Student's Journal of Health Research Africa
Vol. 4 No. 6 (2023): June 2023 Issue
https://doi.org/10.51168/sjhrafrica.v4i6.502
Original article

A RETROSPECTIVE OBSERVATIONAL STUDY ON THE EFFECTS OF TYPE 2 DIABETES AND ITS MANAGEMENT ON INDIVIDUALS WITH SEVERE COVID-19 PATIENTS' PROGNOSIS.

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Abstract

Background :

Type 2 diabetes (T2D) as a worldwide chronic disease combined with the COVID-19 pandemic necessitates improving the management of hospitalised COVID-19 patients with preexisting T2D to reduce complications and the risk of death.

Methods:

In this retrospective study, the clinical characteristics of 193 patients with severe covid-19 were gathered. 48 patients with severe covid-19 had diabetes, while 145 patients (the control group) did not.

Results :

48 (24.9%) of 193 patients with severe covid-19 had diabetes. In comparison to patients with severe covid-19 who did not have diabetes, those with diabetes were elderly, more likely to require mechanical ventilation and ICU admission, and had a higher mortality rate. Moreover, patients with severe covid-19 and diabetes had elevated levels of leukocyte count, neutrophil count, high-sensitivity C reaction protein, procalcitonin, ferritin, interleukin (IL) 2 receptor, IL-6, IL-8, tumour necrosis factor, D-dimer, fibrinogen, lactic dehydrogenase, and N-terminal pro brain natriuretic peptide. Among patients with severe covid-19 and diabetes, men were more likely to not survive [30 (76.9%) vs. 9 (23.1%)].

Conclusion:

The mortality rate among patients with severe covid-19 and diabetes is substantial. Diabetes may increase the likelihood of mortality.

Keywords: Diabetes Mellitus, COVID-19, SARS-Cov-2, Cytokine Storm, Glycemic Control,
Submitted: 2023-06-23 Accepted: 2023-06-25

1. Introduction:

More than 126 million persons have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), and more than 2.76 million deaths have been reported worldwide [1]. This virus is a new enveloped beta-coronavirus with a single stand that shares 82% of genomic similarities with the virus responsible for the 2003 SARS pandemic [2]. SARS-CoV-2 reproduces faster than other beta-coronaviruses such as SARS-CoV and Middle East Respiratory

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Syndrome (MERS-CoV), posing a greater threat to global health [3]. The COVID-19 outbreak has caused significantly more deaths (2.76 million total deaths through March 28, 2021) than the other coronavirus respiratory syndromes (8,096 cases with 774 total deaths for the 2003 SARS outbreak and 2,519 confirmed cases and 866 total deaths for the 2012 MERS outbreak) [1, 4, 5]. As the number of confirmed cases and deaths increases exponentially, the use of epidemiological data to characterise COVID-19 patients could aid in controlling the disease's spread and in the development of treatments. Lungs, heart, and kidneys are frequently the most affected organs when a respiratory virus causes injury to multiple organs.

According to studies, the presence of one or more comorbidities is associated with the increased severity of COVID-19. Hypertension and diabetes are the most prevalent comorbidities among COVID-19 patients, according to a systematic review and meta-analysis with a total of 46,248 confirmed cases [6]. Personal history of diabetes or newly diagnosed diabetes was typically determined from medical records or a self-reported diagnosis using the WHO diagnostic criteria: fasting plasma glucose ≥ 7.0 mmol/L (≥ 126 mg/dL) or 2-h plasma glucose 11.1 mmol/L (≥ 200 mg/dL) or HbA1c ≥ 48 mmol/mol (6.5%) [7, 8]. Also, older age, hypertension, obesity, diabetes, cardiovascular disease, and chronic obstructive pulmonary disease are most frequently observed in patients with severe COVID-19 and those who died, according to studies [9, 10]. Individuals with diabetes have a higher risk of viral respiratory infections [11]. Although diabetes does not appear to increase the risk for COVID-19 in some European regions, such as Italy [12], it does increase the risk for COVID-19 and mortality rates in the majority of the world. In addition, diabetes can cause lung dysfunction, such as a reduction in forced expiratory volume and forced vital capacity. Consequently, diabetes may be a risk factor for covid-19. Our study seeks to examine the clinical characteristics of patients with severe covid-19 and diabetes mellitus, as well as the relationship between diabetes and the prognosis of patients with severe covid-19.

2. Materials and Methods:

2.1. Study design and population:

This is a retrospective, single-center, observational study. All participants were diagnosed with covid-19 in accordance with interim WHO recommendations. A total of 198 patients were treated for one year at Shree Hospital & Maternity Center, Bihar, India. 5 were excluded due to exclusion criteria. This study was conducted for around 16 months from May 2021 to September 2022.

2.1.1. Inclusion criteria:

- Adults (18 years or older)
- Real-time PCR laboratory confirmation of covid-19
- Chest CT findings meeting diagnostic criteria for covid-19

2.1.2. Exclusion criteria:

- Clinical characteristic data were missing.
- Lack of laboratory characteristics data.
- Type 2 diabetes.
- Type 1 diabetes.

Eventually, 193 patients who had concluded their medical records and follow-up were included. All of the patients lived in the community. All procedures were in accordance with the provisions of the Helsinki Declaration. Every participant gave verbal informed consent.

2.2. Data Collection:

We evaluated the patient's clinical records and laboratory results. Two independent researchers examined the collected data. Age, gender, chronic medical history (diabetes, hypertension, cardiovascular disease, cerebrovascular disease, chronic kidney disease, chronic pulmonary disease, chronic liver disease, treatment for diabetes and other comorbidities), clinical symptoms (fever, cough, dyspnea, pectoralgia, diarrhoea, nausea, vomiting, anorexia, headache, fatigue), and living status were collected. In addition, we gathered laboratory information, including blood routine, liver and renal function, random blood glucose, glycated haemoglobin, lipid,

cardiac troponin I, high-sensitivity C reactive protein (hsCRP), ferritin, coagulation function, IL-2 receptor, IL-6, IL-8, IL-10, and TNFα.

2.3. Case definition:

All patients were diagnosed with COVID-19 based on interim WHO recommendations [12]. Patients infected with SARS-CoV-2 may exhibit a variety of clinical manifestations, and their clinical status may evolve over time. According to the National Institutes of Health (US) Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [13], the patients were grouped into the following severity of illness categories based on their clinical presentation on admission: nonsevere, severe and critical. On the basis of the patient's medical history and according to the guidelines of the Indian Diabetes Society [14], T2D status was determined. On admission, none of the T2D patients exhibited symptoms of acute cardiac injury despite the fact that they had all taken diabetes medication routinely over the past year. Electrocardiographic and echocardiographic abnormalities or cardiac biomarker (hypersensitive troponin I or creatine kinase) elevation above 99 percent of the upper reference limit [15] were used to define acute cardiac injury. Disease favourable outcome was defined as full recovery and discharge, progression from critical/severe to nonsevere disease status, and/or maintenance of nonsevere disease status; disease unfavourable outcome was defined as death, progression from nonsevere to severe/critical or severe to critical, and/or maintenance of severe or critical disease status.

2.4. Statistical Analysis:

Categorical variables were summarised with figures and percentages, while continuous variables were presented with medians and interquartile ranges (IQR). For continuous variables, a Student's t-test or Wilcoxon rank-sum test was utilised. For categorical variables, the chi-square test or Fisher exact test was used as appropriate. Using univariate and multivariate Cox proportional hazard regression models, HRs and 95% confidence intervals (CIs) were calculated. A final model was chosen using a backward sequential selection procedure [16, 17]. The discrimination potential of the Cox regression model was characterised by the time-dependent receiver operating characteristic curve (ROC) and the calculated time-dependent area under the curve (AUC). A predictive nomogram was created to generate a combined indicator for estimating the risk of mortality, and it was validated by 1,000 bootstrap resamplings. Using Harrell's concordance index (C-index) [18, 19], discrimination was used to evaluate the model's capacity to distinguish between patients with differing outcomes. By displaying calibration curves, calibration was used to determine how closely predictions matched actual results. The variables were excluded if the number of events was insufficient to calculate the HR. Using the Kaplan–Meier method and Log-rank test, cumulative rates of in-hospital fatalities were calculated. The duration of survival was measured from the date of admission to the date of mortality. 'e analyses were conducted using R software (version 3.6.1, R Foundation, Vienna, Austria) or Statistical Analysis System (SAS) software (version 9.4, SAS Institute Inc., Cary, NC), with two-sided $p < 0.05$ used to determine statistical significance.

3. Results:

Our study included 193 patients hospitalised with severe covid-19. The median age was 64 (IQR: 49–73), and 114 (59.1%) of the population were men. Among these patients, 76 (39.4%) reported exposure to patients with confirmed or highly suspected covid-19 infection, and 92 (47.7%) were admitted to the intensive care unit. During hospitalisation, 110 (57.0%) patients were treated with non-invasive or invasive mechanical ventilation, and 108 (56.0%) critically ill patients passed away. The median hospitalisation duration was 13 (IQR 7–16) days (Table 1). At the onset of illness, fever (89.6%), cough (69.9%), dyspnea (59.6%), and lethargy (52.3%) were the most prevalent symptoms. Additionally, some patients manifested with anorexia (35.2%) and diarrhoea (26.4%). Also present were headache, pectoral pain, nausea, and vomiting. Table 1

demonstrates that 94 patients (48.7%) had comorbidities, including hypertension (37.8%), cardiovascular disease (16.1%), cerebrovascular disease (4.1%), chronic pulmonary disease (7.3%), chronic renal disease (2.1%), and chronic liver disease (0.5%) (Table 2).

48 (24.9%) of all patients had diabetes, while 145 (75.1%) did not. Patients with diabetes were older (median age, 70 (IQR 62–77) years vs. 60 (IQR 43–71) years) and more likely to have hypertension (24 (50.0%) patients vs. 49 (33.8%) patients), cardiovascular disease (13 (27.1%) patients vs. 18 (12.4%) patients, and cerebrovascular disease (5 (10.4%) patients vs. 3 (2.1%) patients. Neither the symptoms nor other comorbidities differed significantly between diabetic and non-diabetic patients. Compared to patients without diabetes, more patients with diabetes were admitted to the intensive care unit (32 (66.7%) vs. 60 (41.4%)) and received mechanical ventilation (39 (81.3%) vs. 71 (49.00%)) (Table 2). In addition, patients with diabetes had a shortened hospital stay (10 (IQR 6–13) days vs. 13 (IQR 9–18) days) and a higher mortality rate (81.3% vs. 47.6%).

4. Discussion:

The objective of this retrospective study was to determine the clinical characteristics of patients with severe covid-19 who also had diabetes and to assess the impact of diabetes on the prognosis of patients with severe covid-19. Patients with severe covid-19 and diabetes were elderly and exhibited a more severe inflammatory response than patients with severe covid-19 and no diabetes. In addition, the Kaplan-Meier survival curve revealed that the survival rate of patients with severe covid-19 and diabetes was substantially reduced.

Previous research indicated that patients with severe covid-19 had a high prevalence of diabetes [8, 9, 14], which was approximately 20% compared to 11.6% in Indian adults [15]. Few studies, however, have examined the clinical characteristics of patients with severe covid-19 who also have diabetes, as well as the direct relationship between diabetes and survival rate in patients with severe covid-19. Our findings were consistent with previous research indicating that up to 24% of patients with severe covid-19 have diabetes. Patients with diabetes were more likely to develop covid-19, which may have been a result of their poor pulmonary function [13]. However, the mechanisms underlying diabetes-related pulmonary dysfunction remain unclear. Animal studies indicated that alveolar capillary microangiopathy and interstitial fibrosis were induced by glycosylation of lung tissue collagen in the diabetes model, and that this process was mediated by angiotensin II and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [16, 17]. Patients with diabetes were also found to have a thickening lung basal lamina [18], which may impact pulmonary diffusion function.

According to our study, the clinical profile of patients with severe covid-19 and diabetes was comparable to that of patients with severe covid-19 and no diabetes. Patients with severe covid-19 and diabetes had a high proportion of wheeze and dyspnea symptoms, but the difference was not statistically significant due to the small sample size. Our findings corroborated previous findings that more non-survivors were male [7]. The specific mechanism for covid-19 susceptibility in men was the nearly threefold higher expression of ACE2 in men compared to women [2, 3]. In line with previous research [7, 8, 20], non-survivors exhibited a severe inflammatory response as well as cardiac, hepatic, renal, and coagulation impairments.

5. Conclusion:

In conclusion, our findings revealed that patients with severe covid-19 and diabetes were more likely to require mechanical ventilation and ICU admission and had a greater risk of death. Patients with diabetes and severe covid-19 exhibit a severe inflammatory response. Moreover, our findings imply that diabetes is a risk factor for mortality in patients with severe covid-19. In conclusion, comprehensive diabetes treatment should be considered in the management of covid-19.

Table 1: **Patients' characteristics (age, sex, symptoms) both with and without diabetes**

	Diabetes (n=48)	Non-diabetes (n=145)	Total (n=193)
Age	70	60	64
Sex			
Male	33	81	114
Female	15	64	79
Symptoms			
Fever	43	130	173
Cough	37	98	135
Dyspnea	33	82	115
Pectoralgia	1	9	10
Diarrhea	10	41	51
Nausea	2	12	14
Vomiting	2	3	5
Anorexia	21	47	68
Headache	5	16	21
Fatigue	28	73	101

Table 2: **Comorbidities in patients with and without diabetes**

Comorbidities			
Hypertension	24	49	73
Cardiovascular Disease	13	18	31
Cerebrovascular disease	5	3	8
Chronic kidney disease	0	4	4
Chronic pulmonary disease	4	10	14
Chronic liver disease	0	1	1
Exposure to disease	17	59	76
ICU patients	32	60	92
Mechanical ventilation treatment	39	71	110
Length of hospital stay	10	13	13
Mortality	39	69	108

6. Limitation:

Lack of a control group- either as a matched control to compare patient groups or as a randomised control for the evaluation of treatments- is one of the limitations of this study, which was conducted within the context of an emergency outbreak. Moreover, our research is based on a limited sample of diabetic patients. However, our research provided evidence for clinical decision-making.

7. Recommendation:

We recommend aiming fasting blood glucose at for better survival.

8. Acknowledgement:

None

9. List of abbreviations:

T2D- Type 2 Diabetes Mellitus
IL- Interleukin
SARS- Severe acute respiratory syndrome
COVID-19- Coronavirus disease 2019
MERS- Middle East Respiratory Syndrome
PCR- Polymerase chain reaction
CT- Computed tomography
hsCRP- high-sensitivity C reactive protein
TNF- Tumor necrosis factor
IQR- interquartile ranges
HRs- hazard regression
ROC- receiver operating characteristic
AUC- area under the curve
NADPH- Nicotinamide adenine dinucleotide phosphate

10. Source of funding:

Nil

11. Conflict of Interest:

None declared

12. References:

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13. Publisher details:

Publisher: Student's Journal of Health Research (SJHR)
(ISSN 2709-9997) Online
Category: Non-Governmental & Non-profit Organization
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