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Original Article

Comparison of Survival Analysis of COVID-19 Patients with Known Diabetes

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ABSTRACT

Objective: To compare the survival rate of COVID-19 patients with diabetes versus without diabetes COVID-19 patients.
Study Design: Comparative, prospective study.
Place and Duration of Study: The patients were selected from the special ward established for COVID-19 patients came in Federal Government Polyclinic Hospital, Islamabad Pakistan, from Dec 2020 to May 2021.
Methodology: 50 without diabetes (control) and 50 with diabetes (study) confirm cases of COVID-19 patients, who fulfill the inclusion and exclusion criteria, were included in the study through consecutive sampling. Independent sample t test, chi square test and Kaplan-Meire survival analysis was used to compile the results.
Results: Out of 100 majority 75 patients were male. The average age of the patients was 52.08±14.85 years. Both the groups were equal with respect of gender with *p*-value >0.05. The average age of the patient was significantly higher in study group with *p*-value <0.001. Overall percentage of patients of oxygen dependency, mechanical ventilation required, and use of Angiotension receptor inhibitor were higher in study group as compared to the control group patients with *p*-value <0.001. The survival rate was lower in study group as compared to the control group but the difference was not significant with *p*-value >0.05.
Conclusion: The COVID-19 patients with diabetes, need extra care and attention before and after infection in the current COVID-19 pandemic. They are at higher risk and with respect of prolong hospital stay due to severe attack of COVID-19 and also higher risk of mortality too.

Keywords: Association of COVID-19 and diabetes, Kaplan-meire survival analysis, Oxygen dependency in COVID-19, Survival rate in COVID-19.

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INTRODUCTION

One of the major causes of fatality in the whole world is diabetes mellitus. The disease has also shown its close association with different diseases such as cardiovascular diseases and renal problems. According to the estimates, global prevalence of this disease observed to be 9.3% in 2019, whereas this percentage is increasing further with a very rapid pace.[1]

In the year 2017, diabetes was recorded to be the contributing or underlying cause of death over 270,702 certificates of deaths, corresponding to a crude rate of 83.1/100,000 individuals.[2] The studies have identified that the number of sufferers of this disease will become approximately 700 million by the year 2045.[3]

In the recent years the world has seen a new viral disease with the name of COVID-19. The disease appeared for the first time in early days of December 2019 in China. Symptoms of the identified disease were alike pneumonia having an unknown origin. The initial studies bean and the pathogen involved in spreading the disease rapidly among human population was a novel enveloped RNA beta-coronavirus.[4] However, the extent of severity and negative impacts on individual's health may vary from one person to another. In a national study, up to April 2020, out of 4695 confirmed cases of COVID-19, 66 (1.4%) deaths were noted.[5]

To control the spread of COVID-19 the governments all over the world asked to maintain the social distancing and impose lockdown where the situation out of control. In the result, physical activities were restricted which caused great troubles for patients suffered from diabetes. All these factors are playing their role in increasing the level of risk of infections and hospitalizations, amputations, and death in patients suffering from diabetes.[6]

In a study conducted in China the researchers were identified the risk factors and comorbidities of COVID-19 infection. They concluded that hypertension was the most common comorbid with 21.1%, then diabetes 9.7%, cardiovascular disease 8.4% and only 1.5% were respiratory system disease.[7]

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The continuously increasing number of patients suffering from diabetes along with increasing rate of prevalence of COVID-19 endorses the need of increased care for such patients for minimizing any further complications and risk of death. Since the current knowledge about the linkage between COVID-19 and diabetes is quite limited, it is very difficult to identify the direction in which these patients must be looked after. Therefore, this study was designed for the comparison of survival analysis as well as the behavior of the COVID-19 on the diagnosed cases of COVID-19 with and without diabetes.[8]

METHODOLOGY

This comparative prospective study was planned in COVID-19 ward of Federal Government Polyclinic Hospital (FGPCH), Islamabad Pakistan, from December 2020 to May 2021. The study was approved in 76th meeting of FGPCH Ethical Committee with letter no. FGPC.1/12/2020/Ethical Committee.

Inclusion Criteria: All confirmed COVID-19 patients were included having age 18-60 years; of either gender male/female were included in the study.

Exclusion Criteria: Patients with other comorbidities i.e. asthma or other pulmonary diseases, lung diseases, patients having any cardiac disease, and pregnant women, were excluded in this study.

The sample size was calculated with the help of WHO sample size calculator 2.2b on the basis of the results of a study conducted in Wuhan China. In that study the researchers reported that there was significant difference in mortality between COVID-19 patients with diabetes and COVID-19 patients without diabetes (16.5-0%) with *p*-value 0.038. The minimum sample size required to test the hypothesis "The survival rate among COVID-19 patients with diabetes and COVID-19 patients without diabetes are not equal" based on the survival rate of both type of COVID-19 patients (0.001 and 0.165), keeping level of significance 5% and power of test 80%, is 50 in each group. Hence we were included 100 confirmed COVID-19 patients in our study through consecutive sampling.

Patients came with common symptoms of COVID-19 i.e. Fever, Headache, Cough, Loss of taste, Diarrhea, Sore throat, Congestion and Shortness of breath were recommended for COVID-19 test. The confirmation of COVID-19 were made through Polymerase Chain Reaction (PCR) test. The patients got positive result were admitted till the patient got negative PCR test report. Complete clinical history was taken from all patients admitted in the COVID-19 ward. The repeated PCR was recommended for discharge of the patient on the advice of doctor with respect of patient's clinical symptoms.

Data was analyzed through SPSS version 23.0. Patients age, gender, duration of Diabetes, glycemic control before and after admission in hospital from COVID-19, Duration of hospital stay due to COVID-19, requirement for NIV, mechanical ventilation requirement and final outcome was noted down on a self-designed peforma. Chi square test, and student t test was used for analysis. For survival analysis Kaplan-Meire technique was used to compare the probability of survival between two groups. *p*-value ≤0.05 was considered as significant.

RESULT

In overall 100 patients included in this study there were majority 75(75%) were male and 25(25%) were female. 50 patients of COVID-19 with diabetes were included in Group-A and 50 patients of COVID-19 without diabetes were included in Group-B. In Group-A, there were 37(74%) were male whereas in Group-B 38(76%) patients were male and the both group were independent with respect of gender of the patient with *p*-value >0.05. The patients included in the study have a mean duration of diabetes 5.39±6.29 years with a minimum 0.5 year and maximum 25 years. Similarly out of 50 patients of Group-A, only 16(32%) patient's glycemic was control/normal during their hospital stay that may affect the main outcome of the study.

The average age of the patient was significantly different between two groups as the patients of Group-A were older having higher mean age 59.28±9.84 years as compared to the control group having mean age 44.88±15.58 years with *p*-value <0.001. The comparison of lab profile, hospital and duration of the disease is mentioned in Table-I.

The Table-I showed that the COVID-19 patients already affected with diabetes were equally showed non-seriousness as the patients without diabe-tes and try to get cured through desi/herbal treatment in the initial stage of the disease hence *p*-value >0.05. It was also showed that the duration of hospital stay and the total duration of treatment was significantly higher in group A as compared to the Group-B with *p*-value <0.001 which was an evidence that COVID-19 infection severely damaged the health condition of patients with diabetes as compared to the patients without diabetes. Hence the diabetes is a risk factor of severe attack of COVID-19.

Table-I: Comparison of lab parameters, duration of hospital stay and total treatment duration between two groups

Lab Variables and Duration of Treatment	Group-A (n=50)	Group-B (n=50)	*p*-value
C-Reactive Protein (CRP) (mg/dL)	110.978±70.999	38.292±43.398	<0.001
ESR (mm/hr)	99.68±42.597	43.14±38.089	<0.001
Ferritin (ng/mL)	811.82±640.846	313.97±187.855	<0.001
D. Dimers (mg/L)	3.29±1.02	2.589±1.886	<0.001
Lactate Dehydrogenase (LDH) (IU/L)	535.30±241.171	348.22±311.715	≤0.001
Bed rest at home after symptoms appear or after positive result of COVID-19 test	7.02±3.761	6.94±4.377	>0.05
Duration of hospital stay (days)	11.72±4.513	6.82±2.89	<0.001
Total duration of treatment since COVID-19 positive result	18.74±3.002	13.76±4.516	<0.001

The table-II showed that due to COVID-19 the patients with diabetes were severely ill and required extra cure i.e. oxygen, ventilator and angiotension receptor for treatment of COVID-19 as compared to the patients with non-diabetes. The proportion of death due to COVID-19 was also significantly higher in Group-A (44%) as compared to the Group-B (18%) with *p*-value 0.005.

Table-II: Comparison of patient's requirements and final outcome between two groups

Variables	Categories	Group-A n (%)	Group-B n(%)	*p*-value
Oxygen dependency	Yes	44(88)	14(28)	<0.001
	No	6(12)	36(72)	
Need Mechanical ventilation	Yes	23(46)	10(20)	0.006
	No	27(54)	40(80)	
Use angiotension receptor inhibitor	Yes	22(44)	4(8)	<0.001
	No	28(56)	46(92)	
Final outcome	Survive	28(56)	41(82)	0.005
	Death	22(44)	9(18)	

The survival analysis through Kaplan-Meire technique showed that the probability of survival at different time duration after COVID-19 positive was greater in patients with no history of diabetes, but the difference of survival probability was not significant as the log rank (Mental-Cox) chi square statistics was 0.117 with *p*-value >0.05, although the survival curve of COVID-19 patients without diabetes was just slightly above then the survival curve of COVID-19 patients with diabetes in Figure-1.

We also separately analyze the cases of Group-A and divided the patients into further two groups on the basis of glycemic control during the time of admission in hospital. The result showed that the patients with glycemic control showed a much better resistant against COVID-19 infection. The oxygen dependency ratio, need mechanical ventilator, use angiotensin receptor inhibitor and mortality percentage was less in Group-A patients having glycemic control as compared to others (Table-III).

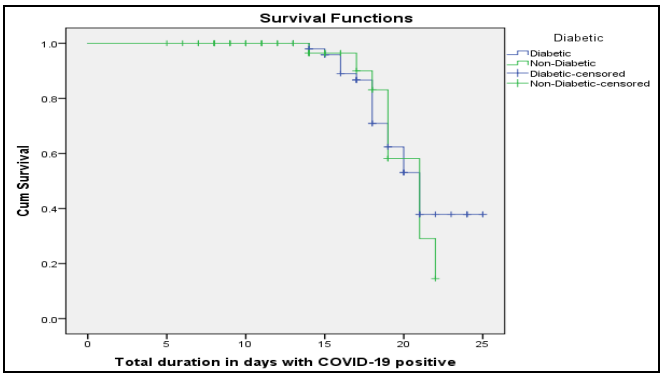

Figure-1: Survival curve with respect of total duration of treatment after COVID-19 positive

Table-III: Comparison of cases with glycemic control and without glycemic control with respect of treatment required and outcome

Variables	Categories	Glycemic control		*p*-value
		Yes n(%)	No n(%)	
Gender	Male	12(75)	25(73.5)	>0.05
	Female	4(25)	9(26.5)	
Oxygen dependency	Yes	11(68.8)	33(97.1)	0.005
	No	5(31.2)	1(2.9)	
Need Mechanical ventilation	Yes	-	23(67.6)	<0.001
	No	16(100)	11(32.4)	
Use angiotensin receptor inhibitor	Yes	3(18.8)	19(55.9)	0.014
	No	13(81.2)	15(44.1)	
Final outcome	Survive	16(100)	12(35.3)	<0.001
	Death	-	22(64.7)	

The comparison of duration of diabetes and duration of hospital stay showed that the patients having good glycemic control and a short diabetes history cured very fast as compared to the patients who have a prolong diabetes history and have no glycemic control. (Figure-2)

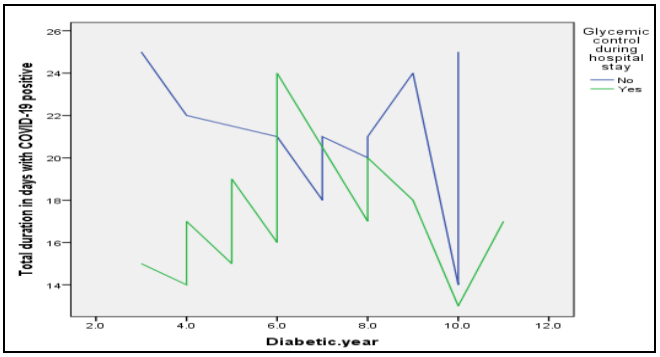

Figure-2: Line chart of duration of COVID-19infection and duration of diabetes with respect of glycemic control during hospitalization.

DISCUSSION

The average age of survivors was 46.49±13.02 years and non-survivors was 64.52±10.57 years with *p*-value <0.001. In a study conducted in Wuhan China, the average age of the critically ill patients infected from COVID-19 was 59.7±13.3 years. Yang *et al*. also revealed that age of the patients was also related to the mortality of the patient as the average age of the patient who did not survive was higher 64.6±11.2 years as compared to the survivors aged 51.9±12.9 years.[9]

In the studies conducted by Zhang *et al.* & Yan *et al.* the COVID-19 patients with diabetes have higher leucocyte and neutrophil count, fasting blood glucose, serum creatinine urea nitrogen and creatine kinase isoenzyme.[10,11] In England, a study conducted by Ebekozien *et al.* consisting 64 patients of type-1 diabetes, 33 were COVID-19 positive and the remaining 31 were have symptoms of COVID-19. The results showed that the adverse outcome diabetic Ketoacidosis (KDA) were found 45.5% in COVID-19 confirmed cases group whereas 13.3% were in COVID-19 suspected group.[12] Similarly in our study, CRP, ESR, ferritin, D. Dimers and LDH was higher in COVID-19 patients with diabetes.

In a cohort study conducted by Williamson et al. studied the 5638 deaths due to COVID-19 to find out the associated factors of death. The results showed that uncontrolled diabetes was a significant risk factor of COVID-19 patient's death with hazard ratio 2.36.[13] Similar observations were noted down in the study conducted by Recalcati in which an increased risk of death and other severe complications were found in patients with diabetes.[14] In another study conducted by Scheen *et al.* the result showed that the proportion of patients with diabetes was almost three times in ICU admission cases of COVID-19 and the mortality rate of COVID-19 patients with diabetes was also double as compared to the patients without diabetes.[15]

Various other issues have also been reported which are associated with the COVID-19 disease such as skin and ocular disorders. The results of a cohort study of Italy identified cutaneous manifestations in almost 20% of positive-COVID-19 patients.[16]

In a retrospective multicenter study conducted by Zhu *et al.* the researchers included 7337 confirmed cases of COVID-19 from which 952 had pre-existing type-2 diabetes. They concluded that the cases of COVID-19 with type-2 diabetes required more interventions in treatment and the mortality rate was also high in such patients.[17]

In another study conducted in England, the researchers observed the death ratio of COVID-19 patients having type-1, type-2 and other type diabetes. They concluded that almost one third deaths 31.4% were of type-2 diabetes, 1.5% deaths observed in those patients having type-1 diabetes and only 0.3% deaths occurred in other type of diabetes. The odds ratio of "in hospital mortality" of COVID-19 patients with type-1 diabetes was 3.51 whereas 2.03 in patients with type-2 diabetes.[18]

In a population based cohort study conducted by Holman *et al.* the researchers revealed that post COVID-19 attack, the death ratio of type-1 and type-2 diabetes patients were increased with 50.9% and 64.3% respectively with respect of the last 3 years average mortality. From Feb-May 2021, total deaths of 1604 and 36291 patients respectively due to type-1 diabetes and type-2 diabetes were recorded. Out of them, 464 (28.93%) of type-1 diabetes patients and 10525(29%) of type-2 diabetes patients' death were related with COVID-19.[19]

In a meta-analysis of 33 studies consisting 16003 patients concluded that the diabetes is associated with the mortality and the severity of the disease having odds ratio 1.9 and 2.75 respectively, as compared to the non-diabetic COVID-19 patients.[20] In another meta-analysis the researcher clinched that after 1382 COVID-19 cases reviewed the diabetes mellitus was the second most frequent comorbid. The results showed that the risk of admission in ICU was higher in patients with ongoing treatment of diabetes having odds ratio 2.79 and have a higher mortality risk with odds ratio 3.21 as compared to the other non-diabetic COVID-19 patients.[21]

Sardu *et al.* applied cox regression and concluded that the patients with hyperglycemia and diabetes have higher risk of severely infected from COVID-19 as compared to the patients with normoglycemia and without diabetes.[22]

A very similar results to our study was reported in a two center retrospective study conducted in China, where the proportion of patients admitted in intensive care unit and mortality was higher in patients with diabetes as compared to the patients without diabetes but the cox hazard ratio 1.58 of COVID-19 patients with diabetes was not associated with in hospital mortality.[23] In our study the survival curve is not much deviated of patients with diabetes as compared to the patients without diabetes.

Reversely, in a univariate analysis conducted by Cariou *et al*. in which they included 1317 confirmed cases of COVID-19 with diabetes. Majority 88.5% of the patients were of type-2 diabetes. The univariate analysis showed that age, type of diabetes, HbA1c, diabetic complication were not significantly associated with primary outcome of the study.[24] Similar result was found in the study conducted by Li *et al.* where they concluded that the duration of diabetes is negatively associated with the admission in COVID-19 ICU. They observed that 11.7% patients with a short history of diabetes were required IMV for treatment of COVID-19 and all were admitted in ICU whereas the patients with a prolong history of diabetes only 9(9.2%) were received IMV treatment and only 4(4.1%) were admitted in ICU.[25]

The result of our study also revealed that the diabetes is not increase the mortality risk in COVID-19 patients if the patients with diabetes manage his/her disease and having good glycemic control. Hence the diabetes itself is not a real risk factor for severity of COVID-19 but its duration and the disease control.

CONCLUSION

COVID-19 patients with diabetes are at higher risk with respect of prolong hospital stay and also mortality. It is also concluded that the probability of survival of the patient not associated with the duration of the COVID-19 positive in both patients with or without diabetes.

LIMITATIONS OF STUDY

Some confounders that observed after the data collection for this study is missing i.e. go in fresh air for at-least 2 hours with the treatment of COVID-19, Physio-therapy/ lung exercise with the treatment of COVID-19 and complete duration of COVID-19 positive as initially due to few fake news spread by social media patients were afraid to report and start the treatment at home. Hence we just mentioned and analyzed the hospital stay in days due to COVID-19.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

SB & SM: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

GK & FUI: Data acquisition, data analysis, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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