

Evaluation of some Hematological and Inflammatory Factors in Iraqi Patients Suffering from COVID-19 and Type 2 Diabetes Mellitus

Qusay Abdulwahab Khalaf^{1*}, Khetam Habeeb Rasool¹, Eman Natiq Naji¹,
Mohamad Merhi Nasser²

¹Department of Biology, College of Science, Mustansiriyah University, 10052 Baghdad, IRAQ.

²Faculty of Pharmacy, Limoges University, BP 23204, Limoges, France.

*Correspondent contact: qusay.wah@gmail.com

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COVID-19 is a newly recognized sickness spreading rapidly worldwide and causing many consequences and deaths. Diabetes Mellitus (DM) is suggested as a risk factor that contributes to the severity and mortality of COVID-19. The present study investigates the levels of Lymphocytes, Neutrophils, C-reactive protein, D-dimer, and ferritin, in COVID-19 patients who suffer from type 2 diabetes mellitus (T2DM) and those without T2DM. 80 participants enrolled in this study, distributed into 4 groups; Group 1 (G1) included 20 patients with COVID-19 and T2DM; Group 2 (G2) comprised of 20 patients with COVID-19; Group 3 (G3) included T2DM patients. In addition, 20 individuals were taken as a healthy control group. The patient samples were obtained from Ibn-AlKhateeb Hospital /Baghdad in the period between February to April 2022. A hematology automated device was utilized to count lymphocytes and neutrophils, while a biochemical automated device was employed to measure D-dimer, CRP, and ferritin. Regarding the blood immune cells, there was a significant decrease in lymphocyte counts and a significant increase in neutrophil counts in G1 and G2 groups compared to the healthy control group. The serum levels of the studying markers (CRP, D-dimer, and ferritin) were increased in the G1, G2, and G3 compared to the control group. Furthermore, patients in the G1 group had higher levels of these markers than in other groups, which are considered prognostic markers for COVID-19 infection.

KEYWORDS: COVID-19, T2DM, Lymphocytes, Neutrophils, CRP, D-dimer, Ferritin.

الخلاصة

مرض كوفيد-19 من الأمراض التي تم تمييزها حديثاً والذي انتشر سريعاً عبر العالم مسبباً عدة مشاكل صحية وكذلك عدة وفيات بين المرضى. يشكل داء السكري عامل خطورة على مرضى كوفيد-19، حيث ساهم بتفاقم حدة المرض تارة وبالوفيات تارة أخرى. في هذه الدراسة تم اختبار مستويات الخلايا اللمفاوية والمتعادلة (كأجزاء من كريات الدم البيضاء)، والبروتين التفاعلي CRP، D-dimer، ومخزون الحديد Ferritin في دم المرضى المصابين بكوفيد-19 وداء السكري النوع الثاني. شملت الدراسة 80 عينة دم، وتم جمع عينات المصابين بكوفيد-19 من المرضى الراقدين في مستشفى ابن الخطيب /بغداد في الفترة ما بين شباط ولغاية آذار من العام 2022. تم توزيع العينات على 4 مجموعات وكل مجموعة تألفت من 20 شخص وكالاتي: المجموعة الأولى اشتملت على المرضى المصابين بكوفيد-19 وبالسكري النوع الثاني، المجموعة الثانية تكونت من المرضى المصابين بكوفيد-19 فقط، أما المجموعة الثالثة فكانت متألفة من مرضى السكري النوع الثاني. بالإضافة إلى ذلك تم اخذ 20 فرداً سليماً كمجموعة تحكم صحي. أظهرت الدراسة انخفاض ملحوظ في معدل أعداد الخلايا اللمفاوية وزيادة ملحوظة في أعداد الخلايا المتعادلة في المجموعة الأولى والثانية مقارنة بمجموعة التحكم الصحي. ازدياد مستويات CRP و D-dimer و ferritin بين مجاميع الدراسة الثلاث. بالإضافة إلى ذلك فإن المجموعة الأولى سجلت أعلى المستويات لهذه العوامل وبذلك تعتبر هذه العوامل عوامل تنبؤية لحدوث مرض كوفيد-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a contagious respiratory disease caused by the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) virus, which first appeared in Wuhan, China. The World Health Organization (WHO) claimed COVID-19 a pandemic on March 11, 2020, due to its fast spread in a short period, affecting a large number of people and causing mortality. SARS-CoV-2 infection might be asymptomatic or accompanied by viral respiratory infection symptoms such as fever, weakness, cough, and dyspnea. [1-3]. The pathogens can be transmitted by droplets that contaminate the air, hands, and surfaces or from person to person by fomites [4]. Respiratory failure, kidney failure, septic shock, hemorrhage, and heart failure are the primary causes of death associated with COVID-19. It was observed that COVID-19 risk factors included arterial hypertension, coronary heart disease, obesity, and diabetes. 90–95 % of all diabetes is type 2 diabetes mellitus (T2DM) worldwide [5]. Due to their compromised immune systems, people with T2DM may suffer from worse consequences more quickly after they become infected with COVID-19 [6]. This large vulnerable population is seriously threatened by the COVID-19 pandemic [7].

Lymphocyte cells control immune responses by destroying the virus-infected cell and producing antibodies to eliminate pathogens. Also, neutrophils are used as an indicator of COVID-19 severity, they are innate immune cells and have a role in the clearance of pathogens by phagocytosis [8][9].

Plasma ferritin is an indicator of immune dysregulation related to COVID-19 severity and cytokine storm syndrome [10]. D-dimer is used as a predictive biomarker for coagulation disorders that associate with COVID-19 infection. Furthermore, elevated CRP level was significantly related to severe conditions of diabetic and Covid-19 patients [11-13]. This study aims to evaluate the counts of the blood cell; lymphocytes and neutrophils; as well as some biomarkers such as CRP, D-dimer, and ferritin in COVID patients with T2DM.

MATERIALS AND METHODOLOGIES

This study included 80 participants obtained from the Ibn Al-Khateeb Hospital/ Baghdad from February to April 2022. The ages of all studied groups were 41 – 85 years (an average of 63 years). The cases were classified according to infection by COVID-19 and T2DM. Study groups were classified as the following; the first group of 20 patients with diabetes mellitus type 2 suffered from COVID-19 infection (G1). The second group of 20 patients with COVID-19 but without diabetes (G2), and the third group of 20 diabetic patients without COVID-19 infection (G3). In addition to these groups, 20 individuals were taken as a healthy control group. T2DM diagnosis was performed according to the specialist, while infections with COVID-19 were determined by PCR and computerized tomography (CT) scan followed by fluorescent immunoassay (FIA) as a confirmatory test. FBS and HbA1C tests were detected for all the study groups.

Ten milliliters of blood samples were collected from all the participants of this study. The blood was placed in a 2.5 ml sodium citrate tube for the D-dimer test and rotated in a centrifuge (at 4000 rpm for 5 minutes). After that, the upper portion of the plasma was separated. Two ml of blood sample was placed in an EDTA tube for a complete blood count test. The remaining 5.5 ml of blood was transferred into a gel tube and left for 15 minutes until clotted at room temperature. Then, samples were centrifuged at 4000 rpm for 10 minutes to separate the serum for assessments of CRP and ferritin levels. Serum samples were separated from the tested tubes and stored at -40°C until used [14]. An automated blood analyzer (Sysmex XN350/USA) analyzed the blood lymphocytes and neutrophils. The inflammatory factors (C-reactive protein, D-dimer, and ferritin) were estimated using a chemical auto-analyzer (BECKMAN COULTER AU / USA).

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 21 is used to interpret the data. The information is given in the form of a mean,

standard error, and ranges. Frequencies and percentages are used to display categorical data. ANOVA was used to compare between tested mean. Data expressed mean±SE. LSD test was used to calculate the significant differences between tested means. The letters A, B, and C LSD for rows represented the levels of significant, and highly significant starting from the letter (A) and decreasing with the last one. Similar letters mean there are no significant differences between the tested mean. Values of

p>0.05 were considered statically non-significant while p≤0.05 considered significant results.

RESULTS AND DISCUSSION

The statistical analysis showed that at P<0.05 level, there was a significant decrease in lymphocyte percent in G1 & G2 (12.41±1.87 and 12.77±2.32, respectively) in comparison with G3 and the control group (35.49±1.03 and 31.03±1.11 respectively) as shown in Table 1.

Table 1: Mean of lymphocyte levels among study groups.

Lymphocyte Percentage	G1	G2	G3	Control
Mean ± SE (%)	12.41±1.87	12.77±2.32	35.49±1.03	31.03±1.11
P-value	C	C	A	B
		0.01**(S)		

S.E: Standard Error ; P:Probability; S: Significant; G:group; The letters (A,B, and C) LSD for rows represented the levels of significance; highly significant begin with (A) and decrease with (C). Similar letters indicate that there are no significant differences in the tested means.

The present study showed an increase in neutrophil cells in G1(81.74±2.52) and G2 (73.60±5.10), compared to the control group (p=0.05). Also, the neutrophils in G3 were higher than that in G1 and G2 groups.

There were no significant differences between G3 (64.18±1.30) and the control group (60.08±0.82), as observed in Table 2.

Table 2: Mean of neutrophil levels among the study groups.

Neutrophil percentage	G1	G2	G3	Control
Mean ± SE (%)	81.74±2.52	73.60±5.10	64.18±1.30	60.08±0.82
P-value	A	B	C	C
		0.05		

S.E: Standard Error ; P:Probability; S: Significant; G: group; The letters (A,B, and C) LSD for rows represented the levels of significance; highly significant begin with (A) and decrease with (C). Similar letters indicate that there are no significant differences in the tested means.

CRP levels were increased in G1, G2, and G3 compared to the healthy control group (105.23±11.88,96.13±15.41,11.73±0.59 versus 4.42±0.35, respectively) in a significant manner (P<0.001). CRP level in G3 was higher than that

in the control group (11.73±0.59 vs 4.42±0.35, respectively).G2 group had more CRP concentration than G3 and the control group (96.13±15.41 vs 11.73±0.59,4.42±0.35 respectively), as illustrated in Table 3.

Table 3: Mean of CRP levels among the study groups.

CRP	G1	G2	G3	Control
Mean±SE (mg/L)	105.23±11.88	96.13±15.41	11.73±0.59	4.42±0.35
P-value	A	B	C	D
		0.001**(S)		

S.E: Standard Error ; P:Probability; S: Significant; G:group; The letters (A,B, C, and D) LSD for rows represented the levels of significance; highly significant begin with (A) and decrease with (C). Similar letters indicate that there are no significant differences in the tested means.

Concerning D-dimer levels, there was highly significant elevation ($P<0.05$) in G1 (1955.40 ± 466.77), G2(1533.57 ± 344.09), G3(28.97 ± 15.34) compared to the healthy control group (223.25 ± 12.41). The D-dimer levels were shown to be higher significantly in G1 than in G2. The level of G3 was significantly

higher than that in the control group, as denoted in Table 4.

A significant increase in ferritin serum levels ($p<0.05$) in G1, G2, and G3 groups in comparison with the healthy individual's group, as declared in Table 5.

Table 4: Mean of D-dimer levels among the study groups.

D-Dimer	G1	G2	G3	Control
Mean±SE (mg/L)	1955.40±466.77 A	1533.57±344.09 B	248.97±15.34 C	223.25±12.41 D
P-value	0.001**(S)			

S.E:Standard Error ; P:Probability; S:Significant; G: group; The letters (A,B, C, and D) LSD for rows represented the levels of significance; highly significant begin with (A) and decrease with (C). Similar letters indicate that there are no significant differences in the tested means.

Table 5: Mean of ferritin levels among the study groups.

Ferritin	G1	G2	G3	Control
Mean ± SE µg/L	492.32.70±2.44 A	1533.57±48.17 B	248.97±15.34 C	233.25±12.41 D
P-value	0.001**(S)			

S.E:Standard Error ; P:Probability; S:Significant; G:group; The letters (A,B,C, and D) LSD for rows represented the levels of significance; highly significant begin with (A) and decrease with (C). Similar letters indicate that there are no significant differences in the tested means.

Discussion

Leukocytes are an essential part of the immune system against infections such as viruses and bacteria that invade the body. An elevated or reduced level of them indicates an abnormal condition. Lymphocyte cells control immune responses by destroying the virus-infected cell and creating antibodies to neutralize viruses and bacteria [8]. Furthermore, neutrophils are used as an indicator of the severity of COVID-19, they are innate immune cells, and have a role in the clearance of pathogens by phagocytosis[9].

The findings of this study were in line with numerous studies, which stated that lymphopenia was reported in about 40% of hospitalized COVID-19 patients, even lower than the normal reference values [15][16]. Cheng *et al.* (2021) suggested that COVID-19 patients with T2DM are more likely than those without T2DM to develop severe COVID-19, and hyperglycemia is associated with inflammatory responses and lymphopenia in COVID-19 patients with T2DM [17].

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can enter lymphocytes via ACE2-independent mechanisms. SARS-CoV-2 and immune-mediated pathways both have the potential to cause lymphopenia by altering lymphocyte production, survival, or tissue re-distribution. Lymphopenia causes general immune suppression and can promote cytokine storms. Both contribute to viral persistence, replication, multi-organ failure, and death [18]. Most studies demonstrated that COVID-19 severity is associated significantly with increased neutrophil cells, decreased lymphocytes, and raised risk of death [16][19][20]. Neutrophil cells are the first line of cell-mediated defense against pathogens, eliminating them through fusion with cytoplasmic granules containing proteases, defensins, antimicrobial peptides, or reactive oxygen species (ROS) [21]. Neutrophilia has been considered an indicator of severe respiratory symptoms and poor outcomes in patients infected by COVID-19 [22]. The results of this study agreed with various studies

regarding elevated CRP levels in COVID-19 patients compared with healthy control individuals [12][23-25].

The results obtained by Debi *et al.* showed that diabetic Covid -19 patients compared to non-diabetic patients had higher CRP concentrations, which might be due to inflammatory reactions and then tissue destruction [13].

CRP is a plasma protein produced by hepatocytes, and many inflammatory mediators like IL6 can trigger its products. It has shown recently to be associated with chronic inflammations, such as Type II diabetes mellitus and cardiovascular diseases besides being a biomarker of acute inflammation [23].

The serum CRP level may be a biomarker of disease severity and progression in COVID-19 patients since it rises during inflammatory reactions and may be elevated by viral or bacterial infections. [26][27].

A local study (in Anbar Governorate) demonstrated there was significant an increase in D-dimer level in severe cases of COVID-19 infection. Thus, it can be used as an indicator in early diagnosis of COVID-19 infection [28].

Additionally, Several investigations have found that COVID-19 patients are predisposed to vein and artery thrombosis. Evidence of coagulopathy in COVID-19 infection indicated higher D-dimer levels in the early stages of the disease, a three to fourfold increase that was connected to a bad prognosis. Furthermore, COVID-19 individuals may have elevated D-dimer levels due to underlying conditions such as diabetes, cancer, and stroke. Diabetic patients with higher D-dimer levels had more severe illness. Persistent hyperglycemia can result in endothelial dysfunction and inflammation, which can contribute to thrombus development. As a result, severe COVID-19 infection combined with diabetes is more likely to result in coagulopathy and poor outcome [29]. Debi *et al.* [12] noticed that the development of COVID-19 diseases was associated with irregular coagulation activity with increased D-dimer levels. Through a meta-analysis, the D-dimer level in diabetic Covid-19 patients was notably higher than in non-diabetic ones.

The present study showed that D-dimer levels were significantly higher in diabetic patients than in the control group, suggesting they were more likely to have a hypercoagulable state than patients without diabetes. This result explains that hyperglycemia causes a pro-thrombotic status. The formation of thrombi is due to an imbalance between pro-coagulation, anticoagulation, and fibrinolysis due to hyperglycemia. Activation of host defense systems leads to the activation of coagulation [30].

The result showed a statistically significant elevated ferritin levels in COVID-19 patient groups. Previous studies detected similar results that increased ferritin concentration is associated with COVID-19 infection [27][30].

However, serum ferritin is used as a clinical biomarker to evaluate the reduction or overload of iron stores. Also, ferritin represents an upregulated acute-phase protein and raised concentration in infectious inflammation [32]. Ferritin is an intracellular protein iron storage protein; it is found in the liver, spleen, and bone marrow for hematopoiesis. Ferritin is used in iron recycling, and it is one of the biomarkers of inflammation in bacterial or viral infection [32][33]. Higher serum ferritin level was found to be correlated with more severe disease and poor outcome in COVID-19 patients. Therefore, the serum ferritin level can be an essential predictive biomarker in COVID-19 management [34].

CONCLUSIONS

Patients with both COVID-19 and T2DM exhibited significantly decreased lymphocyte counts and a significant increase in neutrophil counts compared to COVID-19 patients and T2DM patients. Also, the levels of CRP, D-dimer, and ferritin were significantly different among the study groups, and the patients with both COVID and T2DM showed more levels than other groups. Therefore, diabetes might be considered as a risk factor for the outcome of SARS-CoV-2 prognosis. More intensive attention should be given to diabetic patients in case of rapid deterioration.

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