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The "D" Word And Covid-19; Outcome Of Indoor Diabetics With Covid-19 In Tertiary Care Hospital

Nadia Shams[1], Lubna Meraj[2], Muhammad Aqeel[3], Hina Andaleeb[4], Lama Qadri[5], Syed Muhammad Hameez Qadri[6]

1. Professor & HOD Medicine, Rawal Hospital/RIHS, Islamabad 2. Professor of Medicine, Benazir Bhutto Hospital, Rawalpindi 3. Assistant Professor, PIMS Hospital, Islamabad 4. Assistant Professor, Rawal Hospital, RIHS Islamabad 5,6. 4th Year Medical Student.

Corresponding author: Dr. Nadia Shams, nadia_shams@yahoo.com.

Abstract

Objective: COVID-19 has been a global challenge. Diabetes is a frequent co-morbid in Covid cases having a complex bidirectional relationship. This study aims to determine the outcome of COVID-19 cases with diabetes vs. non-diabetics.

Methods: This observational study was conducted at RIHS Islamabad (June–Dec. 2020) after ethical approval. Adult indoor confirmed (PCR positive) COVID cases of both genders were included by consecutive sampling. Patients <18 years of age, having gestational diabetes, drug-induced diabetes and Cushing's syndrome were excluded. The study included 75 Covid cases with diabetes (group A) and 75 Covid non-diabetics (group B). Diabetes was labelled based on glycated haemoglobin and blood sugars. Patients were managed as per recommendations and followed till discharge or expiry. Details are documented on a specially designed proforma. Data was analyzed by SPSS V-22 with significant $p<0.05$. The chi-square test was applied to study the association of diabetes in Covid cases with expiry, duration of hospital stay, disease severity and need for mechanical ventilation.

Results: Among 150 cases of Covid; there were 54(36%) females and 96(64%) males. The mean age was 58+13 years (range 27-92 years). The mean age of those cases who expired was 60.77+12.78 years vs. 56.73+13.40 years in those who were discharged ($p>0.05$). Obesity was observed in 41(27.3%), hypertension in (35.3%), ischemic heart disease in 26(17.3%), asthma in 11(7.3%), COPD in 7(4.7%), chronic kidney disease in 7(4.7%), hypothyroidism in 5(3.3%), These co-morbid conditions had no association with mortality. 9(6%) cases had mild Covid, 97(64.7%) moderate and 44(29.3%) had severe Covid. Higher frequency of moderate 41(54.7%) and severe 29(65.9%) Covid was found in diabetics. Death was observed in 14(14.4%) moderate and 34(77.3%) severe Covid ($p<0.0001$). The mean duration of hospital stay was 13+7.7 days (1-45 days) having no association with mortality. The need for invasive ventilation and duration of admission were comparable between the two groups. Total 102(68%) cases were discharged and 48(32%) expired. 30(62.5%) of deceased were diabetics vs. 18(37.5%) non-diabetics ($p=0.036$).

Conclusion: Diabetes is commonly observed comorbidity in COVID-19 cases and is significantly associated with disease severity and mortality. Patients with both diabetes and COVID-19 require close monitoring and careful management. Additionally, older age and obesity are important risk factors that further contribute to the severity of the disease and the risk of mortality in diabetic patients with COVID-19.

Keywords: Covid-19. Type II Diabetes Mellitus. Glycated Hemoglobin

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Introduction

Covid-19 has been a global challenge. Diabetes, hypertension and ischemic heart disease are frequently observed co-morbidities in Covid cases. International Diabetes Federation (IDF) reports a 26.7% prevalence of diabetes in Pakistan. In diabetics; hypertension, ischemic heart disease, obesity, altered ACE-2 expression, dysregulated immune response & endothelial dysfunction impose greater risk in terms of Covid severity and outcome. The relationship between COVID-19 and diabetes is complicated and bidirectional; either may worsen the other.

In COVID-19-infected individuals, diabetes mellitus is linked to a considerable risk of complications, prolonged hospital admissions, and death. Glycemic management in diabetes is hampered by COVID-19 infection due to increased inflammation and altered immune response. Diabetics with COVID-19 are more likely to experience consequences, such as thrombosis or respiratory and cardiovascular failure. The best way to treat individuals with COVID-19 and diabetes has to be investigated further. Hence, in the diabetic patient population, it appears to be crucial to encourage COVID-19 immunization The increased susceptibility to COVID-19 in diabetics has been explained by elevated basal levels of cytokines, such as IL1-β and IL-6, and with a state of low-grade chronic inflammation that seems to further intensify the hyperinflammation observed in response to COVID-19. This "cytokine storm", particularly with the increase in IL-6, is also suggested to alter the AMPK/mTOR signalling pathway in patients with diabetes, possibly aggravating insulin resistance and diabetes-induced complications. Obesity, Positive family history, high fasting lipid profiles, fatty liver, and higher steroid dosage during acute infection are important factors to accelerate the onset of diabetes.

Severe COVID-19 should probably be considered as an independent risk factor for diabetes. Metabolic profiles are needed to determine a correlation, aetiology, risk factors, prognosis, and treatment for diabetes in post-COVID-19 cases Whether in those with diabetes or not, hyperglycemia is a significant risk factor for COVID-19 mortality. Therefore, insulin is preferred to oral hypoglycemic medications in hospitalized COVID-19-infected diabetics. Frequent blood sugar monitoring, and prompt management of hypoglycemia, hyperglycemia, and diabetic ketoacidosis (DKA) is recommended. Its importance upon hospital admission is emphasized by the CORONADO study stating that that hyperglycemia seems to worsen the COVID-19 prognosis. Hyperglycemia in Covid cases has been associated with a considerable increase in morbidity and mortality. This increases the overall cost of treatment and the length of in-hospital stay.

Hyperglycemia may improve or return to normal glycemia in prediabetic or non-diabetic patients once they recover from acute illness and may not require antidiabetic medications. However, long-term follow-up is the key to better outcomes in such cases. Important prognostic factors include early diagnosis, comorbidities, interventions, and longer surveillance of patients with stress hyperglycemia and/or new-onset diabetes. Hence, ensuring risk factor management and good glycemic control.

Understanding the outcomes of indoor diabetic patients with COVID-19 in tertiary care hospitals in underdeveloped countries is crucial due to the high prevalence of diabetes, limited healthcare resources, unique socioeconomic factors, and the potential for health disparities. These factors can significantly influence the course of the disease and treatment outcomes. This study was conducted to examine the impact of COVID-19 on diabetic patients in such settings, aiming to provide valuable insights that can inform targeted interventions and shape public health policies to address the specific needs of this vulnerable population.

Materials And Methods

This observational study was conducted at Rawal Institute of Health Sciences (RIHS) Islamabad over a month duration (1st June 2020 to 31st December 2020) after ethical approval. The study aimed to determine the outcome of Covid cases with diabetes as compared to non-diabetics. During the epidemic, the COVID positivity was reported to change daily varying from 2-5%, keeping the precision at 5%, with a 95% confidence interval and 5% positivity, the sample size was calculated to be 73 cases for each group. A total of 75 adult indoor confirmed Covid cases (PCR positive) of both genders were included by consecutive sampling. Informed consent was obtained from all the cases. Group A included the diabetics that were diagnosed based on previous records including fasting, random blood sugars and HbA1c. Patients <18 years of age, pregnant women, gestational diabetes cases, drug-induced diabetes, Cushing's syndrome and patients who left against medical advice were excluded.

Seventy-five confirmed COVID cases (PCR positive) with no evidence of diabetes were included in group B. Patients <18 years of age and those who left against medical advice were excluded.

Demographic data and detailed clinical evaluation were performed. The fasting blood sugars, random blood sugars, HbA1c and Covid PCR were performed. Age, gender, body mass index (BMI) and co-morbid conditions were documented. COVID-19 infection was classified as mild, moderate or severe as per the criteria of the National Institutes of Health. Cases were admitted and managed in isolation wards and critical care units as per protocol. They were followed till discharge or expiry. Details were documented and data was analyzed via SPSS V-22 with significant $p<0.05$. The chi-square test was applied to study the association of diabetes in Covid cases with expiry, duration of hospital admission, disease severity and need for mechanical ventilation. Data was presented as tables and graphs.

Results

Among 150 cases of Covid; there were 54(36%) females and 96(64%) males. The mean age was 58$\pm$13 years (range 27-92 years). The mean age of those cases who expired was 60.77$\pm$12.78 years vs. 56.73$\pm$13.40 years in those who were discharged (p=0.807).

Other than diabetes, common co-morbid conditions seen were obesity 41(27.3%), hypertension (35.3%), ischemic heart disease 26(17.3%), asthma 11(7.3%), COPD 07(4.7%), chronic kidney disease 07(4.7%) and hypothyroidism 05(3.3%) (fig.1). Amongst these, obesity was significantly higher in diabetics 27(36%) as compared to non-diabetics 14(18.7%) (p=0.017)

As per Covid severity, 09(6%) had mild Covid, 97(64.7%) had moderate and 44(29.3%) had severe Covid. Death was observed in none of mild disease, 14(14.4%) of moderate and 34(77.3%) of severe Covid (p<0.0001). The frequency of mild Covid was comparable between diabetics 04(5.3%) and non-diabetics 05(6.7%); however higher frequency of moderate 41(54.7%) and severe 29(65.9%) Covid was found in diabetics (p=0.010 & 0.012).

Table 1: The demographic variables, disease severity and outcome in COVID-19 cases with and without diabetes (n=150)

Variable	Among all n=150	Diabetics with Covid n=75	Non-diabetics with Covid n=75	p-value
Age (years) mean ± SD	58 ± 13 (27-92 years)	60.24 ± 11.77	55.80 ± 14.40	0.122
Gender				
• **Males**	96(64%)	40(53.3%)	56(74.7%)	**0.006**
• **Females**	54(36%)	35(46.7%)	19(25.3%)	
Obesity				
• **Obese**	41(27.3%)	27(36%)	14(18.7%)	**0.017**
• **Non-obese**	109(72.7%)	48(64%)	61(81.3%)	
Severity				
• **Mild**	09(6%)	05(6.7%)	04(5.3%)	0.731
• **Moderate**	97(64.7%)	41(54.7%)	56(57.7%)	**0.010**
• **Severe**	44(29.3%)	29(65.9%)	15(34.1%)	**0.012**
Invasive ventilation	42(28%)	22(52.4%)	20(47.6%)	0.716

The need for invasive ventilation was comparable between the two groups (p=0.716). The mean duration of hospital stay was 13±7.7 days (1-45 days). Duration of admission had no association with mortality (p=0.337). The mean duration of stay before expiry was 11.6±8.42 days in diabetics vs. 14.02±7.30 days in non-diabetics till discharge. Also, the duration of hospital stay was comparable between the two groups (p=0.062). Total 48(32%) cases expired while 102(68%) were discharged on recovery. Amongst the expired cases with Covid, 30(62.5%) were diabetics vs. 18(37.5%) were non-diabetic (p=0.036, fig 2).

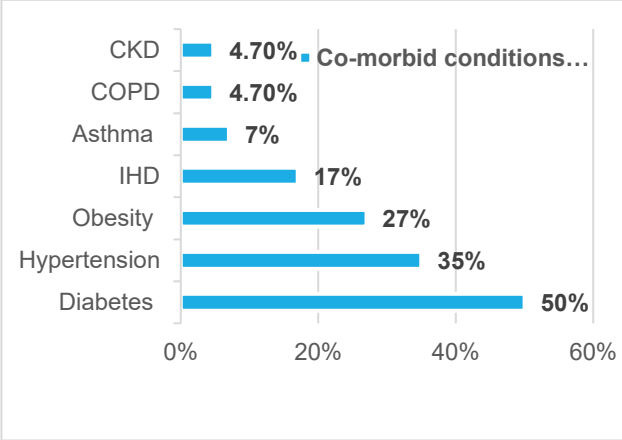

Figure 1: Bar graph presenting co-morbid conditions observed in indoor Covid cases (n=150)

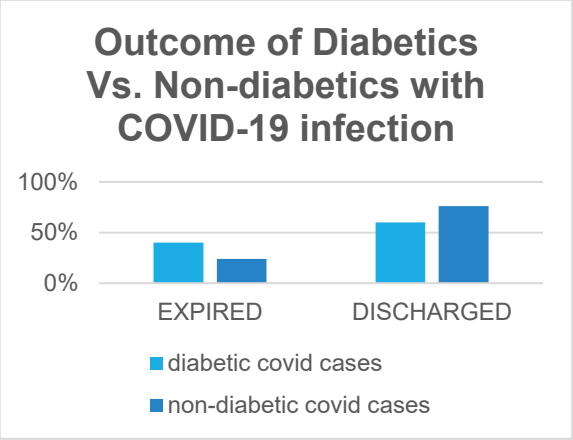

Figure 2: Bar graph presentation of outcome in COVID cases with and without diabetes (n=150)

Discussion

This study was conducted during the ongoing COVID-19 epidemic in 2020. Pakistan reported the first case of Covid-19 on 26th February 2020. This was followed by the exponential rise of Covid cases within two months. The data was updated daily on the Covid-19 dashboard. The case fatality rate (CFR) was observed to be 1.67% in 2020. The geriatrics, immunosuppressed and those with multiple co-morbid conditions were found to be at high risk for fatal illness. It was a novel disease for the whole globe. The

preventive and management guidelines were evolving day by day. Amidst the myths and perceptions regarding COVID-19, the national policies regarding prevention, quarantine and management were implemented.

During this wave of COVID-19, every effort was made to identify a possible escape from this devastating situation. The physicians and researchers gathered data to detect the risk factors for fatality. Diabetes mellitus has been an independent leading cause of mortality and morbidity worldwide. We consider that the COVID-19 infection in the background of diabetes may be labelled as a sinister alliance. The history of viral epidemics including SARS-CoV, H1N1 and MERS-CoV records a significantly higher mortality in diabetics. This could be explained by the vicious circle of raised inflammatory markers, endogenous glucocorticoids and therapeutic interventions including the use of corticosteroids leading to worsening glycemic control and vice versa. Hyperglycemia leads to the recruitment of pro-inflammatory monocyte cells, and platelet dysfunction that contributes further to the adverse cardiovascular events in diabetics.

Most of the cases were managed by home isolation during the epidemic to cope with the exhaustion and burnout of the healthcare system. The mean age observed was 58 years in our indoor patients. Hence, advanced age is an added risk factor for the indoor requirement in COVID-19. Comparatively higher mortality was observed in geriatrics as compared to the younger cases though the difference wasn't statistically significant. Phillips et reported that advanced age, long-term health care facility (LTC) and high burden of co-morbid conditions are the greatest risk factors for mortality in COVID-19. We observed a wide range of ages in our admitted cases, the eldest case was 92 years old in our study.

There was a predominance of males in the admitted cases in both the groups, i.e., 2/3rd of the cases were males. The diabetic Covid group had a higher number of females as compared to non-diabetics. The gender-based mortality matched in both the groups in this study. Literature shows worldwide regional variation in gender-related fatality rates.

Approx. 40% of our admitted cases were obese based on BMI. Obesity was significantly higher in the diabetic group. Obesity is reported by the Centers for Disease Control and Prevention (CDC) to triple the risk of severe COVID-19 infection. Obesity may be the consequence of COVID-19 infection in the post-COVID phase as well.

As per severity, 65% of cases had moderate and 29% had severe Covid. There were fewer (6%) cases of mild COVID-19, the reason being that most of the mild Covid was managed by home isolation and didn't need admission. The frequency of diabetes as a co-morbid was significantly associated with the severity of COVID-19. In a multicenter review, Kristan et al reported diabetes to be an independent predictor of Covid severity. Additional contributing factors in diabetics were glycemic control, insulin dependency, diabetic complications, obesity and other comorbid conditions.

In this study, we observed quite high mortality of 32% in the admitted cases. This data was collected in 2020, when the COVID management and prevention strategy was evolving day by day and we lost many precious lives in the early wave of epidemic. Kania et al reported a mortality of 16% in diabetics as compared to non-diabetics (8%). The underlying postulated mechanisms are complex. Diabetes is considered equivalent to an immunocompromised state with impaired leukocyte phagocytic mechanism, neutrophilic chemotaxis and bactericidal action of the immune system. Also, the pro-inflammatory cascade studied in diabetics with COVID-19 demonstrated that elevated interleukin-6, d-dimers, C-reactive proteins and fibrinogen further contributed to the cytokine storm leading to severe disease and fatality.

The need for invasive ventilation was statistically similar in both groups. There is variable data regarding invasive ventilation, Farzan et al found that advanced age and pre-existing hypertension were associated with the need for mechanical ventilation, while diabetes wasn't found to be associated. Contrary to these, Zakirkesh et al found a four-fold need for invasive ventilation in diabetics as compared to non-diabetics.

Among the expired cases in this study, sixty-two per cent were diabetics. The risk of death as per literature is 2-3.5 folds in diabetics with Covid. The reported mortality is high both in type-I and type-II diabetes. One of the major contributing factors is the pre-existing ischemic heart disease in the majority of diabetics. There is the role of elevated inflammatory markers, aggressive cytokine storm, impaired immune response, altered expression of ACE receptors, coagulation cascade and many more complex mechanisms contributing to outcomes in terms of severity of COVID and mortality. In addition to this, the high likelihood of diabetics catching COVID-19 infection, complex management of diabetes and unpredictable level of protection after the vaccine are other significant factors in diabetics.

There are limited studies from Pakistan about diabetes in COVID-19. Aijaz W et al conducted a study on Covid cases with diabetes and prediabetes. This Karachi-based study reported a mortality rate of 20% in Diabetics with Covid. However, there was no proven association of glycemic control with Covid severity or outcome in this study. Contrary to this Nasim A. et al concluded that there is a need to focus on glycemic control and strict monitoring in diabetics with COVID-19. The study found 31% mortality in their Covid cases.

Our study is valuable in terms of contributing to the local data that can be used for international comparison. The study reports the Covid related mortality in the early wave of the epidemic. Certain limitations were that the study included few cases of mild COVID-19 as they didn't need admission. The mortality that occurred outside the hospital settings might have been missed leading to an underestimation of the figures. Studies published in recent times assessed the findings of hospitalized COVID-19 patients, while there is none or limited data available from asymptomatic cases, or mild Covid managed in the community, COVID care

centres or in-home isolation. So, there might be a greater number of real-time cases of newly detected diabetes in COVID-19 patients worldwide. Hence, a large population of patients needs to be followed up globally to have a better understanding of this phenomenon, involving an epidemiological and interventional approach. Contrary to the usual recommendations for future studies, we wish that humanity never faces a COVID epidemic in future. Though retrospective data may be used for further research.

Conclusions

Diabetes is a common comorbidity in COVID-19 cases and is significantly associated with increased disease severity and mortality. Patients with both diabetes and COVID-19 require close monitoring and careful management. In addition, older age and obesity are key risk factors that further contribute to disease severity and increased mortality in diabetic patients with COVID-19. We recommend that such patients be closely monitored and regularly screened to mitigate the risk of adverse outcomes and reduce mortality.

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