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DIABETES CONTRIBUTES IN INCREASING RISK OF MORBIDITY AND MORTALITY RELATED TO COVID-19 DURING PATIENTS' HOSPITALIZATION

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ABSTRACT

Background: diabetes mellitus is a complex chronic disease characterized by glucose dysregulation and is associated with significant complications. It is considered one of the most important risk factors for a severe course of COVID-19. Diabetes comorbidities such as increased risk of severe pneumonia and a more pronounced pro-inflammatory response and hypercoagulability or pro-thrombotic status in patients with COVID-19 during hospitalization can be associated with disease deterioration with poor outcomes even death. ***Aim:*** to determine the effect of diabetes on hospitalized patients diagnosed with COVID-19. ***Materials and methods***: In this retrospective cohort study, 85 critically ill COVID-19 patients with an age ranging between 34-90 years admitted to the ICU in the isolation centres were selected to perform this research during the period from September 2020 to May 2021. Patients were classified based on the history of diabetes mellitus disease into 47 diabetic, and 38 non-diabetic COVID-19 patients. Routine laboratory tests include haematological, inflammatory, coagulation and renal function biomarkers were collected three times from all patients, upon admission and continued throughout the hospitalization stay. ***Results:*** Patients with DM had higher WBCs and neutrophils counts and lower lymphocytes counts than non-diabetic, which were statistically significant ($P<0.05$). As long as the diabetic patient stayed longer in the ICU, the WBCs and NEU count were getting higher and LYM getting lower. In diabetic COVID-19 patients, glucose was positively significant correlated with WBC and NEU and negatively significant with lymphocytes ($P<0.05$). CRP, ESR and D-dimer levels were increased abnormally in all patients, but were significant only among diabetic COVID-19 patients ($P<0.001$). A strong positive significant relation was seen between the sugar and CRP ($r=0.367$ and $P=0.023$), and D-dimer ($r=0.314$ & $P=0.032$) in diabetic patients, while no relation was seen in non-diabetic patients. Urea and creatinine increased significantly in diabetic rather than in non-diabetic patients ($P<0.05$), their levels continued in increase as long as the diabetic patients remained longer in the ICU. Patients with DM had greater mortality rate compared to patients without diabetes (66% vs 23.7%). ***Conclusion:*** diabetes and hyperglycaemia are associated with poor outcomes and increased mortality rate among hospitalized COVID-19 patients. Therefore, regulate glucose levels in COVID19 patients may improve disease outcomes and diminish the mortality rate.

KEYWARDS: ■ Diabetes Mellitus ■ Corona Virus ■ Hospitalised Patients ■ Morbidity and Mortality.

1.0 INTRODUCTION

Diabetes mellitus (DM) is a complex chronic disease characterized by glucose dysregulation caused by an absolute or relative insulin deficiency (Landstra and de Koning 2021). It is one of the leading causes of morbidity and mortality worldwide and the global burden of diabetes is high, with an overall prevalence of 9.3% and 463 million people suffering from the disease worldwide (Saeedi *et al.*, 2019). DM is associated with significant cardiovascular and renal complications, obesity, hypertension, vasculopathy, a proinflammatory and hypercoagulable state and cardiovascular disease (CVD) (Harding *et al.*, 2019). Infectious diseases are more frequent and can be associated with worse outcomes in patients with diabetes (Casqueiro, Casqueiro and Alves 2012). Therefore, it is not surprising that diabetes has been considered as a possible risk factor or a predictor for worse outcomes in patients with coronavirus disease 2019 (Palaiodimos *et al.*, 2020).

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global pandemic that initially started in Wuhan, China, and spread extremely quickly throughout the world

(Sanyaolu *et al.,* 2020). The clinical spectrum of SARS-CoV-2 infection ranges from mild to critically ill cases, manifesting as asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and even death (Li *et al.,* 2021). About 5% to 16% of the patients who tested positive for SARS-CoV-2 required hospitalization in intensive care units (ICU), mainly for respiratory distress associating dyspnea, high respiratory rate, low oxygen saturation, or rapid increase in lung infiltrates (Barragan *et al.,* 2021). Mortality rate associated with ICU hospitalizations ranged from 49% to 67% (Bhatraju *et al.,* 2020).

Indeed, most infected people are thought to have a favourable prognosis, however chronic diseases commonly seen in elderly people, such as diabetes mellitus, hypertension, cerebral vascular disease, and their susceptibility conditions, may lead to poor clinical outcomes, in time of prepandemic (Li *et al.,* 2020). A meta-analysis showed that the most prevalent comorbidities in people with COVID-19 were hypertension 21.1 % and diabetes 9.7 %, followed by cardiovascular diseases 8.4 %, and respiratory system disease 1.5 % (Yang *et al.,* 2020). This build-up of epidemiologic evidence made it increasingly clear that DM and other chronic, non-communicable diseases appear to negatively influence COVID-19 clinical outcomes (Sardu *et al.,* 2020).

Although the relationship between COVID-19 and diabetes mellitus is complicated and bidirectional, diabetes mellitus is considered one of the most important risk factors for a severe course of COVID-19 (Holman *et al.,* 2020). Several factors that are often present in diabetes mellitus are likely to contribute to this risk, such as older age, a pro-inflammatory and hypercoagulable state, hyperglycemia and underlying comorbidities (hypertension, cardiovascular disease, chronic kidney disease and obesity) (Landstra and deKoning 2021). Hyperglycaemic COVID-19 patients have severe clinical problems including increased ICU admittance, machine-driven ventilation, and substantial rise in inflammatory markers (Gazzaz 2021). It is considered that level of plasma glucose is an independent predictor for increasing mortality and morbidity in COVID-19 patients (CDC 2020). Among all patients, those with diabetes or hyperglycaemia have a two- to four-fold increase in mortality and severity of COVID-19 than those without diabetes. The primary cause of comorbidities and mortality in COVID-19 patients with diabetes is compromised immune response to viral infections (Ng and Rickard 2020).

It is known that SARS-CoV-2 enters the host cell through the binding of the SARS-CoV-2 spike (S) protein, which is the major determinant of the virulence to the angiotensin-converting enzyme 2 cell surface receptor ACE2 on host cells and the internalization of complex by the host cell. Subsequently, the virus enters the host cell through endosomal pathways (Hoffmann *et al.,* 2020). Upon virus entry, the host immune system will respond through stimulating the immune response to eliminate the corona virus. The attachment of SARS-CoV-2 spike glycoprotein with ACE2 triggers complex molecular events that lead to hyper-inflammation and burst of cytokine storm, which is known as a hallmark of COVID-19 infection (Mahmudpour *et al.,* 2020). Noticeably, however Roca-Ho *et al.,* (2017) pointed out that ACE2 increase its expression in the lung, heart, kidney and pancreas of diabetes mellitus of rodent model making it easier for the virus to bind and enter the body. As a result, diabetic patient have higher affinity cellular binding and efficient virus entry, diminished T cell function, increased susceptibility to hyper-inflammation, cytokine storm syndrome, decreased viral clearance and presence of cardio vascular disease (Yang *et al.,* 2020).

Importantly, several clinical studies have shown that patients with COVID-19 are prone to notable glucose dysregulation (Landstra de Koning 2021). It is found that COVID-19 patients in particular critically ill patients developing hyperglycaemic (hyperosmolar syndrome) during hospital admission leading to negative outcomes and most often ending with deaths (Bode *et al.,* 2020). This hyperglycaemia in COVID-19 patients is likely because the SARS-CoV-2 binds to ACE2 receptors that are expressed in pancreatic tissue and β-cells in particular. Therefore, an acute loss of insulin secretory capacity along with a stress condition and the cytokine storm could lead to a rapid metabolic deterioration with development of hyperglycaemic hyperosmolar syndrome or diabetic ketoacidosis (Rayman *et al.,* 2020). Simultaneously, Apicella *et al.,* (2020) reported that the direct effect of SARS-CoV-2 on β-cell function and survival, causing worsening rapid and severe deterioration of metabolic control in people with pre-existing diabetes or leading to the development of new-onset diabetes.

In addition, insulin resistance (IR) is due to reduced tissue sensitivity to insulin and refers to the inability of the pancreas to secrete sufficient insulin for blood glucose regulation. Exocrine and endocrine pancreatic expression of angiotensin-converting enzyme 2 (ACE2) is likely to be associated with an exaggerated manifestation of diabetes in subsets of severely ill SARS-CoV-2 infected patients. The SARS-CoV-2 leads to pancreatic β-cells islet of Langerhans injury, damage islets and reduces insulin release and acute diabetes onset by binding to the ACE2 receptor on pancreas (Yang *et al.,* 2020). SARS-CoV-2 also worsens diabetic ketoacidosis (DKA), thereby creating a proinflammatory cytokine storm milieu where IL-6 and TNF levels are increased (Trevisani *et al.,* 2020). It is reasonable that the proinflammatory storm milieus created by COVID-19 and DM coexist and exacerbates severity (Govender *et al.,* 2021). It is noted that hyperglycaemia during hospitalization was noted to contribute to worse prognosis for patients with COVID-19 in Wuhan (Wang *et al.,* 2020). According to Apicella *et al.,* (2020) among

1122 patients with COVID-19 admitted to hospital in the USA, the mortality rate was four times higher in those with diabetes or hyperglycaemia during the hospital stay (28·8%) than those with normoglycaemia (6·2%).

In diabetic patient, a cytokine storm was highly associated with fatal cases of COVID-19, and is considered as the main factor that promotes disease progression rather than non-diabetic patient (Xie *et al.,* 2021). A recent clinical study reported that people with diabetes had activated inflammatory response that represented in the elevated levels of white blood cells (WBCs), neutrophils, tumour necrosis factor alpha (TNFα), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and suppressed immunity; as markedly decreased levels of lymphocytes due to apoptosis incidence of CD3, CD4 and CD8 of T-lymphocytes by the viral infection (Guo *et al.,* 2020).

In several clinical studies in patients with diabetes and COVID-19, worse inflammatory profiles with higher inflammatory markers such as CRP, D-dimer, IL-6 and ferritin were identified compared to patients without diabetes (Coppelli *et al.,* 2020). Additionally, elevated CRP and D-dimer levels, as well as higher IL-6, TNF-a and ferritin levels were found in non-survivors as compared to survivors with diabetes (Shi *et al.,* 2020). A high CRP was independently associated with increased risk of mortality for patients with diabetes hospitalized with COVID-19 (Mahmudpour *et al.,* 2020).

Further, Landstra and deKoning (2021) indicated that hypercoagulation in COVID-19 is thought to occur due to the profound inflammatory response and cytokine storm observed in some patients. Because patients with diabetes have a more pronounced inflammatory response, they may be at greater risk to suffer from thromboembolic events in the case of COVID-19 (Abu-Farha *et al.,* 2020). Diabetes causes an increase in risk of thromboembolic events as it is tied to a prothrombotic state that results from an imbalance of clotting factors and fibrinolysis. COVID-19 increases coagulation activity even further. The endothelial dysfunction linked to hypoxia can cause intravessel coagulation during an infection. Anticoagulation therapy in patients with COVID-19 seems to improve prognosis (Apicella *et al.,* 2020).

COVID-19 has been widely associated with thromboembolic events such as pulmonary embolism, deep-vein thrombosis (DVT), ischemic stroke and myocardial infarction, which represent a predominant cause of death in critically ill patients with severe COVID-19 (Sardu *et al.,* 2020). Patients with diabetes in general have an increased risk of thromboembolic events represented by high D-dimer level, which, in the case of COVID-19, can add to a high risk of death (Landstra and deKoning 2021). In two studies, longer prothrombin times and higher D-dimer concentrations were found in COVID-19 non-survivors as compared to survivors in hospitalized Chinese patients with diabetes (Yan *et al.,* 2020). However, this was not the case in the French nationwide cohort study in which D-dimer levels were not a significant predictor of 7-day mortality in patients with diabetes hospitalized with COVID-19 (Landstra and deKoning 2021).

In addition, diabetes contributes to increase the risk for a severe course of COVID-19 in hospitalized critically ill patients through affecting other organs such as kidney. The SARS-CoV-2 infection leads to 5% to 16% hospitalization in intensive care units (ICU) and is associated with 23% to 75% of kidney impairments, including acute kidney injury (AKI) (Barragan *et al.,* 2021). The SARS-CoV-2 is thought to have a direct renal toxicity via entry into proximal tubular cells and podocytes where ACE2 receptors and transmembrane serine proteases (TMPRSS) are highly expressed in the kidneys (Pan *et al.,* 2020). In critically ill diabetic patients, other factors may be implicated, such as cytokine storm, angiotensin II pathway activation, and dysregulation of complement, hypercoagulation, and microangiopathy (Barragan *et al.,* 2021).

Chronic kidney disease (CKD) is one of the well-known long-term complications of diabetes. The prevalence of chronic kidney disease (CKD) among patients with diabetes is around 40%. In patients hospitalized with COVID- 19, CKD has been shown to be an independent risk factor for death in hospital (Cheng *et al.,* 2020). Recent studies have demonstrated that this association is also present in patients with diabetes. In the French nationwide cohort study on hospitalized COVID-19 patients, diabetic kidney disease was a predictor for early death in patients with diabetes (Cariou *et al.,* 2020). Increasing stages of CKD were associated with incrementally increasing risks of COVID-19-related mortality (Holman *et al.,* 2020). Thus, the aim of this study is to investigate whether diabetes is associated with poor outcomes and mortality of hospitalized patients with COVID-19.

2.0 MATERIAL AND METHODS

2.1 Study design and participants

In this retrospective cohort study, a total of 85 critically ill COVID-19 patients with an age ranging between 34-90 years were selected to perform this research during the period from September 2020 to May 2021. All the confirmed cases with COVID-19 were defined as a positive result to real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay using nasal and pharyngeal swab specimens.

All 85 COVID-19 patients were critically ill and were admitted to Intensive Care Units (ICU) at Alnaser Isolation Centre and Abosora Isolation Centre, which were designated centres by the government for COVID-19 patients' admission in Zawia/Libya. Patients were classified based on the history of diabetes mellitus disease into 47 diabetic, and 38 non-diabetic COVID-19

patients. Routine laboratory biomarkers were collected three times from the isolation centres for all patients, upon admission and continued throughout the hospitalization stay. The admission period lasted from a week to almost a month for some patients before they recovery and discharges the centre or death.

2.2 Data collection

All demographic data including age, gender, history of diabetes and laboratory test results including sugar results (glucose level), hematological biomarkers results (complete blood count), inflammatory biomarkers results (C-reactive protein and erythrocyte sedimentation rates levels), coagulation biomarkers results (D-Dimer level) and renal function tests results (urea and creatinine levels) were obtained three following times for each patient before recovery and discharge the centre or death from the available medical records in the isolation centre. The laboratory test results of this study were analysed by using hematology analyzer (sysmex ks21) to obtain the complete blood count results (CBC). CRP and D-Dimer were tested on an I-CHROMA analyser. ESR was measured by using Westrengate method. Urea and creatinine was measured by using Biosystems BTS 350 Biochemistry Semi Auto Analyser.

3- Statistical analysis

All data obtained were calculated and analysed by using Microsoft Office Excel 2010 and SPSS 19.0 software (statistical package for statistical analysis). Descriptive analysis was performed on all the variables. Categorical variables results were described as counts and percentages, continuous variables results were expressed as mean ± SEM and qualitative variables were expressed as frequency and percentage. Differences between the two critically ill COVID-19 groups (diabetic and non-diabetic) were determined using the independent sample t-test analysis. Statistical significance was considered as $P < 0.05$ and $P < 0.001$. Pearson's correlation coefficient (r) analysis was used to ascertain possible associations between the sugar levels and routine blood biomarkers in diabetic and nondiabetic critically ill COVID-19 patients during hospitalization.

4.0 RESULTS

In this study a total of 85 critically ill COVID-19 patients who admitted to the ICU in the isolation centres with an age ranging between 34-90 years were participated. Based on the patients' medical history records, 47 of these patients were diabetic and the rest 38 were non-diabetic. During hospitalization, blood routine parameters were conducted three times for diabetic and non-diabetic patents before recovery and discharge the centre or death. The admission period lasted from a week to almost a month for some patients in the isolation centre based on the disease severity progression.

4.1 The overall values of three tests of haematological biomarkers in diabetic and non-diabetic COVID-19 patients during hospitalization

4.1.1 The values of three tests of WBCs, neutrophils and lymphocytes in diabetic and non-diabetic COVID-19 patients during hospitalization

Three time blood routine tests were conducted for all patients on the admission and during all the period of hospitalization stay. WBCs counts were abnormal and significantly increased in diabetic patients in comparison to the non-diabetic patients, where their WBCs count was almost normal ($P<0.001$). Regarding the morbidity, it is noted that as long as the diabetic patient stayed longer in the ICU, the WBCs count is getting higher and vice versa with non-diabetic. During hospitalization the WBCs count in diabetic patients was increased gradually along with the admission period, while in non-diabetic patients decreased gradually. Among diabetic patients the first WBCs test was 12.29±0.66 and increase in the last WBCs teat to reach 14.68±0.66, and in non-diabetic patients WBCs count was 11.39± 0.64 on the admission and decreased to 11.01±0.60 in the last test (Table1 and Figure1).

Table 1: shows the values of three tests of WBCs, neutrophils and lymphocytes in diabetic and non-diabetic COVID-19 patients during hospitalization (P-value ≤0.001 and *P≤0.05).**

Blood routine parameters	Three haematological biomarker tests	Diabetic Mean±SEM	Non-Diabetic Mean±SEM	P-value
WBCs 3900-10900 x10^6/L	First WBCs test	12.29 ±0.66	11.39± 0.64	0.330
	Second WBCs test	14.66±0.63	11.21±0.49	0.000**
	Last WBCs test	14.68±0.66.	11.01±0.60	0.000**
Neutrophils 1.5-8 x10^6/L	First NEU test	11.12±0.70	10.33±0.70	0.436
	Second NEU test	12.46±0.68	11.46±0.58	0.283
	Last NEU test	13.55±0.77	10.29±0.56	0.002*
Lymphocytes 1.2-3.3 x10^6/L	First Lym test	0.98±0.08	1.06±0.08	0.484
	Second Lym test	0.91±0.06	0.95±0.08	0.708
	Last Lym test	0.74±0.04	1.01±0.27	0.025*

Moreover, at the beginning of admission stay, there was non-significant difference in neutrophils and lymphocytes count between diabetic and non-diabetic patients ($P>0.05$). In the last test during hospitalization stay, neutrophils count in diabetic was significantly higher than non-diabetic ($P=0.002$). While, lymphocytes

count in diabetic was significantly lower than non-diabetic (P=0.025). It is noted from the three blood tests performed during the admission stay period that there was steadily increase in neutrophils and gradually decrease in lymphocytes count in diabetic patients, whereas in non-diabetic these cells did not show much differences (table1 and Figure1).

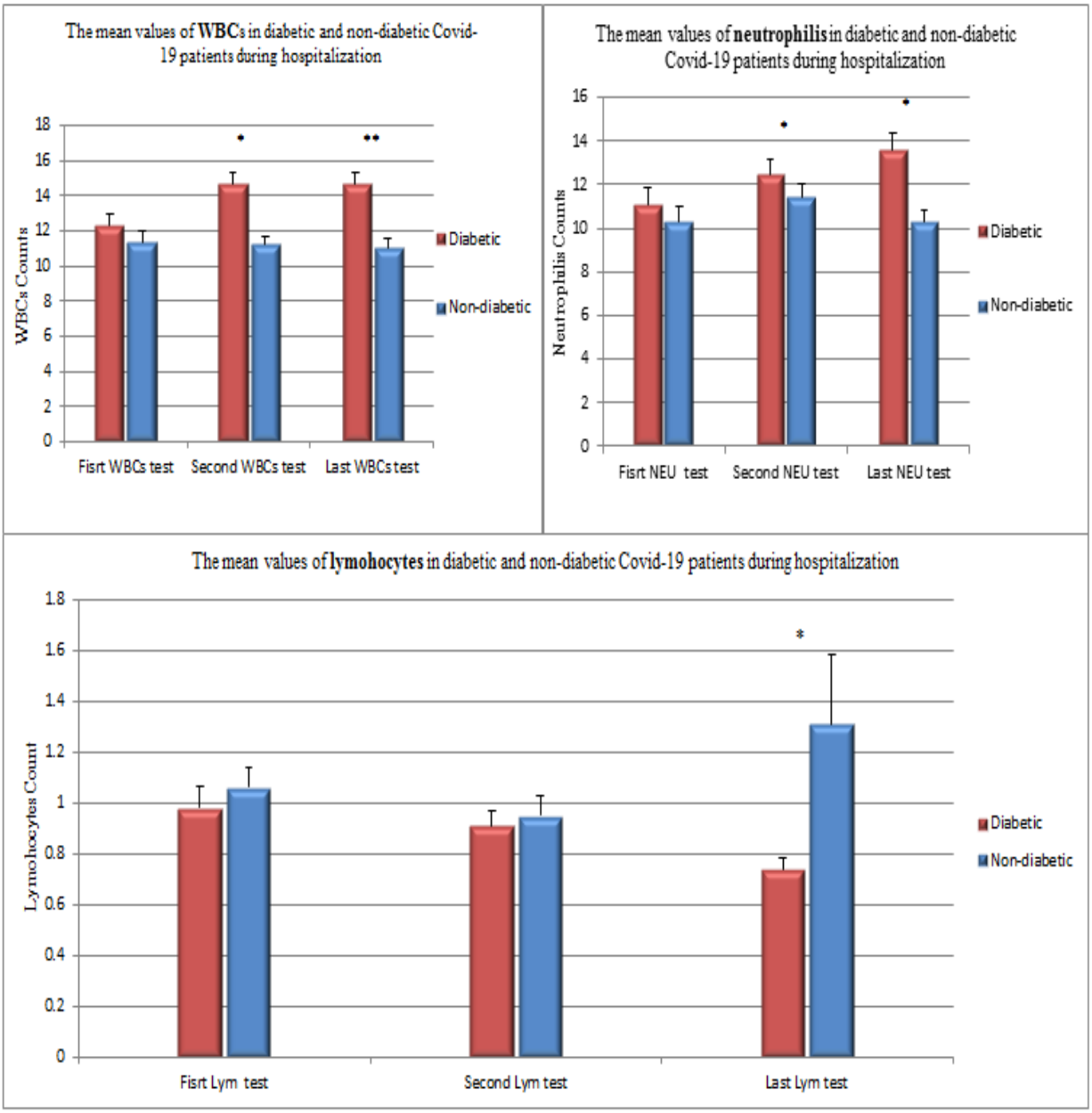


Figure 1: shows the values of three tests of WBCs, neutrophils and lymphocytes in diabetic and non-diabetic COVID-19 patients during hospitalization.

4.1.1.1 The relation between sugar and haematological biomarkers (WBCs, neutrophils and lymphocytes) in diabetic and non-diabetic COVID-19 patients during hospitalization

In non-diabetic patients, the sugar was positively correlated with WBCs and neutrophils, where the r = 0.173 and 0.258 respectively, but this relation was non-significant (P > 0.05). Nevertheless, in diabetic patients, there was a strong positive significant relation between sugar and WBCs (r= 0.377, P=0.020) and between sugar and neutrophils (r= 0.482, P= 0.002). In addition, the relation between sugar and lymphocytes in non-diabetic patients was negative but non-significant (r= -0.254, P=0.124), while in diabetic patients this relation was strong negative and significant (r= 0.341, P= 0.019) (Figure2).

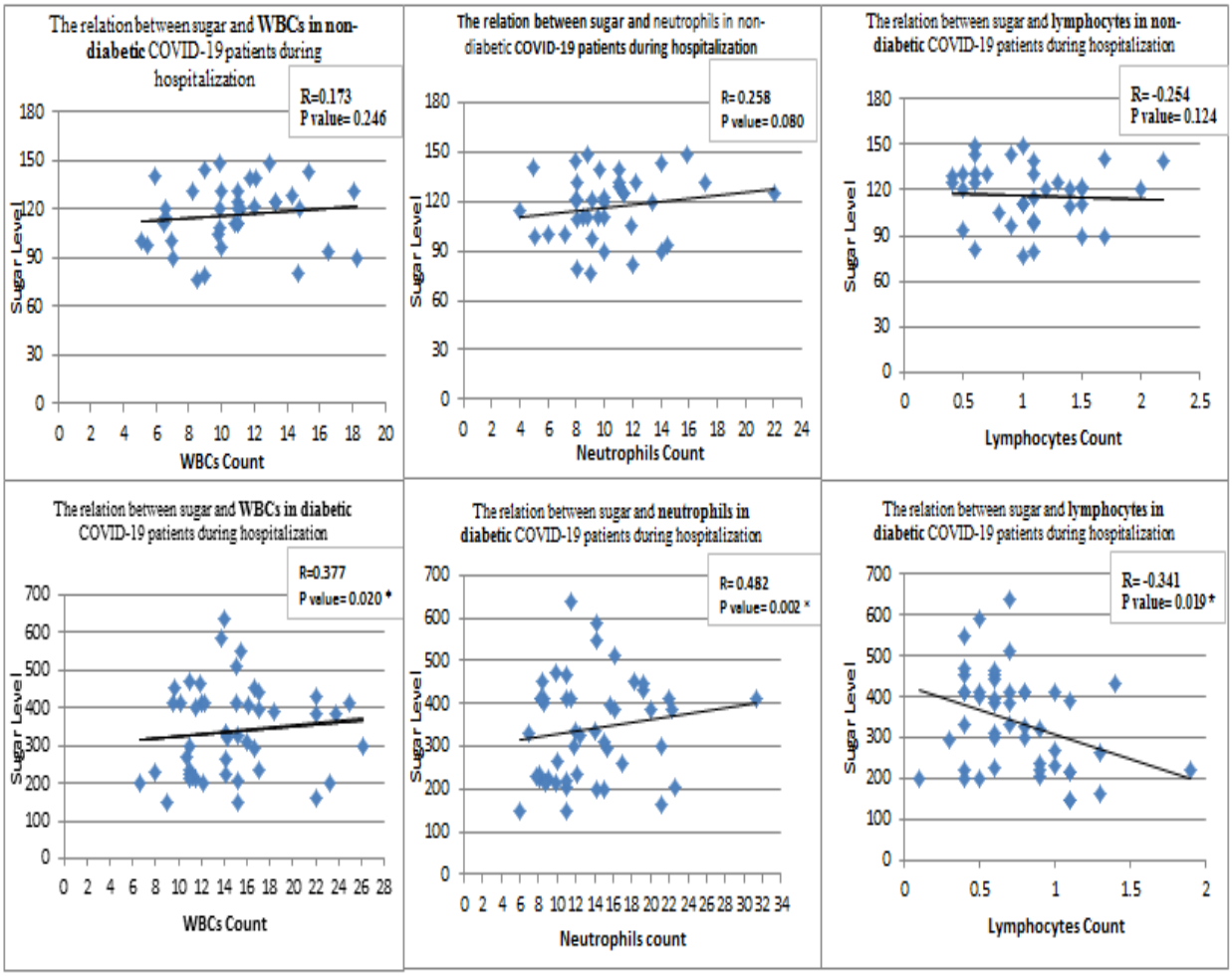


Figure 2: Shows The Relation Between Sugar And Haematological Biomarkers (Wbcs, Neutrophils And Lymphocytes) In Diabetic And Non-Diabetic COVID-19 Patients During Hospitalization.

4.1.2 The values of three tests of RBCs, haemoglobin and platelets in diabetic and non-diabetic COVID-19 patients during hospitalization

There was non-significant differences in the RBCs and haemoglobin between diabetic and nondiabetic patients (P>0.05). However, Platelets in diabetic patients showed a significant low count than in non-diabetic patients (P=0.001). It is seen that during admission the platelets count decreased dramatically (from 187.34 to 141.76) in diabetic patients, simultaneously, in non-diabetic patients, platelets count did not show much decrease (Table 2 and Figure 3).

Table 2: shows the values of three tests of RBCs, haemoglobin and platelets in diabetic and non-diabetic COVID-19 patients during hospitalization (*P≤0.05).

Blood routine parameters	Three haematological biomarker tests	Diabetic Mean±SEM	Non-Diabetic Mean±SEM	P-value
RBCs	First RBCs test	4.66±012	4.63±0.12	0.871
	Second RBCs test	4.76±0.13	4.67±.012	0.628
	Last RBCs test	4.61±0.12	4.41±0.15	0.319
Hemoglobin	First HB test	14.66±1.08	13.41±0.30	0.407
	Second HB test	14.01±1.02	13.24±0.32	0.306
	Last HB test	13.80±0.31	12.29±3.32	0.273
Platelets	First PLT test	187.34±14.45	192.81±18.79	0.381
	Second PLT test	179.76±17.54	188.73±17.54	0.334
	Last PLT test	141.76±16.35	187.31±18.18	0.001*

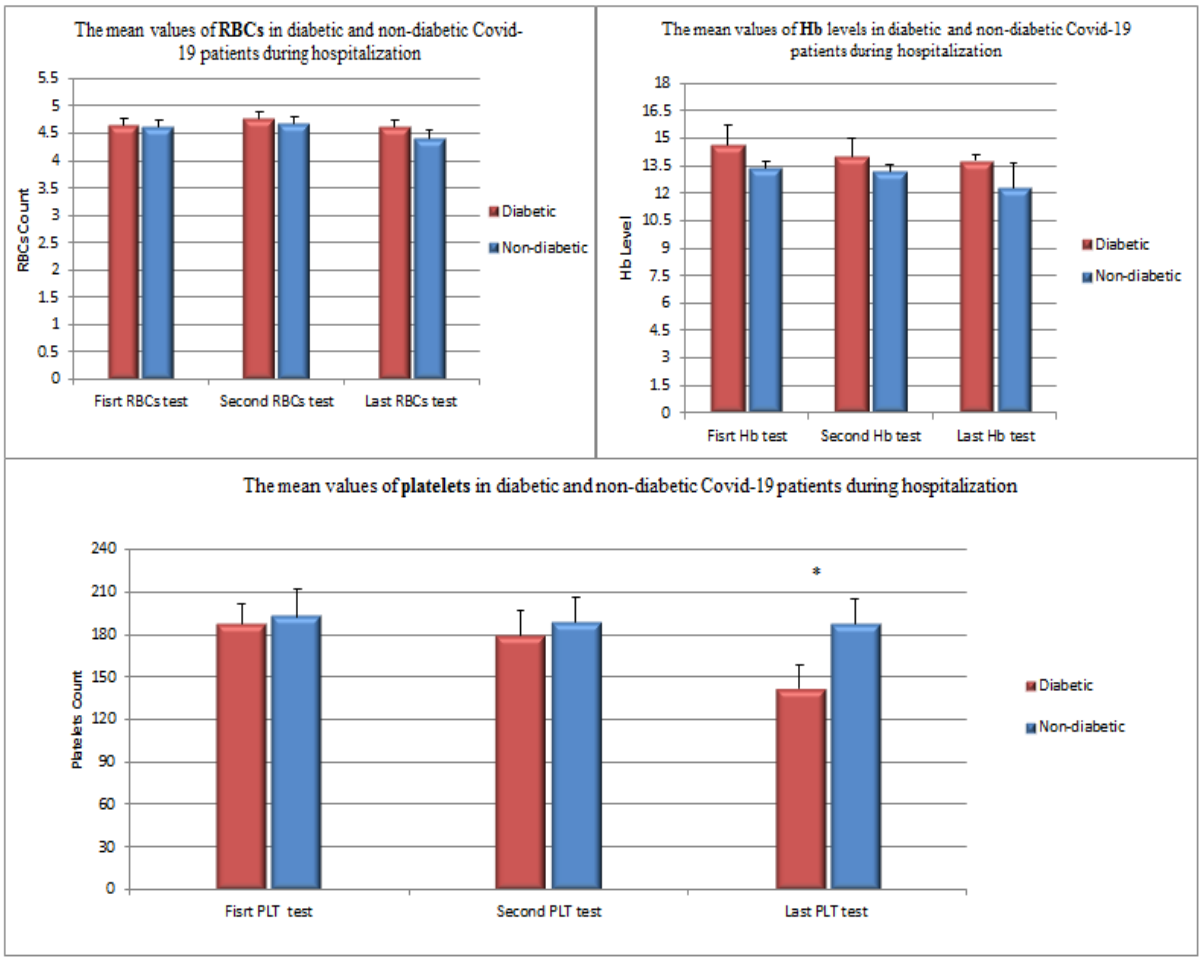


Figure 2: shows the values of three tests of RBCs, haemoglobin and platelets in diabetic and non-diabetic COVID-19 patients during hospitalization.

4.2 The mean levels of three tests of inflammatory biomarkers (CRP and ESR) in diabetic and non-diabetic COVID-19 patients during hospitalization

The levels of CRP and ESR were increased abnormally in both diabetic and non-diabetic, but their levels were significantly higher in diabetic (P<0.001). It is noticeably that, as long as diabetic patients stayed longer in the ICU, their CRP and ESR levels were getting elevated massively and worse. Clearly, for the duration of staying in hospital, the levels of CRP and ESR in diabetic patients were elevated dramatically from131.91±11.15 to 193.23±15.16 and from 61.85±2.98 to 81.08±3.98 respectively. On the other hand, in non-diabetic patients, CRP was decreased regularly in comparison to the level of ESR, which was increased slightly (Table 3 and Figure 4).

Table 3: shows the mean levels of three tests of inflammatory biomarkers (CRP and ESR) in diabetic and non-diabetic COVID-19 patients during hospitalization (P-value ≤0.001 and *P≤0.05).**

Blood routine parameters	Three inflammatory biomarkers level tests	Diabetic Mean±SEM	Non-Diabetic Mean±SEM	P-value
CRP level 0—10 mg/dl	First CRP level test	131.91±11.15	97.20±12.52	0.041*
	Second CRP level test	143.78±11.48	80.69±9.73	0.000**
	Last CRP level test	193.23±15.16	70.34±11.25	0.000**
ESR level 0—20 mm/1h	First ESR level test	61.85±2.98	50.31± 4.20	0.024*
	Second ESR level test	66.97±3.12	52.26±3.77	0.000**
	Last ESR level test	81.08±3.98	61.02±4.54	0.000**

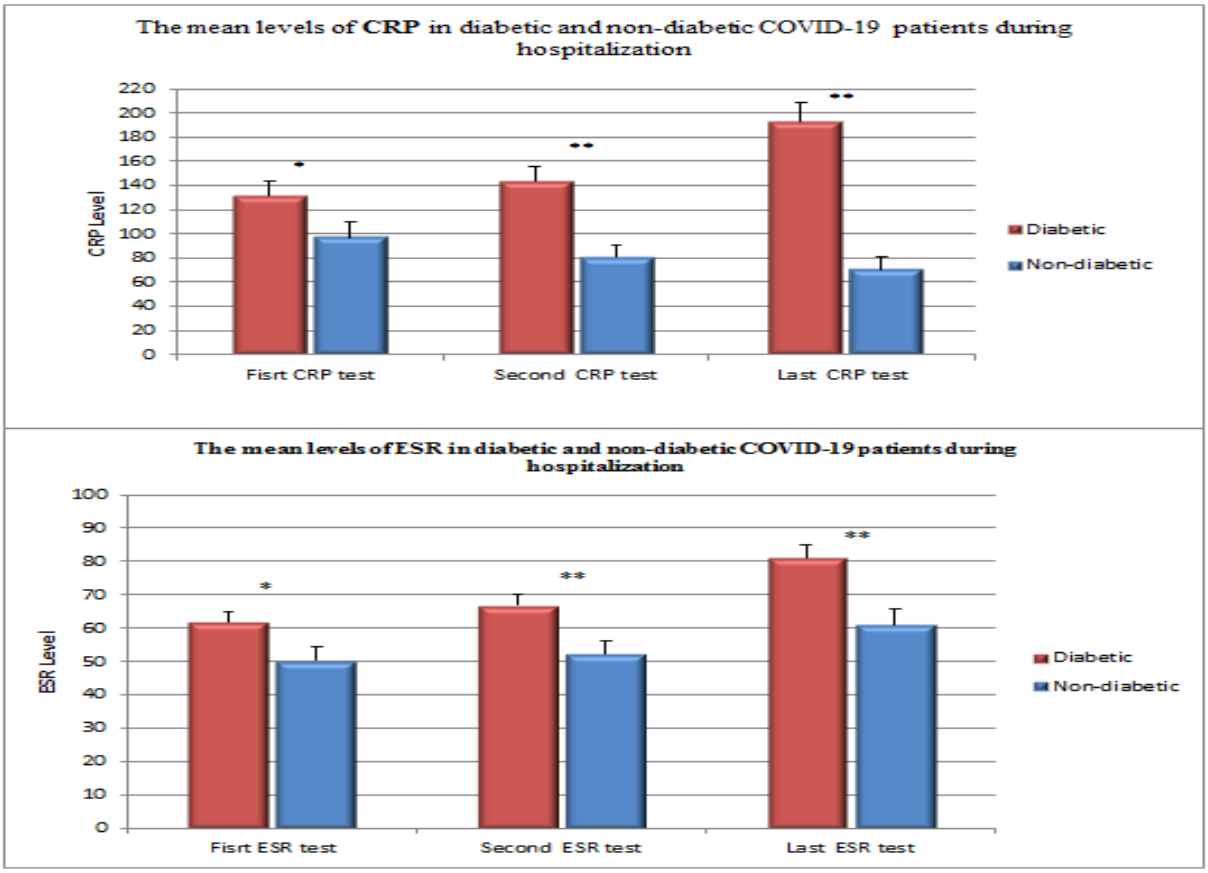
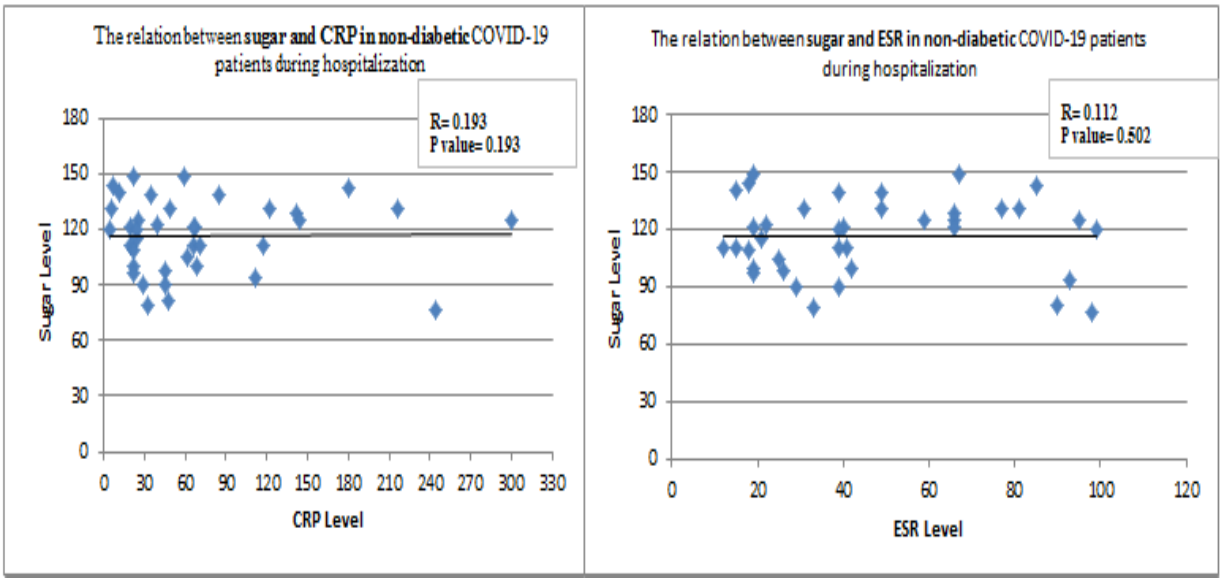


Figure 3: Shows She Mean Levels Of Three Tests Of Inflammatory Biomarkers (CRP And ESR) In Diabetic And Non-Diabetic COVID-19 Patients During Hospitalization.

4.2.1 The relation between sugar and inflammatory biomarkers (CRP and ESR) in diabetic and non-diabetic COVID-19 patients during hospitalization

In non-diabetic patients, there was no relation between sugar and CRP, where r= 0.193 and P value >0.05, whereas a strong positive significant relation was seen between the sugar and CRP in diabetic patients, where r= 0.367 and P value = 0.023. Furthermore, no relation was seen between the sugar and ESR in non-diabetic patients (r=0.112), in contrary, in diabetic patients this relation was positive but not significant, where r= 0.237 and P value = 0.109 (Figure5).



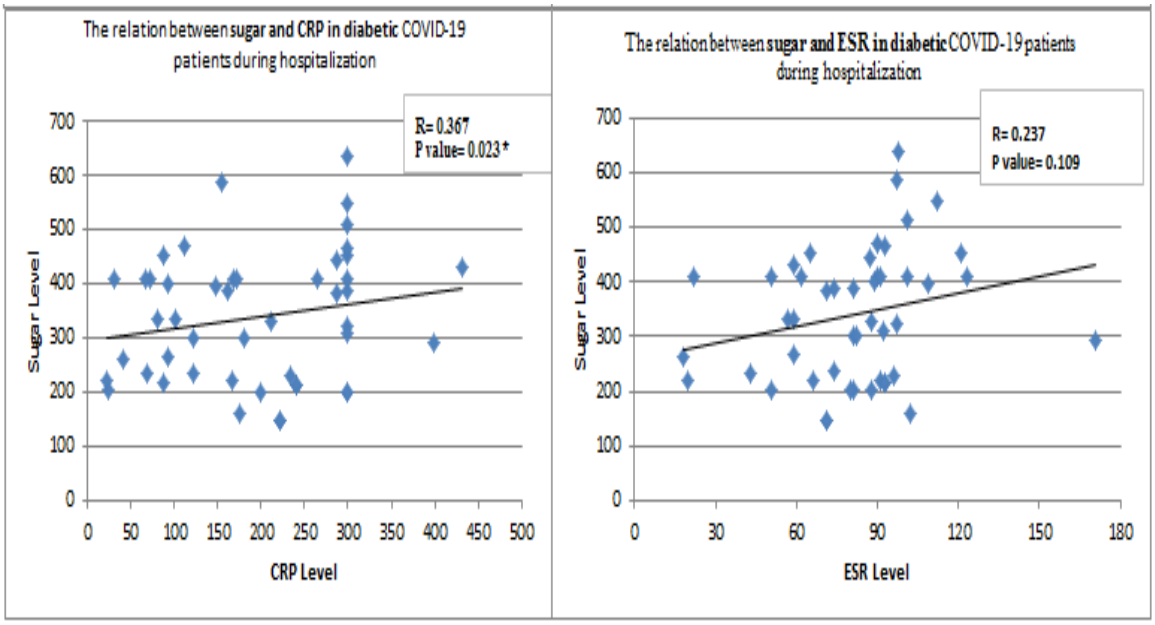


Figure 4: Shows The Relation Between Sugar And Inflammatory Biomarkers (CRP And ESR) In Diabetic And Non-Diabetic COVID-19 Patients During Hospitalization.

4.3 The mean level of three tests of coagulation biomarker (D-dimer) in diabetic and non-diabetic COVID-19 patients during hospitalization

A significant abnormal higher level of D-dimer was seen in diabetic patients in compare with non-diabetic patients, where the P=0.000. In diabetic patients, according to the three tests done during the admission stay, level of D-dimer was increased noticeably from 3090.21±478.22 to 3982.29±477.21. In contrast, in non-diabetic patients, the D-dimer level wan not changed remarkably during the hospitalization (Table 4 and Figure 6).

Table 4: shows the mean level of three tests of coagulation biomarker (D-dimer) in diabetic and non-diabetic COVID-19 patients during hospitalization (P-value ≤0.001).**

Blood routine parameters	Three D-dimer level tests	Diabetic Mean±SEM	Non-Diabetic Mean±SEM	P-value
D-dimer level 0—500 mg/dl	First D-dimer level test	3090.21±478.22	1109.21±192.94	0.000**
	Second D-dimer level test	3335.38±454.74	1174.26±168.68	0.000**
	Last D-dimer level test	3982.29±477.21	1679.18±379.46	0.000**

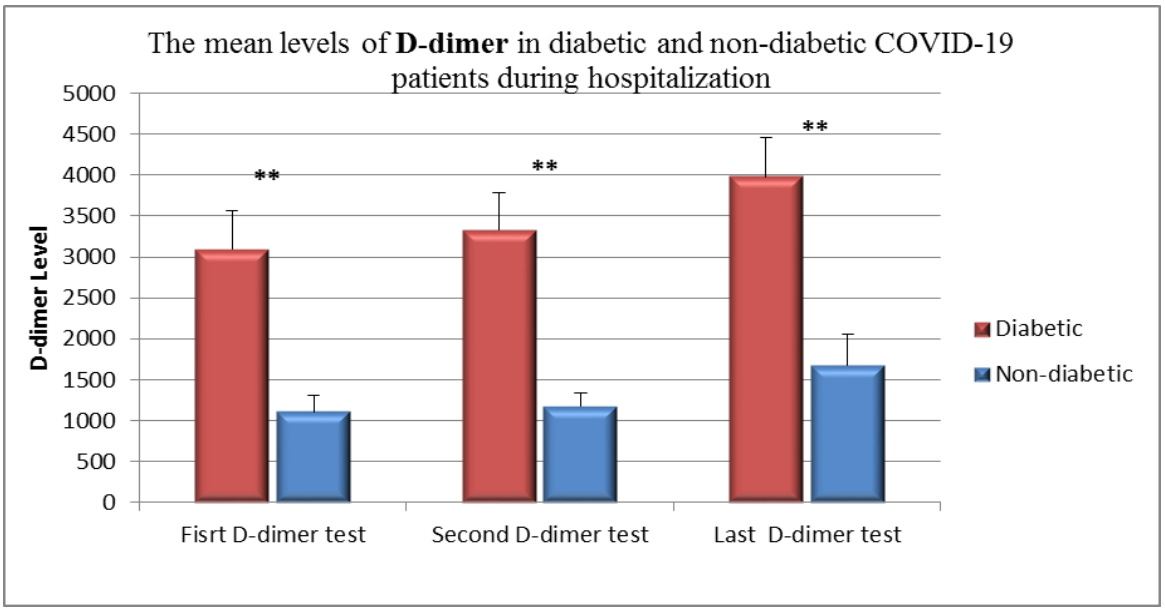


Figure 5: shows the mean level of three tests of coagulation biomarker (D-dimer) in diabetic and non-diabetic COVID-19 patients during hospitalization.

4.3.1 The relation between sugar and D-dimer in diabetic and non-diabetic COVID-19 patients during hospitalization

In non-diabetic patients, there was no relation between sugar and D-dimer, where r=0.144 and p value = 0.388, while in diabetic patients sugar was positively correlated with D-dimer and this relation was significant (r=0.314 and P value =0.032) (Figure 7).

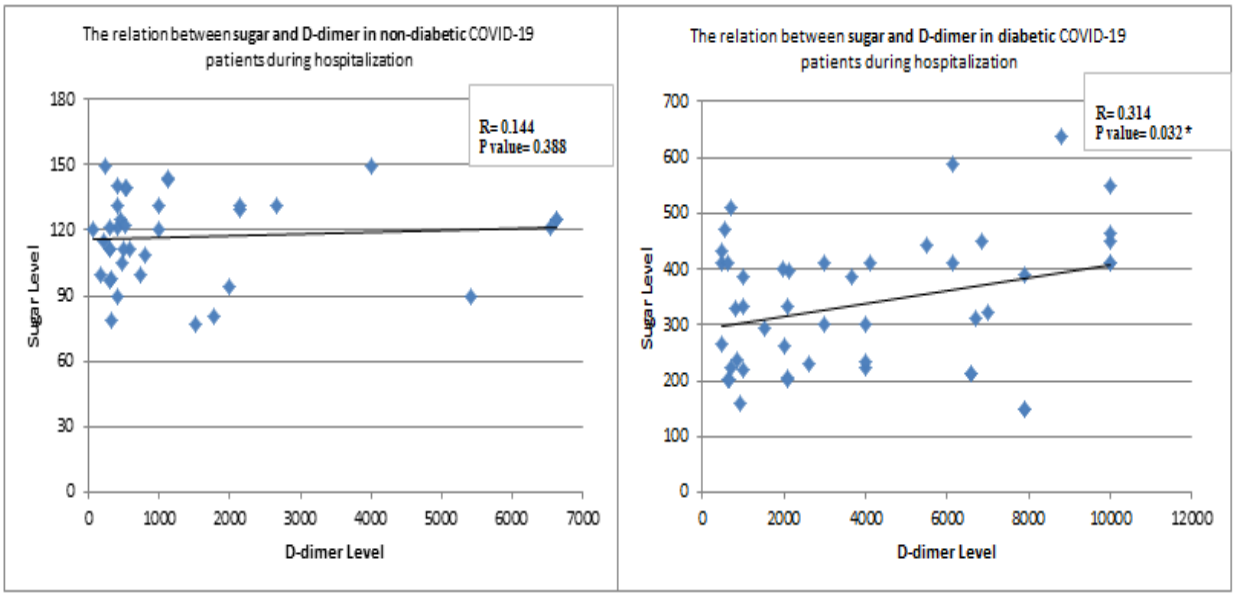


Figure 6: Shows The Relation Between Sugar And D-Dimer In Diabetic And Non-Diabetic COVID-19 Patients During Hospitalization.

4.4 The mean levels of three tests of renal function (urea and creatinine) in diabetic and non-diabetic COVID-19 patients during hospitalization

The renal function test results were abnormal and high only in diabetic patients. Urea and creatinine increased significantly in diabetic rather than in non-diabetic (P<0.05 and P<0.001). In regard to morbidity, it is observed that as long as the diabetic patients remained longer in the ICU, their urea and creatinine levels became elevated and worse which may indicate kidney failure. Upon admission and until the last test done, the level of urea and creatinine increased dramatically from 60.14±7.0 to 95.12±11.41 and from 1.49±0.14 to 2.05±0.21 respectively. However, in non-diabetic patients the level of urea and creatinine stayed normal during all the admission stay period (Table5 and Figure 8).

Table 5: shows the mean levels of three tests of urea and creatinine in diabetic and non-diabetic COVID-19 patients during hospitalization (P-value ≤0.001 and *P≤0.05).**

Blood routine parameters	Three renal function level tests	Diabetic Mean±SEM	Non-Diabetic Mean±SEM	P-value
Urea level 10-50mg/dL	First urea test	60.14±7.0	37.26±3.77	0.009*
	Second urea test	86.80±11.02	38.34±4.32	0.000**
	Last urea test	95.12±11.41	40.28±4.24	0.000**
Creatinine level 0.3-1.2mg/dL	First creatinine test	1.49±0.14	1.05±0.10	0.018*
	Second creatinine test	1.77±0.19	1.12±0.12	0.010*
	Last creatinine test	2.05±0.21	1.13±0.13	0.001*

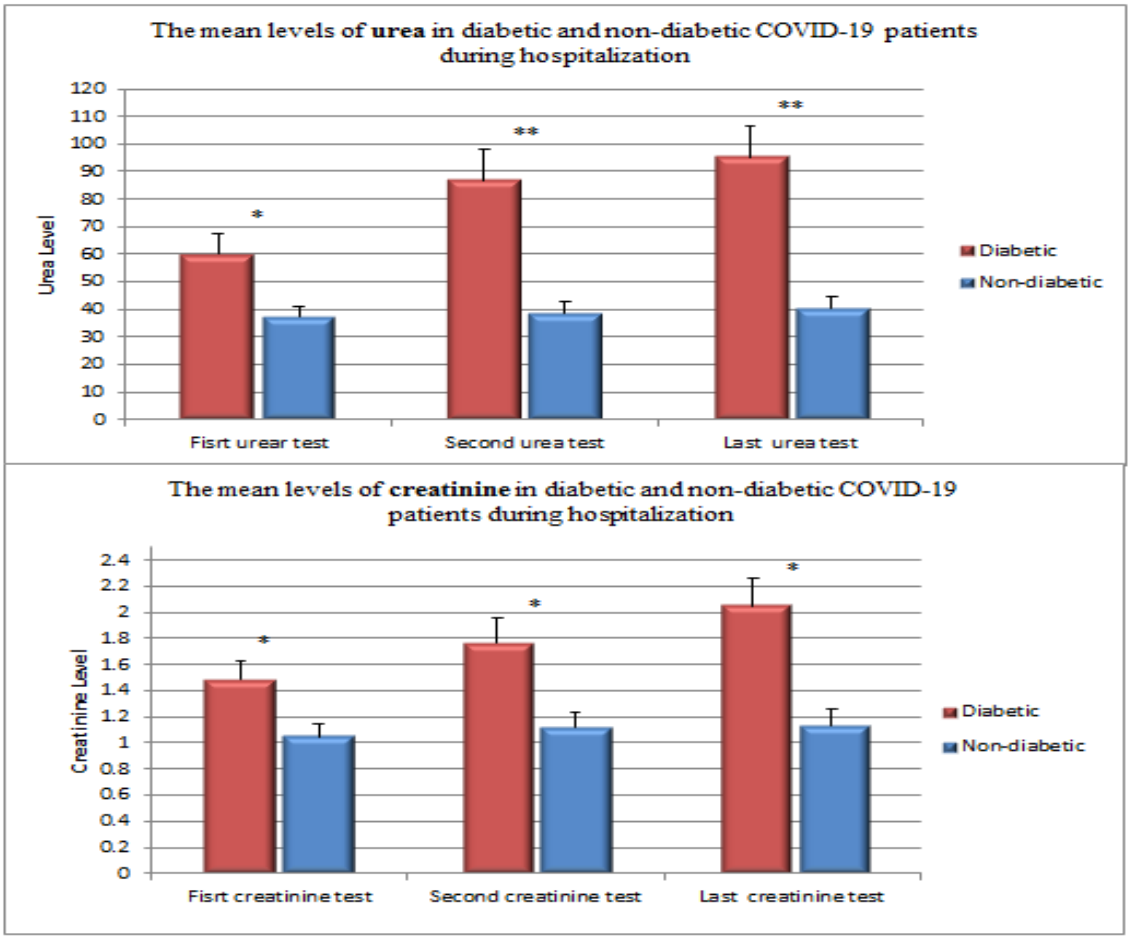
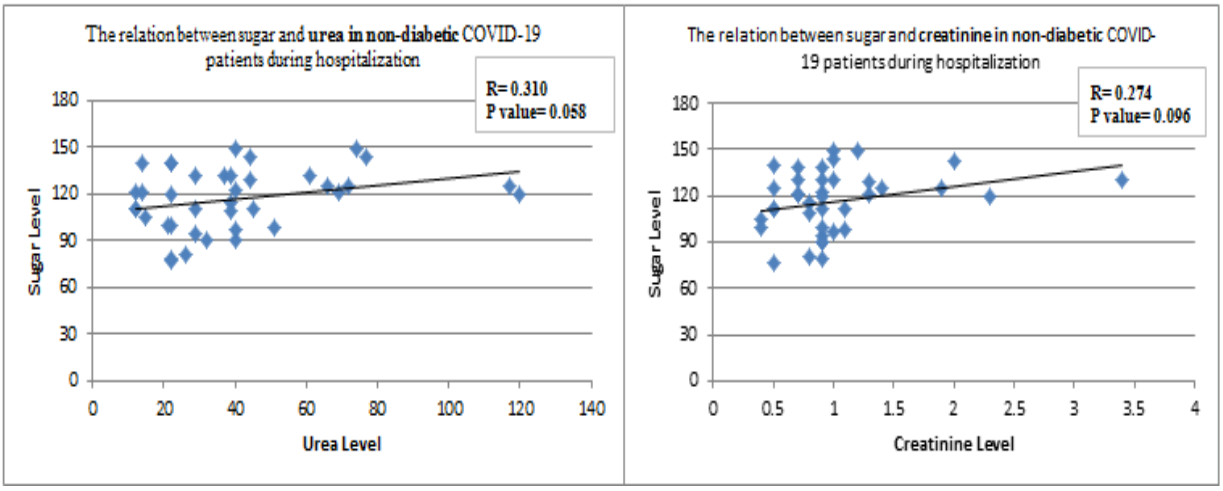


Figure 7: shows the mean levels of three tests of urea and creatinine in diabetic and non-diabetic COVID-19 patients during hospitalization.

4.4.1 The relation between sugar and renal function test (urea and creatinine) in diabetic and non-diabetic COVID-19 patients during hospitalization

There was positive relation between sugar and urea in both diabetic patients (r= 0.310) and non-diabetic patients (r= 0.302), but this relation was only significant among diabetic patients, where P value= 0.039. Moreover, the correlation between sugar and creatinine was positive in diabetic and non-diabetic patients, where r= 0.274 and 0.244 respectively, but not significant (p value >0.05) (Figure 9).



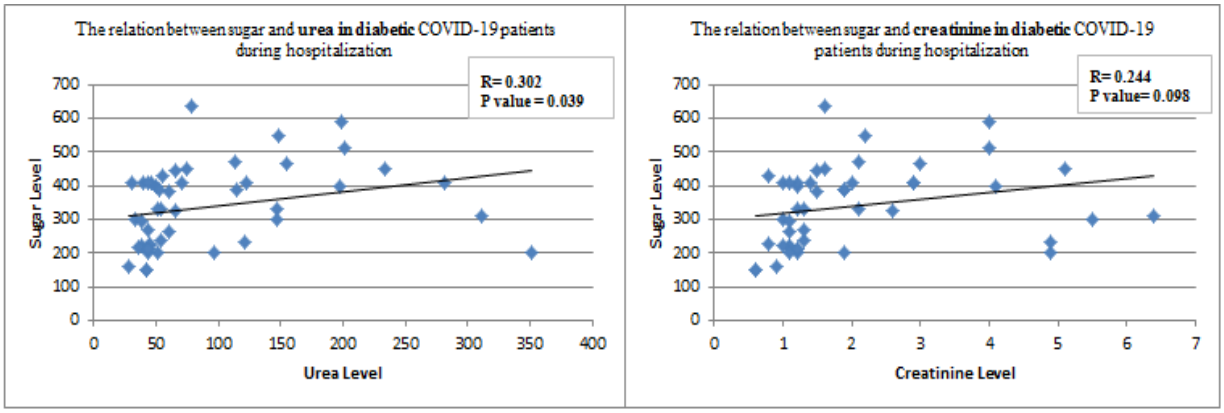


Figure 8: shows the relation between sugar and renal function test (urea and creatinine) in diabetic and non-diabetic COVID-19 patients during hospitalization.

4.5 The mortality rate among diabetic and non-diabetic COVID-19 patients during hospitalization in the isolation centre

The mortality rate among all critically ill COVID-19 patients who were admitted to the ICU was high, where forty out of the eighty five patients died, means nearly half of the patients died (47.1%). Shockingly, DM patients have much higher death rate (66%) and lower survival rate (34%) than non-DM patients during all the period of admission to the ICU, 31 out of the 47 diabetic patients died. Regarding the non-diabetic patients, the mortality rate was 23.7%, where only 9 out of 38 patients died and the survival rate reached 76.3%, where 29 out of 38 patients recovered and discharged the ICU (Table 6 and Figure 10).

Table 6: Shows The Mortality Rate Among Diabetic And Non-Diabetic COVID-19 Patients During Hospitalization In The Isolation Centre.

Critically ill COVID-19 Patients	Mortality	Frequency (n=85)	Percentage (100%)
All patients	Recovery (survivors)	45	52.9%
	Death (non-survivors)	40	47.1%
	Total number	85	100.0%
Diabetic patients	Recovery (survivors)	16	34%
	Death (non-survivors)	31	66%
	Total number	47	100%
Non-diabetic patients	Recovery (survivors)	29	76.3%
	Death (non-survivors)	9	23.7%
	Total number	38	100%

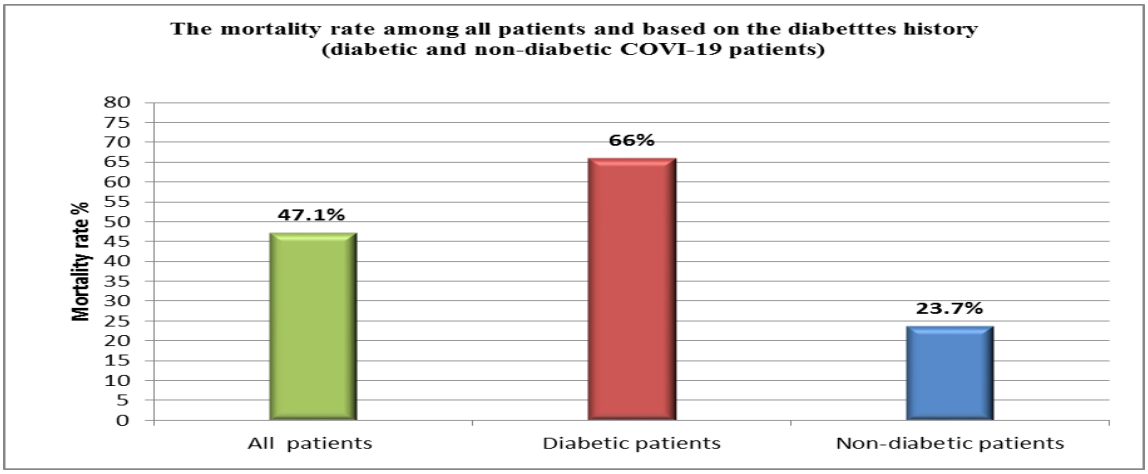


Figure 9: Shows The Mortality Rate Among All Patients And In Diabetic And Non-Diabetic COVID-19 Patients During Hospitalization In The Isolation Centre.

5.0 DISCUSSION

The primary aim of this study was to investigate whether the diabetes mellitus contributes in increasing the morbidity and mortality in hospitalized critically ill patients with COVID-19. In this study, obvious abnormal patterns of hematological, inflammatory, coagulation and renal function biomarker tests were revealed in all diabetic and somewhat in non-diabetic critically ill COVID-19 patients.

The present study showed diabetic patients infected with covid-19 have higher WBCs and neutrophils count than non–diabetic during staying in ICU at the isolation centre (figure &table 1). This is in an agreement with Yan *et al.,* (2020) study who showed that diabetic patient have higher level of leukocytes count (WBC 7.99×10^9/L) than non-diabetic (WBC5.55×10^9/L), and neutrophils count in diabetic were also higher than non-diabetic (7.25×10^9/L vs 3.94×10^9/L). Simultaneously, another supported study done by Li *et al.,* (2020) reported that white blood cell is significantly higher in diabetic than non-diabetic where p value is 0.011. This increase could be due to the high expression of ACE2 receptor on epithelial cells of airway and pancreatic cell in diabetic patient. This ACE2 receptor binds and facilitates the SARS-CoV-2 entry to the host cells, then this virus will replicate inside these cells causing high apoptotic host cells. Death of host cells may subsequently trigger inflammatory response represented by activation of pro-inflammatory cytokines or chemokines that in turn bring more WBCs particularly macrophages and neutrophils to the infections or apoptosis site (Erener 2020).

Moreover, the current study showed that high blood glucose level was positive significant correlated with WBC and neutrophils count in COVID-19 diabetic patients in comparison to non-diabetic patients, the correlation was positive but non-significant (Figure2). This result agrees with a study in China, which indicates that high blood glucose was positively correlated with higher inflammation levels (accumulation of WBC and Neutrophils), and it is a risk factor for the increased severity of COVID-19 (Zhang et al, 2021). In addition, the result of the current study found that most of hospitalized diabetic and non-diabetic covid-19 patients have low lymphocytes count at the first days of hospitalization. As soon as the patients stayed in the ICU, lymphocyte showed more decrease in its count only in diabetic patients (Table& figure1). These results were supported by findings from a multicentre study16 in a Chinese population of patients with COVID-19 (952 with diabetes and 6385 without diabetes), showing that those with diabetes had a higher incidence of lymphopenia (44·5% vs 32·6%) (Zhu *et al.*, 2020).

Gao *et al.,* (2020) research also showed that type 2 diabetic patients had lower lymphocyte count, reached the minimal count faster, and had longer hospital stays than the non-diabetic group, where lower minimal lymphocyte count $0.67 \pm 0.36 * 10^9$/L vs. $1.30 \pm 0.54 * 10^9$/L. The reason behind this may be that lymphocytes count predominately decline after viral infection and this decrease could as result of direct killing of lymphocytes by the virus, the consumption of lymphocytes after virus invasion, apoptosis of lymphocytes and inhibition in function of immunity by virus (Muniyappa & Gubbi, 2020). Furthermore, in some cases, dysregulation of immune response induces an insufficient type I interferon (IFN) production and its responses to virus, abnormally secretion of pro-inflammatory cytokine by alveolar macrophages, and subsequent $CD4^+$ and $CD8^+$ T cell dysfunction (Acharya, Liu and Gack 2020).

The current study displayed that blood glucose was negatively correlated with lymphocytes and was significant in diabetes patients and non-significant in non-diabetic COVID-19 patients (Figure2). This result is supported by Cheng *et al.,* (2021) who reported the correlation analysis showed that hyperglycemia was associated with lymphopenia and deceased lymphocyte subset. COVID-19 patients with DM are more likely to develop severe COVID-19 than those without DM and that hyperglycemia associated with the lymphopenia and inflammatory responses in COVID-19 patients with DM. These indicate that hyperglycemia may affect the lymphocyte and its subsets numbers in COVID-19 conditions (Cheng *et al.,* 2021). This is probably due to that the presence of hyperglycemia weakens the body's innate and immune systems, thereby limiting the body's ability to resist any infection (Zumla *et al.,* 2015).

In addition, in this study hemoglobin and RBCs showed non-significant difference between diabetic and non-diabetic Covid-19 patients (table 2& figure 2). A supported study stated that there were no significant differences among red blood cell count (4.04×10^9/L) vs. (4.14×10^9/L) and haemoglobin 12.4 vs. 12.8 mg/dL P = 0.28; between non-DM and DM patients (Sun *et al.,* 2020). However, a contrary study reported that the assessment of hemoglobin levels was found to be lower in the blood of Covid-19 diabetic (12.63±2.110) individuals compared to non-diabetics (13.43±1.839, p<0.01) (Elemam *et al.,* 2021). Furthermore, platelets count in the present study was significantly lower in diabetic than non-diabetic Covid-19 patients (table 2 & figure 2). This study is in discrepancy with a study conducted in Libya which reported that although significant thrombocytopenia has been found in diabetic patients with severe COVID-19 infection, only around 8% of hospitalized intensive care unit (ICU) patients with DM exhibited decreased platelet counts, perhaps due to serious infective/inflammatory conditions where endogenous and iatrogenic factors affect the count, also Coronaviruses may also infect bone marrow elements, resulting in abnormal haematopoiesis (Jaat *et al.,* 2021).

The finding of the current study revealed that the levels of CRP and ESR were increased abnormally in both

diabetic and non-diabetic, but their levels were significantly higher in diabetic (P<0.001). It is noticeably that, as long as diabetic patients stayed longer in the ICU, their CRP and ESR levels were getting worse and elevated massively (table 3 and figure 4). These results were supported by study carried out in China on severe patients with COVID-19 infection (952 with diabetes and 6385 without diabetes), and found that diabetic COVID-19 patients had elevated level of inflammatory biomarkers (C-reactive protein 57·0% vs 42·4% and ESR 33·3% vs 20·3%). Diabetic COVID-19 patients are more susceptible to the destructive effect of the cytokine storm than those without diabetes (Apicella *et al.*, 2020). Indeed, in several clinical studies in patients with diabetes and COVID-19, worse inflammatory profiles with higher inflammatory markers such as CRP, ESR, IL-6 and ferritin were identified compared to patients without diabetes (Zhu *et al.*, 2020).

The underlying reason might be that diabetes is associated with a proinflammatory state of COVID-19 patients, which results to a higher risk of experiencing a cytokine storm, and this contributes to the risk of a more severe course of COVID-19 patients ending with deterioration or even death (Landstra and de Koning 2021). The proinflammatory cytokines and toxic metabolites that are present in a cytokine storm are already chronically elevated in individuals with diabetes as part of the low-grade chronic inflammation (Hodgson *et al.*, 2015). This is associated with exaggerated macrophage, monocyte and T-cell recruitment, and with decreased regulatory T-cell function, which promotes further inflammation and leading to a more rapid progression of COVID-19 (Landstra and de Koning 2021).

Furthermore, the present research showed no relation between sugar and CRP (P >0.05) in non-diabetic patients, whereas a strong positive relation was seen between the sugar and CRP in diabetic patients (P=0.023) (figure 5). This agrees with Zhang et al (2020) who stated that hyperglycemia was an independent predictor of a high CRP level in patients with COVID-19. Apicella *et al.*, (2020), also confirm that a higher erythrocyte sedimentation rate was seen in patients with COVID-19 with diabetes, compared with patients with COVID-19 without diabetes. Thus, hyperglycemia was positively correlated with higher inflammation levels and more severe illness, and it is a risk factor for the increased severity of COVID-19. After hospitalization of diabetic patients, the massive release of cytokines and glucocorticosteroids during an overwhelming viral infection induced the stimulation of gluconeogenesis and increased insulin resistance, as well as the possibility of acute pancreatic β-cell damage via angiotensin-converting enzyme 2, which might contribute to this elevation in blood glucose levels (Lu *et al.*, 2020). Based on those results, it was suggested hyperglycemia would be a symptom of severe illness (Zhang *et al.*, 2021).

The current study showed level of D-dimer was a significantly higher in diabetic than non-diabetic Covid-19 patients (P=0.000) (Table4 and figure4). This result is in line with study done by Mishra *et al.*, (2020) who identified that patients with diabetes had significant higher D-dimer levels than non-diabetic (p value =0.002), peak D-dimer levels were 1509 ± 2420 ng/mL (Mean ± SD) in people with diabetes and 515 ± 624 ng/mL (Mean ± SD) in patients without diabetes. More supportive study found that increased D-dimer levels have been found in people with hyperglycemia and COVID-19, reducing hyperglycemia is followed by a decrease of the D-dimer (Sardu *et al.*, 2020). Li *et al.*, (2020) pointed out that For patients with diabetes with COVID-19, D-dimer levels increased dramatically during admission, we found patients with COVID-19 especially those with diabetes with a higher level of D-dimer at admission, their D-dimer continues to increase intensively and are significantly associated with the risk of death (Li *et al.*, 2020).

Simultaneously, the present research showed in diabetic patients glucose level was positively correlated with D-dimer and this relation was significant (p =0.032) (Figure 7). This is in clear similarity with sardu *et al.*, (2020) who reported that D-dimer levels were correlated with blood glucose levels, where D-dimer levels were higher in patients with hyperglycemia than in those with normoglycemia (P = 0.001). Therefore, it is possible that COVID-19 infection with diabetes is more likely to cause activation of extrinsic coagulation pathway and increase blood viscosity leading to hypercoagulable state with a worse prognosis (Gupta *et al.*, 2019). This is because diabetes is associated with a prothrombotic state, with an imbalance between clotting factors and fibrinolysis and an increased risk of thromboembolic events. Persistent hyperglycemia can lead to endothelial dysfunction and inflammation which can lead to thrombus formation (Domingueti *et al.*, 2016). D-dimer is an activation marker of fibrinolysis. Some studies have shown that D-dimer was a robust prognostic predictor in pneumonia and sepsis patients (Li *et al.*, 2020).

The renal function test results were abnormal in diabetic and normal in non-diabetic patients, where the level of urea and creatinine increased significantly increase in diabetic rather than in non-diabetic COVID-19 patients (P≤0.05) (Table5 and Figure8). This is in agreement with Khalili *et al.*, (2021) who reported that among 254 patients hospitalized for COVID-19 (127 with diabetes and 127 without diabetes), 58 patients (22.8%) developed acute kidney disease or injury (AKI) during hospitalization; patients with diabetes were more likely to develop AKI and also experienced more severe AKI compared with patients without diabetes. Moreover, it is confirmed that patients with diabetes had a greater prevalence of comorbidities than non-diabetes (hypertension 83·9% vs 50·0%; cardiovascular disease 45·2% vs 14·8%; chronic pulmonary disease 12·9% vs 3·3%; and chronic kidney disease 6·5% vs 3·3%)

(Apicella *et al.*, 2020). This could be due to dehydration after several days of high fever and diarrhea, to a high level of positive end expiratory pressure, or direct viral cytopathic injury of renal cells (Cecconi *et al.*, 2020). SARS-CoV-2 might directly target the kidney through an angiotensin-converting enzyme (ACE) 2-dependent pathway, causing acute renal impairment and increased lethality (Apicella *et al.*, 2020).

There was positive relation between sugar and renal function test (urea and creatinine) in diabetic patients and non-diabetic patients but this relation was only significant among diabetic patients (0.039) (Figure 9). This finding is in clear similarity with other studies which found that diabetes mellitus is independent risk factors for AKI development in COVID-19 pneumonia patients, and the severity of AKI in these patients is positively associated with older age, higher BMI, and diabetes mellitus (Khalili *et al.*, 2021). Leon-Abarca *et al.*, (2020) found that diabetes has significant additional impacts on Covid-19 patients with CKD compared to patients with CKD alone; such impacts include the high rate of infection, increased ICU admissions and high fatality rate. The direct virus entry into the kidneys through ACE2 receptors, which are overexpressed in renal tubular cells of diabetic CKD patient, is one of the potential mechanisms of SARS-CoV-2-induced kidney injury. This is supported by the presence of SARS-CoV-2 in the urine swabs of infected patients as well as the observation of viral particles on histopathological examination (Khalili *et al.*, 2021).

The current study showed that DM patients have much higher mortality rate (66%), where 31 out of 47 diabetic patients died than non-DM patients, where the mortality rate was 23.7% and only 9 out of 38 non-diabetic patients died during all the period of admission to the ICU (Table 6 and Figure 6). This result is corresponding very closely to study's findings in Wuhan found that in 1122 patients with COVID-19 admitted to hospital in the USA, the mortality rate was four times higher in those with diabetes or hyperglycaemia during the hospital stay (28·8%) than those with normoglycaemia. The mortality was higher in those with hyper glycaemia and without known diabetes than in patients with known diabetes (6·2%) (Bode *et al.*, 2020). Another supported study showed that patients with diabetes and uncontrolled hyperglycemia had a mortality rate of 28.8% compared to a mortality rate of 6.2% in other patients, they also had an increased length of stay (Rao *et al.*, 2020). More closed study reported that death occurred in 40 of 96 uncontrolled patients with hyperglycaemia (41·7%) compared with deaths in 13 of 88 patients without diabetes (14·8%, p<0·001) (Apicella *et al.*, 2020).

In addition, evidence from epidemiological observations in regions heavily affected by SARS-CoV-2 and reports from the Centers for Disease Control and Prevention (CDC) and other national health centres and hospitals showed that the risk of a fatal outcome from COVID-19 is up to 50% higher in patients with diabetes than in those who do not have diabetes (Bornstein *et al.*, 2020). A retrospective study of 451 people with COVID-19 with diabetes from the U.S. reported that people with uncontrolled hyperglycemia had longer length of stay and higher mortality compared with people without diabetes (Hartmann-Boyce *et al.*, 2020). In general, people with diabetes are at increased risk death because of defects in innate immunity affecting phagocytosis, neutrophil chemotaxis, and cell-mediated immunity. Acute hyperglycemia can have important metabolic effects. High glucose levels lead to an osmotic diuresis with electrolyte loss and hypovolemia and can inhibit host defences (Muniyappa and Gubbi 2020). However, a French observational study in hospitalized diabetic patients with COVID-19 did not find an association between long-term glucose control and COVID-19 outcomes and deaths but had a smaller sample (Hartmann-Boyce *et al.*, 2020).

6- Study limitations

Several limitations of the current study are worth mentioning. First, this study involved a relatively small number of critically ill patients admitted to 2 isolation centres. Therefore, a large sample size could give a more comprehensive understanding of diabetes and its impact and complications on Covid-19 patients. Second, a prior diagnosis of diabetes was identified through the patient history from the medical record review and haemoglobin A1c levels were not obtained to detect the onset of diabetes. Finally, the study assessed only the laboratory biomarkers tests of COVID-19 during patient's admission to ICU; more detailed information from other laboratory tests and clinical outcomes were unavailable at the time of analysis. Thus, it is recommended to involve more precise investigations to draw an accurate conclusion. Further studies are still needed.

7- CONCLUSION

Diabetes mellitus has been one of the most consistent risk factors for severe disease in patients with COVID-19 and uncontrolled hyperglycemia has been associated with poor outcomes and mortality. This study found that hospitalized COVID-19 patients with DM have poor outcomes and a higher mortality rate than non-DM patients. This could be due to diabetes being associated with worsening several blood parameters which could serve as predictable markers to assess the COVID-19 severity and mortality risks. Diabetes in patients with COVID-19 poses a great clinical challenge, one that requires a great effort, and an indispensable strategy to reduce the risk of medical complications and death among hospitalized COVID-19 patients as much as possible. Consequently, analysis and control in glucose levels of patients with COVID-19 seems important to keep glucose levels in a "safer" range, and perhaps improve outcomes.

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