High Mortality Unaffected by Age, Gender and Steroid Use is the Hallmark of COVID-19 in Diabetes: Observations from a Retrospective Analysis during Peak of 2020 Pandemic in India

Ramesh Aggarwal¹, Aparna Agrawal², Anil Gurtoo³, Vivek Suman¹, Shivraj Meena¹, Anupam Prakash⁴*

Abstract


Methods: Records of admitted COVID-19 patients suffering from diabetes or having admission hyperglycemia (random plasma glucose ≥200 mg/dL) between March to August 2020 were analysed for severity and outcomes of COVID-19, presence of comorbidities, steroid use, and correlated with hyperglycemia.

Results: 71 COVID-19 patients (severe disease - 35, moderate- 17, mild- 19) were studied. Mortality was 52.1% (mild disease-27.3%, moderate- 43.5% and severe- 72.7%). Mortality was similar across age and gender. Prevalence of comorbidities was similar in survivors (20.6%) and non-survivors (24.3%). Newly detected hyperglycemia at admission was noted in 9 patients, two-thirds of which had severe COVID-19 and 5 expired (55.5%). Higher values of plasma glucose at admission (295.9 vs. 236.4 mg/dL, p=0.047) and high fasting plasma glucose values (210.3 vs. 166.5 mg/dL, p=0.043) were observed among non-survivors. Mortality rates were statistically similar in those who received steroids and those who did not.

Conclusion: COVID-19 in diabetes patients requiring admission carries high mortality, irrespective of age, gender, presence of comorbidities and steroid use. However, admission hyperglycemia and high fasting plasma glucose values are associated with higher mortality.

Introduction

Diabetes is one of the major illnesses affecting 8.8% of the world population representing almost 415 million people.¹ Diabetes is known to predispose an individual to increased risk for infections. Studies in the past have shown a J-curve type of relationship between HbA1c and the chances of being admitted in hospital with respiratory infection. COVID-19 pandemic seized the world in 2020, but diabetes impacted COVID-19 as one of the prime adverse prognostic factors. An increased risk of infection in diabetics was reported during previous outbreaks of severe acute respiratory syndrome, Middle East respiratory syndrome and H1N1 influenza virus. Evidence is gradually emerging that not only diabetes but hyperglycemia in the early phase of the disease may determine the severity of the disease. However, published literature is lacking on how Diabetes patients getting admitted with COVID-19 have behaved. The present study outlines the severity and outcomes in patients

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This retrospective observational study collected data of COVID-19 patients who were admitted to our dedicated COVID-19 set-up at a tertiary care centre in Delhi, India between the months from March to August 2020. The study was approved by the Institutional Ethics Committee. A total of 71 COVID-19 patients presented with hyperglycemia during the referenced period. Hyperglycemia was defined as random blood sugar ≥180mg/dL at admission. Only RT-PCR/CBNAAT confirmed cases of COVID-19 were included in the study. Patients who were already known to be suffering from diabetes were also included. New onset hyperglycemia was defined as random blood sugar at admission ≥200mg/dL without any previous evidence of preexisting diabetes. HbA1c was not done at baseline in these patients.

Records were analysed for information which was transcribed on a pre-structured proforma which included baseline demographic data, clinical features including severity of COVID-19 (based on MoHFW guidelines),

#### Results

A total of 71 RT-PCR confirmed nCoV-2019 positive patients who presented with hyperglycemia or were known diabetes mellitus patients during the period (March –August 2020) formed the study group. 37 patients (52.1%) succumbed and constituted the non-survivor group (Group A). Table 1 shows the various characteristics among the non-survivors (Group A) and the survivors (Group B).

In up to 60 years age group, 14/32 (43.75%) males and 11/20 (55%) females survived, while in the > 60 years age group, 7/12 (58.3%) males and 2/7 (28.6%) females survived, and the difference was not statistically significant age wise or gender wise.

Mortality did not differ significantly in between the genders, irrespective of the severity of COVID-19. 2/12 (16.7%) males and 1/7 (14.3%) females suffering from mild COVID-19 failed to survive, compared to 3/5 (60%) males and 5/9 (55.5%) females suffering from moderate COVID-19, and 18/24 (66.7%) males and 8/11 (72.7%) females suffering from severe COVID-19.

Prevalence of comorbidities in the study group was also similar (p>0.05) in the non-survivors (24.3%) and survivors (20.6%).

#### Methods

The study collected data of COVID-19 patients who were admitted to our dedicated COVID-19 set-up at a tertiary care centre in Delhi, India between the months from March to August 2020. The study was approved by the Institutional Ethics Committee. A total of 71 COVID-19 patients presented with hyperglycemia during the referenced period. Hyperglycemia was defined as random blood sugar ≥180mg/dL at admission. Only RT-PCR/CBNAAT confirmed cases of COVID-19 were included in the study. Patients who were already known to be suffering from diabetes were also included. New onset hyperglycemia was defined as random blood sugar at admission ≥200mg/dL without any previous evidence of preexisting diabetes. HbA1c was not done at baseline in these patients.

#### Table 1: Comparison between Group A (Non Survivors) and Group B (Survivors)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A Non Survivors (n=37)</th>
<th>Group B Survivors (n=34)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>55.1 ± 11.9 (33-82)</td>
<td>55.1 ± 12.63 (33-85)</td>
<td>0.475</td>
</tr>
<tr>
<td>Male to Female ratio</td>
<td>23:14</td>
<td>21:13</td>
<td>0.972</td>
</tr>
<tr>
<td>Age of Males (Mean ± SD in years)</td>
<td>53.3 ± 12.34 (33-82)</td>
<td>56.5 ± 13.03 (33-85)</td>
<td>0.2</td>
</tr>
<tr>
<td>Age of Females (Mean ± SD in years)</td>
<td>58.0 ± 10.94 (40-80)</td>
<td>52.9 ± 12.12 (42-85)</td>
<td>0.13</td>
</tr>
<tr>
<td>Comorbidity &gt; 1</td>
<td>9 (24.3%)</td>
<td>7 (20.6%)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

#### Table 2: Covid-19 mortality in relation to plasma glucose at admission and severity of COVID-19 (n=60)

<table>
<thead>
<tr>
<th>Admission plasma glucose values</th>
<th>N</th>
<th>Mild (n=13)</th>
<th>Moderate (n=17)</th>
<th>Severe (n=30)</th>
<th>P value (Chi square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200 mg/dL</td>
<td>19</td>
<td>2/6 (33.3%)</td>
<td>2/5 (40%)</td>
<td>4/8 (50%)</td>
<td>0.147</td>
</tr>
<tr>
<td>≥200 mg/dL</td>
<td>41</td>
<td>Nil/7 (0%)</td>
<td>5/9 (55.5%)</td>
<td>20/25 (80%)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

#### Table 3: Patients on steroids: Comparison of blood sugars and outcome (all values are in Mean ± SD)

<table>
<thead>
<tr>
<th>Plasma glucose (mg/dL)</th>
<th>Non-survivors (n=15)</th>
<th>Survivors (n=9)</th>
<th>P value (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting (within 24 hours of admission)</td>
<td>213 ± 95.95 (97-321)</td>
<td>203.7 ± 58.79 (128-286)</td>
<td>0.80</td>
</tr>
<tr>
<td>Prior to discharge/ death</td>
<td>251.46 ± 74.02 (144-396)</td>
<td>174 ± 114.41 (116-293)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

#### Table 4: Duration of stay (Days)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A Non Survivors (n=37)</th>
<th>Group B Survivors (n=34)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>31-40 years</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>41-50 years</td>
<td>10</td>
<td>9</td>
<td>0.988</td>
</tr>
<tr>
<td>51-60 years</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Data is presented as Mean ± SD and proportions. Statistical analysis was performed. Two-group and three group comparisons were respectively made with unpaired Student’s t-test and ANOVA. Chi-square test was used for non-parametric data. P<0.05 was taken as level of significance.
Table 4: Fasting plasma glucose values before and after steroids in Survivors (n=9)

<table>
<thead>
<tr>
<th>Fasting plasma glucose</th>
<th>Before Steroid</th>
<th>After Steroid</th>
<th>Last Day of Steroids</th>
<th>48 hours after Steroid stopped</th>
<th>72 hours after Steroid stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=3</td>
<td>n=9</td>
<td>n=6</td>
<td>n=5</td>
<td>n=4</td>
</tr>
<tr>
<td>Range (mg/dl)</td>
<td>133-206</td>
<td>128-286</td>
<td>116-246</td>
<td>93-165</td>
<td>100-152</td>
</tr>
<tr>
<td>Mean ± SD (mg/dl)</td>
<td>161.3 ± 46.23</td>
<td>203.7 ± 58.79</td>
<td>160.3 ± 44.49</td>
<td>121.8 ± 26.76</td>
<td>122 ± 26.29</td>
</tr>
</tbody>
</table>

(1).

Plasma glucose at presentation ≥200 mg/dL (25 out of 41, 60.9%) when compared to those who had plasma glucose at presentation between 71-200 mg/dL (6 out of 17, 35.3%), did not show a significant difference (p=0.07). Mortality rates did not differ significantly in relation to severity of COVID-19 when compared in the two groups with admission plasma glucose values <200 mg/dL and values ≥200 mg/dL (Table 2). Two patients had presented with hypoglycemia (plasma glucose < 70 mg/dL), and both did not survive. Average duration of stay was 3.7 days among non-survivors compared to 13.2 days for those who survived.

When a cut-off of 126 mg/dL and 200 mg/dL were used, then no significant difference was noted in the mortality percentages below and above these cut-offs, for admission plasma glucose values or fasting plasma glucose values.

There were 24 patients who received steroids out of which 19 (79%) had severe presentation at admission. Of the 24 patients who received steroids, 15 (62.5%) expired. In our study, there was no significant difference in mortality in patients who received steroids and those who did not receive steroids. All those patients who expired despite receiving steroids had significantly higher plasma glucose levels at expiry than the patients who survived (Table 3).

We also observed that the average increase in blood sugar values in patients after receiving steroids (usual dose was Inj Dexamethasone 6 mg IV OD) was 42.4 mg/dL. This rise in blood sugar came within normal range 48 hours after stopping steroids (Table 4). The mean insulin requirement which was 50 units per day in patients receiving steroids dropped down to 43 units 48 hours after stopping steroids.

**Discussion**

The present study reveals that COVID patients having pre-existing diabetes or admission hyperglycemia had 52.1% mortality across the severity spectrum of COVID-19, though mortality increased with severity of COVID-19 viz. 27.3% in mild cases, 43.5% in moderate cases and 72.7% in severe cases. Poor outcomes of COVID-19 in patients suffering from diabetes have been reported in other studies as well. Data analysis of 153 people revealed in-hospital mortality of 20% in patients having diabetes compared with 10.5% in patients without diabetes (3). Increasing odds of in-hospital death or poor prognosis in patients with COVID-19 were found to be associated with diabetes in an analysis of 904 hospitalised patients (in-hospital death: OR 2.51 (95% CI 1.53, 4.13), poor prognosis: OR 2.21 (95% CI 1.50, 3.26), p< 0.001 for both). Chinese Centre for Disease Control and Prevention (CCDC) reported a case fatality rate (CFR) of 7.3% in patients with diabetes, compared to 2.3% in overall population of 44,672 COVID-19 patients. In a retrospective study of 7337 COVID-19 patients, a significant 49% relative increase in all-cause mortality (HR 1.49; 95% CI, 1.13–1.96; p = 0.005) was reported in patients with diabetes (n = 810), compared to the groups without diabetes (n = 6385) even after adjustment for multiple confounding factors. In our initial published experience in 182 COVID-19 patients, all-cause mortality was 32.9% (n=60) but mortality in diabetes was 58.5% (31 of the 53 diabetic patients expired). Bode et al. studied 1122 patients from 88 U.S. hospitals and observed that amongst 570 patients who died or were discharged, the mortality rate was 28.8% in 184 diabetes and/or uncontrolled hyperglycemia patients, compared with 6.2% of 386 patients without diabetes or hyperglycemia (p < 0.001).

In the present study, a much higher mortality (37/71) i.e. 52% has been witnessed in diabetic patients (known diabetics as well as newly onset). The average age in the non-survivor and survivor groups was similar [(55.1±11.9 years (33-82) vs 55.1±12.63 years (33-85), Table 1]. Also, we did not find any significant difference in mortality between the patients aged ≤60 years and those aged >60 years. Naomi et al. (9) studied patients of COVID-19 in England and observed that older age was associated with increased COVID-19-related mortality in patients with type 2 diabetes. Out of 10525 deaths, 94.23% were in over 60 years age whereas 5.7% were in patients less than 60 years of age. In our study, diabetes seemed to offset the protective effect that young age may offer against COVID-19. This finding is supported by a cohort study of total population of Scotland (10). It reported a statistically significant interaction between diabetes and age on risk of fatal or critical care unit-treated COVID-19 (p=0.001); odds ratio (OR) being 2.494 for age 0-59 years, OR of 1.764 for 60-69 years age group and OR of 1.327 for age ≥70 years.

Naomi et al. reported male sex (vs female sex) was associated with increased COVID-19-related mortality for both people with type 1 and type 2 diabetes (p = 0.0001). In our study mortality rates were similar among males and females, and did not vary with age. However, it was noted that more males presented with severe COVID-19 (58.97% vs 40% in females) though mortality in both the genders was similar.

We observed that more than half of the diabetic patients (52.38%) had severe disease at presentation and almost three-fourth (72.27%) of these patients expired. Studies have shown that the disease is more severe in patients with diabetes. In a recent meta-analysis it was observed that the pooled ratio of those suffering from a severe course compared with a milder course in diabetic patients was 2.26. As we did not include patients who were not admitted to the hospital and were sent for home isolation, there is a higher percentage of severe COVID-19 in our hospitalized diabetic population. In another study of 339 patients from China, it was observed that diabetic patients had 4-fold increased risk of having severe/critical COVID-19 illness and this association persisted even after adjustments for age, sex, smoking and other comorbidities.

We observed that the number of patients with more than one comorbidity was greater among non-survivor group than the survivor group but this difference was not
than 60 ml/min per 1.73 m². They observed that 288 (34.4%) subjects had one or more past diseases (hypertension, chronic heart disease, chronic liver disease, chronic kidney disease, cerebrovascular disease, carcinoma) of which hypertension was the most common comorbidity. Naomi et al (9) studied comorbidities in COVID-19 patients with type 2 diabetes. They observed that out of 10525 deaths, 425 (4.0%) had either cardiovascular or renal morbidity (defined as previous myocardial infarction, stroke, hospital admission for heart failure or eGFR less than 60 ml/min per 1.73 m²).

We compared the fasting plasma glucose values within first 24 hours of admission and random plasma glucose (RPG) at admission between the two groups. Using a cut-off value of 200 mg/dL for both random plasma glucose at admission, and fasting plasma glucose performed within 24 hours of admission, our data did not show any statistically significant difference in mortality between the groups which had plasma glucose values below 200 mg/dL compared to group having values above 200 mg/dL (Table 2). However, higher admission plasma glucose values as well as higher fasting plasma glucose values were observed in those who expired, compared to the survivors.

Recent studies including a meta-analysis14-18 have suggested that hyperglycemia is an independent risk factor for mortality. However, different studies have used different cut-off values viz. 126 mg/dL or 200mg/dL, and almost all are retrospective studies like ours, and thus harbour the limitations of such studies. Hyperglycemia particularly an acute increase in blood sugar levels is associated with a steep increase in inflammatory mediators including a procoagulant effect. This may lead to cytokine storm as seen in COVID-19 patients. Also, SARS-CoV2 virus binds to ACE2 receptors and this binding is facilitated by hyperglycemia induced glycosylation of ACE2 receptors.

Studies have also shown that in patients with COVID-19 and diabetes, the mortality is related to the preceding levels of hyperglycemia. The higher the HbA1c levels, the greater the risk of mortality. COVID-19-related mortality was significantly higher in those with an HbA1c ≥7.6% than in those with an HbA1c of 6.5-7.0%, and the risk increased with increasing HbA1c levels: (HR 1.22 [95% CI 1.15-1.30, p<0.0001] for 7.6-8.9% and 1.36 [1.24-1.50, p<0.0001] for 9.0-9.9% (9). HbA1c levels were not analysed in our study, so the contribution of preceding levels of hyperglycemia to the mortality or severity could not be assessed and could be an important confounder in our study results.

Bode et al8 studied 1122 patients and found 451 (38.5%) of these patients had either diabetes or suffered from uncontrolled hyperglycemia. It was found that 28.8% of patients having diabetes or uncontrolled hyperglycemia did not survive hospitalization, representing a more than four-fold higher in-hospital mortality rate compared with the mortality rate for COVID-19 inpatients without diabetes or uncontrolled hyperglycemia (6.2%).

Hyperglycemia can have poor outcomes in COVID-19 patients. Targher et al12 retrospectively studied a cohort of 339 patients with COVID-19 and found that the proportion of severe COVID-19 illness increased progressively (p < 0.0001) in relation to glucose abnormalities at admission: from 7.1% in patients with random plasma glucose < 100.9 mg/dL, 20.3% in those with random plasma glucose 100.9-198.2 mg/dL and 65% in those with random plasma glucose ≥200 mg/dL at hospital admission, respectively. Coppelli et al17 studied 271 hospitalised COVID-19 patients and reported mortality rate of 16.8% among 149 with normal glycaemia, 28.6% among 56 who had diabetes and 39.4% of the 66 who had new-onset hyperglycaemia, indicating poorer outcomes in new-onset hyperglycaemia. Wang et al13 studied the relationship between fasting blood glucose (FBG) and 28-day mortality in COVID-19 patients not previously diagnosed as having diabetes. They found that in comparison to patients with FBG <6.1 mmol/l, mortality within 28 days was higher in those with FBG of 6.1–6.9 mmol/l (crude HR 2.06 [95% CI 1.20,3.54]) and ≥7.0 mmol/l (crude HR 3.54 [95% CI 2.33, 5.38]) respectively.

In our 9 patients who had newly detected hyperglycaemia at admission, 66.6% (n=6) of them had severe presentation and 55.5% (n=5) of these patients with new onset hyperglycaemia expired and this mortality was similar to that observed in known diabetic patients. All patients with new onset hyperglycaemia required insulin in the hospital and all except one patient required either OAD or insulin at discharge. We are not in a position to say whether the new onset hyperglycaemia was due to unmasking of latent diabetes or stress hyperglycaemia due to acute stress of COVID-19, release of inflammatory mediators, steroid induced if the patient received steroids or due to direct effect of the virus on pancreas.

There were 24 patients who received steroids out of which 79% (n=19) had severe presentation at admission. 62.5% of these patients expired in the hospital. In our study we also observed that steroids did not improve the outcome in diabetic patients as there was no significant difference in mortality in patients who received steroids and those who did not receive steroids. The numbers of course are small. We also studied the effect of steroids on blood sugar levels (Table 3). All those patients who received steroids and expired had fasting plasma glucose and plasma glucose (at expiry) significantly higher than the patients who survived. (p value <0.007 and 0.02 respectively).

We also observed that the average increase in blood sugar values in patients after receiving steroids (usual dose was Inj Dexamethasone 6 mg IV OD) was 42.4mg%. This rise in blood sugar came back to normal range 48 hours after steroids were stopped. The mean insulin requirement which was 50 units per day in patients receiving steroids dropped down to 43 units 48 hours after stopping steroids. Attention is drawn to the fact that COVID-19 patients were not given steroids initially, as in the initial part of the pandemic, it did not form part of the standard protocol.

Studies have shown that patients with diabetes and COVID-19 require insulin on admission. In a study from China it was observed that 29.2% of diabetic patients were on insulin at admission and another 37.5% received
insulin after admission, indicating presence of dysglycemia during the course of disease. Stress hyperglycemia, drugs like steroids and virus induced autoimmunity can be the contributing reasons for higher insulin requirements in these patients.

This study had inherent limitations expected of a retrospective study. Besides, the study was conducted among hospitalized patients, so data may not be generalizable to non-admitted population. Also, the sample size is small. However, this is the whole sample that had presented to hospital during the period of study, without any exclusions. Baseline or recent HbA1c was not available for most patients, and hence preexisting diabetes was defined only on the basis of patients’ history and records. Biochemical markers of severity like cytokines, D-dimer and ferritin were not available for the study group, which in future studies can give some insights for management of these patients.

Conclusions

Diabetes patients suffering from COVID-19 requiring admission irrespective of severity of COVID-19 have high mortality rates, mortality being higher with increasing severity of COVID-19. Mortality rates are similar in the elderly (>60 years) and ≤60 years age groups, and in both genders.

Patients having admission hyperglycemia (≥ 200 mg/dL), who are not previously known diabetics have similar mortality rates as diabetics. Hyperglycemia at presentation, even among known diabetics is associated with higher mortality rates than those who have random plasma glucose < 200 mg/dL.

Diabetic patients with COVID-19 who received steroids did not show a reduced mortality in our study. Steroids exacerbate hyperglycemia and its withdrawal led to euglycemic state by 48 hours in treated patients.

References