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EFFECT OF DIABETES ON OUTCOME OF COVID-19 PATIENTS IN INTENSIVE CARE UNIT OF A TERTIARY CARE CENTRE – A HOSPITAL BASED CASE CONTROL STUDY

Medicine

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ABSTRACT

Background The World Health Organization (WHO) declared the outbreak of novel coronavirus disease (COVID-19) as a pandemic on March 11, 2020. The first case of COVID-19 in India, which originated from China, was reported on 30 January 2020. India has a climbing prevalence rate of diabetes in recent decades. Patients with diabetes are more susceptible to be infected by bacteria, viruses and fungus than individuals without diabetes relatively because of lower immune function. As a result, these patients might be at an increased risk of SARS-CoV-2 infection and consequently poor prognosis. **Aims** To study the effect of diabetes on outcome of COVID-19 patients in Intensive Care Unit of a Tertiary Care Centre. **Results** In the present study, the mean age group of cases (COVID-19 Patients with Diabetes) and controls (COVID-19 Patients without Diabetes) were 48.6±7.99 years and 49.17±8.53 years respectively. The ratio of males: females was 1.72:1 in cases while the same for controls was 1.5:1. Different variables that indicate disease severity in SARS-CoV-2 such as Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Serum Lactate Dehydrogenase (LDH), Ferritin and D-dimer were in higher level in large number of cases as compared to controls. 18.3% of cases were in Reservoir Bag oxygen therapy whereas in controls, 10% of patients were in Reservoir Bag. Also 16.7% of patients in case group and 11.7% of patients in control group were in Non-Invasive Ventilation. Mechanical Ventilatory Support was in 26.7% of cases and 18.3% of controls. Mortality rate of COVID-19 patients in case group was 23.3%, which is significantly higher than the mortality rate in control group which was 13.3%. **Conclusion** Diabetes is associated with adverse outcome and increased mortality rate in patients with COVID-19 and is considered as a major risk factor for COVID-19 infection, posing a major public health challenge for health policymakers in managing and controlling the disease. Therefore, development of prevention and treatment strategies aimed at reducing COVID-19 morbidity and mortality in diabetes patients is of significant importance.

KEYWORDS

COVID-19, Diabetes, Disease Severity, Airway, Mortality.

INTRODUCTION

Emerging and reemerging pathogens are global challenges for public health.[1] The World Health Organization (WHO) declared the outbreak of novel coronavirus disease (COVID-19) as a pandemic on March 11, 2020. The first case of COVID-19 in India, which originated from China, was reported on 30 January 2020.

India currently has the largest number of confirmed cases in Asia and has the second-highest number of confirmed cases in the world after the United States with more than 11.3 million reported cases of COVID-19 infection and more than 158,600 deaths as of March 14, 2021.[2] The per day cases peaked mid-September in India with over 90,000 cases reported per day and have since come down to below 20,000 as of March 2021 which is fluctuating since then.

Coronaviruses are RNA viruses that are divided into four genera; Alpha-coronaviruses and Beta-coronaviruses are known to infect humans.[3] SARS-CoV-2 is related to beta coronaviruses and the SARS-CoV, the virus that causes SARS.[4] Similar to SARS-CoV, SARS-CoV-2 enters human cells through the angiotensin-converting–enzyme 2 (ACE2) receptor.[5] _Coronaviruses typically cause common cold symptoms, but two beta-coronaviruses SARS-CoV and Middle East respiratory syndrome coronavirus MERS-CoV can cause pneumonia, respiratory failure, and death. In late 2019, infection with a novel beta-coronavirus, subsequently named SARS-CoV-2, was reported in people who had been exposed to a market in Wuhan, China, where live animals were sold. Since then, there has been rapid spread of the virus, leading to a global pandemic of Covid-19.

India has a climbing prevalence rate of diabetes in recent decades. Patients with diabetes are more susceptible to be infected by bacteria, viruses and fungus than individuals without diabetes relatively because of lower immune function.[6,7] Excessive fluctuations in blood glucose levels in patients with diabetes can cause glucose, fat, and protein metabolic disorders with long-term hyperglycemic conditions, which lead to a decline in the body's immune function and reduction in respiratory organ function. Thus, intrapulmonary infection is very common and prone to severe pneumonia in patients with diabetes.[8] The severe stress response triggered by severe pneumonia will lead to proinflammatory and anti-inflammatory balance disorders in the body. The immense release of catecholamines and glucocorticoids induces blood glucose elevation, further aggravating the infection, leading to a vicious cycle of the disease. When it becomes severe, pneumonia is a threat for patients with diabetes.[9] Severe pneumonia and diabetes induce each other; diabetes will promote the onset of pneumonia, and the patient's infection is difficult to control. As a result, these patients might be at an increased risk of SARS-CoV-2 infection and consequently poor prognosis. Here, we discuss the effect of diabetes on the outcome of covid 19 patients in intensive care unit of a tertiary care centre.

AIMS

To study the effect of diabetes on outcome of COVID-19 patients in Intensive Care Unit of a Tertiary Care Centre.

METHODS

Study Design

Monocentric retrospective Case Control study.

Study Place

The study was conducted in the Department of Medicine at Assam Medical College and Hospital, Dibrugarh, in North east India. We enrolled patients from COVID Intensive Care Unit in this study.

Ethics

The study was approved by the ethics committee of Assam Medical College and Hospital, Dibrugarh. We obtained a written informed consent from all study participants before enrolling them in the study.

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Sample Size

In this study, 60 SARS-CoV-2 pneumonia patients with known or newly-diagnosed diabetes (HbA1c ≥ 6.5% on admission) who were admitted in COVID Intensive Care Unit from 1st October 2020 to 15th November 2020 were identified within the institutional registry. Oral or telephone informed consent was obtained from all patients or the first-degree relatives of patients. The diagnosis was based on the positive result of real-time reverse transcription polymerase chain reaction (RT-PCR), which is the presence of SARS-CoV-2 in both the nasal and pharyngeal swab specimens and Rapid Antigen Test (RAT). The clinical outcomes were followed up through November 30, 2020. These 60 diabetic patients with SARS-CoV-2 pneumonia were compared to 60 non-diabetic patients with SARS-CoV-2 pneumonia admitted in Intensive Care Unit during same period matched for age and sex.

Inclusion Criteria

The following criteria were included in the study:

1. Patients above the age of 18 years.
2. Patients diagnosed with SARS-CoV-2 pneumonia either by Real time Reverse Transcription Polymerase Chain Reaction (RT-PCR) or Rapid Antigen Test (RAT) with respiratory symptoms.
3. Patients admitted in Intensive Care Unit.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients below 18 years of age.
2. Patients with SARS-COV-2 positive, but without pneumonitis.
3. Patients with multiple comorbidity.

We collected clinical data including basic information (age, gender), comorbidities (classified by systems), symptoms and signs, laboratory findings, chest radiological images, primary outcomes including disease severity at admission (patient condition), therapeutic effect and mortality. Biological data on admission included glycated hemoglobin A1c (HbA1c) level, plasma glucose level, white blood cells count (WBC), lymphocytes count, neutrophils-to-lymphocytes ratio (NLR), platelets count, C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), lactate dehydrogenase (LDH), Ferritin, D-dimer, Renal Function Test (RFT), aspartate-aminotransferase (AST), and alanine-aminotransferase (ALT). Treatments for COVID-19 (oxygen therapy, antibiotics, corticosteroids), and requirement for non-invasive ventilation, requirement for invasive mechanical ventilation (IMV) were recorded. The short-term outcome of COVID-19 patients (discharge or in-hospital death) were registered.

Statistical Analysis

Data was entered into computer Microsoft Excel and exported to SPSS version 20 for analysis. Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as frequency and percentage. Differences between groups were assessed by Student-T test or Mann-Whitney test according to the distribution of continuous variables, and by Chi-square test (for 2 x 2 tables) for discrete variables as test of significance for qualitative data. P-value was considered statistically significant when it was less than 0.05.

RESULTS

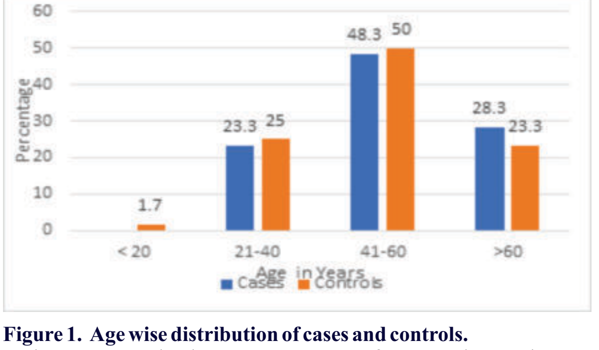

Figure 1. Age wise distribution of cases and controls.

In the present study, the mean age group of cases and controls were 48.6±7.99 years and 49.17±8.53 years respectively. Among the cases, prevalence was maximum in 40 – 60 years of the age group which comprises 48.3% of total patients. In the control group, prevalence was maximum in 40 – 60 years of the age group which comprises 50% of total patients.

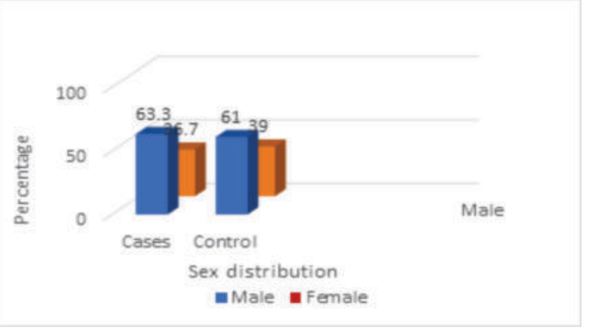

Figure 2. Sex wise distribution of Cases and Controls.

In our study, the ratio of males: females was 1.72:1 in while the same for controls was 1.5:1.

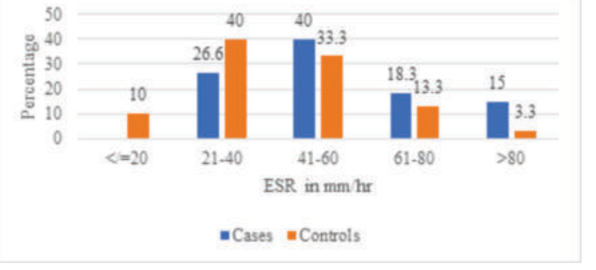

Figure 3. Level of ESR in Cases Vs Controls.

In our study, it was found that maximum number of patients in case group i.e. 24 patients (40%) have ESR level between 41-60 mm whereas in control group, maximum number of patients i.e.24 patients (40%) have ESR level between 21-40 mm. Also 18.3% of cases have ESR level between 61-80 mm whereas in controls, it was only 13.3%. Only 3.3% of controls have ESR greater than 80 mm whereas it was 15% for cases.

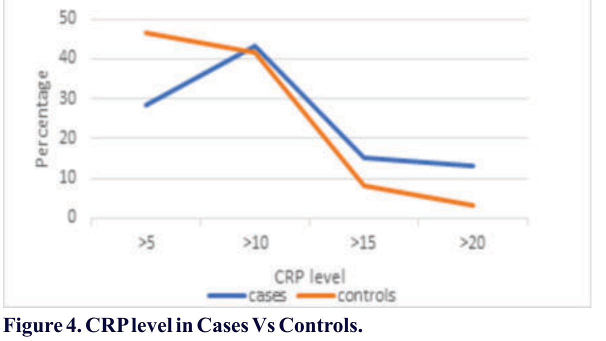

Figure 4. CRP level in Cases Vs Controls.

In our study, it was found that larger number of patients in case group have CRP value in higher level (28.3% have CRP <5 and 13.3% have CRP >15) as compared to patients in control group where larger number of patients have CRP value in lower level (46.6% have CRP <5 and only 3.3% have CRP >15).

Table 1. Different variables that correlate disease severity in cases and controls.

Variables	Cases n(%)	Controls n(%)	P-value (P)
Serum LDH level in Cases and Controls (A Disease Severity Marker)			
</=250	6(10%)	11(18.3%)	0.363
251-500	24(40%)	29(48.3%)	
501-750	17(28.3%)	12(20%)	
750-1000	10(16.6%)	7(11.6%)	
>1000	3(5%)	1(1.7%)	
Serum Ferritin level in Cases and Controls (A Disease Severity Marker)			
</=500	18(31.6%)	33(56.6%)	0.014
501-1000	30(48.3%)	22(35%)	
>1000	12(20%)	5(8.3%)	
Serum D-dimer level in Cases and Controls (A Disease Severity Marker)			

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</=2.5	28(46.6%)	43(70%)	0.001
2.6-5.0	21(35%)	17(30%)	
>5.0	11(18.3%)	0	

**P value calculated by Chi square test.*

In our study, it was found that different variables that indicate disease severity in SARS-CoV-2 such as Serum Lactate Dehydrogenase (LDH), Ferritin and D-dimer were in higher level in large number in cases as compared to controls.

Table 2. Comparison of mean of different variables in cases and controls.

	Case	Control	P- value*
LDH	579 ±247	414 ±227	< 0.001
Ferritin	847 ±336	510± 227	< 0.001
d-dimer	3.50 ±1.78	1.75 ±1.03	< 0.001

**P value is calculated by T-test*

In our study, it was found that the mean of Sr LDH, Sr Ferritin and D-dimer show significant differences in cases and controls.

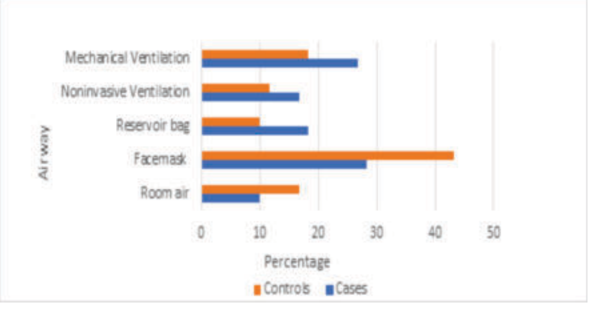

Figure 5. Percentage of patients on different modes of airway.

In our study, it was found that 6% of cases were maintaining oxygen saturation above 95% in Room air whereas it was 10% in controls. 28.3% of cases were in Face mask oxygen therapy and in controls, it was 43.3% who were in Face mask. 18.3% of cases were in Reservoir Bag oxygen therapy whereas in controls, 10% of patients were in Reservoir Bag. Also 16.7% of patients in case group and 11.7% of patients in control group were in Non-Invasive Ventilation. Mechanical Ventilatory Support was in 26.7% of cases and 18.3% of controls.

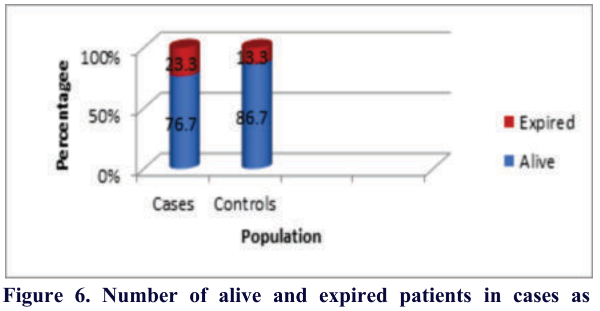

Figure 6. Number of alive and expired patients in cases as compared to controls.

From the figure, it was found mortality rate of COVID-19 patients in case group is 23.3 %, which is significantly higher than the mortality rate in control group which is 13.3 %.

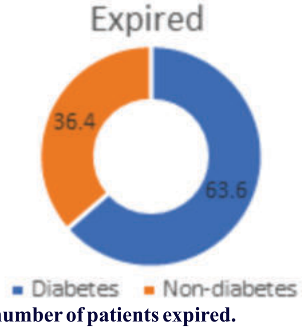

Figure 7. Total number of patients expired.

From our study, it was found that, out of 120 patients who received treatment in Intensive Care Unit, total 22 patients expired (18.3%). Among who expired,14(63.6%) patients were from case group and 8(36.4%)patients were from control group.

DISCUSSION

People with diabetes are more likely to have serious complications from SARS-CoV-2 Pneumonia and their therapeutic effects are much poorer than in patients without T2DM. Past viral pandemics have witnessed the association of diabetes to increased morbidity and mortality. Diabetes was considered as independent risk factor for complications and death during 2002-2003 outbreak of Severe Acute Respiratory Syndrome (SARS-CoV-1).[10] Similarly, the presence of diabetes tripled the risk of hospitalization and quadrupled the risk of intensive care unit (ICU) admission during Influenza A (H1N1) infection outbreak in 2009.[11] During the 2012 outbreak of Middle East Respiratory Syndrome Coronavirus (MERS-CoV), diabetes was prevalent in nearly 50% of population and the odds ratio (OR) for severe or critical MERS-CoV ranged from 7.2 to 15.7 in diabetic cohort [12] as compared to overall population. Mortality rate in patients with MERS who had diabetes was 35%.[13]

In general, people with diabetes are more likely to have more severe symptoms and complications when infected with any virus. This is because, the pulmonary vascular bed and alveolar surfactants in patients with diabetes are often damaged. Diabetic patients will have diminished synthesis of cytokines such as Interferon Gamma, responsible for innate and adaptive immunity against viral infections. Hence it will impair the host's immune response. Diabetes results in a proinflammatory homeostatic immune response skewed toward helper T cell 1 (Th1) and T17 cells and a decrease in regulatory T cells.[7] Immune dysfunction of diabetes alone or following infection has been reported for a wide variety of immune cells, not just macrophages, monocytes and CD4+ T cells. Recently, a phenome-wide Mendelian randomization study found diabetes to be causally related to ACE-2 expression[14] which shows increased ACE-2 expression might predispose people with diabetes to infection with SARS CoV-2. Several cytokines are increased in COVID19 infection. Amongst these, IL-6 is increased in diabetes and may play a more deleterious role in Covid-19 infection.[15]

In our study, the mean age of cases was 48.6±7.99 years whereas in study by Xiaoli Wang et al.[16] in Wuhan, China, it was 66 years and in study by Laura Orioli et al.[17] in Belgium it was 67±14 years. This is because, the elderly population in China and Belgium are more when compared to the elderly population in India.

Laura Orioli et al.[17] showed sex ratio of 0.9:1 in Belgium, whereas Xiaoli Wang et al.[16] in Wuhan demonstrated a ratio of 1.68:1 which is similar to our study with ratio of 1.72:1. In our study, it was found that maximum number of patients in case group i.e.24 patients (40%) have ESR level between 41-60 mm whereas in control group, maximum number of patients i.e.24 patients (40%) have ESR level between 21-40 mm. Also larger number of patients in case group have CRP value in higher level (28.3% have CRP <5 and 13.3% have CRP >15) as compared to patients in control group where larger number of patients have CRP value in lower level (46.6% have CRP <5 and only 3.3% have CRP >15). Saloua Elamari et al.[18], in their study have found diabetic patients had higher levels of CRP than non-diabetics (28 versus 5.8mg/l), This is similar to CORONADO study[19], which shows inflammatory markers of disease severity such as ESR, CRP, AST, ALT got significantly increased in COVID-19 patients with diabetes as compared to non-diabetes. Gregory JM et al.[20] in their study have made similar observations.

The observations made in our study were similar to study by Laura Orioli et al.[17] and CORONADO study, which shows different variables that indicate disease severity in SARS-CoV-2 such as Serum Lactate Dehydrogenase (LDH), Ferritin and D-dimer were in higher level in large number of COVID-19 patients with diabetes as compared to non-diabetes. Saloua Elamari et al.[18], in their study have found ferritin similar results in diabetes versus non-diabetes patients (501 versus 140ng/ml), lactic dehydrogenase (268 versus 226 IU/l), and D-dimer (665 versus 444µg/l).

In our study, it was found that 6% of cases were maintaining oxygen saturation above 95% in Room air whereas it was 10% in controls. 28.3% of cases were in Face mask oxygen therapy and in controls, it was 43.3% who were in Face mask. 18.3% of cases were in Reservoir Bag oxygen therapy whereas in controls, 10% of patients were in Reservoir Bag. Also 16.7% of patients in case group and 11.7% of patients in control group were in Non-Invasive Ventilation. Mechanical Ventilatory Support was in 26.7% of cases and 18.3% of

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controls. In the study by Laura Orioli et al.[17], 53% of COVID-19 patients with diabetes were in Mechanical Ventilation Support. Saloua Elamari et al.[18], in their study have found diabetic patients required more oxygen therapy than non-diabetics (60% versus 26.9%), more mechanical ventilation (20% versus 8.3%). Christopher J. Nicholson et al.[21] in 2021 have found four factors to be independently predictive for mechanical ventilation requirement (diabetes mellitus, SpO2:FiO2 ratio, C-reactive protein, and lactate dehydrogenase).

Mortality rate of COVID-19 patients in case group is 23.3 %, which is significantly higher than the mortality rate in control group which is 13.3 % in our study. Moftakhar L et al.[22], in their study have reported mortality rate among diabetics as 28.3% when compared to non-diabetics (14.3%).

Gregory JM et al.[20] have reported COVID-19 Severity Is Tripled in the Diabetes Community in their study. Another metanalysis of 9 studies from China (n=1936) by Chen et al.[23] found a significant correlation between COVID-19 severity and diabetes (OR, 2.67, 95% CI; 1.91 to 3.74; p<0.01).

We acknowledge that this study has limitations, including a single-center retrospective design, small and heterogeneous population of diabetic patients, and some missing data regarding diabetes duration, complications and management of diabetes.

CONCLUSION

Diabetes is associated with adverse outcome and increased mortality rate in patients with COVID-19 and is considered as a major risk factor for COVID-19 infection, posing a major public health challenge for health policymakers in managing and controlling the disease. Therefore, development of prevention and treatment strategies aimed at reducing COVID-19 morbidity and mortality in diabetes patients is of significant importance. This is the first report describing the outcomes of COVID-19 patients with diabetes from North East India.

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