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Article

Evaluation the Role of Ghrelin Hormone, D-Dimer and Biochemical Variable in Covid - 19 Patients

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Abstract: This study was directed in the epidemiological unit of Kirkuk General Hospital - Kirkuk Health Directorate, Iraq, from January 10, 2024, to May 12, 2024. It included 83 individuals, both male and female, aged between 17 and 66 years, divided into two groups. The first group included 58 patients with confirmed COVID-19 infection, while the control group consisted of 25 healthy individuals. Tests were conducted in the virology laboratory at Kirkuk General Hospital. The results of the study indicated that COVID-19 infection significantly affected the levels of the studied variables, leading to increased levels of Ghrelin, D-Dimer, WBC, S.T-cholesterol, S.TG, S.LDL-C, S.VLDL-C, and S.Glucose, with average values of 3.757, 1949.03 ng/ml, 11.71 × 10^3 cells/ml, 251.40, 176.83, 197.36, 35.44, and 358.33 mg/dl for each variable, respectively. In contrast, the infection significantly reduced the levels of PCV and S.HDL-C, reaching 37.26% and 19.51 mg/dl, respectively. Additionally, the interaction between gender and age significantly affected the levels of Ghrelin, D-Dimer, PCV, and WBC, while it had no significant effect on the other studied variables.

Keywords: COVID – 19, Ghrelin, D-Dimer, Lipid profile

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1. Introduction

Coronaviruses are a large family of viruses that can cause diseases in animals or humans (Lu et al., 2020). There are seven coronaviruses that can infect people worldwide, but humans are usually infected with four human coronaviruses: 229E, NL63, OC43, and HKU1 are coronaviruses that typically lead to respiratory infections, which can range from mild illnesses like the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Additionally, the coronavirus identified in recent years, COVID-19, results in a significant infectious disease. This zoonotic disease is caused by the coronavirus responsible for Severe Acute Respiratory Syndrome 2 (SARS-CoV-2). Initially, the World Health Organization (WHO) referred to this infectious disease as Novel Coronavirus Pneumonia (NCIP), and in 2019, the virus was named Novel Coronavirus (2019-nCoV). On February 11, 2020, the WHO officially renamed this clinical condition to COVID-19 (short for Coronavirus Disease-19). As knowledge about this virus continues to evolve rapidly, it is recommended that readers frequently update their information (Ahmad et al., 2020).

COVID-19 is a respiratory infection caused by SARS-CoV-2, leading to a cascade of systemic events that impact various organs and tissues. Understanding the pathophysiology of COVID-19 is essential for effective patient treatment and for comprehending the causes of complications in many individuals who have recovered (Manta et al., 2022). The majority of the pathophysiological effects of this virus arise from its entry point, which is the Angiotensin-Converting Enzyme 2 (ACE2), a critical component of the Renin-Angiotensin System (RAS) (Ryan and Caplice, 2020). Additionally, the pathophysiological bases that determine that pre-existing conditions such as cardiovascular diseases (CVD), diabetes, and obesity, which increase patients' susceptibility to worse outcomes, are also associated with alterations in ACE2 levels or the function of the Renin-Angiotensin System (RAS). (Logette et al., 2021).

Although COVID-19 is primarily a respiratory disease, it can impact multiple organ systems, including the gastrointestinal system, liver, heart, nervous system, and kidneys (Zhou et al., 2020). Thrombotic complications and coagulopathy, such as disseminated intravascular coagulation, are prevalent in COVID-19. These issues likely result from the activation of the coagulation cascade due to the presence of the virus in the bloodstream, a cytokine storm, or possibly secondary infections and organ dysfunction (Wool and Miller, 2021).

Numerous reports have highlighted the most common clinical symptoms in individuals infected with COVID-19, including the loss of smell and taste (Giacomelli et al., 2020). This loss could theoretically negatively impact the patient's appetite. A multicenter European study indicated that some COVID-19 patients experienced a loss of appetite in conjunction with other symptoms (Lechien et al., 2020). However, the mechanism by which the coronavirus affects appetite in patients remains unclear (Hakami et al., 2021).

The human appetite hormone, ghrelin, is typically secreted into the bloodstream to stimulate food intake and enhance appetite through a complex neurohormonal mechanism (Disse et al., 2010). Ghrelin is a peptide made up of 28 amino acids and is primarily secreted by the stomach lining. It is also present in saliva, where it can influence taste (Groschl et al., 2005). For instance, ghrelin has been shown to reduce the perception of sour taste while enhancing the sweetness of flavors. Although the exact role of ghrelin in saliva is not yet fully understood, its secretion appears to have an impact on both taste and appetite (Shin et al., 2010).

Ghrelin-producing cells are located not only in the gastrointestinal organs but also in various other tissues (Sato et al., 2012). In addition to its role in appetite regulation, ghrelin influences many other biological processes, including glucose homeostasis, hormone secretion, cell proliferation, and survival. It also plays a significant role in regulating immune function and inflammation (Mathur et al., 2021). Recent studies indicate that ghrelin has protective effects in models of acute lung injury (Valle et al., 2021). Previous reports have shown that ghrelin treatment improves morphological damage and pulmonary parameters while reducing pro-inflammatory cytokine levels in serum in models of acute lung injury induced by pancreatitis (Zhang et al., 2020).

D-dimer is a fibrin degradation product commonly used as a biomarker for thrombotic disorders. A D-dimer level below 0.5 micrograms/mL is generally considered normal, with values increasing with age and during pregnancy. D-dimer levels also rise with the severity of community-acquired pneumonia (Querol-Ribelles et al., 2004). Following the outbreak of the COVID-19 pandemic, D-dimer was identified as a potential prognostic indicator in COVID-19 patients. Studies have shown that D-dimer values on the day of admission can be promising predictors of disease severity (Soni et al., 2020).

Accurate and widely available predictive biomarkers can be very helpful in managing COVID-19; therefore, the current study aims to assess ghrelin hormone levels and some other biological variables in patients with coronavirus.

2. Materials and Methods

Study Sample: This study was conducted at the Epidemiological Unit of Kirkuk General Hospital - Health Directorate of Kirkuk Province, Iraq, from January 10, 2024, to May 12, 2024. The study sample included 83 individuals, both males and females, aged between 17 and 66 years, divided into two groups. The first group consisted of 58 patients with confirmed COVID-19 infection, while the control group included 25 healthy individuals. Tests were conducted in the Virology Laboratory at Kirkuk General Hospital.

Blood Collection: Blood samples were collected at the sample collection station of the Epidemiological Unit, where 5 mL of blood was drawn using a sterile syringe through venipuncture and collected in glass tubes inside a gel tube for separation. The tubes were centrifuged for 10 minutes at a speed of 1500 RPM. The serum was separated from the cells, and the supernatant was removed. The serum was then taken for testing several targeted biochemical parameters in this study.

Studied Variables

Ghrelin Test: Total ghrelin was measured in all samples using a human ghrelin testing kit in a 96-well format (BT, Shanghai, China), following the manufacturer's procedures. Each sample was diluted four times in a dilution solution, and 100 µL of this dilution was transferred to the corresponding wells. Then, 50 µL of the compound was added to each well, except for the blank well. The plate was covered and incubated for 60 minutes at 37°C. Afterward, 50 µL of substrate A and B were added to each well, including the blank well. The plate was covered again and incubated for an additional 20 minutes at 37°C. The reaction was then stopped, and the optical densities of the standards and samples were measured at 450 nm using the Bio Tek EL 340-microplate reader. The detection limit for the ELISA technique ranged from 0.0 picograms/mL to 100 nanograms/mL. A graph was plotted using the absorbance values of the standards and their corresponding concentrations (Hakami et al., 2021).

D-Dimer: Blood samples from the study participants were collected and sent to the laboratory within twenty-four hours for D-dimer evaluation. D-dimer was measured using fluorescent immunoassay technology with the STANDARD F200 analysis kit (SD Biosensor, Korea), and the Getein 1100 device for quantitative fluorescent immunoassay (Getein Biotech Inc., China), as Additionally, the mispa-i2 (Agappe Diagnostics Ltd., India) was used. All kits employed had a biological reference range of less than 0.5 micrograms/mL, and all results were reported in fibrinogen equivalent units (FEU, nanograms/mL) (Poudel et al., 2021).

Measurement of Packed Cell Volume (PCV): A small sample of blood was drawn and preserved in a tube containing an anticoagulant. This sample was then placed in a PCV capillary tube, filling two-thirds of the tube with blood. One end of the tube was sealed, and it was placed in a microhematocrit centrifuge for 5 minutes at a speed of 5000 revolutions per minute. After centrifugation, the capillary tube was analyzed using a PCV Hematocrit Reader, which indicates the percentage of packed cell volume relative to the total blood volume (Turgeon, 1990).

White Blood Cell Count (WBC): The count of white blood cells was determined using a hemocytometer. A specified volume of blood was diluted with a dilution solution (Turk's Solution), which lyses red blood cells and stains the nuclei of white blood cells, making them easier to count and differentiate. This procedure is crucial for reducing the cell density visible under the microscope, allowing for clearer observation of individual cells. Blood was drawn up to the 0.5 mark, and then diluted with the solution up to the 11 mark. The diluted blood was mixed thoroughly, and a drop was placed on a slide cover (Talaro, 2005).

Lipid profile: The levels of total cholesterol and triglycerides were measured using ready-made kits provided by Biolabo France (Burtis and Ashwood, 1999). HDL-C was measured using the enzymatic method with a ready-to-use Biolabo kit, following the procedure outlined by Kostner (1976). LDL-C levels were calculated using the formula: LDL-C (Conc.) = Total cholesterol Conc. - HDL-C Conc., based on the concentration of low-density lipoprotein cholesterol, adhering to the previously described method (Fischbach, 2000).

S. glucose: A method utilizing 4-aminophenazone as a color coupler in combination with sulphonated 2,4-dichlorophenol is presented for measuring hydrogen peroxide generated from glucose using glucose oxidase. This method demonstrates sensitivity such that a concentration of 20 μg of glucose in a final volume of 4 mL yields an optical density of 0.61 at 515 nm with 10-mm cuvettes, corresponding to a molecular absorption of twenty-two thousands (Barham and Trinder, 1972).

Statistical Analysis: Once the required data for the studied variables was collected, it was input into a computer and organized using Microsoft Office Excel. Statistical analysis and comparisons of the means among the various groups and categories were performed using Duncan's multiple range test with the Statistical Analysis System (SAS). Additionally, graphical representations were created using Microsoft Office Excel (Al-Zubaidi and Al-Jubouri, 2022).

3. Results

Impact of COVID-19

Table (1) indicates a significant effect of COVID-19 infection on all studied variables, according to the results of Duncan's multiple range test at a 5% significance level. The infection led to elevated levels of Ghrelin, D-Dimer, WBC, S.T-cholesterol, S.TG, S.LDL-C, S.VLDL-C, and S.Glucose, with mean values of 3.757, 1949.03 ng/ml, 11.71 × 10^3 cells/ml, 251.40, 176.83, 197.36, 35.44, and 358.33 mg/dl for each variable, respectively. Conversely, the infection significantly reduced levels of PCV and S.HDL-C, which reached 37.26% and 19.51 mg/dl, respectively.

Table 1. The effect of infection with Covid-19 on the studied variables.

Groups / Variable	Patients		Control		Range
	Mean	±STD	Mean	±STD	
Ghrelin (ng / ml)	3.757 a	0.77	0.352 b	0.10	1-0.5
D – Dimer (ng/ml)	1949.03 a	481.73	171.08 b	20.62	<250
PCV (%)	37.26 b	3.88	41.04 a	3.17	40-50
WBC (×10^3 cell/ ml)	11.71 a	2.08	8.20 b	0.89	4-11
S.T- cholesterol (mg/dl)	251.40 a	13.16	146.80 b	11.73	<200
S.TG (mg/dl)	176.83 a	13.83	82.52 b	30.60	<150
S.HDL-C (mg/dl)	19.51 b	1.36	38.84 a	8.31	>40
S.LDL-C (mg/dl)	197.36 a	11.43	90.92 b	8.02	<100
S.VLDL-C (mg/dl)	35.44 a	2.84	16.41 b	6.12	<30
S. glucose (mg/dl)	358.33 a	90.56	83.20 b	10.23	<100

Means with the same letter are not significantly different.

These data show a variation in Ghrelin hormone levels in COVID-19 patients compared to non-infected individuals, suggesting a potential role for this hormone in the disease process. However, further studies are needed to confirm these findings and to understand the underlying mechanisms of this association.

Impact of the Interaction Between Gender and Age on the Studied Variables

Ghrelin Hormone: Ghrelin is a hormone primarily produced in the stomach and is often referred to as the "hunger hormone" due to its significant role in appetite regulation. It stimulates hunger and increases food intake, while also contributing to the stimulation of growth hormone secretion. Some studies have shown a potential link between levels of this hormone and various medical conditions, including COVID-19.

Figure (1) illustrates significant differences in Ghrelin hormone levels among COVID-19 patients across different gender and age categories. Male patients over 40 years old recorded the highest mean Ghrelin level at 4.36 ng/ml, while the lowest mean level of Ghrelin, at 3.35 ng/ml, was observed in females under 30 years old. The results indicated that males exhibited higher Ghrelin levels compared to females, and older age groups (30-40 years and over 40 years) had higher Ghrelin levels compared to those under 30 years. It appears that age and gender play a role in determining Ghrelin hormone levels. For instance, there was a difference in mean Ghrelin levels between males and females within the same age group, particularly noted in the age group over 40 years. The presence of statistical differences among certain groups suggests that these differences are not random but may be related to other factors such as disease severity or the presence of chronic illnesses. In the study by Kuliczkowska-Płaksej et al. (2023), a statistically significant effect of gender was found in the relationship between COVID-19 and ghrelin concentration, with lower levels observed in men.

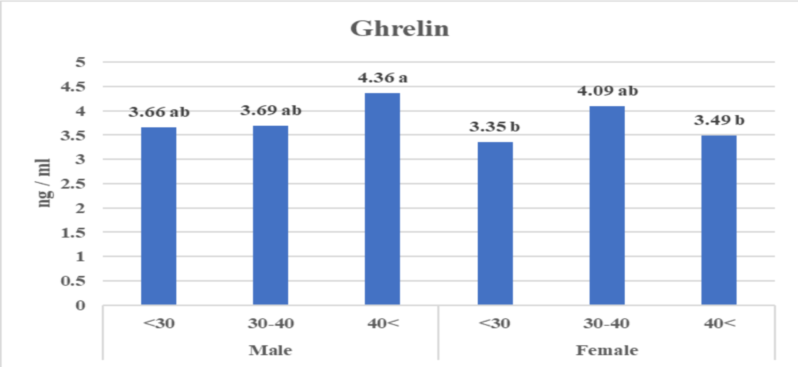

Figure 1. The effect of the interaction between gender and age on ghrelin levels in COVID-19 patients.

Means with the same letter are not significantly different.

D-dimer: Is a protein produced when blood clots break down and is used as a marker in testing for coagulation disorders. A D-dimer level is considered elevated when blood clots are present in the body, such as in deep vein thrombosis (DVT) or pulmonary embolism (PE). However, D-dimer levels can also rise due to other conditions such as infections, surgery, or pregnancy.

The figure displays D-dimer levels in a studied group of COVID-19 patients, divided by gender and age group. It shows a general increase in D-dimer levels, with significant differences between the averages of the studied groups. Elevated D-dimer levels were observed in all patient categories, both male and female, compared to normal levels, which should not exceed 250 ng/ml. The averages ranged from 1875.9 to 2194.5 ng/ml, indicating an increased risk of blood clots in COVID-19 patients. Moreover, it appears that females generally have higher D-dimer levels compared to males, especially in the age group of 40 years and older, where this group recorded an average of 2194.5 ng/ml, suggesting that females may be more susceptible to blood clots compared to males in the context of COVID-19 infection. Overall, there does not seem to be a significant impact of age group on D-dimer levels. However, a slight increase in levels was noted among females in the age group of 40 years and older.

The elevation of D-dimer levels in COVID-19 patients indicates an increased risk of blood clotting, which can occur in both small and large blood vessels and may lead to serious complications such as pulmonary blood clots, deep vein thrombosis, and stroke.

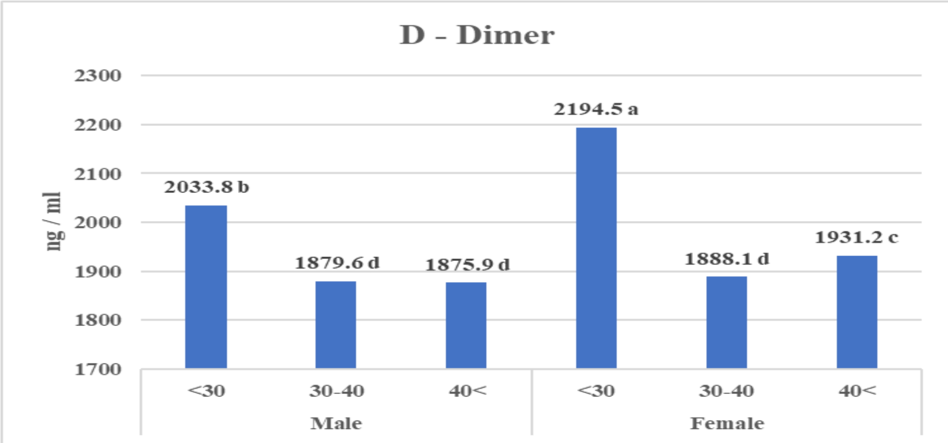

Figure 2. The effect of the interaction between gender and age on D-Dimer levels in COVID-19 patients.

Means with the same letter are not significantly different.

Packed Cell Volume (PCV): It is a medical test used to measure the ratio of red blood cells to the total volume of blood. It helps determine the concentration of red blood cells in the blood. It is a simple and inexpensive test that measures the ratio of red blood cells to the total volume of blood. In other words, it measures the ratio of red blood cells to plasma (the fluid that carries blood cells).

The results shown in the figure indicate some minor differences in PCV values among COVID-19 patients; however, overall, there are no significant differences, with average values ranging from 36.5 to 39 in the age group under 30 years for both males and females, respectively. These results may be useful in understanding the impact of the coronavirus on blood. Regarding the effect of gender, the results show that the average PCV value is slightly higher in females compared to males in the age groups under 30 and 30-40 years. This difference may be related to natural biological factors such as variations in blood volume and hemoglobin levels between the sexes.

The results also indicate a slight decrease in PCV values in some groups, especially among males under 30 years. This decrease may be associated with respiratory inflammation caused by the coronavirus, which can lead to hypoxia and changes in blood volume.

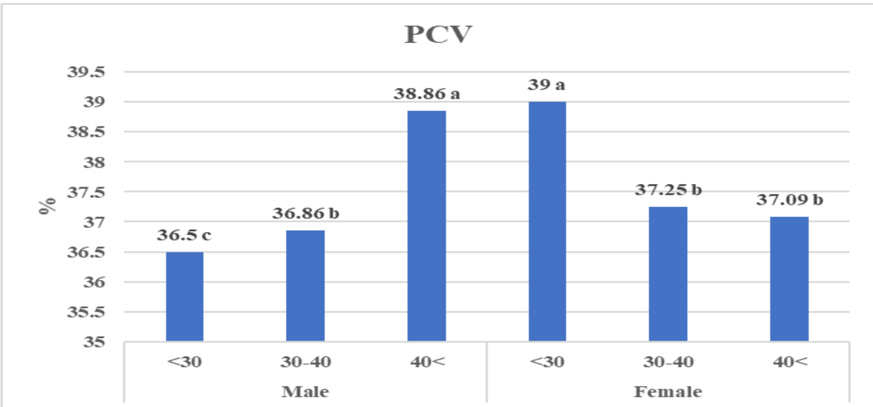

Figure 3. The effect of the interaction between gender and age on PCV levels in COVID-19 patients.

Means with the same letter are not significantly different.

White Blood Cells (WBC): Are important cells in the immune system that play a vital role in defending the body against infections and diseases. White blood cells are present in the blood and are part of the immune system that protects the body from bacteria, viruses, parasites, and other foreign substances.

The figure displays the results of the white blood cell (WBC) count analysis in a sample of patients infected with the coronavirus, divided by gender and age group.

Overall, the results of this study indicate that COVID-19 infection leads to an increase in the white blood cell count, reflecting the immune system's response to the infection. A slight increase in the average white blood cell count was observed in most groups, both males and females, compared to normal reference values.

Regarding gender, there were no significant differences in the average white blood cell count between males and females within the same age group, although it was significant according to the Duncan multiple range test. As for age, there were some minor differences in the average white blood cell count among different age groups, but these differences were not significantly pronounced; the averages ranged between 11.29 and 12.29 × 10^3 cells/ml in males aged 30-40 and under 30 years, respectively. This increase in average white blood cell counts indicates the immune system's response to COVID-19 infection. When the virus enters the body, the immune system is stimulated to produce more white blood cells to combat the infection. The slight differences among the various groups may also be influenced by other factors such as disease severity, the presence of chronic illnesses, or individual responses to the infection.

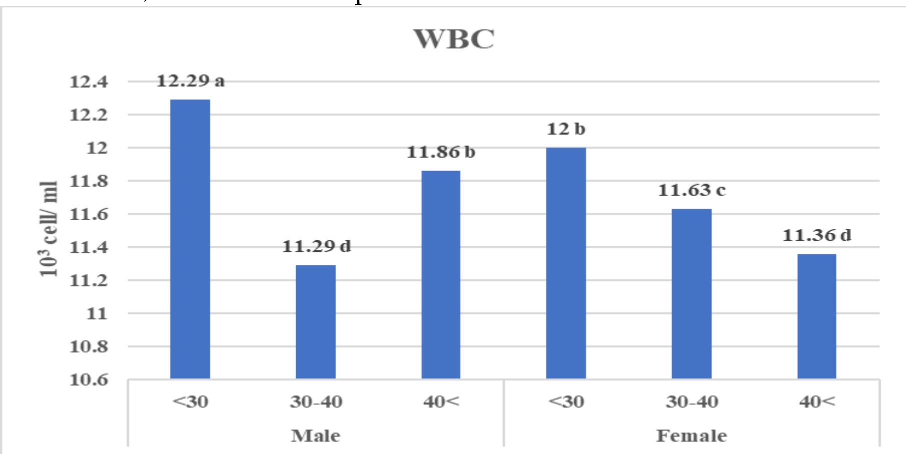

Figure 4. The effect of the interaction between gender and age on WBC levels in COVID-19 patients.

Means with the same letter are not significantly different.

Total Cholesterol (S.T. Cholesterol): Is a measurement of all types of cholesterol in the blood, including low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very low-density lipoprotein (VLDL). This test is used to assess the risk of cardiovascular diseases and helps determine the risk of heart disease and strokes.

The figure shows the results of total cholesterol levels (S.T. cholesterol) in COVID-19 patients, categorized by gender and age groups. A slight decrease in cholesterol levels is observed in males over 40 years compared to the younger age groups. In contrast, an increase in cholesterol levels with advancing age is noted among females, with the age group over 40 years having the highest average cholesterol levels. Overall, cholesterol levels appear to be similar between genders in the 30-40 age group. However, there is a notable difference in the impact of age on cholesterol levels between genders, as levels decrease with age in males, while they increase in females.

Generally, all reported values are considered relatively high, with averages ranging between 248 and 253.18 in patients over 40 years, for both males and females, whereas the normal total cholesterol level is generally considered to be below 200 mg/dl. This indicates that COVID-19 patients in this study have elevated cholesterol levels regardless of gender and age group.

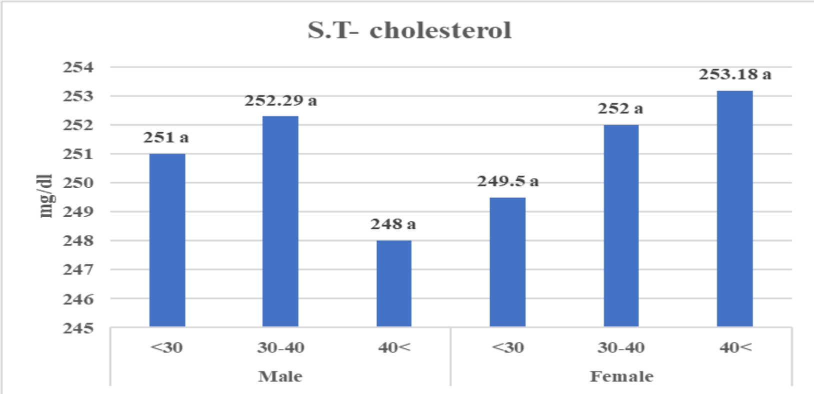

Figure 5. The effect of the interaction between gender and age on S.T-cholesterol levels in COVID-19 patients.

Means with the same letter are not significantly different.

Triglycerides (S.TG) This is a type of fat (triglycerides) found in the blood. The level of triglycerides in the blood is measured as part of an assessment of cardiovascular health. Triglycerides are an important source of energy in the body, but elevated levels can indicate health risks. High triglyceride levels may be associated with an increased risk of heart disease and strokes.

The figure (6) shows the results of triglyceride (S.TG) levels in the blood of patients infected with the coronavirus, classified by gender (male and female) and age groups (<30 years, 30-40 years, >40 years). It is noted that there is no significant effect of the interactions between gender and age on triglyceride levels in patients, with the lowest mean being 168.27 mg/dl for females over 40 years of age, while the highest mean is 181.07 mg/dl for males aged 30-40 years. A noticeable increase in triglyceride levels is observed in males in the 30-40 age group, which then slightly decreases in the older age group over 40 years. Conversely, a significant decrease in triglyceride levels is noted in females over 40 years compared to the younger age groups. Overall, triglyceride levels appear similar between genders in the younger age groups (<30 and 30-40). However, there is a significant difference in the effect of age on triglyceride levels between genders, with levels increasing with age in males (up to a certain age) while decreasing in females after the age of forty. Most of the values mentioned are relatively high, as the normal triglyceride level is generally considered to be less than 150 mg/dl. This indicates that COVID-19 patients in this study have high triglyceride levels regardless of gender and age group, except for females over forty who have levels closer to normal compared to the others.

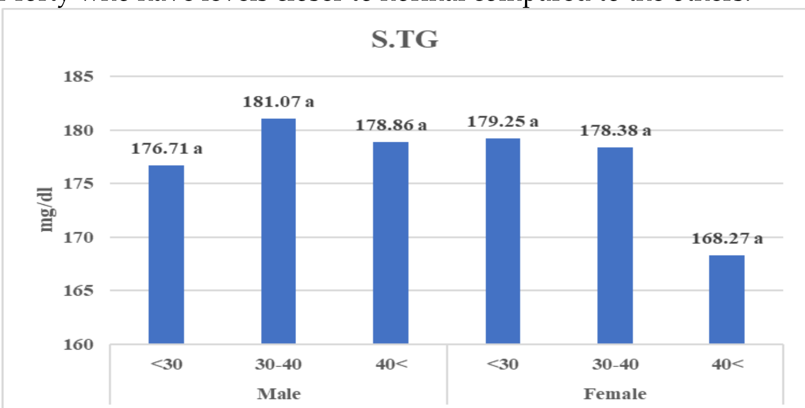

Figure 6. The effect of the interaction between gender and age on S.TG levels in COVID-19 patients.

Means with the same letter are not significantly different.

High-density lipoprotein cholesterol (S.HDL-C): Refers to the level of high-density lipoprotein cholesterol (HDL-C) in the blood, measured in milligrams per deciliter (mg/dl). HDL-C is important because it helps remove harmful cholesterol from the body, thereby reducing the risk of heart disease. A high HDL-C level is considered a healthy indicator, while low levels may signal an increased risk of cardiac issues.

The figure (7) shows the results of HDL cholesterol levels among COVID-19 patients, categorized by gender and age. It is noted that there is no significant effect of the interactions between gender and age on HDL-C levels, with values ranging from 18.88-19.99 mg/dl for patients aged 30-40 years for females and males, respectively. The figure indicates a slight increase in HDL-C levels in males in the 30-40 age group compared to the other two groups, while a decrease in HDL-C levels is observed in females in the same age group, followed by a slight increase in the older age group over 40 years. It shows that HDL-C levels in males are generally higher than in females across most age groups, except in the >40 age group where the difference is minimal. The values presented are within the normal range.

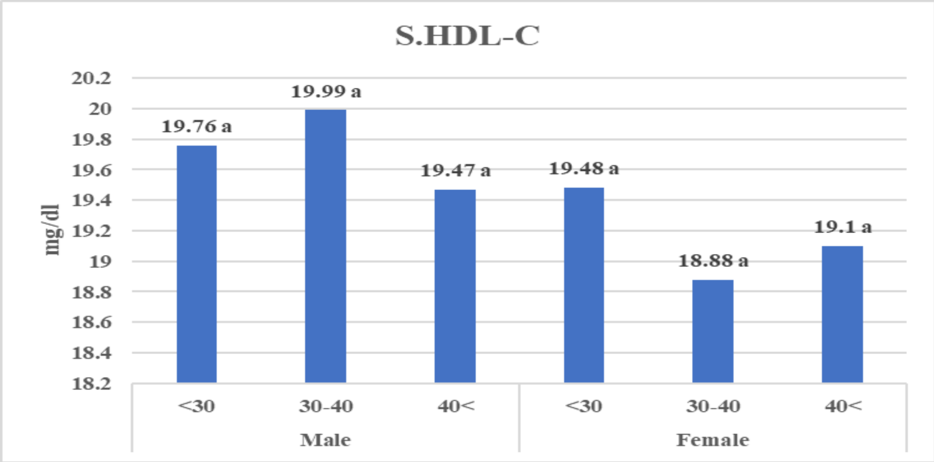

Figure 7. The effect of the interaction between gender and age on S.HDL-C levels in COVID-19 patients.

Means with the same letter are not significantly different.

Low-density lipoprotein cholesterol (S.LDL-C): Refers to the level of low-density lipoprotein cholesterol (LDL-C) in the blood, measured in milligrams per deciliter (mg/dl). LDL-C is the type of cholesterol that can accumulate in the walls of arteries, leading to blockages and increasing the risk of heart disease and strokes. It is preferable for LDL-C levels to be low to maintain cardiovascular health.

The figure (8) shows the results of low-density lipoprotein cholesterol (LDL-C) levels, also known as "bad cholesterol," among a group of COVID-19 patients. It is noted that there is no significant effect of gender and age on LDL-C levels, with means ranging from 191.5-200.9 mg/dl for females under 30 years and those over 40 years, respectively. It is observed that LDL-C levels are higher in males in the 30-40 age group, followed by a decrease in the older age group over 40 years. In contrast, LDL-C levels increase with age in females, with the highest average LDL-C in the age group over 40 years. Overall, LDL-C levels in males are higher than in females in the younger age groups (<30 and 30-40), but the opposite is true in the older age group over 40 years, where females exhibit higher LDL-C levels. All presented values are relatively high, as the optimal level for LDL-C is generally considered to be less than 100 mg/dl. Values between 100-129 mg/dl are close to optimal, while values between 130-159 are considered slightly elevated, 160-189 are high, and over 190 are very high. This indicates that COVID-19 patients in this study have elevated LDL-C levels regardless of gender and age group.

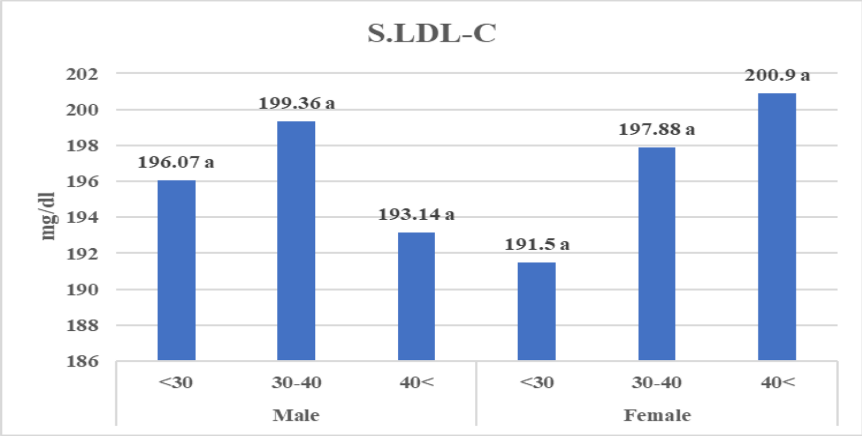

Figure 8. The effect of the interaction between gender and age on S.LDL-C levels in COVID-19 patients.

Means with the same letter are not significantly different.

Very Low-Density Lipoprotein Cholesterol (S.VLDL-C): Refers to the level of very low-density lipoprotein cholesterol (VLDL-C) in the blood, measured in milligrams per deciliter (mg/dl). VLDL-C is a type of fat that carries triglycerides in the blood. Elevated levels of VLDL-C may be associated with an increased risk of cardiovascular diseases, as they can contribute to the accumulation of fats in the arteries. Therefore, monitoring VLDL-C levels is essential as part of cardiovascular health assessment.

The figure (9) shows VLDL cholesterol levels among COVID-19 patients, categorized by gender and age groups. It indicates that there is no significant effect of the interactions between gender and age on VLDL-C levels, which ranged from 33.65-36.54 mg/dl for females over 40 years and males aged 30-40 years, respectively. A higher VLDL-C level is observed in males in the 30-40 age group, followed by a slight decrease in the older age group over 40 years. In contrast, VLDL-C levels decreased in females over 40 years compared to the younger age groups. Overall, VLDL-C levels appear similar between genders in the younger age groups (<30 and 30-40). However, there is a notable decrease in VLDL-C levels among females in the older age group compared to males in the same group. It is important to note that there are no specific and fixed values considered "normal" for VLDL-C levels like there are for LDL and HDL, as VLDL is typically calculated as a fraction of triglycerides (TG/5). Nevertheless, elevated VLDL levels indicate an increased risk of cardiovascular diseases, as VLDL converts to LDL in the bloodstream.

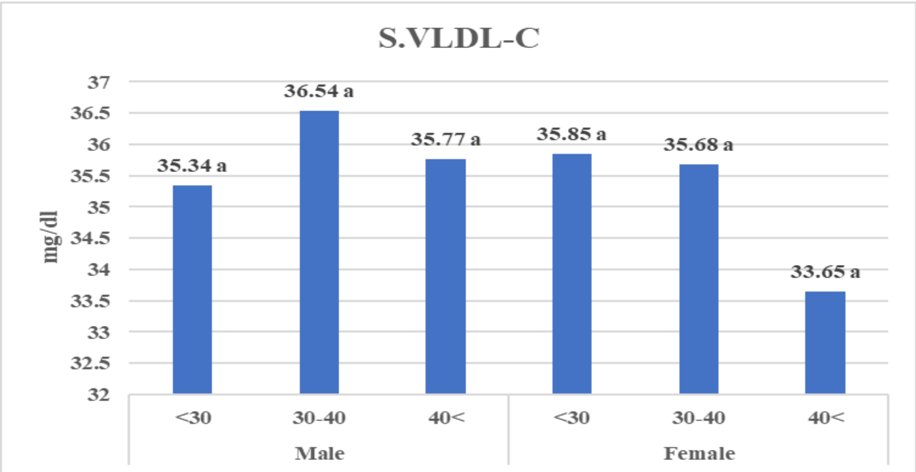

Figure 9. The effect of the interaction between gender and age on S.VLDL-C levels in COVID-19 patients.

Means with the same letter are not significantly different.

S. Glucose: refers to blood sugar levels, measured in milligrams per deciliter (mg/dl). Measuring blood glucose levels is important for diagnosing and monitoring conditions such as diabetes. Blood glucose levels may be measured at different times, such as after fasting or after eating. Normal glucose levels vary, but levels between 70 and 99 mg/dl after fasting (for 8 hours) are typically considered normal, while levels exceeding 126 mg/dl may indicate diabetes.

Figure (10) displays the results of blood glucose levels (S. glucose) in COVID-19 patients, classified by gender and age, showing a significant effect of the interactions between gender and age on blood glucose levels. The highest mean was significantly 388.1 mg/dl in the male group aged 30-40 years, while the female group in the same age range recorded the lowest mean significantly at 327.5 mg/dl. It is noted that glucose levels are significantly higher in males aged 30-40 years, then slightly decrease in the group older than 40, but remain elevated. In contrast, glucose levels in females aged 30-40 years are lower compared to the other two groups, then increase slightly in the group older than 40 years. Overall, glucose levels in males are higher than in females in the younger age groups (<30 and 30-40). However, the opposite is observed in the older age group over 40 years, where glucose levels are similar. All displayed values are considered very high, as normal fasting blood glucose levels are typically between 70-100 mg/dl. Values above 126 mg/dl (fasting) are considered indicative of diabetes. This suggests that COVID-19 patients in this study have significantly elevated blood glucose levels, which may indicate complications related to diabetes or glucose regulation issues due to COVID-19 infection.

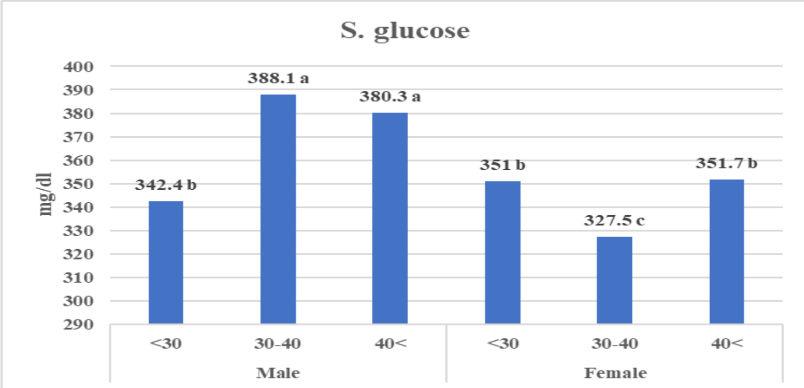

Figure 10. The effect of the interaction between gender and age on S. Glucose levels in COVID-19 patients.

Means with the same letter are not significantly different.

4. Discussion

A study by Leshin et al. indicated that more than half of the reported COVID-19 cases had anorexia as a symptom (Leshin et al., 2020). Similarly, other studies have shown appetite loss in more than 50% of COVID-19 cases along with gastrointestinal symptoms (Pan et al., 2020). Furthermore, appetite loss has been reported to be one of the three most common symptoms of COVID-19 infection (Mao et al., 2020). Thus, a European multicenter study confirmed that appetite loss is a major clinical symptom in COVID-19 positive cases (Leshin et al., 2020).

Individuals across all age groups can contract COVID-19; however, according to the National Health Commission of China (NHC), approximately 80% of deaths have been reported among patients over 60 years old, with 75% of them having pre-existing health issues, including diabetes and cardiovascular diseases (Baloch et al., 2020). According to the WHO situation report No. 7, dated January 27, 2020, the average age of cases detected outside of China was 45 years (ranging from 2 to 74 years). Males predominated among these detected cases (71%). A study involving 138 patients hospitalized due to pneumonia caused by coronavirus (2019-CoV) found that the average age was 56 years (interquartile range: 42-68 years; range: 22-92 years), with 75 (54.3%) being male and 63 (45.7%) female (Wang et al., 2020a). Elderly individuals, especially those with pre-existing health conditions such as asthma, diabetes, or heart diseases, are more likely to die from COVID-19 (CCDC, 2020).

The current results are not consistent with those of Hakami et al. (2021), who did not report significant differences in ghrelin levels between COVID-19 patients and the control group. However, the current results are consistent with those of Kulichkovska-Blasig et al. (2023), who found significantly higher ghrelin concentrations in the COVID-19 group compared to the control group. In the study by Podell et al. (2021), the mean D-dimer level among surviving patients was 1067 μg/mL (±1705 μg/mL), while the mean level among deceased patients was 3208 μg/mL (±2613 μg/mL). This indicates a significant difference between the two means. Furthermore, subgroup analyses of male and female patients revealed different optimal cutoff values for D-dimer levels; 1.90 (0.759–0.94) for males and 1.46 (0.583–0.880) for females, with a significant difference between the genders for D-dimer levels. They also found a significant effect of age categories in their patient sample, which included those younger than 60 years and those older than 60 years, with mean D-dimer levels of 1.01 and 1.92 μg/ml for the two groups, respectively. They confirmed that the disease significantly affects elderly patients who have comorbid conditions, such as hypertension, diabetes, and cardiovascular diseases, increasing the likelihood of thrombosis. They found that WBC values ranged from 7.29-9.95 $\times 10^3$ cells/ml without significant differences, and that high D-dimer values upon hospital admission were significantly associated with in-hospital mortality from COVID-19.

Joan et al (2020) reported that D-dimer levels greater than 0.5 μg/mL were found in 260 of 560 patients (46%). A study by Zhang et al. (2020) in China, which included 343 patients, found that D-dimer might be a useful early marker for predicting in-hospital mortality. They determined that the optimal cutoff for D-dimer was 2 μg/mL. In a retrospective study conducted in the United States with 1065 hospitalized patients, each 1 μg/mL increase in D-dimer on admission was associated with a hazard ratio of 1.06 (95% CI 1.04–1.08, $p < 0.001$) for death from any cause. However, they found that bi-D was a poor predictor of mortality, with an area under the ROC curve for bi-D of 0.678 (Naymagon et al., 2020).

The results of the study by He et al. showed that. (2021) In COVID-19 patients in China, through ROC analysis of the risk of death, the area under the curve of bi-D was 0.909 and the YI was 0.765 at the last laboratory test. A D-dimer value of 2.025 mg/L was considered the optimal cut-off point for mortality. They observed that older male patients who had symptoms of dyspnea and had certain chronic diseases had higher 2D values ($p < 0.05$).

Rezaei et al. (2022) observed that viral infection alters the lipid profile and metabolism of host cells, leading to changes in the lipid profile associated with COVID-19. The most common changes were decreased serum cholesterol and ApoA1 levels, along with increased triglycerides. They also reported that the cytokine storm-mediated hyperinflammatory state disrupts several essential lipid biosynthetic pathways, as virus replication dramatically alters the host cell lipid metabolic program and excessively utilizes lipid resources. Low HDL-C levels have been associated with higher rates of severity and mortality, along with elevated levels of inflammation markers.

Hu et al. found. (2020) Reduced total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels in a retrospective lipid profile study of 248 COVID-19 patients. Furthermore, patients had lower levels of total cholesterol and LDL-C on admission, which gradually recovered with clinical improvement. A study by Osuna-Ramos et al. suggested that. (2020) included 102 patients in Mexico who found that lower levels of total cholesterol and LDL-C could predict more severe disease. Mohammed Saeed et al. (2020) reported elevated triglyceride levels along with elevated LDL-C levels. A study conducted in Saudi Arabia on 80 patients with COVID-19 indicated an increased risk of cardiovascular disease due to changes in lipid profiles among patients: decreased levels of total cholesterol (good and bad cholesterol) and increased total cholesterol.

The study by Ali et al. (2023) showed that the age group most affected by the coronavirus infection was between 50-59 years old. Regarding gender, males were more affected by the disease. The study by Mohammed and Maulood (2023) indicated that females (82, 55%) were affected more frequently than males (68, 45%). Hematological parameters including white blood cell (WBC) count, granulocyte count, and red blood cell distribution width (RDW%) were significantly increased ($p < 0.05$), while lymphocyte count was significantly decreased compared with the control group. There were significant differences in hemoglobin concentration, red blood cell volume, red blood cell count, and red blood cell indices compared with the control group in both genders. Regarding biochemical parameters including serum vitamin D, ferritin, D-dimer, procalcitonin (PCT), and liver function tests, serum vitamin D was significantly decreased, while serum ferritin, D-dimer, procalcitonin, and liver enzymes were significantly increased in COVID-19 patients. The patient group compared with the control group. A comprehensive study on serum lipids at the cellular level suggested that the alteration of cholesterol metabolism caused by COVID-19 is responsible for the decrease in circulating cholesterol levels (Song et al., 2020). Researchers hypothesized that SARS-CoV-2 infection reduces levels of Apo-A1 and HDL-C, both of which are associated with disease severity. They also reported that blood lipids in COVID-19 patients closely resembled those of a specific type of extracellular vesicle membrane enriched with GM-3 (monosialodehexosylganglioside) and sphingomyelin (SM). In a series of 46 COVID-19 patients, a decrease in 100 lipid species was observed, especially in lipoproteins associated with macrophage regulatory processes (Shen et al., 2020). There was a downregulation of ApoA, sphingolipids, glycerophospholipids, and some steroid precursors (such as 21-hydroxypregnenolone), along with ApoM and choline, the latter two being observed in severe cases. Choline, a precursor of phospholipids, is an essential molecule in the de novo biosynthesis of phosphatidylcholine, the main phospholipid of cell membranes (Sanchez-Lopez et al., 2019). They suggested that decreased choline levels may be due to increased macrophage activity and activation (Shen et al., 2020; Song et al., 2020).

In the study by Sivri et al. (2023), a total of 1435 patients were divided into two groups: 712 patients in the non-survivor group and 723 in the survivor group. While there was no difference between the two groups in terms of gender, there was a statistically significant difference in age, with the non-survivor group being older. Age, lactate dehydrogenase (LDH), C-reactive protein (CRP), triglycerides, D-dimer, and low-density lipoprotein (LDL) cholesterol were identified as independent risk factors for death in regression analyses. In correlation analysis, age, C-reactive protein, and low-density lipoprotein were positively associated with LDL cholesterol. In ROC analysis, the sensitivity of LDL cholesterol was 61.6% and the specificity was 89.2%.

5. Conclusion

Elevated or decreased levels of ghrelin in COVID-19 patients indicate a relationship between this hormone and the disease course. Ghrelin may also affect the immune response to infection, thereby influencing the severity and duration of the disease. COVID-19 significantly affected the levels of the studied variables, leading to increased levels of ghrelin, D-dimer, WBC, S.T-cholesterol, S.TG, S.LDL-C, S.VLDL-C, and S.glucose, while decreasing levels of PCV and S.HDL-C. The interaction between sex and age significantly affected the levels of ghrelin, D-dimer, PCV, and WBC, although it did not have a significant effect on the other studied variables. It may be possible that ghrelin shows potential changes in saliva compared to its effect in blood. Therefore, we recommend analyzing ghrelin hormone levels in the saliva of patients in future studies. Additionally, a larger sample size than in the current study would certainly enhance the generalizability of the findings.

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