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ORIGINAL ARTICLE

Glycemic control and risk factors of mortality in patients with diabetes mellitus and COVID-19: A single center experience from Pakistan.

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ABSTRACT… Objective: To highlight the effect of COVID-19 and DM on each other by studying glycemic control and risk factors for mortality. **Study Design:** Retrospective Observational Review. **Setting:** Sindh Institute of Urology and Transplantation Karachi Pakistan. **Period:** March 2020 till March 2021. **Methods:** Covid-19 diagnosed patients admitted were enrolled. They were divided into DM and non-DM. Demographics, clinical variables and outcome were compared. Glycemic control during hospitalization was noted. Fasting glucose level >120 mg/dl, and random >200 mg/dl were considered as poor glycemic control. Survivors and non- survivors among DM patients were compared. **Results:** A total of 366 patients were included, 113(30.87%) DM and 253(69.12%) non-DM. Mean age was higher in DM group (58yrs vs 49.6yrs p <0.001). Significantly more patients with hypertension (p <0.001) and ischemic heart disease (p=0.001) developed Covid-19 in DM group. There was no difference in mortality (p = 0.295). In DM patients, the significant risk factors for mortality were age >60years, hypertension and chronic kidney disease. The mean high fasting and pre-dinner blood glucose levels at admission and day 5 were significantly associated with mortality. **Conclusion:** Diabetic patients with advanced age, hypertension and chronic kidney disease were associated with increased risk of death. More attention should be focused on dynamic monitoring and strict glycemic control as uncontrolled diabetes is associated with severe infection and mortality.

Key words: Covid-19, Diabetes, Developing Countries, Mortality, Risk Factors.

INTRODUCTION

The pathophysiology of diabetes mellitus (DM) and Covid-19 is interlinked. DM is characterized by glucose dysregulation by insulin deficiency or resistance. DM has been reported as a strong predictor for severe infections before as well as during the current pandemic of Corona virus disease-19 (Covid-19) resulting in lengthy hospitalization, elevated morbidity and mortality.[1] DM patients outnumbered the proportion of cases and mortality during the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) outbreak occurred in 2012.[2] Risk of hospitalization was three times while ICU admission four times higher among DM patients during the 2009 Influenza-A (H1N1) outbreak while similar complications were noted during 2002-2003 in severe acute respiratory syndrome (SARS-CoV-1) outbreak.[3] Zhu et al. assessed nearly 1,000 Covid-19 patients having DM and reported uncontrolled blood glucose (upper limit > 10 mmol/L) had significantly higher mortality rates.[4] Rafique et al. also observed that "Covid-19 can precipitate hyperglycemic emergencies like diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) in patients with DM."[5]

The management of Covid-19 in patients with poorly controlled DM is challenging. From administration of corticosteroids for cytokine storm causing uncontrolled blood sugars to development of ketoacidosis due to sepsis are some of the major management issues in patients with DM.[6]

According to the second National Diabetes Survey of Pakistan, the prevalence of diabetes is around 26%.[7] Because DM is highly prevalent

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in our county, the data on diabetes and Covid-19 and their effect on each other are needed for accurate management and treatment. There is limited data from Pakistan on DM and Covid-19. Our aim is to identify the effect of DM on Covid-19 by studying glycemic control and risk factors for mortality.

METHODS

This retrospective observational study was conducted Sindh Institute of Urology and Transplantation (SIUT) in department of Medicine. As the study is retrospective involving only medical records therefore; ethical review was taken (SIUT-ERC-2021/A-260) and written informed consent waived by the ethical review committee.

We reviewed records of Covid-19 polymerase chain reaction (PCR) positive patients admitted during the months of March 2020 till March 2021 and were included in analysis. We admitted patients who had oxygen saturation of <94% on room air i.e. severe disease. Transplant recipients and patients who were dialysis dependent were excluded from the study.

Overall 366 patients were enrolled and further comparison was done between two groups: DM (n=113) and non-DM (n=253). Diabetic patient was defined as those who had a history of diabetes and/or who were on antidiabetic medications. Demographics, clinical variables, comorbidities, need of intensive care unit (ICU) care, duration of hospitalization and all cause in-hospital mortality was compared between DM and non-DM group. Blood sugar monitoring during hospital stay (blood sugar level fasting and pre-meal twice a day) were noted, fasting glucose level (FBS) >120 mg/dl, and random (RBS) >200 mg/dl were considered as poorly controlled blood glucose levels.(8) In diabetic group, survivors (n=78) and non- survivors (n=35) were compared regarding age, comorbid condition and glycemic control.

Data Analysis

Data was entered into SPSS version 23. Continuous variables like age, weight, height, BMI, duration of DM, duration of hospital stay, blood sugar level and vitals were analyzed as mean (±SD). Frequencies & percentages were calculated for gender, residence, educational status, occupation, comorbid, need of ICU admission, complication like DK and outcome of patient' disease.

Stratified analysis was followed by the application of $\chi 2$ test, Fisher's exact test or Cochran–Mantel–Haenszel $\chi 2$ test (for categories) while student's t-test was used between groups for comparison of continues variables. P value <0.05 was considered significant. Strict criteria were used for selection of study participants to control confounding factors.

RESULTS

During the study period, a total of 366 patients were included, 113 (30.87%) were DM and 253 (69.12%) were non-DM. The comparison of demographics, clinical characteristics and outcome between DM and non-DM is shown in Table-I. Patients were older in DM (mean age 58.14± 11.42 vs 49.69± 16.44, p<0.001) than comparative group. We observed significantly more number of patients with hypertension (p value<0.001) and ischemic heart disease (p value=0.001) with Covid-19 in DM group. The most significant symptoms in DM group were fever (100% vs 81%), cough (63.7% vs 53%) and shortness of breath (79.6% vs 62.8%) with almost all patients presented with fever. There was no difference in ICU stay and mortality between DM and non-DM group.

On the other hand, when we compared the risk factors for mortality in DM group, age >60 years (p=0.001), hypertension (p=0.025) and chronic renal failure (p=0.025) were found significantly associated with increased mortality. Significantly more patients were on antibiotics who expired among DM group (p<0.001). (Table-II)

Regarding glycemic control during admission, a high mean fasting and pre-dinner blood glucose levels obtained on arrival and on day 5 were significantly associated with death. (Table-II)

	Diabetes Mellitus (n=113)	Non Diabetes Mellitus (n=253)	P-Value*	OR (95% C.I)
Age mean (+S.D)	58.14± 11.42	49.69±16.61	<0.001	-
Age groups n (%)				
< 30 years	3 (2.7)	30 (11.9)	0.005	0.203 (0.061 – 0.679)
30 – 45 years	6 (5.3)	68 (26.9)	<0.001	0.153 (0.064 – 0.363)
45 – 60 years	56 (49.6)	88 (34.8)	0.008	1.842 (1.174 – 2.890)
>60 years	48 (42.5)	67 (26.5)	0.002	2.050 (1.286 – 3.267)
Gender n (%)				
Male	77 (68.1)	172 (68.0)	0.976	1.007 (0.626 - 1.621)
Female	36 (31.9)	81 (32.0)		
Comorbid conditions n (%)				
Hypertension	77(68.1)	97(38.3)	<0.001	3.440 (2.150 - 5.503)
Ischemic heart disease	21(18.6)	18(7.1)	0.001	2.980 (1.519 - 5.848)
Renal disease	43(38.1)	85(33.6)	0.409	1.214 (0.766 - 1.925)
Clinical features n (%)				
Fever	113(100)	205(81)	<0.001	1.550 (1.434 - 1.683)
Cough	72(63.7)	134(53)	0.055	1.560 (0.988 - 2.461)
Myalgia	16(14.2)	52(20.6)	0.146	0.638 (0.346 - 1.174)
Difficulty in breathing	90(79.6)	159(62.8)	0.001	2.313 (1.370 - 3.907)
Diarrhea	12(10.6)	17(6.7)	0.202	1.649 (0.760 - 3.580)
Treatment given n (%)				
Antibiotics	75(66.4)	156(61.7)	0.388	1.227 (0.771 - 1.954)
Steroid	113(100)	240(94.9)	0.012[t]	1.470 (1.37-1.58)
Methylprednisolone	89(78.8)	165(65.2)	0.009	1.978 (1.176 - 3.326)
Dexamethasone	25(22.1)	72(28.5)	0.205	0.714 (0.424 - 1.203)
Tocilizumab	40(35.4)	69(27.3)	0.116	1.461 (0.909 - 2.349)
Anticoagulation	91(80.5)	199(78.7)	0.683	1.122 (0.645 - 1.954)
Remdesivir	24(21.2)	97(38.3)	0.001	0.434 (0.259 - 0.727)
ICU admission n (%)	59(52.2)	113(44.7)	0.181	1.354 (0.868 - 2.112)
Outcome n (%)				
Mortality	35(31.0)	65(25.7)	0.29	1.298 (0.796 - 2.115)

Table-I. Demographics, Clinical characteristics and outcome of diabetes mellitus and non-diabetes mellitus patients

*t test used for comparison of continues variables. Chi square and fisher exact test for categorical variables [t]: fisher exact test

	Expired (n=35)	Alive (n=78)	P-Value*	OR (95% C.I)
Age mean(+S.D)	64.09+9.96	55.47+11.08	<0.001	-
Age groups n (%)				
<30 years	0 (0.0)	3 (3.8)	0.551[t]	-
30-45 years	0 (0.0)	6 (7.7)	0.175[t]	-
46-60 years	14 (40)	42 (53.8)	0.173	0.571 (0.254 - 1.284)
>60 years	21 (60)	27 (34.6)	0.012	2.833 (1.246 – 6.443)
Gender n (%)				
Male	25 (71.4)	52 (66.7)	0.615	1.250 (0.523 - 2.988)
Female	10 (28.6)	26 (33.3)		
Comorbid conditions n (%)				
Hypertension	29(82.9)	48(61.5)	0.025	3.021 (1.122 - 8.133)
Ischemic heart disease	9(25.7)	12(15.6)	0.192	1.904 (0.717 - 5.053)
Renal disease	18(51.4)	25(32.1)	0.050	2.245 (0.993 - 5.075)
Chronic kidney disease	18(51.4)	23(29.5)	0.025	2.532 (1.113 - 5.762)
Acute kidney injury	4(11.4)	3(3.8)	0.200	3.226 (0.682 - 15.264)
Treatment given n (%)				
Antibiotics	34(97.1)	41(52.6)	<0.001	30.683(3.999-35.413)
Methylprednisolone	27(77.1)	62(79.5)	0.778	0.871 (0.333 - 2.278)
Dexamethasone	7(20.0)	18(23.1)	0.716	0.833 (0.312 – 2.224)
Tocilizumab	15(42.9)	25(32.1)	0.267	1.599 (0.699 - 3.614)
Anticoagulation	30(85.7)	61(78.2)	0.351	1.672 (0.563 - 4.967)
Remdesivir	6(17.1)	18(23.1)	0.476	0.690 (0.248 - 1.922)
Glycemic characteristics (Blood glucose mean (+SD)				
Fasting blood glucose (day 1)	254 (133)	192 (109)	0.051	-
Fasting blood glucose (day 5)	232 (86)	151 (81)	0.004	-
Blood glucose pre-lunch (day 1)	264 (151)	213 (122)	0.192	-
Blood glucose pre-lunch (day 5)	226 (96)	179 (84)	0.145	-
Blood glucose pre-dinner (day 1)	277 (99)	218 (111)	0.037	-
Blood glucose pre-dinner (day 5)	267 (102)	180 (77)	0.004	-

Table-II. Risk factors for mortality in diabetes mellitus patients

*t-test used for comparison of continues variables. Chi square and fisher exact test for categorical variables [t]: fisher exact test

DISCUSSION

The current study investigated the relationship of Covid-19 infection with outcomes among diabetic in comparison with non-diabetic patients.

Diabetic patients who had Covid-19 had a significantly higher mean age than non- DM patients with odds of getting Covid-19 was 2 times higher among those who were more than 45 years of age. Tamura et al. also found that significantly higher frequency of patients with diabetes, who had Covid-19 were over 60 years of age.[9] A meta-analysis of 22 studies from Germany observed that age >65 years has 1.67 times higher risk of severe infection with each 5 year increase in age cause 25% increase in severity.[10]

We found a significant association of comorbidities like hypertension [OR = 3.440 95% CI (2.150 -5.503)] and coronary heart disease [OR = 2.980 95%CI (1.519 -5.848)] with diabetic Covid-19 patients as compared to non-diabetics patients. Diabetes remains as an independent risk factor for severe Covid-19[11], however patients with diabetes usually have associated comorbidities that may further increase the risk of severe infection. A study from China showed hypertension to be an independent risk factor for death among patients with diabetes and Covid-19.[12] In a nationwide study on diabetic patients from France, microvascular and macrovascular complications of diabetes are independently associated with severe Covid-19 disease and death.[13]

Regarding clinical symptoms, fever, cough and difficulty in breathing was significantly more observed among diabetic as compared to non-diabetic patients. Shi et al also found that patients with diabetes presented more with symptoms like cough.[12]

We did not find statistically significant increase in ICU admission and mortality between diabetic and non-diabetic patients. On the contrary studies have noted a much higher mortality among diabetic covid-19 patients.[1,9,12] A nationwide study from Sweden found that type 2 diabetes is significantly associated with frequent hospitalization, ICU care and increased mortality.[14] Likewise; in a meta-analysis by Mahamat et al found that the absolute risk of Covid-19 death was increased by 14% among diabetic patients.[15] The reason of no difference in mortality in our cohort is the fact that our center caters to patients with renal disease. The mortality in these patients due to organ failure is already high even if non-diabetic.[16]

We evaluated the risk factors associated with death in patients with Covid-19 and diabetes. We found that age was a statistically significant factor with patients > 60 years had 4 times higher risk of mortality [OR = 4.071 95% CI (1.756 - 9.442)]. Tamura et al. also found that diabetic patients with age >60 years had significantly high mortality.[9] In a study from China, diabetic patients aged ≥ 70 years was found to be an independent associated with in-hospital death for patients with Covid-19.[12] Regarding co-morbidities, we found that patients with hypertension had 3 times and those with chronic kidney disease (CKD) had 2.5 times higher risk of mortality. A study from China reported hypertension as risk factor for mortality (HR 3.10, 95% CI 1.14–8.44) in patients with Covid-19 and diabetes.[12] As our center mainly caters to patients with renal failure, we found CKD as a major risk factor for mortality. A large study from United Kingdom showed an increased mortality among CKD patients with Covid-19 (adjusted hazard ratio ranging from 1-4 among different stages of CKD).[17] Another study from Germany also found that diabetic nephropathy is associated with increase morality risk among Covid-19 patients.[18] Hence according to our study diabetic patients with older age, hypertension and CKD need to be managed closely to prevent mortality.

We also assessed glycemic control and correlate it with mortality. We found that poorly controlled diabetes who had high fasting and pre-dinner blood glucose levels on presentation as well as at day 5 of hospitalization showed increased mortality. It is a well-known fact that poorly controlled diabetes leads to an increased risk of infections mainly due to hyperglycemic environment leading to immune dysfunction.[19] A population based study from Denmark did show an increase risk of infections among patients with high HbA1c levels.[20] Zhu et al did a detailed

analysis of glycemic control and outcome of Covid-19 among 810 diabetic patients. They found that patients with well controlled diabetes had considerably lower mortality (adjusted hazard ratio 0.14) as compared to poorly controlled diabetics.[4] A study from United States also reported a significant high mortality among patients with uncontrolled hyperglycemia.[21]

The limitations of this study are, it was a single center observational study with a limited sample size and retrospective study design however; it has highlighted very significant aspect of care of diabetic patients.

In conclusion, advanced age diabetic patients with concomitant hypertension and CKD have with increased risk of death with Covid-19. Clinician should emphasis on dynamic monitoring and strict glycemic control as uncontrolled diabetes is associated with severe COVID 19 infection and mortality.

CONCLUSION

Diabetic patients with advanced age, hypertension and chronic kidney disease were associated with increased risk of death. More attention should be focused on dynamic monitoring and strict glycemic control as uncontrolled diabetes is associated with severe infection and mortality.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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3	Sunil Kumar Dodani	Conceptualization, Data analysis and interpretation.	
4	Fakhir Raza Haidri	Data analysis, Supervision of manuscript.	
5	Maryam Mushtaq	Data collection.	
6	Asma Nasim	Data interpretation, overall manuscript writing and supervision.	