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Prevalence of COVID-19 associated cytokine storm in diabetic versus non diabetic patients

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Abstract

Introduction: COVID-19, a global pandemic has created a worldwide disaster since its first outbreak in December 2019 in Wuhan, China. Diabetic patients with COVID-19 have a worse prognosis and increased mortality. Cytokine storm is an aggressive inflammatory response to the SARS-CoV-2 virus and is associated with lung damage, multiple organ failure, and a bad COVID-19 prognosis.

Aim of the study: The study aimed to evaluate the levels of some cytokine storm parameters in COVID-19 infection, besides a comparison of these levels between diabetic and nondiabetic Egyptian patients.

Subjects and Methods: the current cross-sectional study recruited 80 adult individuals. All patients were divided into two groups: 42 diabetic patients with COVID-19 and 38 nondiabetic patients with COVID-19. Patients with diseases of inappropriate cytokine inflammatory load, such as autoimmune diseases or malignancies, were excluded. The medical history and clinical examination were performed. The cytokine storm inflammatory markers, such as C-reactive protein (CRP), Ferritin, Lactate dehydrogenase (LDH), D-dimer, Neutrophil-Lymphocyte Ratio (NLR), and Interleukine-6 (IL-6) were tested, in addition to the examination of the Glycemic state: HBA1C, FBS, and 2HPP. Duration of hospital admission and mode of respiratory support were recorded.

Results: The results showed that 61% of diabetic patients needed more intensive care unit (ICU) admission than 36.8% of non-diabetics ($P=0.025$). The mean serum level of IL-6 was 126.55 ± 45.65 pg/ml in diabetic patients compared to 99.58 ± 52.77 pg/ml in non-diabetic, which was statistically significant ($P=0.033$). The ROC curve analysis showed that IL-6 was a significant marker of mortality ($P<0.001$) with a cut-off level >136 pg/mL at 95.65% sensitivity and 87.72% specificity. Furthermore, HBA1C was a significant marker of mortality ($P<0.001$) with a cut-off value >7.8 % at a sensitivity of 65.22 % and specificity of 63.16 %.

Conclusion: Our study confirmed that diabetic patients had significantly earlier onset of cytokine storm, higher inflammatory response, longer hospital admission duration, higher admission rate to ICU, and more need for mechanical ventilation compared to non-diabetics.

1. Introduction

Coronaviruses were first discovered in the 1960s. The name was derived from the outer fringe or “corona” of embedded envelope

protein [1]. COVID-19 is an acute respiratory disease, which is caused by a novel coronavirus, the so-called severe acute

respiratory syndrome coronavirus-2 or SARS-CoV-2. The high spread rate of the SARS-CoV-2 caused an enormous number of deaths and made a huge negative impact on the economical and health systems [2].

SARS-CoV-2 infection symptoms ranged from asymptomatic to mild and severe symptoms. The most common symptoms include fever, cough, and shortness of breath. However, there is increasing evidence that many patients with COVID-19 are asymptomatic or have only mild symptoms, but they are able to transmit the virus to others [3].

Cytokine storm is an example of a hyperactive immune response. Cytokine is a small protein that acts as a signaling molecule between the immune system cells for conveying signals (mostly when foreign invaders attack) from one immune system cell to another. Excessive production of pro-inflammatory cytokines leads to the acute

2. Subjects and methods

2.1. Subjects

That was a single-center cross-sectional study. The study included eighty patients with COVID-19 infection from the COVID Department of Fayoum University hospital.

2.2. Inclusion criteria:

That included PCR positive COVID-19, any age, both genders, diabetic, and non-diabetic patients.

The population in the study was divided into two groups: 42 diabetic and 38 non-diabetic patients, all were diagnosed with COVID-19.

respiratory distress syndrome (ARDS) aggravation and widespread tissue damage resulting in multi-organ failure and death [4]. Targeting cytokines during the management of COVID-19 patients could improve survival rates and reduce mortality [5].

Patients with Diabetes mellitus (DM) are more susceptible to infections, including those of the respiratory tract. The chronic hyperglycemic state and chronic inflammatory state are the two pathophysiological elements of immune-suppression, which take place in diabetic patients at higher risk of COVID-19 infection [6].

Cytokine storm is severe in diabetic patients diagnosed with COVID-19, who need high ICU admission and reported higher mortality and morbidity rate [7].

2.3. Exclusion criteria

Exclusion of other diseases of inappropriate cytokine inflammatory load such as autoimmune and Auto-inflammatory diseases, such as (SLE, RA, IBD...), or malignancies.

2.4. Methods

All patients were subjected to:

Full medical history and clinical examination. Date about the onset of cytokine storm, duration of hospital admission, mode of oxygen therapy, or ventilator support were recorded.

The Biochemical Measurements included:

- Hemoglobin A1C (HbA1c) was measured using high-performance liquid chromatography (HPLC).
- Neutrophil-Lymphocyte Ratio (NLR) were measured by an auto hematology analyzer.
- C-reactive protein (CRP), Ferritin, and D-Dimer were measured using Turbilatex (Certest Biotec Inc., Spain), where the values were determined photometrically.
- Lactate dehydrogenase (LDH) was measured using LDH-LQ kit (SPINREACT Inc., Spain) by kinetic UV method.
- Interleukine-6 (IL-6) was measured by the enzyme-linked immunosorbent assay (ELISA).

2.5. Statistical Analysis

Data were collected in a standardized sheet for each subject. Collected data were rechecked for errors, coded to facilitate manipulation, computerized, and statistically analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. The Shapiro-Wilk test was used to verify the normality of distribution. Quantitative data were

described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The significance of the obtained results was judged at the 5% level. The used tests were *Chi-square* test for categorical variables, to compare between different groups, *Student t-test* for normally distributed quantitative variables, to compare between two studied groups, *Mann Whitney* test for abnormally distributed quantitative variables, to compare between two studied groups, *One-way ANOVA* test for normally distributed quantitative variables, to compare between more than two groups, and Post Hoc test (Tukey) for pairwise comparisons, *Pearson coefficient* to correlate between two normally distributed quantitative variables, *Kruskal Wallis* test for abnormally distributed quantitative variables, to compare between more than two studied groups and Post Hoc (*Dunn's* multiple comparisons test) for pairwise comparisons, and *Spearman* coefficient to correlate between two distributed abnormally quantitative variables. Receiver operating characteristic curve (ROC) was generated to plot sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at different cut off values. The area under the curve (AUC) denotes the diagnostic performance of the test.

3. Results

3.1. Demographic and clinical features

A total 80 patient were included (mean age, 60.81 ± 10.76 years; 52.5% male), of whom

42 patients were diabetics (mean age, 58.11 ± 11.29 ; 52.4 % male) and 38 patients were non-diabetics (mean age, 63.26 ± 9.76 years; 52.6% male) (**Table 1**).

Table 1: Demographic data of diabetic and non-diabetic groups.

		Diabetic patients (n=42)	Non-diabetic patients (n=38)	Total (n=80)	<i>P-value</i>
Sex	Male	22 (52.4%)	20 (52.6%)	42 (52.5%)	0.982
	Female	20 (47.6%)	18 (47.4%)	38 (47.5%)	
Age (years)	Min.-Max.	35.0 – 80.0	37.0 – 85.0	35.0 – 85.0	0.031*
	Mean± SD	58.11 ± 11.29	63.26 ± 9.76	60.81 ± 10.76	

n: number. Values are presented as mean ± SD, * statistically significant.

The onset of cytokine storm was recorded (**Table 2**). The mean time for cytokine storm onset was 9.05 ± 1.59 and 10.55 ± 2.11 days in diabetic and non-diabetic patients, respectively. That was significantly earlier in diabetics ($P=0.001$).

In the course of hospital admission, 40 (50 %) patients needed ICU. That included 26 (61.9%), diabetic patients, compared to 14 (36.8%) non-diabetic patients with a significantly higher ICU admission rate in diabetic patients ($P=0.025$).

Regarding respiratory support, 61.9% of diabetic patients needed mechanical ventilation compared to 36.8 % of non-diabetic patients. That difference was statistically significant ($P=0.025$).

The mean length of hospitalization was 13.60 ± 6.12 days in diabetic patients compared to 7.0 ± 2.22 days in non-diabetic patients ($P<0.001$). The mortality rate was 28.8% (n=23). Mortality was higher in diabetic patients (n=15, 35.7%) than in non-diabetic (n=8, 21.1%).

Table 2: Comparison between diabetic and non-diabetic patients regarding hospital course.

		Diabetics (n=42)	Non-diabetics (n=38)	Total (n=80)	<i>P-value</i>
Onset (days)		9.05 ± 1.59	10.55 ± 2.11	9.76 ± 2.0	0.001*
Admission duration (days)		13.60 ± 6.12	7.0 ± 2.22	10.46 ± 5.72	<0.001
ICU admitted	Yes	26 (61.9%)	14 (36.8%)	40 (50%)	0.025*
	No	16 (38.1%)	24 (63.2%)	40 (50%)	
Intermediate ICU	Yes	16 (38.1%)	24 (63.2%)	40 (50%)	0.042*
	No	26 (61.9%)	14 (36.8%)	40 (50%)	
Mechanical ventilation		26 (61.9%)	14 (36.8%)	40 (50%)	0.025*
Mortality	Yes	15 (35.7%)	8 (21.1%)	23 (71.3%)	0.148

No	27 (64.3%)	30 (78.9%)	57 (28.8%)
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n: number. Values are presented as mean ± SD, * statistically significant.

It was found that the mean value of IL-6 was significantly higher in diabetic patients (126.55 ± 45.65 pg/ml), while it was 99.58 ± 52.77 pg/ml in non-diabetics ($P=0.033$). The mean serum Ferritin level was 1348.60 ± 295.42 ng/ml in diabetics, while it was 1059.26 ± 220.99 ng/ml in non-diabetics ($P<0.001$). Furthermore, mean LDH was 642.43 ± 166.51 U/L in diabetic, while was 623.55 ± 146.46 U/L in non-diabetic with no significant difference

between diabetic group and non-diabetic group ($P=0.594$). The median neutrophil: lymphocyte ratio was 16.70 (IQR 10.90 – 23.70) in diabetic while was 13.80 (IQR 8.0 – 19.50) in non-diabetic with no significant difference between diabetic group and non-diabetic group ($P=0.101$), median CRP was 96.0 mg/L (IQR 48.0 – 96.0 mg/L) in diabetic while was 48.0 mg/L (IQR 48.0 – 96.0 mg/L) in non-diabetic with no significant ($P=0.088$) (Table 3).

Table 3: Parameters of cytokine storm of both diabetic and non-diabetic patients.

	Diabetic patients (n=42)	Non-diabetic patients (n=38)	Total (n=80)	<i>P-value</i>
NLR	16.70 (10.90 – 23.70)	13.80 (8.0 – 19.50)	15.15 (9.03 – 23.05)	0.101
IL-6 level (pg/ml)	126.55± 45.65	99.58± 52.77	113.74± 50.69	0.033*
Ferritin (ng/ml)	1348.6± 295.42	1059.26± 220.99	1211.16± 298.84	<0.001*
CRP (mg/L)	96.0 (48.0 – 96.0)	48.0 (48.0 – 96.0)	64.0 (48.0 – 96.0)	0.088
LDH (ng/ml)	642.43± 166.51	623.55± 146.46	633.46± 156.61	0.594

In the ROC analysis, HBA1C was identified as a significant marker of COVID-19 mortality ($P<0.001$). The cut-off (>7.8%) for HBA1C showed the best combination of sensitivity and specificity. In all patients,

baseline HBA1C >7.8% predicted mortality with a sensitivity of 65.22% and specificity of 63.16%. The positive predictive value (PPV) was 41.7%, and the negative predictive value (NPV) of 81.8% (Figure 1, Table 4).

Table 4: Validity (AUC, sensitivity, specificity) for HBA1C as a predictor of COVID-19 mortality.

	AUC	<i>P-value</i>	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
HBA1C	0.753	<0.001*	0.609–0.897	>7.8	65.22	63.16	41.7	81.8

C.I.: Confidence of intervals.

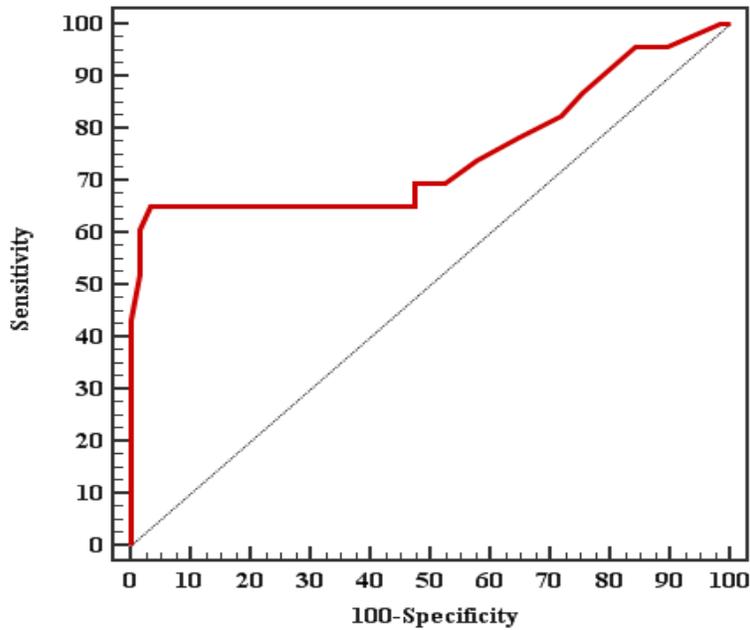


Figure 1: ROC curve for HBA1C as a predictor of mortality.

In the ROC analysis, IL-6 was identified as a significant marker of mortality ($P < 0.001$), and the cut-off of >136 pg/mL for IL-6 showed the best combination of sensitivity and specificity. In all patients,

baseline IL-6 concentration >136 pg/mL predicted mortality with a sensitivity of 95.65% and specificity of 87.72%. PPV was 75.9%, where NPV was 98.0% (**Figure 2, Table 5**).

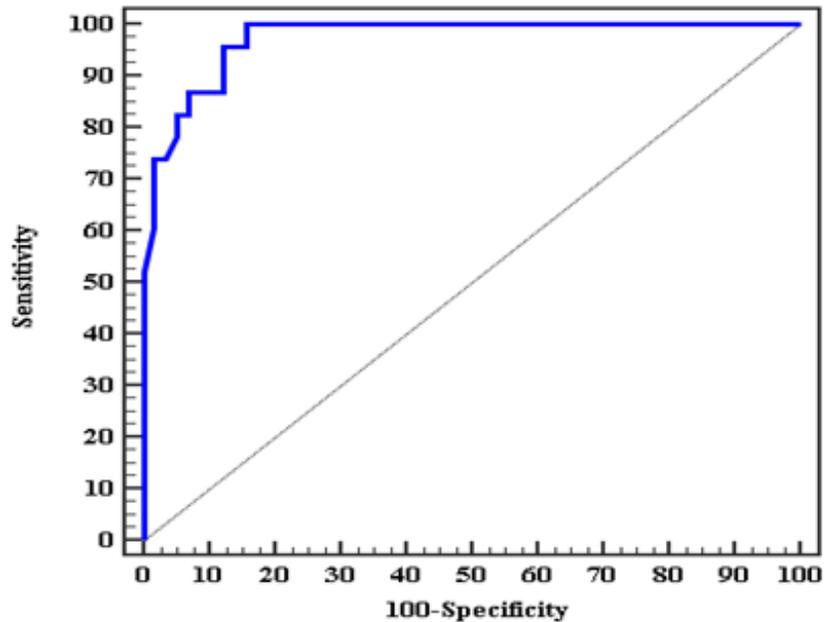


Figure 2: ROC curve for IL-6 as a predictor of mortality.**Table 5:** Validity (AUC, sensitivity, specificity) for HBA1C as a predictor of COVID-19 mortality.

	AUC	P-value	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
IL-6	0.972	<0.001*	0.943 – 1.001	>136	95.65	87.72	75.9	98.0

C.I.: Confidence of intervals.

4. Discussion

The current study included 80 patients with positive COVID-19 test (mean age, 60.81, 52.5% male), of whom 42 patients were diabetics (mean age, 58.11, 52.4 % male) and 38 patients were non-diabetics (mean age, 63.26, 52.6% male).

In the current study, most patients were diagnosed with severe and critical COVID-19 pneumonia. That contradicted the studies that reported that the expected severity pattern of most COVID-19 patients was mild or moderate, while a minority of patients had severe-critical disease [8]. That might be explained as the current study was hospital-based rather than community-based, where the inclusion criteria included only patients with severe infections. These findings were close to a previous study of 663 hospitalized COVID-19 patients, admitted to a university hospital in Wuhan city, where 60% of them had severe-critical disease [9].

The current study on symptomatic patients with COVID-19 confirmed that diabetic patients had significantly earlier onset of cytokine storm, longer hospital admission duration, and higher admission rate to ICU. That required more mechanical ventilation compared to non-diabetic

patients. Furthermore, diabetic patients had a higher mortality rate than non-diabetic patients but were insignificant. These findings correlated with the hypothesis that diabetic patients are more susceptible to infections in general and exhibit a worse prognosis once infected compared to non-diabetics [10]. That came in harmony with other studies that found diabetes was associated with adverse outcomes, high ICU admissions, elevated rates of ventilation, and increased mortality in COVID-19 patients [8]. A previous study reported a longer median length of stay in COVID-19 infections in diabetic patients compared to non-diabetic [10]. In contrast, other small studies did not find a clear association between diabetes and disease severity and mortality among COVID-19 patients. For instance, Zhang *et al.* (2020) showed that DM was not associated with disease severity in COVID-19 patients [12]. Similarly, another study did not report any association between DM and COVID-19 deaths in 274 hospitalized patients [13]. Moreover, in another prospective study, DM was not associated with a higher mortality rate [14].

Regarding the comparison between inflammatory responses in diabetic and non-

diabetic patients, the current results revealed that diabetic patients had higher inflammatory responses than non-diabetic patients. That was expressed by significantly the high IL-6 and Ferritin levels in diabetic patients. The mean IL-6 was 126.55 ± 45.65 pg/ml in diabetics, while it was 99.58 ± 52.77 pg/ml in non-diabetics ($P=0.033$). The mean Ferritin level was 1348.60 ± 295.42 ng/ml and 1059.26 ± 220.99 ng/ml in diabetic and non-diabetic patients, respectively ($P<0.001$). However, NLR, CRP, LDH, and D-Dimer levels were higher in diabetic than non-diabetic patients, the results were insignificant.

These findings correlated with Yan *et al.* (2020), who confirmed that the immune, inflammatory, and coagulation abnormalities of COVID-19 patients were more significantly pronounced in diabetic than non-diabetic individuals, independently of other comorbidities [15]. Also, Guo *et al.* (2020) recorded that the diabetic patients diagnosed with COVID-19 had more IL-6 and CRP than non-diabetics [16]. Furthermore, Yujun *et al.* (2020) revealed that the serum levels of some inflammation-related biomarkers, such as IL-6, serum Ferritin, and CRP, were much higher in diabetic than non-diabetic patients [17].

Several laboratory parameters might facilitate the assessment of disease severity. Clinicians should consider abnormalities in the levels of NLR, CRP, D-dimer, Ferritin, and IL-6 in risk stratification to predict severe and fatal COVID-19 in hospitalized patients. It is more likely that the course of the disease was unfavorable if some or all of these parameters were altered. Furthermore,

the Identification of laboratory biomarkers associated with COVID-19 shed light on the pathological mechanisms of the disease. Increased cytokine loads inflammatory markers, such as CRP, LDH, Ferritin, IL6, D-dimer, and NLR indicated the poor prognosis of patients at the early stages of the disease [18].

Laboratory tests of glycemic assessment were significantly higher in non-survivors' diabetic patients' than in survivors' diabetic patients. Mean HBA1C was $11.21 \pm 0.82\%$ in non-survivors' diabetic patients, while it was $8.74 \pm 0.85\%$ in survivors' diabetic patients ($P<0.001$). The ROC curve analysis revealed that HBA1C was identified as a significant marker of mortality in diabetic patients ($P<0.001$), the cut-off of $>10\%$ for HBA1C predicted mortality with a sensitivity of 93.33% and specificity of 96.30%. The reason for the increased severity of COVID-19 infections in DM was unclear. Poor glycemic control impairs several aspects of the innate and adaptive immune response to viral infections, besides potentiating the secondary bacterial infection in the lungs is one of the reasons for increased severity [19]. Moreover, the study conducted by Wu *et al.* (2020) found that uncontrolled blood glucose level was an independent risk factor for the progression to critical cases or death in hospitalized COVID-19 patients [8]. A descriptive study by Bode *et al.* (2020) suggested that uncontrolled hyperglycemia was associated with an increased length of hospitalization and higher mortality due to COVID-19 [11]. In contrast, Zhu *et al.* (2020) found that a well-controlled blood glucose level was associated with lower

mortality than a poorly controlled blood glucose level in patients with COVID-19

5. Conclusion

The current study confirmed that diabetic patients had significantly earlier onset of cytokine storm, higher inflammatory response, longer hospital admission duration, higher admission rate to ICU, and more mechanical ventilation than non-diabetic patients. Furthermore, diabetic patients had a higher mortality rate than non-diabetic patients. Furthermore, the findings indicated that IL-6 and HbA1c were good predictors of COVID-19 severity and prognosis in diabetic patients.

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and those with pre-existing diabetes [20].

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