: 12.44 ± 0.52, SD = 5.56)	14.61 days (95% CI: 14.61 ± 1.89, SD = 5.80)	12.25 days (95% CI: 12.25 ± 0.54, SD = 5.33)	*p* = 0.007

#*p* values indicate differences between diabetes and non-diabetes patients. *p* < .05 was considered statistically significant; z value is standardized score which measure distance between the mean and an observation.

recovered patients in isolated diabetes group were lesser (54.79%) than non-diabetes group without comorbidities (72.57%) with a statistically significant difference (p = 0.0014) between the groups. COVID-19 related mortality in isolated diabetes group (19.17%) was significantly higher ($p < 0.001$) as compared to non-diabetes group (2.39%). Mean duration of seroconversion in isolated diabetes group (7.38 days) and non-diabetes group without other comorbidities (6.11 days), did not differ significantly. Isolated diabetes group (14.61 days) required a significantly longer (p = 0.007) duration of hospital stays as compared to non-diabetes group without other comorbidities (12.25 days).

DISCUSSION

Diabetes mellitus predisposes an individual to a certain type of infection and mortality [10] including the COVID-19, although its risk as associated comorbidity in COVID-19 needs further exploration. The prevalence of DM in India is 7.3% [11], thereby predisposing a large proportion of population to COVID-19 and its complications. Type 2 diabetes mellitus as a consequence of metabolic syndrome and obesity predisposes to immune dysfunction with raised inflammatory factors and chemokines [12,13]. ACE2 possessing anti-inflammatory property has been linked to SARS-

CoV-2 invasion in human cells and its expression is found reduced in patients of diabetes mellitus, possibly due to glycosylation. This might explain higher predisposition of COVID-19 patients with diabetes mellitus to severe acute lung injury and ARDS [14]. Immunostaining technique has revealed an enhanced staining characteristic for ACE2 in islet tissue as compared to the exocrine pancreatic tissues suggesting plausible role of coronavirus in islet destruction [15] Thus, COVID-19 adversely affecting the varied clinical presentation of the disease.

In the present study it was observed that patients with underlying diabetes mellitus required more aggressive pharmacological and supportive treatment approach. LPV/r combination therapy, with an action against the viral 3CL protease, has modest antiviral activity against SARS-CoV-2 [16]. The patients of diabetes mellitus required LPV/r therapy more often as compared to non-diabetes group whereas, patients with isolated diabetes without other comorbidities were not significantly dependent on LPV/r combination therapy. Convalescent plasma transfusion was beneficial in the treatment of critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. This is also evident by findings of Shen et al., who reported improvement in critically ill patients with COVID-19 and ARDS using convalescent plasma containing neutralizing antibody [17]. In the present study, proportionally isolated diabetic patients were more dependent on convalescent plasma as compared to non-diabetes group without other comorbidities whereas this need did not differ significantly among groups with underlying other comorbidities. Tocilizumab, is a recombinant humanized antihuman IL-6 receptor monoclonal antibody that is capable of binding to IL-6 receptor with high affinity. It prevents IL-6 itself from binding to its receptor, rendering it incapable of immune damage to target cells, and alleviating the inflammatory responses. Xu et al. [18] in their study suggested tocilizumab as an effective medication against clinical symptoms and prevented the deterioration of severe COVID-19 patients. In the present study, a significantly higher proportion of diabetic patients required tocilizumab therapy. Diabetic patients were significantly dependent upon oxygen therapy and ICU care as well as in comparison to non-diabetes group. Non-invasive ventilation need was also more in the isolated diabetes group.

Outcome of COVID-19 infected patients was estimated by number of recovered patients, duration of seroconversion, duration of hospital stays and mortality. Proportionally, number of recovered patients was slightly lower in the group with underlying other comorbidities, suggestive of negative impact of other comorbidities on the prognosis and progression of disease. Furthermore, the recovery in patients of diabetes group was significantly lower. The number of patients who succumbed to COVID-19 was significantly higher in diabetic group. Patients of non-diabetic group required significantly lesser time for seroconversion when compared to diabetes group while no significant differences were noted for groups in which other comorbidities had been excluded. Happiness on the face of patients reflected by discharge from hospital, in our study patients of non-diabetes group discharged earlier than diabetes group without any impact of other comorbidities. Intensive treatment and monitoring were required for diabetic patients. Moreover, choice of treatment was also influenced by other underlying comorbidities. In our study treatment modalities for diabetes group significantly differ compared to non-diabetes group especially when other comorbidities were excluded. This might be explanation of higher severity of COVID-19 manifestation in other chronic disease also.

CONCLUSION

From the findings of the present study it can be concluded that diabetes mellitus definitely predisposes an individual to a severe and fatal COVID-19 infection. The severity of COVID-19 in diabetics could be attributable to the dysfunctional immune system, with a simultaneous susceptibility to viral infection. Such a status of immunity provides a favorable condition for viral survival and a longer recovery duration in diabetics. Whether other comorbidities are present or not, diabetic patients with SARS-CoV-2 pneumonia require higher attention in terms of pharmacological and supportive treatment than those without diabetes. A high prevalence of DM in India predisposes a large proportion of population to COVID-19 and its complications. Hence, an extreme care for preventing COVID-19 in people with underlying DM is advisable beside an intensive care in already infected individuals.

ETHICAL APPROVAL

This study proved by ethical and research committee of SMS medical college and Hospital, Jaipur, India.

AUTHOR CONTRIBUTIONS

S Bhandari, G Rankawat and A Singh formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript; G Rankawat and A Singh collected and analyzed data for study. G Rankawat write the manuscript. B Patel and S Sharma conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

Availability of Data and Materials

Available from corresponding author upon reasonable request.

Declaration of Competing Interest

All authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential.

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