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Measuring of D-dimer and Other Biochemical Parameters as an Early Markers of Severity in COVID-19 PATIENTS with/without Diabetes Mellitus Type II in Al Muthanna Province

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***Abstract*---**Backgrounds: Since December 2019, when the coronavirus 2019 (Covid-19) first appeared in Wuhan and quickly spread throughout China, data on the clinical characteristics of the infected patients have been needed (Guan et al. 2020). Diabetes mellitus (DM) is a metabolic alteration characterized by chronic hyperglycemia. DM is considered one of the most common comorbidities in COVID-19 patients (Conget 2002). Aim: To identify the clinical variance between Covid-19 patients with and without DM (type II). Methods: The study contain 132 patients divided into four groups, there was 66 patients of them infected by COVID-19 with or without diabetic. The study was started from September 2021 to February 2022. Results: The results of the study appeared elevation the values of the most parameters measured for patients with/without diabetic such as D-dimer, ALT, AST, Blood Glucose, and Ferritin. But no change in Bilirubin and Alkaline phosphate (ALP). Conclusion: The COVID-19 patients with DM (type II) may be have the highest risk factors, which can increase the mortality, elevate the inflammation markers and affect the life enzymes (ALT, AST)..

***Keywords*---**COVID-19, Diabetes mellitus, D-dimer.

Introduction

Since the pandemic began in December 2019 in Wuhan, China, coronavirus has been spread around the world (COVID-19) and infected around 279,764,546 million people worldwide, resulting in 5,412,658 deaths. Hypercoagulability and an increase the risk of venous thromboembolism (VTE) episodes are closely

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connected to COVID-related mortality, which can result in thrombo-inflammation in extreme cases. As a result, coagulation biomarkers may help to define patient triage, therapy methods, and prognosis monitoring, as well as, help to predict disease severity and mortality (Zhan et al. 2021).

Coronaviruses name comes from the crown-like spikes on the virus's outer surface. Coronaviruses contains a single-stranded RNA nucleic material ranging in length from 26 to 32 kilobases (Kbs) and tiny (65–125 nm in diameter) (Shereen et al. 2020).

DM patients maybe at an increased risk when they infected by Coronavirus. DM has been one of the most common diseases in COVID-19 patients. It could also be due to the fact that diabetics have inherent characteristics that make them more susceptible to the cytokine storm. As a result of the imbalance between fibrinolysis and coagulation factors. This condition may be associated with an increased risk of thrombotic events, which can lead to mortality (Miri et al. 2021).

In SARS patients, liver damage was observed, which was primarily characterized in the early stages of the disease by modest to moderate elevations of ALT and/or AST. When compared to moderate instances, patients who were in the critically situation, they were more likely to have liver injury. The research was done to figure out the mechanism of SARS-COV causes liver damage (Xu et al. 2020). COVID-19-related hypoxia and shock-related consequences (such as respiratory distress syndrome, systemic inflammatory response syndrome, and multiple organ failure) maybe also causes hypoxia-reperfusion dysfunction and hepatic ischemia. Experimental data indicate that inflammatory cell (both *in vivo* and *in vitro* models of hypoxia and hepatic ischemia) show hepatic cell death caused by hypoxia (Feng et al. 2020).

The key enzymes in the renin–angiotensin system is angiotensin converting enzyme 2 (ACE2) (RAS) (Wu 2020). It is a homologue of ACE and regulate the fluid, blood pressure, systemic vascular resistance, and electrolyte balance as part of the balancing responses triggered by ACE (Crackower et al. 2002)(Danilczyk and Penninger 2006).

Renin breaks down the globular protein angiotensinogen (inactive) to produce angiotensin I. (Ang I, a decapeptide hormone). Angiotensin I convert to angiotensin II (Ang II, an octapeptide hormone) via Angiotensin-converting enzyme (ACE). Ang II has active effects because it binds to receptors (Paul, Mehr, and Kreutz 2006).

SARS-CoV-2 infects liver cells via binding to the angiotensin-converting enzyme 2 receptor (ACE2), which is found in the liver cells and bile duct. ACE2 expression was found in 59.7% of cholangiocytes and 2.6% of hepatocytes, implying that the virus induces liver function impairment by directly affecting ACE2 expression in cholangiocytes (Ali and Hossain 2020).

Acute-phase reactants are a collection of plasma proteins that are heterogeneous (Malone et al. 2017). D-dimer is a soluble fibrin degradation product (FDP) produced by fibrinolysis, which results in the orderly disintegration of thrombi.

The D-dimer is a useful activated marker for coagulation and fibrinolysis (Weitz, Fredenburgh, and Eikelboom 2017). D-dimer was appeared to be a considerable important indicator of severe pneumonia in the patients with COVID-19 infection. Around 90% of COVID-19 patients with pneumonia had elevated D-dimer levels that predicts the death of patients with pneumonia (Hodges et al. 2020)(Farid et al. 2021). According to several research, patients with diabetes, as well as those with microvascular and macrovascular complications have elevated D-dimer levels (Mishra et al. 2020).

Ferritin is an iron storage protein that serves as the body's major iron storage protein and is essential for maintaining iron homeostasis (Knovich et al. 2009). Serum ferritin levels are increased in both the severe and more severe COVID-19 groups. Increased ferritin levels in COVID-19 might suggest a serious secondary bacterial infection and be used as a predictor of poor outcome (Cheng et al. 2020). In several studies, Individuals with diabetes have high blood ferritin levels, and it is well recognized that they are more likely to have major COVID-19 problems (Khalil et al. 2018).

Materials and Methods

The study included 132 patients divided into four groups, 33 patients have type 2 diabetes mellitus, 33 patients have Covid-19 without diabetic, 33 patients have Covid-19 with diabetic, and 33 patients as control group for comparison, Male or female (40-75) years old. The study was throughout the period since from September 2021 to February 2022.

Results and Discussions

The statistical analysis showed highly significant differences for fasting blood glucose (FBG) when compared DM with (DM+COVID) and control group. As seen before in a study by Abdi *et al* 2020 (Abdi et al. 2020), who was found COVID-19 severity is more likely in diabetics than in other patients and consisted of 14.5% of COVID-19 patients. The increase in severity may be due to uncontrolled DM, as high blood glucose is associated with defective immune response, and increased risk of secondary infection and delayed healing that all contribute to increase the severity of COVID 19 infection. As many of the DM patients are well controlled on oral antidiabetic agents and insulin.

In relation to liver function tests (LFT), the current study showed a significant variance in ALT values means among four groups (Covid and control, DM with Covid+DM), where p value was <0.0001. Also there were a significant variances in ALT values means among (DM, Control) groups when they were compared with (DM&Covid) group, since the p value was <0.0001, and between control group when compared with COVID group, where p value was 0.008. At the time, there was no significant variance between COVID group and DM group, also between control group and DM group, where p value was 0.06 and 0.08, respectively. However, there were a significant differences between Covid and Control groups, As they're found in the study (Chen et al. 2020).

This study also showed a significant variance in AST values means among four study groups (Covid and control, DM with Covid+DM), where p value was <0.0001. The results appeared a significant differences for AST when compared between (Covid+DM) group with control and DM groups, where p value was <0.0001. In addition, there are a non-significant differences among Covid and DM where p value was 0.06 and a significant differences among Control and Covid groups, where p value was <0.0001. As a result the finding is there was a non-significant difference among Covid patients with diabetic and non-diabetic in this study (With, Diabetesin, and Muthanna 2021).

There are many causes for the elevation of AST and ALT in patients with DM and COVID 19 infection, these include pre-existing liver injury in patients with DM, drug side effects, and sepsis (there is mild, transient elevation of liver enzyme that occur in critically ill patients). There is a debate whether COVID 19 can cause hepatitis by itself as many studies referred to that the COVID-19 virus causes a type of liver injury which causes transient hepatitis (Puli, Baig, and Walayat 2020). The Bilirubin test and ALP findings were non-significantly difference among four groups (DM with Covid+DM, Covid and control), were p value was 0.62, as seen in the study by Zoe Reinus *et al* 2021 (Bloom et al. 2021).

Table 1 shows a significant variance in D-dimer values means among four groups (Covid and control, DM with Covid+DM), where p value was <0.0001. Also, the statistical analysis showed a significant differences for D-dimer when compared DM group with (COVID+DM) and COVID groups, which means Covid-19 is associated with increased D-dimer levels that agreed with the previous results carried by Yogendra Mishra 2020 (Mishra et al. 2020), who was found Diabetes patients in COVID-19 exhibited higher D-dimer values. Finally, it's possible that COVID-19 infection that combines with DM will result in a hypercoagulable state with a poor prognosis. D-dimer and other acute phase reactants are elevated in groups with severe COVID19 infection as they reflect markers of systemic inflammatory response syndrome (SIRS). The body response to infection by vasodilation, edema and recruitment of WBC maybe have a relationship between D-dimer and the severity of infection, which is a directional to a severe infection that caused an elevated D-dimer level. The elevated D-dimer is a sign of severity and worse outcome as it’s a fibrin degradation product (FDP) that predict thrombosis risk which is a recognizable complication of severe infection.

Furthermore, this study showed a significant variance in Ferritin values means among four groups (Covid and control, DM with Covid+DM), where p value was <0.0001. The results in this study showed a significant difference in Ferritin levels. There was a considerable difference among (COVID+DM) group when compared with control and DM groups, where the p-value was <0.0001 for Ferritin means. Also, it was found a considerable difference among the COVID group when compared with control and DM groups, where the p-value was 0.009 for Ferritin means. Our results are similar to that observed by Weina 2020 (Guo et al. 2020), Who was found a significant variance between COVID-19 patients with and without DM where the p-value was 0.01 and found a highly significant difference with other groups. Also, this study showed a significant variance in WBC values means among four study groups DM with (Covid and control, DM with Covid+DM), where p value was 0.001., which was comparable with the data

carried by Jingqi Zhou *et al* (Anon 2021). Ferritin as one of the acute phase reactants that increases in cases of infection, inflammation, and liver disease. Its elevation is a marker of active inflammation and its association with worse prognosis as it is one of the criteria of the severity of COVID 19 infection (Huang et al. 2020).

Table 1: Comparison between the values means of different biochemical parameters in four different groups of healthy people and coronavirus patients with/without diabetic.

parameter	Covid+DM Mean±SD	Covid Mean±SD	DM Mean±SD	Control Mean±SD	P-value
FBG	323.45±72	180.52±49.1	163±33.2	89.9±8.04	<0.0001
AST	45.424± 21.8	32 ± 18.7	25.57 ± 8.2	22.4 ± 6.02	<0.0001
ALT	59.36± 48.3	45.12±35.6	32 ±9.7	24.84±6.7	<0.0001
ALP	93.84 ± 33.6	91.93 ± 33.6	87.93 ± 22.2	91.27±21.8	0.863
Bilirubin	0.61 ± 0.16	0.59 ± 0.12	0.56 ± 0.16	0.57 ±0.15	0.62
D-dimer	2596 ± 2397	1901 ± 1988	192 ± 73.8	208 ± 72.5	<0.0001
Ferritin	1016 ± 1737	646 ± 393	65.09 ± 39.5	69.09 ±28.8	<0.0001
WBC	11.46 ±4.5	9.68 ± 6.3	7.95 ± 1.3	7.91 ± 1.7	0.001

Table 2: Comparison between the values means of different biochemical parameters within each two different groups (diabetic with/without Covid) and (healthy and Covid patients).

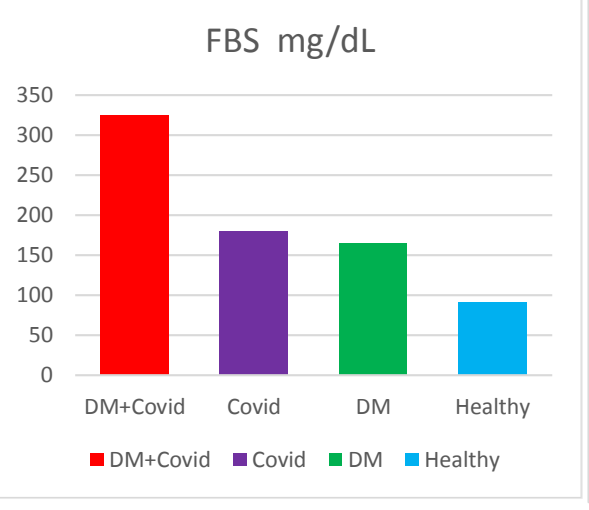
parameter	DM Mean±SD	Covid+DM Mean±SD	P-value	Control Mean±SD	Covid Mean±SD	P-value
FBG	163± 33.2	323.45 ±72	<0.0001	89.9 ±8.04	180.52±49.1	<0.0001
AST	25.57± 8.2	45.42± 21.8	<0.0001	22.4± 6.02	32 ± 18.7	<0.0001
ALT	32 ±9.7	59.36± 48.3	<0.0001	24.84±6.7	45.12±35.6	0.008
ALP	93.84± 33.6	87.93± 22.2	0.40	91.27±21.8	91.93 ± 33.6	0.92
Bilirubin	0.56 ± 0.16	0.61 ± 0.16	0.28	0.57 ±0.15	0.59 ± 0.12	0.18
D-dimer	192 ± 73.8	2596± 2397	<0.0001	208 ± 72.5	1901 ± 1988	<0.0001
Ferritin	65.09± 39.5	1016± 1737	<0.0001	69.09±28.8	646 ± 393	0.009
WBC	7.95 ± 1.3	11.46 ± 4.5	0.001	7.91 ± 1.7	9.68 ± 6.3	0.007

Conclusion

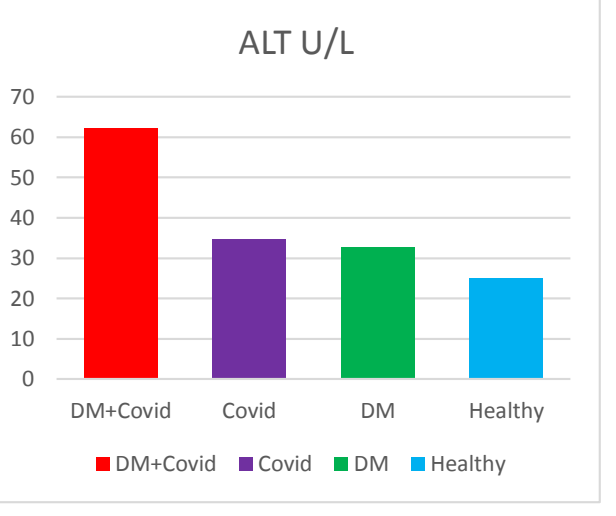
Patients with and without diabetes mellitus were compared in a clinical trial (type II). ALT and AST abnormalities are prevalent, particularly in patients with pre-existing illnesses. Higher liver enzymes might be related to certain medications used for treatments and many other factors including the virus itself can cause transient hepatitis.

Covid-19 patients the level of D-dimer was increased, D-dimer is a sensitive marker of infection, inflammation, and tissue damage and could be used as an indicator of the extent and progression of Covid-19. In addition, Level of ferritin was an increased. The ferritin test is conducted in patients with Covid-19 to determine the extent of inflammation and to predict the prognosis in hospitalized Covid-19 patients.

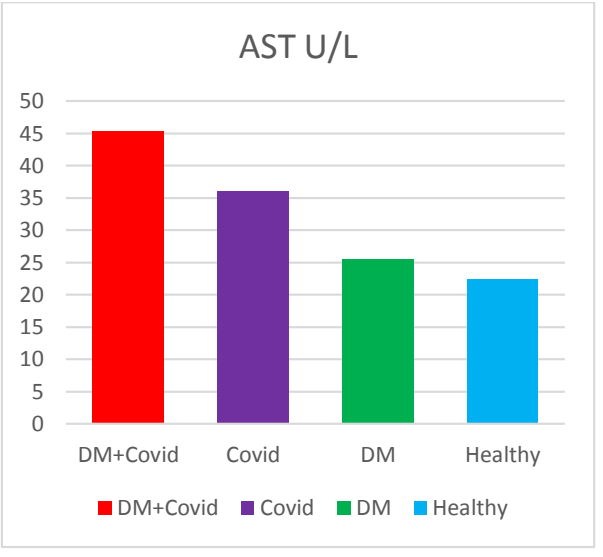
(A) FBS mg/dL



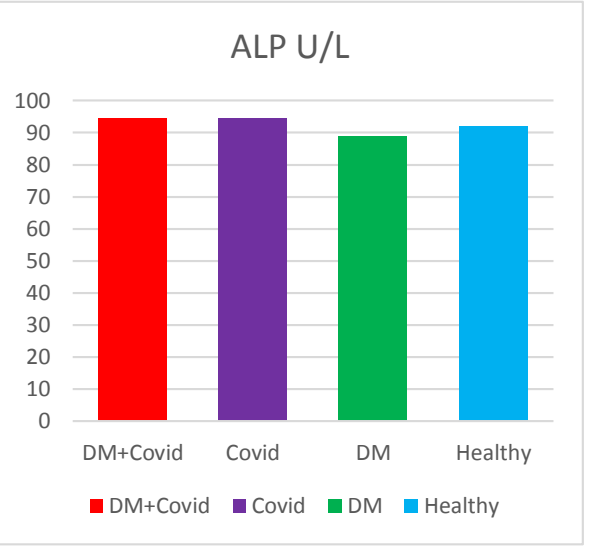
(B) ALT U/L



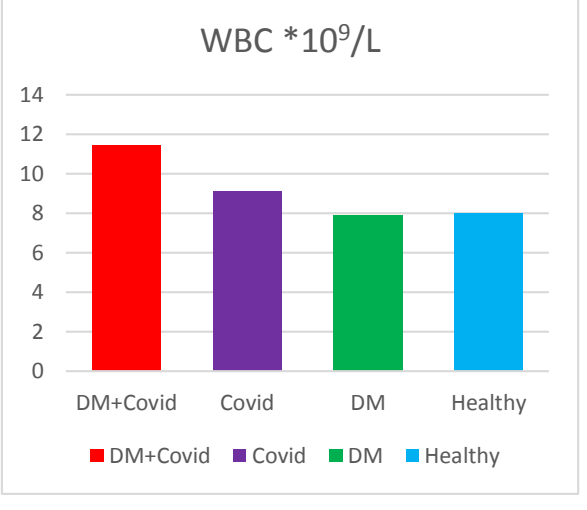
(C) AST U/L



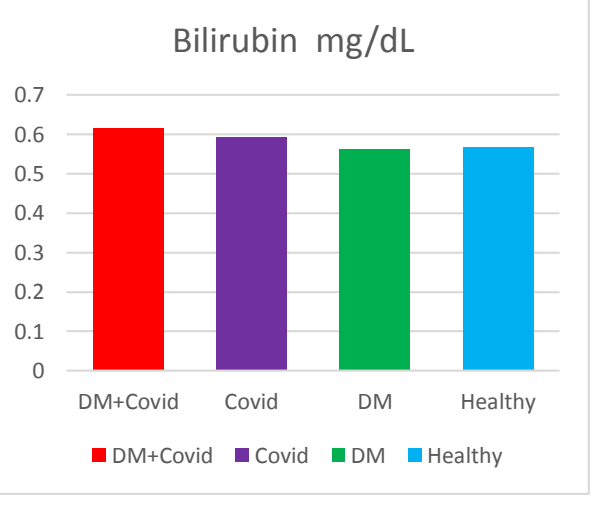
(D) ALP U/L



(E) Bilirubin mg/dL



(F) WBC *10⁹/L



(G) D-dimer ng/mL **(H) Ferritin µg/mL**

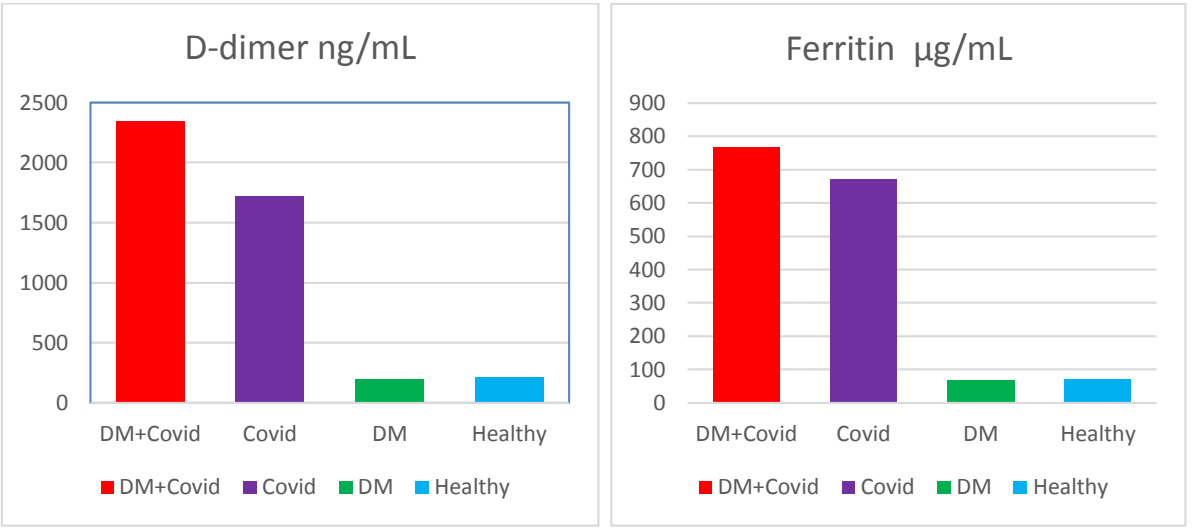


Figure: Comparison between the values means of different biochemical parameters of laboratory tests among four study groups. (1) Control: Healthy persons, Blue color, (2) DM: Diabetes mellitus, Green color (3) COVID: COVID without diabetes, Purple color (4) COVID+DM: COVID with Diabetes, red color. Data are appeared for (A) FBS: fasting blood sugar, (B) ALT: alanine aminotransferase, (C) AST: aspartate aminotransferase, (D) ALP: Alanine phosphate, (E) Total Bilirubin, (F) WBC: White Blood Cells, (G) D-dimer, and (H) Ferritin.

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