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# Correlation of blood sugar levels at the time of admission with the severity of infection and outcome in covid 19 patients admitted to tertiary hospital.

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## Abstract

**Background:** Patients with history of diabetes are known to be more susceptible to infections in general. Moreover, once they get infected, the risk of developing complications is comparatively higher. During the outbreaks of corona virus, the patients with known case of diabetes mellitus was consistently shown to be a predisposing factor for severe COVID-19.

**Objective:** We conducted a prospective study to analyse and compare the association between diabetes and the severity of the disease and the pattern of distribution of COVID markers among the patients with COVID 19 among patients with HbA1C >6.5.

**Results:** The average age of the recruited samples was 53.49±14.49. 94(59.9%) were males. Out of 87 patients with history of DM in the present study, 12(13.8%) were found to be having CT severity score >20. 76/157 (48.4%) and 81/157 (51.6%) of the patients were found to be having HbA1C <6.5% and >6.5% respectively. Prevalence of CT severity score >20 was higher among the patients with HbA1c >6.5%. COVID markers were higher among the study population with >6.5% of the HbA1c. we observed increased in inflammatory markers among the patients with high HbA1c.

**Conclusion:** We conclude that Diabetic patients are more prone for worsening the disease and hence the increased mortality and poor outcome.

**Keywords:** COVID 19, HbA1c, Hyperglycaemia, COVID 19 CT severity

## Introduction

Patients with history of diabetes are known to be more susceptible to infections in general. Moreover, once they get infected, the risk of developing complications is comparatively higher. [1] Fadini GP et al explained that hyperglycaemia will be increasing the viral proliferation in human monocytes which will be associated with

severity of the disease. [2] Hence, elevated glucose levels lead to a direct increase in SARS-CoV-2 replication too. Glycolysis maintains SARS-CoV-2 replication through the production of mitochondrial reactive oxygen species and activation of hypoxia-inducible factor-1α. [2,3]

Also, increased insulin resistance at peripheral tissues and hepatic cells, a combination of increased secretion of hormones such as catecholamines, cortisol, and glucagon will be increasing the hepatic gluconeogenesis, increased availability of lactate, use of carbohydrate-based feeds, glucose-containing solutions, and drugs such as epinephrine, can all contribute to hyperglycaemia. [4,5]

During the outbreaks of corona virus, the patients with known case of diabetes mellitus were consistently shown to be a predisposing factor for severe COVID-19. [6] Several large cohort studies demonstrated a clear association between pre-existing diabetes, HbA1C as well as hyperglycaemia upon admission and COVID-19 related mortality. [7,8]

Many studies suggested that patients with known case of elevated HbA1C were associated with increased risk of prolonged hospitalization and also higher incidence of ICU admissions. [9-12] There were very few Indian and no clinical research articles from Karnataka were found during our study. Hence, we conducted a prospective study to analyse and compare the association between the raised blood sugar levels and HbA1c with the severity of the disease and the pattern of distribution of COVID markers among the patients with COVID 19 among patients with HbA1C >6.5.

**Materials and methodology**

We conducted a prospective observational study at Department of general medicine, Bangalore Medical College and Research Institute for a period of three months from 1st July 2021 to 30th September 2021. After obtaining the ethical clearance [IEC clearance number: BMCRI/PS/103/2021-22], we recruited all patients aged more than 18 years tested positive with COVID 19 and are willing to provide written informed consent to participate in the study. Patients who were presented with known history of cardiovascular diseases were excluded from the study.

**Sample size:** $4pq/d^2$

p = prevalence: Prevalence of DM at our institute in the year 2020 was 9%

q = (100-p)

d is allowable error. We considered 5% allowable error for the given study.

4 (9) (11)/25 So, the approximate sample size is 131.

But as we included the patients who were newly diagnosed (Those who were not previously diagnosed with diabetes/ with no past history of DM) with DM. Hence the sample size of our study increased to 157.

COVID markers such as C reactive protein (CRP) and Lactate dehydrogenase (LDH) were tested for all the recruited population. Also, the Complete blood count (CBC), Random blood sugar (RBS) and glycosylated haemoglobin (HbA1C) was also tested. All the laboratory parameters were noted. Computed tomography (CT) chest was done to analyse the radiographic and symptomatic correlation of the disease. Severity was analysed using CT severity index score based on the percentage and lobes of the lung involved. Score 1 (<5%), Score 2 (6 -25%), Score 3 (26- 50%), Score 4 (51- 75%) and score 5 (> 75%).

Patients with lesser oxygen saturation will be administered with $O_2$ supplementation with suitable mode of oxygenation based on the requirement.

Obtained parameters were noted. The data was tabulated in Microsoft Excel and analysed using SPSS software version 2.0 with suitable statistical tests. The tests used for analysis are mentioned below particular table.

**Results**

The average age of the recruited samples was 53.49±14.49. Majority of the study population were aged between 41 to 60 years accounting for about 78 (49.7%) followed by the patients aged between 61 to 80 years with the prevalence of 44 (28%), which is tabulated in table 1.

Table 1: Distribution of age

| Age in Years | No. of Patients | % |
|---|---|---|
| 21-40 | 32 | 20.4 |
| 41-60 | 78 | 49.7 |
| 61-80 | 44 | 28.0 |
| 81-100 | 3 | 1.9 |
| Total | 157 | 100.0 |

Mean ± SD: 53.49±14.49

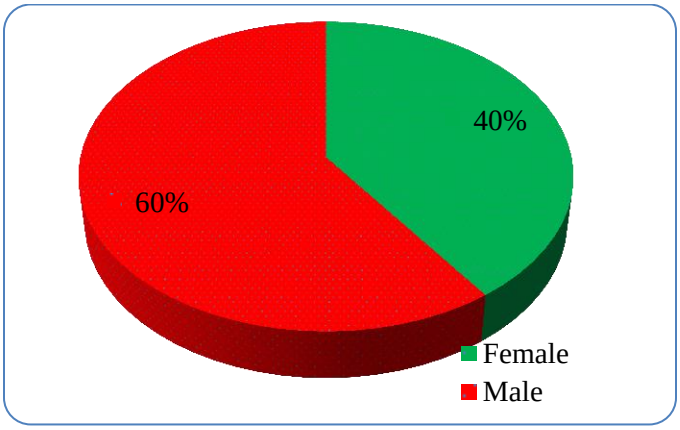


Figure 1: Distribution of gender

Figure 1 illustrates the distribution of gender among the recruited study population. Out of 157 recruited patients, 94(59.9%) were males and 63(40.1%) were female patients.

Table 2: Prevalence of DM among the recruited samples.

| DM | No. of Patients | % |
|---|---|---|
| No | 70 | 44.6 |
| Yes | 87 | 55.4 |

87 (55.4%) of the patients were found to be having DM and the rest 70 (44.6%) were non diabetics.

Table 3: Distribution of random blood sugar and HbA1c among the recruited samples

| Variables | History of DM | | Total | P Value |
|---|---|---|---|---|
| | No | Yes | | |
| HbA1c | | | | |
| <6.5 | 30(42.9%) | 47(54%) | 77(49%) | 0.219 |
| >6.5 | 40(57.1%) | 40(46%) | 80(51%) | |
| RBS | | | | |
| <130 | 3(4.3%) | 6(6.9%) | 9(5.7%) | 0.718 |
| >130 | 67(95.7%) | 81(93.1%) | 148(94.3%) | |

Out of 87 known cases of DM, 46% of the patients were presented with HbA1c >6.5 and approximately 93.1% were with RBS >130 whereas (40/70) 57.1% of the patients with no previous history of DM were found to be having HbA1C >6.5 and 67 (95.7%) were with >130gm/dl of RBS. Here the presence and absence of DM is based on the history of comorbid conditions obtained by the patients. We can observe majority of the patients who were not presented with history of DM also had >6.5% HbA1c these patients might be newly detected.

Table 4: Frequency distribution of CT severity score in the patients studied.

| CT SS | DM | | Total | P value |
|---|---|---|---|---|
| | No | Yes | | |
| Score 1 to 2 | 2(2.9%) | 10(11.5%) | 12(7.6%) | P=0.054+ |
| Score 3 | 62(88.6%) | 65(74.7%) | 127(80.9%) | |
| >Score 3 | 6(8.6%) | 12(13.8%) | 18(11.5%) | |

**Fisher Exact Test**

Table 4 explains that the severity of the disease was significantly high among the patients with diabetes than non-diabetic with the p value of 0.054. Majority of the patients with Score 4 and 5 were among diabetic group.

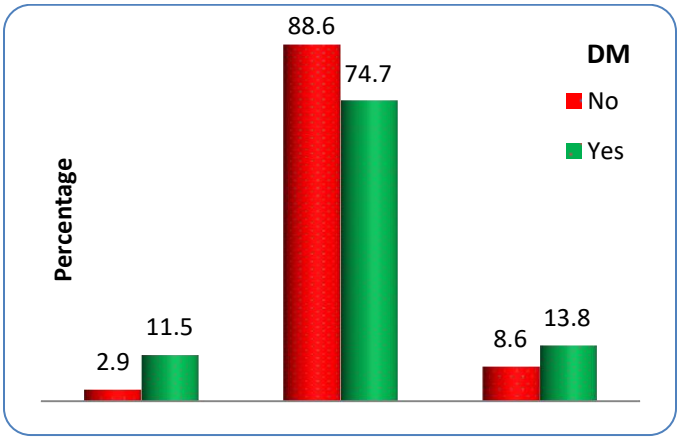


Figure 2: Distribution of CT severity between diabetic and non-diabetic patients

Table 5: Frequency distribution of mode of ventilation patients studied in relation to DM studied

| Mode of ventilation | Dm | | Total |
|---|---|---|---|
| | No | Yes | |
| Face mask | 6(8.6%) | 11(12.6%) | 17(10.8%) |
| High flow nasal oxygen | 15(21.4%) | 20(22.9%) | 32(20.4%) |
| Intubated | 0(0%) | 8(9.2%) | 8(9.2%) |
| Non-invasive ventilation | 4(5.7%) | 9(10.3%) | 13(8.3%) |
| Non rebreathing mask | 30(60%) | 39(44.8%) | 81(51.59%) |
| Nasal prongs | 1(1.4%) | 0 | 1(1.4%) |
| Room air | 15 (21.42%) | 0 | 10(6.4%) |

P=0.179, Not Significant, Fisher Exact Test

Above table 5 illustrates the comparative distribution of mode of ventilation between diabetic and non-diabetic patients. There was no significant difference in the requirement of different mode of ventilation.

Table 6 A: association of crp and ldh according TO hba1c of aptients studied.

| **Variables** | **HbA1C** | | **Total** | **P Value** |
|---|---|---|---|---|
| | **<6.5** | **>6.5** | | |
| CRP | | | | |
| <3.0 | 4(5.3%) | 0(0%) | 4(2.5%) | 0.052 + |
| >3.0 | 72(94.7%) | 81(100%) | 153(97.5%) | |
| LDH | | | | |
| <280 | 27(35.5%) | 15(18.5%) | 42(26.8%) | 0.026 * |
| >280 | 49(64.5%) | 66(81.5%) | 115(73.2%) | |
| Total | 76(100%) | 81(100%) | 115(73.2%) | |

Chi-Square Test/Fisher Exact Test

Inflammatory markers, C reactive protein and Lactate dehydrogenase were significantly elevated among the patients with HbA1C more than 6.5.

Table 6 B: association of D-Dimer, fibrinogen, pt., inr & aPTT according to hba1c of patients studied

| Variables | HbA1C | | P Value |
|---|---|---|---|
| | <6.5 | >6.5 | |
| D DIMER | | | |
| <1.0 | 58(76.3%) | 20(24.7%) | <0.0001 |
| >1.0 | 18(23.7%) | 61(75.3%) | |
| FIBRINOGEN | | | |
| <400 | 49(64.5%) | 23(28.4%) | 0.001 |
| >400 | 27(35.5%) | 58(71.6%) | |
| PT | | | |
| <20 | 55(72.36%) | 33(40.74%) | <0.05 |

| | | | |
|---|---|---|---|
| >20 | 21(27.63%) | 48(59.25%) | |
| INR | | | |
| <2.2 | 28(36.84%) | 27(33.33%) | 0.0001 |
| >2.2 | 48(34.84%) | 54(66.66%) | |

Chi-Square Test/Fisher Exact Test

All the covid markers were found to significantly high among the patients with HbA1C more than 6.5 with significant p value of <0.05 with respect all the parameters.

Table 6 C: IL-6- Frequency distribution in relation to HbA1c of patients studied

| IL-6 | HbA1C | | Total |
|---|---|---|---|
| | <6.5 | >6.5 | |
| <10 | 19(25%) | 1(1.2%) | 20(12.7%) |
| >10 | 57(75%) | 80(98.8%) | 137(87.3%) |
| Total | 76(100%) | 81(100%) | 157(100%) |

P≤0.001**, Significant, Chi-Square Test

IL 6 levels were also found to be higher among the patients with raised HbA1C indicating that these patients are more prone to develop the cytokine storm and related complications than those with lesser HbA1C.

Table 6 D: FERRITIN- Frequency distribution in relation to HbA1c of patients studied

| Ferritin | HbA1C | | Total |
|---|---|---|---|
| | <6.5 | >6.5 | |
| <500 | 38(50%) | 22(27.2%) | 60(38.2%) |
| >500 | 38(50%) | 59(72.8%) | 97(61.8%) |
| Total | 76(100%) | 81(100%) | 157(100%) |

P=0.005**, Significant, Chi-Square Test

Table 7: Comparison of average values of COVID markers

| Variables | HbA1C | | P Value |
|---|---|---|---|
| | <6.5 | >6.5 | |
| D DIMER | 0.88±1.16 | 1.92±1.07 | 0.001 |
| FIBRINOGEN | 407.53±27.42 | 450.1±3.97 | 0.03 |
| PT | 12.53±8.52 | 15.59±9.31 | 0.03 |
| INR | 1.19±0.13 | 1.3±0.11 | 0.0001 |
| APTT | 28.25±7.95 | 29.39±11.49 | 0.474 |
| CRP | 90.06±76.43 | 121.84±72.83 | 0.008 |
| LDH | 373.92±189.95 | 454.96±231.91 | 0.018 |
| IL-6 | 35.58±17.32 | 42.36±13.92 | 0.0075 |
| FERRITIN | 600.3±33.98 | 809.25±48.57 | 0.004 |

Table 8 refers to the comparison of mean values of COVID marker between two groups which illustrates that there was significant raise in the mean values of all the COVID parameters.

Table 8: Comparison of CT SS between the patients with HbA1C <6.5 and >6.5

| CT SS | HbA1C | | P value |
|---|---|---|---|
| | <6.5% | >6.5% | |
| Score 1 to 2 | 44 (57.89%) | 09 (11.11%) | <0.05 |
| Score 3 | 21 (27.63%) | 37 (45.67%) | |
| Score >3 | 11 (14.47%) | 35 (40.69%) | |

Severity of the disease was significantly high among the patients with HbA1C level 6.5% and more

**Discussion**

Diabetic patients are generally at a greater risk of serious infections due to mechanisms including altered immune response, altered metabolism and diabetic complications. HbA1C is the most reliable marker of chronic diabetic status. [9] Meta-analysis by Prattchizzo et al observed HbA1c being linearly associated with an increased COVID-19 mortality with odd's ratio of 1.01 and p <0.00001.[10] But there were no articles who had compared the HbA1c less than and more than the baseline value (6.5%) and seen its association with COVID 19 markers.

Hence, we conducted a study to analyse the association between HbA1C and the severity of COVID 19.

157 patients had met our inclusion criteria, of which 94(59.9%) were males and 63(40.1%) were females. Average age of our recruited study population was 53.49±14.49. Majority of the patients were aged between 41 to 60 years. Whereas the average age of the patients recruited in similar study by Klein SJ et al was 68 years with 71.4% of the male patients. [11]

Out of 87 patients with history of DM in the present study, 12(13.8%) were found to be having CT severity score >20 followed by 65(74.7%) were with 10 to 20 and 10(11.5%) were found to be having <10. After analysing the HbA1C levels among both known case of DM and non-DM patients, we observed that 76/157 (48.4%) and 81/157 (51.6%) of the patients were found to be having HbA1C <6.5% and >6.5% respectively. Similarly, in Klein SJ et al 31.7% of their patients were known cases of DM but later they found a greater number of non- diabetic study participants with 6.5% of HbA1C. There was positive correlation between the increased HbA1C, age and the obesity. [11]

Prevalence of CT severity score >20 was higher among the patients with HbA1c >6.5% than those with <6.5% with statistically significant p value of <0.05 indicating the positive association between the severity of the disease with the increase in HbA1c levels. Elimam H et al and Kulcsar KA et al also have reported increased level of inflammatory markers in diabetic patients than non-diabetic. But these studies were not specific for the COVID 19 positive cases. [12,13]

Similar to our study, Klein SJ et al also observed that the severity of the disease and COVID related complications were extremely high among the patients with HbA1C ≥ 6.5% [11]

In our study, the number of patients with increased COVID markers were higher among the study population with >6.5% of the HbA1c which is illustrated from Table 6A to 6D. After analysing the mean values of the COVID markers, we found mean ±SD of almost all the markers were significantly higher among the patients with HbA1c >6.5% (Table 7) indicating the positive association between the severity and the raise in HbA1c levels. Similar observation was reported in the study conducted by Varikasuvu et al. [14] Also, Spiezia L et al and Di Micco P et al had found significantly increased inflammatory markers, hypercoagulability among the diabetic patients than the non-diabetics. [15,16]

But none of these studies had compared the parameters between the patients with and without the history of DM only. They had not considered the HbA1c alone as the associated factor.

A study by Min JY et al had analysed the severity of COVID 19 among the three different range of HbA1c. [17] In their study, out of 168,803 recruited study population, 50,016 patients had baseline HbA1c 5.7% to

6.4%, 54,729 between 6.5 to 7.4%, 47,640 had HbA1c 7.5% to 9.9% and 16,418 had HbA1c ≥86 (10%). They observed that the patients with HbA1c between 6.5%-7.4% was comparatively lesser and there was risk of hospitalization incrementally higher for those with HbA1c 7.5%-9.9% with the adjusted hazard ratio of 1.19. Similar to our study the risk of COVID-19 in-hospital death was increased in patients with HbA1c 6.5% and more.

As we observed increased in inflammatory markers among the patients with high HbA1c, we could observe that the glycaemic level is directly associated with the infection. Hence, controlling the blood sugar levels specially in the patients with HbA1c level >6.5% helps in reducing the associated morbidity and mortality.

**Conclusion**

The patients with increased level of HbA1c are more prone for COVI 19 infection and also with the increased severity. Diabetic patients are more prone for worsening the disease and hence the increased mortality and poor outcome.

We could have also analysed the associated complication and the other associated risk factors such as obesity and previous history of cardiovascular disease among these patients.

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