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Effect of diabetes mellitus on outcome of critically ill COVID-19 patients: A comparative study

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ABSTRACT

Background: Elderly population, individuals with metabolic derangements such as diabetes mellitus and obesity, and immunocompromised patients are falling prey to the severity of illness caused by the SARS-CoV-2 viral infection. India, deemed as the "Diabetes Capital of the World," has a large population vulnerable to COVID-19 infection and its complications. **Aims and Objectives:** This study was conducted to measure, compare, and describe the clinical and biochemical parameters of COVID-19 patients admitted to the intensive care unit, with and without diabetes mellitus, and their outcomes in terms of morbidity and mortality. **Materials and Methods:** A cross-sectional comparative study was conducted on 146 hospitalized patients with COVID-19 disease confirmed with reverse transcription polymerase chain reaction, 66 of them categorized as diabetic and 80 as non-diabetic. Details of socio-demographic variables, medical history, and comorbidities of the patients were collected using a pre-tested and validated questionnaire. Vital signs and hematological, biochemical, and respiratory parameters were recorded and analyzed among both the groups of COVID-19 patients. **Results:** There were statistically significant differences in the age, sequential organ failure assessment scores at admission, SpO_2, HbA1c, blood urea, creatinine, serum potassium, random blood sugar, ALT, pCO_2, PaO_2, acute respiratory distress syndrome (PaO_2/FiO_2), and the length of hospital stay between the diabetic and non-diabetic patients. **Conclusion:** Hospitalized patients with COVID-19 disease with diabetes mellitus have higher levels of inflammatory markers and of other predictors of severity of illness, need for admission in critical care units, and risk of in-hospital deaths compared to non-diabetic patients.

Key words: COVID-19; Diabetes; HBA1c; Cytokines; Acute respiratory distress syndrome; Immunity; Sequential organ failure assessment score

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INTRODUCTION

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus, first detected in a cluster of unexplained pneumonia cases in Wuhan, China.[1] Largely increasing the global socioeconomic burden; it has turned out to be a major public health concern worldwide. The presentation of illness has a wide spectrum of symptoms varying from mild symptoms like those of common cold or flu to moderate illness in 15–20% of the cases, with 5–10% of the cases exhibiting critical illness leading to respiratory failure and high rate of hospital admissions and deaths.[2] Complications such as acute respiratory distress syndrome (ARDS), pneumonia, acute kidney failure, acute heart failure due to uncontrolled acute inflammation, and cytokine storm have contributed to

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critical illness and death in COVID-19 patients.[3] Several factors such as age, gender, and pre-existing medical conditions such as diabetes, hypertension, ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), obesity, and cancer are associated with a higher risk of mortality in COVID-19 illness.[4] Many observational studies have shown that the patients with diabetes mellitus have high prevalence, severity of disease, and mortality during COVID-19 infection.[4] It was seen that the prevalence of diabetes mellitus was two to threefold higher in patients admitted to intensive care units (ICUs) and the mortality rate was almost double that of the non-diabetic patients.[5] Hyperglycemia in diabetes mellitus interferes with host–viral interactions and host–immune responses through several mechanisms leading to poorer outcomes.[4,5] Furthermore, some studies have reported that COVID-19 has been implicated in the development of new-onset diabetes mellitus.[5] There is a paucity of data regarding the effect of diabetes mellitus and associated comorbidities on the clinical presentation and outcome of symptomatic patients with COVID-19 in comparison with the non-diabetic patients. Thus, the main purpose of this study was to measure, compare, and describe the clinical and biochemical parameters of COVID-19 patients admitted to ICU, with and without diabetes mellitus.

Aims and objectives

This study was done to measure, compare and describe the clinical and biochemical parameters of RT- PCR positive COVID-19 patients admitted to ICU with and without diabetes mellitus and their outcome in terms of morbidity and mortality.

MATERIALS AND METHODS

A longitudinal comparative study was conducted on 146 patients with COVID-19 infection confirmed on reverse transcription polymerase chain reaction, admitted to the ICU of JSS Hospital, Mysuru, Karnataka, India. All patients willing to participate in the study were enrolled and an informed consent was obtained from all of them. There were no specific exclusion criteria, except for the patients not willing to give consent for participation being excluded from the study. The patients were categorized as diabetics (n=66) and non-diabetics (n=80) into two groups. Details of socio-demographic variables, medical history, and comorbidities of the patients were collected using a pre-tested questionnaire with face validity. Vital signs such as pulse rate, blood pressure, respiratory rate, and SpO_2 of all the patients were recorded. The sequential organ failure assessment (SOFA) score at admission was calculated.

Hematological and biochemical parameters including complete blood count, random blood sugar (RBS), HbA1c, procalcitonin, C-reactive protein (CRP), ferritin, D-dimer, lactate dehydrogenase (LDH), renal function tests, liver function tests, and blood gas analysis parameters were obtained from the case records. Respiratory parameters such as fraction of inspired oxygen (FiO_2) were obtained and PaO_2/FiO_2 ratio was calculated.

Ethical committee

The study was approved by the institutional ethical committee, JSS Medical College, Mysuru, and was in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 25 (licensed to the institution). Descriptive statistics were used to calculate mean, median, standard deviation (SD), interquartile range (IQR), proportions, etc., and continuous variables were expressed as mean±SD or median and IQR. Based on the distribution, Chi-square analysis was used to find the association of categorical variables in diabetics and non-diabetics with COVID-19 and parametric (independent t-test) or non-parametric (Mann–Whitney U-test) tests were used to compare the differences in quantitative variables. After the univariate analysis (independent t-test, Mann– Whitney U-test, and Chi-square analysis), variables showing statistical significance were included in binary logistic regression analysis.

RESULTS

Of all the 146 COVID-19 patients admitted to the ICU, 66 patients were categorized as diabetics and 80 patients as non-diabetics. The mean age of all the COVID-19 patients, with or without diabetes, was 54.8±12.2 years, with minimum age being 16 years and maximum being 69 years. Of all the patients, 78.7% were males and 21.3% were females; 74.6% of the patients had one or the other co-morbidities, 69.7% were diabetics, 46.7% were hypertensives, 11.5% had a history of IHD, and 25.4% had other co-morbidities such as asthma, chronic kidney disease, COPD, epilepsy, anemia, pancreatitis, hypothyroidism, and hepatitis B infection. The median SOFA score was 3 (1–14) on the day of admission, 3 (2–10) on day 2, and 5 (2–13) on day 3. Of all the patients, 41.8% expired and the remaining 58.2% were discharged. The median number of days of hospital stay was found to be 11, with minimum of 2 days and maximum of 41 days. The vital, hematological, and biochemical parameters of all the patients are depicted in Table 1.

Table 1: Vital parameters of COVID-19 patients admitted to the ICU

Variable	Mean±SD/ median IQR	Min.	Max.
Vitals			
Pulse (bpm)	99.19±17.7	45	150
Systolic blood pressure (mm/Hg)	135.2±23.1	80	200
Diastolic blood pressure (mm/Hg)	81.9±14	40	110
Respiratory rate (respirations/min)	32.7±9	16	65
SpO_2 (%)	85.3±9.3	45	100
ARDS			
PaO_2/FiO_2	156.6±54.9	62.7	417.5
Blood Parameters			
HbA1c (%)	8.5±2.5	4.9	14.4
Hb (g/dl)	12.6±2.1	5.5	17.8
Total blood cell count (cells/mm^3)	9624.3±4447.7	38	23520
Total platelet	2.3±1.01	0.19	5.9
ESR (mm/h)	676±36.3	5	150
MCV (fl)	83.4±9.9	25.7	104.4
Blood urea (mg/dl)	54.9±40.6	12	183
Creatinine (mg/dl)	2.6±8	0.35	87
Inflammatory markers			
Sodium (mmol/l)	133.4±7.4	86.4	153
Potassium (mmol/l)	4.6±1	3.1	10.5
Chloride (mmol/l)	95.9±26.1	0.3	358
Ferritin (µg/l)	1243.3±1606.1	95.3	15979
LDH (U/l)	439.3±170.7	217	1399
CRP (mg/l)	120.3±110.1	0.41	559.6
D-Dimer (µ/ml)	1.9±2.2	0.2	8.7
Vitamin D (ng/ml)	18.2±7.7	3	58
Procalcitonin (ng/ml)	5.3±26.8	0.012	173
Liver function tests			
Total Bilirubin (mg/dl)	0.9±1.5	0.19	12.8
AST (IU/l)	57.9±152.2	11	1467
ALT (IU/l)	48±103	7	962
Albumin (g/dl)	3.3±0.47	1.9	4.3
ALP (IU/l)	95.9±96.4	27	857.4
Arterial blood gas parameters			
pH	7.3±0.09	6.9	7.5
pCO_2	33.2±8.1	20.8	67.8
PaO_2	66.6±29.1	25.1	207
HCO^3	20.7±7.3	6.9	79.6
Lactate	2±1.2	0.2	10.8
SpO_2 (%)	83.8±14.9	36.8	99.1

The vital, hematological, biochemical, respiratory profiles, and the mortality rates of diabetic COVID-19 patients were compared with those of the non-diabetic COVID-19 patients (Table 2, Figures 1 and 2).

There were statistically significant differences in the age (P<0.001), SOFA scores at admission (P=0.032), SpO_2 (P=0.02), HbA1c (P<0.001), blood urea (P<0.001), creatinine (P=0.002), serum potassium (P=0.004), RBS (P<0.001), ALT (P=0.007), pCO_2 (P=0.009), PaO_2 (P=0.009), ARDS (PaO_2/FiO_2) (P=0.007), and the number of days of hospital stay (P=0.004) among the diabetic and non-diabetic COVID-19 patients. There was also

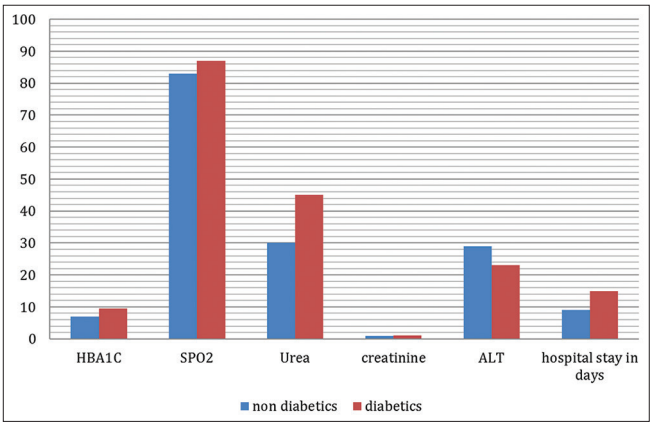

Figure 1: Comparison of various parameters with respect to diabetes status among COVID-19 patients admitted to the ICU

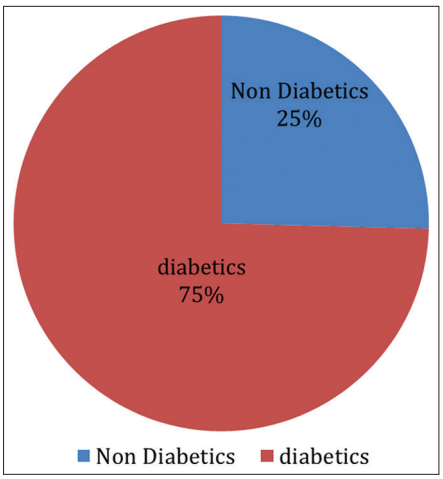

Figure 2: Association of mortality with respect to the diabetes status of the COVID-19 patients admitted to the ICU

significant association between gender and diabetes status seen among the admitted COVID-19 patients. None of the other parameters showed any statistically significant difference among both the groups of patients. On applying binary logistic regression analysis, variables that showed statistically significant differences in univariate analysis, it was found that gender, blood urea, and the duration of hospital stay were statistically significantly related to the outcome (recovery/death) among the diabetic COVID-19 patients admitted to the ICU. With reference to the male diabetic COVID-19 patients, female patients had 6.79 odds of expiry; every one unit increase in the blood urea levels showed 1.02 increase in odds of expiry; and an additional 1 day of hospital stay reduced the odds of expiry among the diabetic patients by 0.23 (Table 3).

DISCUSSION

The present study was conducted to compare and describes the clinical and biochemical parameters of

Table 2: Association and comparison of various parameters with respect to the diabetic status among the COVID-19 patients admitted to the ICU

Variable	Diabetic Status		t/F/Z/Chi-square value	p-value
	No (n=66)	Yes (n=80)		
Age (years)	46.73±14.8	58.3±9	20.7	<0.001
Vitals				
SOFA score at admission	2 (3–4)	2 (–4)	–0.085	0.032*
Pulse (bpm)	99.2±20.6	99.16±16.3	1.7	0.982
Systolic blood pressure (mm/Hg)	129.7±20.7	137.6±23.8	1.1	0.08
Diastolic blood pressure (mm/Hg)	79.9±13.2	82.8±14.3	0.096	0.283
Respiratory rate (respirations/min)	34.2±8.9	32.1±9.1	0.93	0.232
SpO_2	83±11.8	87±7.7	10.1	0.02
ARDS				
PaO_2/FiO_2	176.93±88.1	170.09±63.8	6.5	0.613
Blood parameters				
HbA1c (%)	6.9±2.7	9.5±2	0.98	<0.001
Hemoglobin (mg/dl)	12.8±1.9	12.6±2.1	0.6	0.6
Total blood cell count (cells/mm^3)	8864.9±4338	9962.7±4477.6	0.08	0.2
Total platelet	2.1±0.8	2.4±1.4	2.9	0.198
ESR (mm/h)	60 (40–80)	70 (40–100)	–1.4	0.15*
MCV (fl)	82±13.4	84±7.9	3.4	0.29
Blood Urea (mg/dl)	30 (20–38.5)	45 (33–91)	–4.117	<0.001*
Creatinine (mg/dl)	0.9 (0.7–1.1)	1.06 (0.9–1.8)	–3.1	0.002*
Vitamin D (ng/ml)	18.9±7.5	17.9±7.9	0.003	0.499
Inflammatory markers				
Serum sodium (mmol/l)	133.3±7	132.6±7.4	0.018	0.06
Serum potassium (mmol/l)	4.2±0.73	4.8±1	2.6	0.004
Serum chloride (mmol/l)	95±6.9	96.3±31.1	0.48	0.8
Serum ferritin (µg/l)	810.4 (326.7–1686.5	941.6 (462–1579)	–0.421	0.674*
LDH (U/l)	465±195.5	428±159	0.047	0.27
CRP (mg/l)	77.5 (38–128.3)	94.3 (47.2–160)	–1.4	0.15*
D-Dimer (µ/ml)	0.7 (0.5–2.4)	1.1 (0.4–2.2)	–0.092	0.92*
Procalcitonin (ng/ml)	0.41 (0.14–1.2)	0.15 (0.61–1.4)	–0.738	0.460*
RBS (mg/dl)	147 (112.5–221.5)	257 (188–354)	–4.841	<0.001*
Liver function tests				
Total bilirubin (mg/dl)	0.57 (0.43–0.96)	54 (4–84)	–0.518	0.604*
AST (IU/l)	36 (26.5–54.5)	30 (21–48)	–1.6	0.09*
ALT (IU/l)	29 (21.5–56)	23 (17–35)	–2.7	0.007*
Albumin (g/dl)	3.2±0.5	3.3±0.41	7.4	0.14
ALP (IU/l)	88 (62–112.5)	71 (60–101)	–1.59	0.112*
Arterial blood gas parameters				
pH	7.4±0.07	7.3±0.09	1.02	0.06
pCO_2	33.9±9.2	32.6±7.6	10.1	0.009
PaO_2	70.6±29.4	59.4±16.7	10.1	0.009
ARDS (PaO_2/FiO_2)	176.6±73.5	147.9±42.1	9.9	0.007
HCO_3	22±5.6	20.2±7.9	1.13	0.21
Lactate	2 (1.4–2.3)	1.9 (1.3–2.4)	–0.04	0.968*
SpO_2 (%)	83.8±16.8	82±13.3	2	0.5
Outcome of treatment				
Recovered	24 (33.8%)	47 (66.2%)	0.97	0.32#
Expired	13 (25.4%)	38 (74.6%)		
Gender				
Female	13 (50%)	13 (50%)	6.05	0.014#
Male	24 (25%)	72 (75%)		
Number of days of hospital stay				
Number of days of hospital stay	9 (6–15)	15 (9.5–24)	–2.905	0.004*

Independent t-test and *Mann–Whitney U-Test were used to compare variables which are normally and not normally distributed. #Chi-square analysis was used to find the association between the outcome of treatment and gender with respect to the status of diabetes

Table 3: Binary logistic regression

Variable	AOR (95%CI)	P-value	R^2
Gender (male)	6.79 (1.17–39.2)	0.032	56.5
Blood urea	1.02 (1.01–1.04)	0.001	
Duration of hospital stay	0.77 (0.680–0.88)	<0.001	

COVID-19 patients admitted to the ICU with and without diabetes mellitus. Our study results showed that among the patients hospitalized with COVID-19 infection, the need for admission in critical care units with severe illness and the risk of in-hospital deaths

were higher in patients with diabetes compared to those without diabetes.

In a Chinese retrospective study, patients with diabetes had more severe pneumonia with higher concentrations of inflammatory markers such as LDH, α-hydroxybutyrate dehydrogenase, alanine aminotransferase, and γ-glutamyl transferase, and fewer lymphocytes with neutrophil predominance. A subgroup of 24 patients with diabetes in the same study had greater mortality compared to 26 patients without diabetes (16.5% vs. 0%),[1,2] which is similar to the results of the present study. Likewise, in a prospective cohort study of patients with COVID-19 from New York City (NY, USA), the prevalence of diabetes and obesity was higher in individuals admitted to hospital than those not admitted to hospital (34.7% vs. 9.7%, diabetics vs. non-diabetics; and 39.5% vs. 30.8%, and obese vs. non-obese patients, respectively),[3] which correlates the observation of more severity of symptoms in diabetics in our study compared to those in the non-diabetics. Furthermore, it was evident in a meta-analysis of eight studies that COVID-19 patients with diabetes had an increased need for ICU admission.[4] To further support the finding in our study, we came across a study conducted in Italy that reported the presence of diabetes in 31.1% patients who died of COVID-19.[5] Susceptibility and severity of COVID-19 infection in diabetics may be because of compromised immune system, especially the innate immunity. Even transient hyperglycemia may temporarily affect the innate immune responses to infection.[6,7]

The results of the present study are in accordance with those of the study conducted by Maddaloni and Buzzetti, who showed significant elevation in inflammatory markers in diabetics, resulting in a cytokine storm, further worsening the illness and dictating the need for critical care admissions. Diabetic patients have an elevated pro-inflammatory cytokine level, in particular interleukin (IL)-1, IL-6, and tumor necrosis factor-α. Other inflammatory markers including the CRP, fibrinogen, and D-dimer have also been found to be elevated in diabetic patients with COVID-19 infection. Several explanations of the association between diabetes and worse clinical outcome in COVID-19 patients can be proposed (Figure 3). In general, patients with diabetes are more susceptible to a wide range of infections because of alterations in neutrophil chemotaxis, cytokine production, and impaired T-cell responses because of hyperglycemia.[7,8] In this study, there was a statistically significant difference in SpO_2 and RBS levels in diabetic compared to non-diabetic COVID-19 patients on the day of admission. Diabetic patients had comparatively longer hospital stay, which may be attributable to secondary infections. The present

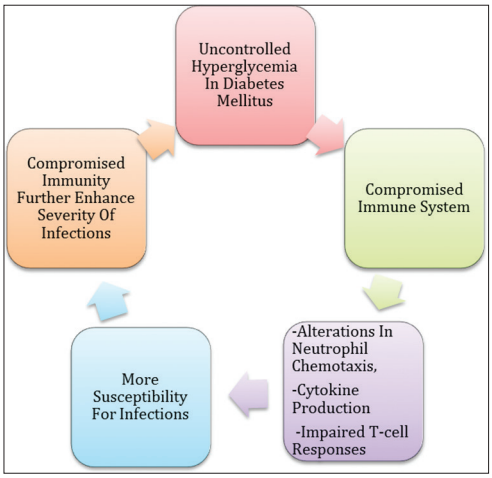

Figure 3: Possible mechanisms of diabetes mellitus complicating the clinical situation in COVID-19 patients

study also reported altered renal functions with statistically significant increase in blood urea and creatinine levels in diabetics with COVID-19 infection, which may be one of the contributors for increased morbidity and mortality in diabetic COVID-19 patients. The PaO_2/FiO_2 ratio was lower in diabetic COVID-19 patients compared to non-diabetic ones, which indicates that diabetics are more prone for faster deterioration, even in terms of oxygenation, due to deregulated immune system.

Mortality was found to be higher in diabetic COVID-19 patients (38 diabetics compared to 13 non-diabetics), which is similar to a meta-analysis done on COVID-19 and diabetes.[9]

Limitations of the study

The present study could not overcome certain limitations like the data on duration and type of diabetes and secondary complications were not recorded, and thus risk stratification in the subgroup analysis within the diabetic population could not be conducted. The study population included was mainly from the South Asian geographical region, and so these conclusions, although significant, cannot be extended automatically to the Caucasian or other populations. Finally, the patients who were diagnosed with COVID-19 had multiple chronic comorbidities such as hypertension, cardiovascular disease, cerebrovascular disease, and COPD, which could have affected the accuracy of the results. Future studies on larger, exclusively diabetic, population with COVID-19 infection are recommended for better implications.

CONCLUSION

Among patients hospitalized with COVID-19 infection, the need for admission in critical care units with severe illness and risk of in-hospital deaths were higher in patients with

diabetes compared to those without diabetes. Predictors of poor prognosis were elder age, COPD, and higher levels of inflammatory markers such as LDH and CRP. The SOFA score, age, length of hospital stay, ALT levels, and lower PaO_2/FiO_2 ratio were statistically significantly higher in diabetic patients compared to the non-diabetics admitted with COVID-19 infection in the ICU. Thus, more intensive surveillance of patients with these conditions may be warranted. Further studies may be required to compare the clinical complications and outcomes among the diabetics admitted with mild to moderate COVID-19 in comparison with a more severe disease.

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Authors' Contributions:
RR- Concept and design of the study; **AHM-** data collection; **DK-** Data collection; **SMC-** Data analysis and interpretation; **NV-** Manuscript drafting.

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