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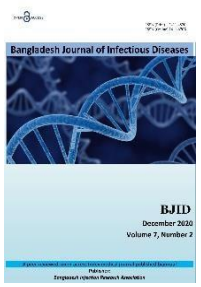

Serum Interleukin-6 (IL-6) Level and Glycemic Control of Covid-19 Exposed Diabetic Patients in a Selected District Diabetic Hospital of Bangladesh

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Abstract

Background: The COVID-19 pandemic worsened diabetes management, increasing the risk of complications like DKA and HHS, requiring close blood glucose monitoring. **Objective:** The objective of this study was to examine the relationship between serum IL-6 levels and glycemic control in COVID-19-exposed diabetic patients in Bangladesh. **Methodology:** This cross-sectional study was conducted at Ahad Diabetic Health Complex, Jessore, from October 2022 to May 2023, involving 85 diabetic patients aged 18 and above, exposed to COVID-19. Data on socio-demographics, glycemic status, and COVID-19 exposure were collected using a semi-structured questionnaire. Blood samples were taken for serum interleukin 6 (IL-6) analysis. The study followed ethical guidelines, with approval from relevant ethical review committees, and used SPSS for statistical analysis. **Results:** Among the respondent's majority were middle and elderly age group people with mean 8.0741±11.45401years with almost equal male female ratio. By nutritional status 48.2% were of Normal weight, followed by 43.5% were Pre obese, and 4.7% were obesed. Among the respondents 52.9% cases had family history of diabetes, 41.2% caseshad COVID symptoms but only 17.6% were COVID-19 positive with having COVID symptoms. Among the respondents, 60.0% were suffering from diabetes for 1 to 5 years, 28.2% for 6 to 10 years, 7.1% for 11 to 15 years and only 4.7% were suffering for 13 – 20 years. The mean Serum IL-6 was 5.66±2.245 among the respondents having COVID-19 positive while it was more 7.10±6.137 among the rests. Mean blood glucose level was 14.7933±7.45381 mmol/L who were COVID-19 positive and 12.9876±5.69122 mmol/L among rests. **Conclusion:** The study found a significant association between serum IL-6 levels and age, suggesting that age may influence inflammation in COVID-19-exposed diabetic patients. [*Bangladesh Journal of Infectious Diseases, December 2024;11(2):131-137*]

Keywords: COVID-19; interleukin 6; type-2 DM; cytokine; TNF-alpha

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Introduction

The COVID-19 pandemic has had a profound impact on global health, with millions of individuals affected by the viral infection. Among the vulnerable populations, diabetic patients face a higher risk of severe illness and complications when exposed to the SARS-CoV-2 virus. Bangladesh, like many other countries, has witnessed a significant number of COVID-19 cases, raising concerns about the management and outcomes of diabetic patients during this pandemic. The concept of coronavirus disease 2019 (COVID-19)-related cytokine storm syndrome (COVID-CSS) emerged early in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic to explain why some patients exposed to this virus become critically ill with acute respiratory distress syndrome, multi-organ failure, and death[1]. Interleukin 6 (IL-6) is one of the key cytokines after activated macrophages. Control of systemic Interleukin 6 (IL-6) levels in SARS-CoV-2 infected patients now-a day is a parameter for COVID-19 disease[2]. The majority of COVID-19 patients ultimately recover, however according to the most recent research, 10% to 20% of patients may continue to have mid- or long-term consequences after their original sickness has passed[3]. Post COVID-19 condition, also referred to as "long COVID," is the collective name for these short- and long-term effects. It's vital to keep in mind that, like COVID-19, post-COVID-19 condition is still developing. In order to better understand the cause, symptoms, and impact of post-COVID-19 conditions, researchers are collaborating with patients who have developed these conditions[4].

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose levels. It is known to impair the immune system and increase the susceptibility to infections. COVID-19, caused by the novel coronavirus SARS-CoV-2, primarily affects the respiratory system but can also lead to systemic inflammation and immune dysregulation. IL-6, a pro-inflammatory cytokine, plays a crucial role in the immune response and has been linked to the severity of COVID-19 infections. Diabetic patients may be more susceptible to severe illness and complications if they contract COVID-19. Diabetic individuals, particularly those with poorly controlled blood sugar levels or underlying diabetes-related complications, are more likely to experience severe COVID-19 symptoms and complications compared to non-diabetic individuals. This includes an increased risk of hospitalization, intensive care unit (ICU) admission, the need for mechanical ventilation, and higher mortality rates. Diabetes can weaken the immune system, making it more difficult for the body to fight off infections, including viral infections like COVID-19. This can lead to a prolonged and more severe illness. Diabetic patients often have other related health complications, such as cardiovascular disease, kidney disease, or obesity, which can further increase the risk of severe COVID-19 outcomes. These comorbidities can worsen the impact of the infection and require careful management. The aim of the study to understanding the relationship between serum Interleukin 6 (IL-6) levels and glycemic control in COVID-19-exposed diabetic patients in Bangladesh is of paramount importance for optimizing their care and improving health outcomes.

The interleukin-6 (IL-6) is a cytokine that plays a crucial role in the regulation of the immune response and inflammation. It is produced by various cells, including immune cells and adipose tissue. IL-6 has been implicated in several physiological and pathological processes, including glycemic control. Elevated levels of IL-6 have been associated with insulin resistance and impaired glycemic control in conditions such as obesity, type 2 diabetes, and metabolic syndrome. IL-6 can interfere with insulin signaling and promote insulin resistance, leading to elevated blood glucose levels. Additionally, IL-6 can stimulate the production of acute-phase reactants, such as C-reactive protein (CRP), which are markers of inflammation.

Chronic low-grade inflammation, characterized by increased IL-6 levels, can contribute to the development of insulin resistance and impair glycemic control. On the other hand, glycemic control can also influence IL-6 levels. Poor glycemic control, characterized by high blood glucose levels over an extended period, can promote inflammation and increase IL-6 production[3]. It's important to note that IL-6 is just one of several cytokines and inflammatory markers involved in the regulation of glycemic control. Other cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1β), also contribute to the complex interplay between inflammation and glucose metabolism[5].

“Cytokine storm” is a catch-all term that has used to describe a range of dysregulated immune reactions with a variety of instigating events ranging from sepsis to stem cell transplant[5]. Interleukin-6 levels $\geq$80 pg·mL^{-1} predict an increased risk of respiratory failure and death[6], and immunomodulatory therapy is an area of urgent investigation. Interleukin (IL)-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by SARS-

CoV-2 induces a dose-dependent production of IL-6 from bronchial epithelial cells[7]. COVID-19-associated systemic inflammation and hypoxemic respiratory failure can be associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin[2-4,8-10]. In some cases of severe COVID-19, a dangerous immune response known as a cytokine storm can occur. Immune response in COVID-19: When the SARS-CoV-2 virus infects the body, the immune system is activated to fight the infection. Immune cells release cytokines as part of the normal immune response to help eliminate the virus. In severe cases of COVID-19, the immune system overreacts and releases large amounts of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-alpha), and others. This excessive cytokine release can lead to widespread inflammation and tissue damage throughout the body.

Cytokine storms can contribute to the development of acute respiratory distress syndrome (ARDS), a severe lung condition characterized by widespread inflammation and fluid accumulation in the lungs[6]. Cytokine storms can also affect other organs, leading to multi-organ dysfunction and failure. Older age, pre-existing health conditions (such as diabetes, cardiovascular disease, or obesity), and a weakened immune system are potential risk factors for developing a cytokine storm[11].

Methodology

Study Settings and Population: The study was a cross-sectional study. The study place was Ahad Diabetic Health Complex, Jhumjhumpur, Jessore. The study was conducted during the period of October 2022 to May 2023. The study population was all the Covid-19 exposed diabetic patients attending in the District Diabetic Hospital (Ahad Diabetic Health Complex, Jhumjhumpur, Jessore). The sample size was 85. The participants were selected through purposive sampling. The inclusion criteria were diabetic patients over 18 years who ever exposed to Covid-19 and also the exclusion criteria participants under 18 years, terminally ill patients, individuals who have co-morbidities were excluded from this study.

Data Collection: Participants were asked to attend the health center on the day of data collection. The objectives and procedure of the data collection were explained, so that they can think whether they will permit the researcher to go through the procedure. Written informed consent will also be obtained from the participants. A semi-structured questionnaire and checklist using the selected variables according to the specific objectives. At the time of recruitment, trained research assistants noted the socio-demographic issues; Age, household size, education, income, employment.

Blood Sample Collection: A trained phlebotomist took venous blood samples in the morning. The serum separator sample were collected in a red-top tube. The tubes were then kept in a cold box for four hours before being sent to a reference laboratory to be measured for serum interleukin 6 (IL-6). After a 4 to 6 hour overnight fast, trained phlebotomists gathered venous blood in the morning. The serum separator was used to collect samples in the red-top tube. Fresh blood samples were centrifuged for 10 min at 2,000g. Serum were collected and tested within 4–6 h. All procedures were performed under level 3 protection.

Laboratory Procedure: Whole blood was collected in tubes containing separation gel (VACUETTE) and transported to the Laboratory of Department of Biochemistry & Cell Biology, Bangladesh University of Health Sciences (BUHS) for next analysis. After centrifugation, the serum was collected and stored at −80°C. IL-6 was quantified using an ELISA kit (reference 430504, Bio Legend, CA, USA), according to the manufacturer's instructions. All other laboratory tests, included in the established protocol, were performed in the HB laboratories, following the standard procedures.

Statistical Analysis: For processing the data, the Statistical Package for Social Science (SPSS) was used. Descriptive (frequency, percentage, mean and standard deviation) analysis were performed as needed for quantitative variables. A chi-square test would be utilized to ascertain the association among socio-demographic, glycemic status and Covid-19 Exposure related variables.

Ethical consideration: Bangladesh University of Health Sciences (BUHS) and Ahad Diabetic and Health Complex Ethical Review Committee (AH/2021/001) approved the research proposal for data collection, the study participants were verbally informed about the study design, the study's purpose, and their right to withdraw from the research project at any time and for any reason. Data were collected anonymously, keeping confidentiality and maintain aseptic precautions during blood sample collection in complete compliance with ethical principles, after receiving written informed consent from the participants.

Results

Among the respondents 49.4% (n=42) were male and 50.6% (n=42) were female. The table 1 shows that among the respondents 43.5% (n=37) were within 36 to 50 years' age, were within 26 to 35 years' age, followed by 42.4% (n=36) were beyond 50 years and rest 14.1% (n=12) within 20 to 35 years' age. Mean age 48.07±11.45 years. Minimum 26 years and Maximum 72 years. Among the respondents 48.2% (n=41) were of Normal weight, followed by 43.5% (n=37) were pre-obese, and 4.7% were obesed. Mean 4.99±1.44. Minimum 2 members Maximum 9 members. Among the respondents, 56.5% (n=48) had 5 to 7 persons in their family, followed by 37.6% (n=32) had up to 4 persons (Table 1).

Table 1: Socio-Demographic Factors of the Study Respondents (N=85)

Variables	Frequency	Percent
Gender		
• Female	43	50.6
• Male	42	49.4
Age group		
• 20 to 35	12	14.1
• 36 to 50	37	43.5
• 51 or above	36	42.4
Nutritional status		
• Under weight	03	3.5
• Normal weight	41	48.2
• Pre obese	37	43.5
• Obese	04	4.7
Family size		
• Up to 4 members	32	37.6
• 5 to 7 members	48	56.5
• 8 and above members	05	5.9

It was shown the respondents 52.9% (n=48) had family history of diabetes. Among the respondents, 60.0% (n=51) were suffering from diabetes for 1 to 5 years, 28.2% (n=24) for 6 – 10 years, 7.1% (n=6) for 11 – 15 years and only 4.7% were suffering for 13 – 20 years. Among them, 55.3% (n=47) are getting insulin and 95.3 (n=81) getting medicine as management of diabetes. Among the respondents 41.2% (n=35) had COVID symptoms and only 17.6% (n=15) were COVID-19 positive (Table 2).

Table 2: Distribution of the Respondent by History of Diabetes and Covid-19 (n=85)

Variables	Frequency	Percent
Family History		
• Yes	45	52.9
• No	40	47.1
Duration of Diabetes		
• 1 to 5 Years	51	60.0
• 6 to 10 Years	24	28.2
• 11 to 15 Years	6	7.1
• 16 to 20 Years	4	4.7
Medication status		
• Insulin Intake	47	55.3
• Medicine Intake	81	95.3
Covid-19 Symptoms		
• Yes	35	41.2
• No	50	58.8
History of COVID-19 infection		
• Yes	15	17.6
• No	70	82.4

the distribution of respondents by COVID-19 vaccination status and vaccine type. All participants received the first dose, 96.5% received the second dose, and 63.5% received the booster dose. AstraZeneca was the most commonly administered vaccine for all doses (Table 3).

Table 3: Distribution of the Respondents by COVID-19 Vaccination Status and Type of Vaccine (n=85)

Vaccine Type	First Dose		Second Dose		Booster Dose	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
AstraZeneca	56	65.9	53	62.4	12	14.1
Pfizer	3	3.5	2	2.4	9	10.6
Moderna	1	1.2	1	1.2	20	23.5
Sinopharm	25	29.4	26	30.6	13	15.3
None	-	-	3	3.5	31	36.5
Total	85		82		54	

The mean Serum IL-6 was 5.66±2.245 among the respondents having COVID-19 positive while it was more 7.10±6.137 among the rests. Mean blood glucose level was 14.7933±7.45381 mmol/L who were COVID-19 positive and 12.9876±5.69122 mmol/L among rests (Table 4).

Table 4: Mean level of Serum IL-6 and Blood Glucose Level Among the Respondents

Index	History of COVID-19 Infection		
	Yes	No	All
Serum IL-6			
• Mean±SD	5.7±2.245	7.1±6.137	6.8±5.639
• Range	2 to 11	0.2 to 41	2 to 41
Blood Glucose (mmol/L)			
• Mean±SD	14.8±7.5	12.9±5.7	13.3±6.1
• Range	6.3-26.2	3.8-26.7	3.8-26.7

The linear regression analysis was done between serum IL-6 levels and variables including age, RBS, COVID-19 history, and COVID symptoms. Age showed a significant positive association with IL-6 (P=0.008), while RBS, COVID-19 positivity, and COVID symptoms did not demonstrate significant associations (Table 5).

Table 5: **Linear Regression Analysis Among Serum IL-6 with Age, RBS, COVID-19 History and COVID Symptoms (n=85)**

Variables	P value	cOR	95% C.I.	
			Lower	Upper
Age	0.008	1.063	1.016	1.111
RBS	0.124	1.066	0.982	1.157
Covid +ve	0.090	3.636	0.819	16.150
Covid Symptom	0.066	0.322	0.096	1.080
Constant	0.006	0.029		

Variable(s) entered on step 1: age, RBS, COVID History, COVID Symptoms.

Discussion

The statistics provided give us an insight into the demographics and health conditions of the respondents. It's interesting to note that the majority of the respondents were middle and elderly aged, and almost an equal number of males and females participated. In terms of nutritional status, the data shows that almost half of the respondents were of normal weight, while a significant percentage (43.5%) were pre-obese. Only a small proportion (4.7%) were obese. It's important to note that obesity is a significant risk factor for many health conditions, including diabetes, heart disease, and COVID-19. The data also shows that the majority of the respondents had a family size of 5 to 7 persons, with a mean family size of 4.99. Additionally, the majority of the respondents had a yearly income of between Tk. 300,000 to 500,000. Income and family size are both important factors that can influence an individual's access to healthcare and their overall health outcomes. It's concerning to note that more than half of the respondents had a family history of diabetes. Diabetes is a chronic condition that requires ongoing management and can lead to serious health complications if left uncontrolled.

It's also noteworthy that a significant proportion of respondents (41.2%) reported COVID-19 symptoms, but only 17.6% of them tested positive for COVID-19. This could be due to several reasons, including false-negative test results or other illnesses that share similar symptoms with COVID-19. The data also shows that all respondents received the first dose of the COVID-19 vaccine, and a high percentage (96.5%) received the second dose. However, only 63.5% of the respondents received the booster dose. This highlights the importance of ongoing vaccination efforts to protect individuals from COVID-19 and prevent the spread of the virus. It's also interesting to note that a majority of the respondents (60.0%) were suffering from diabetes for 1-5 years, indicating a relatively recent diagnosis for many. The majority of respondents were also managing their diabetes with medication, with only a little over half of them receiving insulin.

In Libiya[12], one study was conducted among 60 patients diagnosed with COVID-19 and admitted to the hospitals' Intensive Care Units (ICU) during January to March 2021. They study showed that the IL-6 level was on the rise during the course of COVID-19, whereas that of insulin was on the decrease. One study conducted in Renmin Hospital, in Wuhan, China[13]. The results of that study showed that COVID-19 patients have higher serum level of cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-6 and IL-10) and CRP than control individuals. Within COVID-19 patients, serum IL-6 and IL-10 levels are significantly higher in critical group (n = 17) than in moderate (n = 42) and severe (n = 43) group. The levels of IL-10 are positively correlated with CRP amount ($r = 0.41$, $P < 0.01$). Using univariate logistic regression analysis, IL-6 and IL-10 are found to be predictive of disease severity and receiver operating curve analysis could further confirm this result (AUC = 0.841, 0.822 respectively). Another study also in China[14] which was aimed at investigating the relationship between glucose metabolism and the inflammatory state of inpatients with COVID-19. 71 inpatients with COVID-19 were classified into nondiabetes mellitus (NDM) group, impaired fasting

glucose (IFG) group, and diabetes mellitus (DM) group. The average hospitalization days were significantly shorter in DM patients when compared with patients in the IFG group and NDM group. CD4+ T cell percentage was higher while CD8+ T cells percentage was lower in the DM group than those in the NDM group. The serum levels of IL-6, IL-2, IL-10, and INF-γ in the DM group were upregulated when compared with those in the NDM group. The serum levels of TNF-α, IL-4, IL-2, IL-10, and INF-γ were significantly higher in the DM group than those in the IFG group. A significant difference was observed in CD4+ T cell, CD4+/CD8+ ratio percentage, IL-6, and IL-10 between the NDM group and DM group with adjusted BMI. Several studies have investigated the relationship between serum IL-6 levels and glycemic control in patients with COVID-19 and diabetes. One study[15] published in the journal Diabetes Research and Clinical Practice in 2021 found that COVID-19 patients with diabetes and poor glycemic control had significantly higher serum IL-6 levels compared to those with good glycemic control. The study also found that higher IL-6 levels were associated with increased severity of COVID-19 in patients with diabetes. Another study[16] published in the journal Diabetes/Metabolism Research and Reviews in 2021 also found that COVID-19 patients with diabetes and poor glycemic control had higher serum IL-6 levels compared to those with good glycemic control. The study also found that elevated IL-6 levels were associated with an increased risk of mortality in patients with diabetes and COVID-19.

Overall, these studies suggest that serum IL-6 levels may be useful as a biomarker for assessing the severity of COVID-19 in diabetic patients and that glycemic control may play an important role in modulating the immune response to COVID-19. However, further research is needed to fully understand the relationship between serum IL-6 levels, glycemic control, and COVID-19 outcomes in diabetic patients. The data shows a positive significant association between age and Serum IL-6, a marker of inflammation that has been linked to severe COVID-19 disease. This highlights the importance of taking preventive measures to protect the elderly and those with underlying health conditions from COVID-19.

There are several limitations of study. During conducting the researcher encountered some constraints. Achieving an adequate sample size and recruiting a diverse population of COVID-19 exposed diabetic patients was challenging, especially in a specific district hospital. Limited access to patients, lack of patient cooperation, or unwillingness to participate can affect the sample size and generalizability of the study. Collecting accurate and comprehensive data on serum IL-6 levels and glycemic control required appropriate laboratory testing, access to medical records, and patient information. Ensuring ethical considerations, such as privacy, confidentiality, and protection of participants' rights, were also challenging in a resource-constrained setting. Conducting research involves a considerable time commitment, from study design and implementation to data analysis and interpretation. Limited time availability due to other clinical or administrative responsibilities was also one constrain faced in completion of the study.

Conclusion

The study found that serum IL-6 levels were significantly associated with age, indicating a possible link between age and inflammation in COVID-19 positive individuals. The results also suggest that the population is relatively well-informed about COVID-19 vaccination and is actively seeking vaccination.

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Conflict of Interest
No competing interests exist by the authors. This manuscript has not submitted to, nor is under review at another journal or other publishing venue.

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None

Contribution to authors:
All of the listed authors have reviewed and approved the manuscript. Meer Faizul Islam**:** Conceptualization, Methodology, Software Md. Ashiqur Rahman: Data curation, Writing- Original draft preparation. Md. Biplob Hossain: Visualization, Investigation. Sadia Islam, Shohanur Rahaman: Supervision. Afrin Haque, Chomel Mahbub: Software, Validation.: Arifa Akram**:** Writing- Reviewing and Editing.

Data Availability
Any questions regarding the availability of the study's supporti ng data should be addressed to the corresponding author, who can provide it upon justifiable request.

Ethics Approval and Consent to Participate
The Institutional Review Board granted the study ethical approval. Since this was a prospective study, every study participant provided formal informed consent. Each method followed the appropriate rules and regulations.

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