Association between type-2 diabetes and Outcomes in COVID-19 Patients admitted to Intensive Care Unit: A retrospective Study.

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ABSTRACT

Background: Corona Virus Disease (COVID-19) Pandemic is the last pandemic with significant economic and social impact. The scientific literature also witnessed a pandemic of manuscripts about the pandemic. However, certain areas still to be addressed, especially with the waning of the pandemic. Its association with comorbid disease conditions is a good example of such areas. Here, we retrospectively evaluated the association between COVID-19 and type-2 Diabetes mellites in critically ill patients.

Methodology: This was a retrospective study of 300 patients, admitted to the ICU, with confirmed diagnosis by polymerase chain reaction (half had diabetes and the other half had not). They were selected from different healthcare facilities (e.g., Al-Azhar University Hospitals (Damietta and Assiut)). The collected data included patient demographics (e.g., age, weight, height, sex, smoking status, and residence). Patients were categorized into obese and non-obese for the risk

assessment. Laboratory values just prior to ICU admission were used in analysis. Primary outcomes were the need for mechanical ventilation and mortality during ICU stay.

RESULTS: There was male-sex predilection in both groups (62.7% and 58.7%). Obese subjects significantly increased in diabetic group (48% versus 26.0%). The clinical manifestations (except expectoration) and hypertension, fasting blood sugar, creatinine and glycated hemoglobin were more prominent in diabetic than non-diabetic group. However, lymphopenia was reported among 44.0% and 38.0% of diabetic and non-diabetic groups, with no significant difference. The ICU duration was significantly longer in diabetic than non-diabetic groups (13.48±3.61 vs 11.29±2.79 days). The invasive mechanical ventilation was reported among 58% and 30.0% in diabetic and non-diabetic groups, with significant difference. Also, mortality was significantly increased in diabetic than non-diabetic groups (26.0% vs. 12.0%, respectively).

Keywords: COVID-19; Diabetes Mellitus; Critical Care; Prediction

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the last detected strain of coronaviruses that leads to the coronavirus disease (COVID-19) pandemic due to its high infectivity and transmissibility, leading to a significant economic and social disruption worldwide **(1).**

Healthy individual who contracted COVID-19 infection are usually asymptomatic or have mild respiratory manifestations. However, patients with a concomitant or pre-existing medical disease may develop severe manifestations with significant increase of COVID-19 related morbidity and mortality (e.g., acute respiratory distress syndrome (ARDS), vascular thrombosis, septic shock, and multi-organ failure **(2, 3).**

Diabetes mellitus (DM) is a worldwide health problem. Egypt is ranked globally as the 10th highest age-adjusted regarding prevalence of diabetes. The prevalence is up to 20.9% in the 20-79 years old Egyptians. Type-2 diabetes mellites (T2DM) is the commonest form of DM worldwide as it accounting

for 90.0% of all diabetic patients. T2DM is associated with an increased risk of premature death, different comorbid conditions and psychological disorders, beside its burden from the economic point of view **(4).**

Patients with DM are at increased risk of acquiring COVID-19 infection. In addition, diabetics are at higher risk for the hospitalization, admission to intensive care unit (ICU) and the risk of mortality **(5,6).**

Previous studies addressed the association between COVID-19 infection outcomes and diabetes yielded mixed results. Some trials advocated the association between diabetes and severe COVID-19 (admission to ICU and post-acute COVID-19 complications) **(7,8).** Other studies have not reported such association **(9, 10).** Most studies reported no link between COVID-19 related mortality and diabetes mellitus **(11, 12).**

The current study was design as a retrospective study to examine the possible association between diabetes mellites and COVID-19 outcomes.

Methodology

This is a retrospective study that included reviewing files of 300 patients who were admitted to the intensive care unit, who's infection was confirmed by polymerase chain reaction (half of them had diabetes mellitus and the other half had not). We included adult patients (18 years or older), with their first COVID-19, between April 2020 and December 2021, and they were admitted to Intensive Care Unit of different healthcare centers, whenever the administration consent was obtained.

Type-2 diabetes mellitus (T2DM) diagnosis was based on the known patients' medical history and history of drug intake (anti-diabetic therapy). For confirmation of diagnosis, patients who had HbA1 > 6.5 and fating glucose level > 126 mg/dl were considered diabetics **(13).**

Collected data: files were reviewed for patient demographic data including age, weight, height, sex, smoking status, and residence. The body mass index was calculated from the equation (BMI=weight

(kg)/height $(m)^2$), and patients with BMI > 25kg/m^2 was considered obese and patients were categorized into obese and non-obese for risk assessment.

Laboratory values in the statistical analysis were the recent investigations just prior or at admission of the patient.

Primary outcomes were the need for mechanical ventilation and mortality during ICU stay.

Data analysis:

The collected data were organized, coded, and statistically analyzed by the statistical package for social science, version 16 (SPSS Inc, Chicago, Illinois, USA). The continuous variables were presented by their arithmetic mean and standard deviation (as they were normally distributed); while categorical variables were expressed by the relative frequency and percentages. The two groups were compared by the independent sample's student "t" and Chi square tests, for continuous and categorical variables, respectively. P value ≤ 0.05 was considered significant.

RESULTS

In the current work, the statistical analysis had been performed for a total of 300 patients with confirmed diagnosis of COVID-19; 150 of them had diabetes and 150 had not. Males were highly presented in both groups (62.7% in diabetic and 58.7% of non-diabetic groups). Patient's age ranged between 33 and 69 years and majority of patients were around their fifties. Obese subjects significantly increased in diabetic than non-diabetics groups (48% and 26.0%) respectively. This confirmed the significant increase of body mass index in diabetic than non-diabetic group (28.30±3.65 vs 26.69±3.38 kg/m^2, respectively). The clinical manifestations (fever, cough, and dyspnea) were significantly presented in diabetic than non-diabetic groups. However, expectoration showed non-significant differences between groups. Finally, hypertension significantly increased in diabetic than non-diabetic groups, while smoking, dyslipidemia and COPD/Asthma showed non-significant difference between both groups (Table 1).

Regarding laboratory investigations, there was significant increase of serum fasting glucose levels, creatinine and glycated hemoglobin among diabetic than non-diabetic groups. However, lymphopenia was reported among 44.0% and 38.0% of diabetic and non-diabetic groups respectively, with no significant difference (Table 2).

Regarding outcome, the duration of ICU ranged between 7 and 22 days; the ICU stay duration was significantly longer in diabetic than non-diabetic groups (13.48±3.61 vs 11.29±2.79 days, respectively). The invasive mechanical ventilation was reported among 58% and 30.0% in diabetic and non-diabetic groups, with significant difference. In addition, mortality was significantly increased in diabetic than non-diabetic groups (26.0% vs. 12.0%, respectively) (table 3).

In diabetic groups, mechanical ventilation was significantly associated with obesity, cough at presentation, COPD/Asthma, higher creatinine, poor glycemic control (higher glycated hemoglobin), lymphopenia, longer ICU duration and higher mortality (Table 4).

In diabetic group, mortality was significantly associated with obesity, cough, hypertension, dyslipidemia, COPD/Asthma, higher serum creatinine, poor diabetic control, lymphopenia and longer ICU stay duration (Table 5)

Table (1): Patient demographics, clinical manifestations and associated risk factors among studied populations

		COVID-Diabetic (n=150)	COVID-Non-diabetic (n=150)	Total (n=300)	Test	P value
Gender	Male	94(62.7%)	88(58.7%)	182(60.7%)	0.50	0.47(ns)

	Female	56(37.3%)	62(41.3%)	118(39.3%)		
Age	Mean±SD	53.27±5.13	52.14±6.89	52.71±6.10	1.61	0.11(ns)
	Min. – Max.	38-69	33-65	33-69		
BMI	Mean±SD	28.30±3.65	26.69±3.38	27.49±3.60	***3.96***	***<0.001****
	Min. – Max.	23.59-33.51	22.84-33.91	22.84-33.91		
Obesity	None-obese	78(52.0%)	111(74.0%)	189(63.0%)	***15.57***	***<0.001****
	Obese	72(48.0%)	39(26.0%)	111 (37.0%)		
Clinical manifestations	Fever	132(88.0%)	116(77.3%)	248(82.7%)	***5.95***	***0.015****
	Cough	115(76.7%)	97(64.7%)	212(70.7%)	***5.21***	***0.022****
	Dyspnea	144(96.0%)	129(86.0%)	273(91.0%)	***9.15***	***0.002****
	Expectoration	9(6.0%)	5(3.3%)	14(4.7%)	1.19	0.27(ns)
Smoking		63(42.0%)	53(35.3%)	116(38.7%)	1.40	0.23(ns)
Hypertension		78(52.0%)	57(38.0%)	135 (45.0%)	***5.93***	***0.015****
Dyslipidemia		60(40.0%)	54(36.0%)	114(38.0%)	0.51	0.47(ns)
COPD/Asthma		36(24.0%)	45(30.0%)	81(27.0%)	1.37	0.24(ns)

Table (2): Laboratory investigations among studied groups

		COVID-Diabetic (n=150)	COVID-Non-diabetic (n=150)	Total (n=300)	Test	P value
Glucose	Mean±SD	158.04±10.46	111.22±4.55	134.63±24.79	***50.24***	***<0.001****
	Min. – Max.	140-183	98-121	98-183		

Creatinine	Mean±SD	1.41±0.26	1.06±0.22	1.23±0.29	***12.38***	***<0.001****
	Min. – Max.	0.9-1.8	0.7- 1.6	0.7- 1.8		
HA1c	Mean±SD	7.54±0.84	5.15±0.51	6.35±1.38	***29.59***	***<0.001****
	Min. – Max.	6.22-8.91	4.39-6.30	4.39-8.91		
Lymphopenia		66 (44.0%)	57(38.0%)	123 (41.0%)	1.12	0.29(ns)

Table (3): Outcome among study groups

		COVID-Diabetic (n=150)	COVID-Non-diabetic (n=150)	Total (n=300)	Test	P value
ICU Stay	Mean±SD	13.48±3.61	11.29±2.79	12.39±3.40	***5.89***	***<0.001****
	Min. – Max.	8-22	7-20	7-22		
Invasive MV		87(58.0%)	45 (30.0%)	132 (44.0%)	***23.86***	***<0.001****
Mortality		39(26.0%)	18(12.0%)	57(19.0%)	***9.55***	***0.002****

Table (4): Factors associated with invasive mechanical ventilation in diabetic group

		Invasive MV (n=87)	No MV (n=63)	Test	P value
Sex	Male	54 (62.1%)	40(63.5%)	0.032	0.85
	Female	33(37.9%)	23(36.5%)		
Age		53.27±5.37	53.26±4.83	0.007	0.99
BMI		29.14±3.41	27.15±3.67	***3.42***	***0.001****
Overweight/Obesity		65(74.7%)	30(47.6%)	***11.55***	***0.001****
Clinical manifestations	Fever	75(86.2%)	57 (90.5%)	0.23	0.64
	Cough	72(82.8%)	43(68.3%)	***4.29***	***0.038****
	Dyspnea	83(95.4%)	61(96.8%)	0.19	0.66
	Expectoration	6(6.9%)	3 (4.8%)	0.29	0.58
Smoking		36(41.4%)	27(42.9%)	0.03	0.85
Hypertension		51(58.6%)	27(42.9%)	3.63	0.07
Dyslipidemia		33(37.9%)	27(42.9%)	0.36	0.54
COPD/Asthma		27(31.0%)	9(14.3%)	***5.62***	***0.020****
Glucose		158.64 ±10.98	157.20±9.72	0.83	0.40
Creatinine		1.46±0.23	1.32±0.26	***3.17***	***0.002****
HA1c		7.66±0.78	7.39±0.90	***1.99***	***0.048****
Lymphopenia		51(58.6%)	15(23.8%)	***17.97***	***<0.001****
ICU Stay		14.51±3.86	12.06±2.65	***4.60***	***<0.001****
Mortality		31(35.6%)	8(12.7%)	***9.98***	***0.002****

Table (5): Factors associated with mortality in the diabetic group

		Died (n=39)	Live (n=111)	Test	P value
Sex	Male	28(71.8%)	66(59.5%)	1.87	0.17
	Female	11(28.2%)	45(40.5%)		
Age		53.07±6.49	53.34±4.59	0.23	0.81
BMI		30.10±3.34	27.67±3.55	***3.74***	***<0.001****
Overweight/Obesity		30 (76.9%)	65(58.6%)	***4.19***	***0.041****
Clinical manifestations	Fever	37(94.9%)	95(85.6%)	2.35	0.12
	Cough	35(89.7%)	80(72.1%)	***5.04***	***0.028****
	Dyspnea	36(92.3%)	108(97.3%)	1.87	0.18
	Expectoration	0(0.0%)	9(8.1%)	3.36	0.11
Smoking		13(33.3%)	50(45.0%)	1.62	0.25
Hypertension		36(92.3%)	42(37.8%)	***34.30***	***<0.001****
Dyslipidemia		30(76.9%)	30(27.0%)	***29.23***	***<0.001****
COPD/Asthma		23(59.0%)	13(11.7%)	***35.34***	***<0.001****
Glucose		159.69±10.49	157.45±10.43	1.14	0.25
Creatinine		1.65±0.18	1.31±0.22	***9.52***	***<0.001****
HA1c		7.98±0.77	7.39±0.81	***3.89***	***<0.001****
Lymphopenia		27(69.2%)	39(35.1%)	***13.61***	***<0.001****
ICU Stay		18.53±2.04	11.71±1.99	***18.26***	***<0.001****

DISCUSSION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged, spread globally and nominated as an epidemic. The identification of different mechanisms included in severe (critically-ill) COVID-19 and its associated risk factors are crucial to improve the management. Diabetes is considered a risk factor for COVID-19 **(14-16),** but the underlying mechanisms and other confounding factors remain largely unknown.

In the current work, COVID-19 patients with diabetes had significantly higher body mass index (BMI), obese subjects, fever, cough, dyspnea, hypertension, creatinine, long ICU stay, increased need for mechanical ventilation, and higher mortality. Males were more prevalent than females. In diabetic group, mechanical ventilation was associated with higher BMI, Cough, COPD/asthma, serum creatinine, poor diabetic control, lymphopenia, longer ICU stay and increased mortality. However, mortality in diabetic group was associated with increased BMI, obesity cough, hypertension, dyslipidemia, COPD/Asthma, serum creatinine, poor diabetic control, lymphopenia, and longer ICU stay. Overall, 44% need invasive mechanical ventilation and mortality was reported for 19%. In diabetic group, 58% need IMV compared to 30.0% in non-diabetic group, while mortality recorded for 26% and 12.0% in diabetic and non-diabetic group, respectively. The mortality rate reported in the current work is close to that of **Giorda et al. (17),** who reported a mortality rate of (27.1%). In addition, they reported that, 75% of their patients were overweight or obese, and hypertension was the commonest associated comorbid disease condition.

In a cohort of 58 patients who were admitted to ICU, **Nasrullah et al. (18)** reported that, males represented 63.8%, constitutional symptoms were the commonest (91.4%), then, lower respiratory tract symptoms (87.9%). tachypnea (65.5%) and hypoxia (67.2%). However, cardiovascular disease was the commonest associated comorbid disease condition (74.1%), then, obesity (53.5%), and diabetes (39.7%). About half of the patients need invasive mechanical ventilation. The overall mortality was 32.8% (slightly higher than the current work). The significantly associated factors with mortality were age, comorbidity index, tachypnea, lymphopenia at presentation, acute respiratory distress syndrome (ARDS), mechanical

ventilation, and steroid use. These results are partially comparable to the current work, due to different study design, as they aimed to document characteristics of COVID-19.

The rates of mortality in COVID-19 patients admitted to intensive care units are available from different countries with high variability. For example, **Arentz et al. (19) and Bhatraju et al. (20)** from Seattle, USA, reported a rate of 67.0% and 50.0% respectively, while **Yang et al. (21), Wang D, et al. (22),** and **Huang et al. (23),** from China reported a rate of 62.0%, 30.0% and 38.0% successively. In addition, **Cummings et al. (24)** from New York reported a rate of 40.0%, **Grasselli et al. (25)** from Italy reported a rate of 39.0%, **Auld et al. (26)** from Atlanta reported a rate of 31.0%, and **Ferguson et al. (27)** from California reported a rate of 14.0%. The great variability in the mortality rate could be explained by different etiologies, mainly patient's characteristics, its associated comorbid conditions and resources. The absence of specific treatment and epidemic situations could also explain these variabilities. Thus, the examination of diabetes as a comorbid condition in critically ill-patients is of utmost importance and could help in future planning for proper treatment.

In the current study, diabetic patients with COVID-19, had a higher frequency of dyspnea, which is in agreement with **Shi Q, et al. (16)**. Hypertension was more frequent in diabetics and was nominated as a potential risk factor for severe COVID-19 **(28).** Previous reports suggested that, diabetes and hypertension may play a significant role in the increased rate of mortality in server COVID-19 **(29).**

Unlike the current work, **Bonyek-Silva et al. (30)** reported that, mortality rates and obesity were similar between diabetic and non-diabetic patients with COVID-19. The small number of included patients in each group in the study of Bonyek-Silva et al. (29 diabetic and 24 non-diabetic) could be the explanation for the absent differences between groups regarding the effect of obesity and mortality rate. In addition, they included all COVID-19 patients admitted to their hospital, while we confined the study to specific group of critically-ill patients. However, they confirmed the potential role of diabetes on severe COVID-19 patients and explained these effects by the proinflammatory profile induced by

diabetes on the circulating immune cells with increased expression of different inflammatory mediators and genes like (ACE2 and ALOX5 genes) rendering these cells more prone to invasion by SARS-CoV-2.

In a nationwide study from Brazil**, de Jesus Silva et al. (31),** highlighted that, obesity with diabetes mellitus and/or cardiovascular disease (CVD) were associated with significantly higher rates of invasive mechanical ventilation, and death in adults. The possible mechanism of obesity-related harmful effects in diabetic and or non-diabetic SARS-CoV-2 patients include: 1) reduced elasticity of the chest wall, reduced total compliance of respiratory system, with restriction of the diaphragmatic ventilation, leading to difficult airway management **(32)**; 2) Obesity, associated obstructive sleep apnea, that lead to dysfunction of surfactant and reduced the proper function of the airway **(33),** 3) obesity itself is a metabolic and inflammatory condition, and is associated or lead to development of other chronic medical diseases (e.g., hypertension, dyslipidemia and cardiovascular disease), with modification of the normal immune response and increased immune system vulnerability to viral infection, with reduced response to antivirals and antibiotics **(34),** 4) obese subjects are prone to poor glycemic control, that is associated with impaired overall ventilatory function **(33).**

Intestinally, **de Jesus Silva et al. (31)** found that 49.5% of the effect of diabetes mellitus on COVID-19 mortality was mediated by obesity, specifically in early-onset cases (<40 years of age).

In the line with the results of the current work, it had been reported that, diabetes has been associated with significant increase of intubation among COVID-19 **(35),** and elevated levels of glycated hemoglobin (HbA1c) had been linked with the increased risk of hypercoagulability, worse oxygen saturation and mortality **(36). Zhu L. et al. (37)** reported a significant association the intubation risk and death with poor glycemic control during hospitalization of COVID-19 with type 2 DM, specifically those with higher BMI.

Results of the current work, is in line with **Charoenngam et al. (38)** who observed that COVID-19 patients with T2D had significantly higher odds of in-hospital mortality and morbidity than patients

without T2D and in those with hyperglycemia than normoglycemic patients in non-diabetic group. patients with T2D had an approximately 5-time higher odds of mortality. **Windham et al. (39)** concluded that, in a hospitalized COVID-19 patient, poor glycemic control evidenced by higher HbA1c was associated with an increased risk of intubation or mortality within 7 days of admission.

In addition to previous factors explaining increased morbidity and mortality in COVID-19 with diabetes, it had been postulated that, patients with T2D suffer a higher degree of stress and systemic inflammation than non-diabetic patients. Acute hyperglycemia seems to have a more important role than insulin resistance in mediation of harmful effects associated with COVID-19. This was confirmed by reduced mortality rate among COVID-19 patients with tight glycemic control. Thus, insulin infusion was recommended to reduce risks of severe COVID-19 **(29).**

Furthermore, cytokine storm and inflammatory mediators, the prominent feature of COVID-19, can lead to impaired insulin singling, and instituted a vicious circle **(40).** SARS-CoV-2 can also infect the pancreatic β-cells, with subsequent β-cell dysfunction and insulin deficiency **(41,42),** which could lead to significantly increased morbidity and mortality **(43-45) .** The beneficial effect of glycemic control was also confirmed by the study of **Prattichizzo et al. (46)** who found that, the use of metformin produced pleiotropic immunomodulatory effects that lead to reduced levels of circulating cytokines.

In COVID-19, neutrophils are thought to react to infection in a different way, with the manufacture of neutrophil extracellular traps as an important viral clearance mechanism **(47).** Previous reports have also shown that higher glucose levels delay the neutrophil extracellular traps formation **(39)**.

The dysfunction of lung endothelial barrier may be associated with an increased edema and respiratory failure seen in COVID-19 **(48, 49).**

In the current work, smoking was not significantly associated with invasive mechanical ventilation or mortality; the results in accordance with previous reports **(5, 12).** However, **Williamson et al. (50)** have reported opposite conclusions

As expected, the poor diabetic control was significantly associated with increased invasive mechanical ventilation and mortality in diabetic patients. These results agree with that of **Giorda et al. (17).**

The current study had some limitations. The first is the retrospective nature of the study, with inevitable limitations of available data. The second is the small number of patients, another inevitable limitation due to national policy and included hospitals for management of COVID-19 patients. The third is the duration of the study (between April 2020 and December 2021), with changes of treatment protocol. Thus, interpretation of these results must be treated with caution, and future studies are recommended.

Conclusion: The results of the present study adds to the growing body of evidence regarding the potential harmful effects of diabetes on the morbidity and mortality of COVID-19 critically ill-patients. Several factors significantly associated with the need for mechanical ventilation and mortality in diabetic patients (e.g., hypertension, obesity, dyslipidemia, COPD/Asthma, poor diabetic control and lymphopenia). Results of the current work adds to and help clarify previous associations between diabetes in COVID-19.

Conflict of interest: None

Financial Disclosure: none

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