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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Research Article

Diabetes as a Risk Factor in Patients with Covid-19 in Tishreen University Hospital - Lattakia-Syria

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Received: August 12, 2023; **Published:** September 26, 2023

Abstract

Background: SARS-CoV-2 infection (Severe acute respiratory syndrome coronavirus2) has created a major and complex problem in health care worldwide since December 2019. Studies have shown that diabetes is associated with an increase in the risk and severity of COVID-19 disease, as it was found that high blood sugar reduces immunity and increases the rate of the virus replication.

On the other hand, some studies have concluded that the SARS-CoV-2 virus may attack pancreatic beta cells, causing a new occurrence of diabetes. Research is still being conducted in this field.

Objective: Studying the impact of diabetes on the course and prognosis of covid-19. And comparing the newly diagnosed diabetes (on admission) with the prior-to-admission diabetes on the prognosis of covid-19.

Materials and Methods: This retrospective analytical study was conducted on patients diagnosed with positive RT-PCR-SARS-COV-2 at Tishreen University Hospital in Lattakia between December 2021-June 2022, where we distributed the patients into diabetic and non-diabetic patients. We compared the need for ventilation and the mortality rate between the two groups.

Statistically significant variables were applied to the multivariate equation for variables and diabetes was determined as a risk factor. Diabetic patients were distributed into two groups, diabetes detected on admission, glucose > 126 mg/dl, and previously known diabetes (prior to admission). Then a comparison was conducted between them on the course and prognosis of covid-19.

Results: The research sample included 197 patients, their ages ranged from 34 to 70, mean age and SD 63.23 ± 14.2 years. 58.4% were males, 36% were diabetics (15.2% diabetes on admission, 20.8% previously known diabetes).

The need for invasive mechanical ventilation (IMV) (32.4% VS 11.1% p = 0.0001) and non-invasive (non-IMV) (39.4% VS 16.7% p = 0.0001) was higher among diabetics compared to non-diabetics. Mortality was also higher (71.8% VS 38.9% p = 0.0001).

Diabetes was associated with an increased rate of death (OR 3.8, 95% CI: 1.1 - 7.3), an increased rate of the need for invasive ventilation (OR 3.3, 95% CI: 1.5 - 9.9) and an increased rate of the need for non-invasive ventilation (OR 2.8, CI: 95% CI: 1.3 - 11.6). We also found that high blood sugar values during hospitalization were associated with an increased mortality (271.88 ± 98.04) VS (117.67 ± 56.5) p = 0.0001.

Comparing the patients with newly discovered diabetes (on admission) to patients with previously known diabetes, we found that the percentage of those who needed invasive ventilation was 46.7% VS 22% p = 0.02, and the death rate was 80% VS 65.9% p = 0.04 which is higher in patients with newly discovered diabetes compared to patients with previously known diabetes.

Conclusion: This study concluded the importance of monitoring and controlling blood sugar levels in diabetic patients due to the association of diabetes with a poor prognosis for COVID-19 in terms of the need for invasive ventilation, the need for non-invasive ventilation and mortality.

Keywords: *COVID-19; SARS-CoV-2; Diabetes; Risk Factor*

Introduction

The global number of diabetes in 2019 was about 463 million, and mortality in the same year was about 1.6 million. With its increasing prevalence in low- and middle-income countries, diabetes is one of the leading causes of death and one of the largest global health and financial burdens [1]. The incidence of diabetes in Syria in 2021 was about 14.9% of the population [2].

Covid-19 is a highly contagious and widespread infectious septic disease caused by a new strain of coronavirus (coronaviridae) associated with the severe acute respiratory syndrome SARS-CoV-2 - first discovered in Wuhan, China on December 2019, and then spread to more than 200 countries. On March 11, 2020, the World Health Organization (WHO) declared the covid-19 pandemic. Until August 2, 2023, (768,983,095) confirmed cases of COVID-19 have been reported globally, according to the official website of the World Health Organization, including (6,953,743) deaths. The death rate from COVID-19 has been estimated at approximately 1.1% as of 2 August 2023, (57,423) confirmed cases and (3,163) deaths have been reported in the Syrian Arab Republic [3].

Patients at high risk of severe COVID-19 infection or death include the elderly, males, and those who suffered from any previous health conditions such as: cardiovascular disease (CVD), obesity and/or type 1 diabetes mellitus (T1DM) or type 2 (T2DM) [4]. Diabetes is a metabolic chronic inflammatory disease that causes several metabolic and vascular disorders that in turn affect the immune response to diseases. High blood sugar and insulin resistance increase the Advanced Glycation End Products (AGES), as well as the inflammatory cytokines and oxidative stress in addition to stimulating the production of adhesion factors and inhibition of lymphocyte response to various factors and causes disruption of the function of neutropenic and macrophages. This inflammatory activity makes the organism more prone to infections with a poor prognosis in these diabetic patients [5].

In addition to the above, uncontrolled diabetes causes an imbalance in the coagulation and fibrinolysis processes with an increase in clotting factors, relative inhibition of the fibrinolytic mechanism as well as damaging the endothelium and increasing the platelet pheresis leading to vascular thrombosis [5] as a result: Diabetes leads to a difficulty controlling SARS-COV-2 replication and amplification of the inflammatory activity leading to a reduction in the survival rate [5].

Recent studies have shown that SARS-CoV-2 has negative effects on the functioning of pancreatic beta cells through the process of replication and binding with ACE2 receptors on their surface, which may lead to: ketoacidosis in diabetic patients, hyperglycemia in patients admitted to the hospital with unknown previous diabetes, or with newly known diabetes (on admission) [5].

Diabetes is one of the most important diseases that increase the risk of COVID-19 in terms of hospitalization, admission to the intensive care unit (ICU), the need for mechanical ventilation, and severely worsens prognosis. Therefore, it is essential to shed light on a deeper understanding of the mutual interrelation between the two diseases' mechanisms and to emphasize the importance of effective management and good control of blood glucose levels.

This research is the first in Syria in terms of studying the interrelationship between Covid-19, diabetes, and studying newly discovered diabetes after being infected with SARS-CoV-2 in terms of prognosis.

Materials and Methods

Materials: Analytic cohort study (Retrospective): This study was conducted in the COVID-isolation department of Tishreen University Hospital in Lattakia Governorate - Syrian Arab Republic. Study data was collected between December 2021-June 2022. This study was applied to a sample of 197 patients with COVID-19 infection, diagnosed with a positive swab based on the RT-PCR-SARS-COV-2 test. Their age ranged between 34 - 70 years. Patients were distributed and followed up as follows: To study the effect of diabetes on the course and prognosis of covid-19. Patients were distributed into two groups: non-diabetic patients and diabetic patients. All variables

(the need for mechanical ventilation invasive and non-invasive, and the outcome) were studied and compared between the two groups. In addition, diabetic patients were distributed into two groups: diabetes detected upon admission and previously known diabetes. Then a comparison has been made between them in terms of the course and prognosis of covid-19. Inclusion criteria: Patients with positive throat swab based on the RT-PCR-SARS-COV-2 test whom were admitted in the COVID-isolation department and followed up to discharge or death in the hospital. Exclusion criteria: Negative RT-PCR-SARS-COV-2 test, oncological patients and a lack of data for some patients.

Tools: We developed a form to collect study data after reviewing the relevant references that included the following variables: personal information, comorbid chronic diseases, clinical symptoms, diabetes: Diagnosed diabetes was defined according to the WHO diagnostic criteria of fasting plasma glucose ≥ 126 ml/dl (≥ 7.0 mmol/l), the need for non-invasive ventilation - the need for invasive ventilation, the course of the disease: survival-death.

Statistical studies

Descriptive statistics: Frequency and percentages for the qualitative variables, measures of central tendency and measures of dispersion for the quantitative variables.

Inferential statistics: All variables were tested according to univariate regression, where the independent T Student was used to study the differences of the averages between two independent groups and the chi-square test or (Fisher Exact) to study the relationship between the qualitative variables. Then, the variables with a statistical value were applied to the logistic regression equation and the odds ratio (OR) a) was determined. To study the risk associated with hyperglycemia on prognosis within the hospital, the results were considered statistically significant with a p-value < 5%.

The program adopted IBM SPSS statistics (version28) to calculate the statistical coefficients and analyze the results.

Results of the Study

General and demographic characteristics of the patients observed in this research: The research sample included 197 patients who had a positive swab for Covid-19. They were admitted to the isolation department at Tishreen University Hospital in Lattakia during the time period December 2021 - June 2022, who fulfilled the inclusion criteria in the research.

The age of the research sample patients ranged from 34 to 70 years, with an average of 63.23 ± 14.2 years.

Sex	Males		115	58.4%
	Females		82	41.6%
	Total		197	100%
Smoking	Smoker		92	46.7%
	Non-Smoker		105	53.3%
	Total		197	100%
Accompanying Diseases	Arterial hypertension		96	48.7%
	Cardiovascular disease		40	20.3%
	Chronic lung disease	Copd	24	12.2%
		Asthma	9	4.6%
	Chronic kidney disease		21	10.7%
	Neurovascular disease		15	7.6%
	Chronic anemia		14	7.1%

Clinical Symptoms	Dyspnea	150	76.1%
	Cough	147	74.6%
	Fever	114	57.7%
	General asthenia	95	48.2%
	Anorexia	47	23.9%
	Nausea or vomiting	34	17.3%
	Headache	13	6.6%
	abdominal pain	11	5.6%
	diarrhea	10	5.1%
Diabetes	Diabetics	71	36%
	Non-Diabetics	126	64%
	Total	197	100%

Table 1: *Distribution of the sample of patients according to sex, smoking, accompanying diseases, clinical symptoms and the presence of diabetes mellitus.*

		Diabetics	Non-Diabetics	P-value
Invasive Mechanical Ventilation	Needed	23 (32.4%)	14 (11.1%)	0.0001
	Not Needed	48 (67.6%)	112 (88.9%)	
Non-invasive mechanical ventilation	Needed	28 (39.4%)	21 (16.7%)	0.0001
	Not Needed	43 (60.6%)	105 (83.3%)	
The Research Sample	Death	51 (71.8%)	49 (38.9%)	0.0001
	Healing	20 (28.2%)	77 (61.1%)	

Table 2: *The need for invasive and non-invasive mechanical ventilation and mortality for the two research groups.*

Table 2 shows that there are statistically significant differences between the two research groups regarding the need for invasive, non-invasive mechanical ventilation and mortality which were higher in the diabetic group, compared to the non-diabetic group.

Variants	OR a [CI95%]	p-value
Death	3.8 [1.1 - 7.3]	0.0001
The need for invasive mechanical ventilation	3.3 [1.5 - 9.9]	0.002
The need for non-invasive mechanical ventilation	2.8 [1.3 - 11.6]	0.0001

Table 3: *Multivariate analysis of hyperglycemia in COVID-19 patients.*

After applying the statistically significant variables to the multivariate analysis equation, we found that hyperglycemia is a risk factor for death, and that we needed to use much more the invasive mechanical ventilation, as well as the non-invasive mechanical ventilation.

	Death	Survival	P-value
Blood sugar during hospitalization	271.88 ± 98.04	117.67 ± 56.5	0.0001

Table 4: *The effect of blood sugar during hospitalization on the final prognosis in patients with Covid -19.*

The table below shows that there are statistically significant differences between the two research groups regarding the average values of blood sugar during hospitalization according to the final prognosis. The blood sugar values were higher in the death group.

Final Prognosis	Diabetes Discovered on Admission (30) 15.2%	Diabetes Known Prior to Admission (41) 20.8%	P-value
The Need for Nasal Cannulas	6 (20%)	9 (22%)	0.8
Non-Invasive Mechanical Ventilation	10 (33.3%)	18 (43.9%)	0.3
Invasive Mechanical Ventilation	14 (46.7%)	9 (22%)	0.02
Death	24 (80%)	27 (65.9%)	0.04

Table 5: *Final prognosis for previously known diabetic patients with COVID-19 and newly discovered diabetic patients.*

Table 5 shows that there are statistically significant differences between the two groups of diabetic patients regarding the invasive mechanical ventilation and death, which was higher in diabetic patients detected on admission.

Discussion

This retrospective study was conducted on 197 patients with a confirmed diagnosis of SARS-CoV-2 by RT-PCR. Patients were randomly selected. The course and prognosis of the disease were determined in relation to diabetes mellitus as a risk factor. The patients were distributed into two groups, diabetic and non-diabetic, and the results were as follows: The percentage of diabetic patients was 36% (71), and non-diabetics 64% (126). The need for invasive and non-invasive ventilation were both higher in diabetic patients compared to non-diabetics, p value = 0.0001. This result is in accordance with Iranian study in terms of non-invasive ventilation (35.8% VS 6.3% $p < 0.001$) and invasive ventilation (10.8% VS 2.7% $p < 0.001$) [6].

And more, our study showed that the death rate for diabetics was higher, and thus the prognosis for covid-19 was worse for them than for non-diabetic patients (71.8% VS 38.9% p = 0.0001). This result is in accordance with the Chinese study (20.2% VS 8.0% p = 0.001) [7] and the Iranian study 17.8% VS 8.7% p = 0.003) [6].

Statistically significant variables were applied to the multivariate analysis equation. We found that high blood sugar is a risk factor for death and that it raises the need of invasive and non-invasive ventilation, 3.8 [1.1 - 7.3], 3.3 [1.5 - 9.9], 2.8 [1.3 - 11.6], respectively. Diabetic patients have a higher risk of developing severe infection with covid-19 due to: The effect of diabetes on immunity and inflammatory activity, which weakens the organism towards infection resistance, in addition to diseases associated with diabetes, such as cardiovascular disease and kidney damage, which increase the severity of the disease. Therefore, these patients are more likely to be admitted to hospitals, intensive care units, and mechanical ventilation, and also more likely to develop complications such as acute kidney damage and secondary infections, and thus a higher death rate.

Previous studies have shown that diabetes is a risk factor for pathogenicity and death in many viral infections such as influenza A 2009 (H1N1), SARS-COV, MERS-COV [8-11].

To investigate more about the effect of high blood sugar on the Covid-19 prognosis, we divided the group of diabetic patients according to the data we obtained into two groups: previously known diabetes and diabetes detected on admission (fasting blood glucose ≥ 126 ml/dl). They were compared in terms of: The need for invasive and non-invasive mechanical ventilation and prognosis: As a result, we found that there were statistically significant differences between the two groups in terms of the need for invasive mechanical ventilation - (46.7% VS 22% p = 0.02) and death (80% VS 65% p = 0.04).

Where it was higher in patients with diabetes detected on admission compared to previously known diabetics. We must note that diabetes detected on admission may be related to Covid-19 or undiagnosed diabetes, therefore untreated, which gives a worse prognosis.

This result was consistent with the Chinese study (Huiqingli., *et al*.), for the need for invasive ventilation (11.7% VS 9.2% VS 2.3% p = 0.018) and death (21.3% VS 11.2 VS 1.5% p < 0.001) [12].

The American study (Sara J. Cromer., *et al*.) [13] found statistical differences between the two groups of newly discovered diabetes and pre-diagnosed diabetes in terms of admission to intensive care (72.73% VS 36.17% p < 0.01), while no significant differences were found in terms of prognosis and death (15.58% VS 19.34% p = 0.53).

The relationship between diabetes and COVID-19 is bidirectional: On the one hand, the association of diabetes with an increased risk of severe infection with COVID-19, and on the other hand, the occurrence of new-onset diabetes and severe associated metabolic complications such as ketoacidosis and hyperosmolar state in patients with COVID-19.

One of the possible mechanisms for the occurrence of the newly discovered diabetes in patients with COVID-19 is the attachment of the SARS-CoV-2 virus to the angiotensin-converting enzyme (ACE2) receptors present in the basic metabolic organs and tissues such as pancreatic beta cells, adipose tissue, the small intestine and the kidney, which leads to many changes in glucose metabolism. Newly discovered diabetes is associated with a higher risk of mortality, as compared to chronic diabetes:

- The severity of high blood sugar and the difficulty controlling its levels in patients with newly discovered diabetes, which leads to a greater risk of complications such as ketoacidosis (DKA) and acute respiratory distress syndrome (ARDS).
- The delay of the diagnosis of the newly discovered diabetes, thus the treatment was delayed. While patients with chronic diabetes were receiving appropriate treatment and their sugar levels were controlled.
- One of the mechanisms of infection with diabetes in COVID-19 patients is the damage the virus causes to beta cells, and this activity has acute and severe effects on the organism compared to the mechanism of chronic diabetes that occurs over a longer period of time [4,14-16].

To study the effect of the blood sugar level during hospitalization on the Covid-19 prognosis, the highest blood sugar value was recorded for patients during hospitalization and the statistical significance was determined in terms of prognosis. As a result, the average blood glucose values were higher in the death group (271.88 ± 98.04 VS 117.67 ± 56.5 p = 0.0001) compared to the US reference study Sanjana Rao., *et al*.

Where it reached the same result and the same statistical significance between the two prognosis groups (297.2 ± 108.6 VS 204.2 ± 112.5 p = 0.006) [17].

The most important determinants of the study were the lack of glycosylated hemoglobin (HbA1c) for most patients that prevented us from knowing their diabetes control level, the inability to accurately determine whether the diabetes newly discovered diabetic patients (when hospitalized with Covid-19) compared to pre-diagnosed diabetic patients. The high blood sugar level during hospitalization was associated with a high death rate in covid-19 patients.

Diagnosed on admission was previously undiagnosed diabetes or diabetes caused by infection with the SARS-CoV-2 virus.

Conclusion

Death rate was higher in diabetic covid-19 patients compared to non-diabetic patients, and their need for invasive and non-invasive mechanical ventilation was higher. The need for invasive ventilation and the death rate were higher in newly discovered diabetic patients

(when hospitalized with Covid-19) compared to pre-diagnosed diabetic patients. The high blood sugar level during hospitalization was associated with a high death rate in covid-19 patients.

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Volume 12 Issue 9 September 2023