ISSN: 1343-4292
Volume 140, Issue 06, September, 2022

Assessment of Serum Level of Ghrelin and IL-6 as Predictor Markers of Severity in Obese Patients with COVID-19

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ABSTRACT— COVID-19 or coronavirus disease 2019 which first appeared in China, become a global health issue. Ghrelin is a peptide hormone that increases food intake and decreases fat utilization, resulting in weight gain. Ghrelin influences nutritional intake and the release of growth hormone, and therefore development and growth. IL-6 is the common pro-inflammatory cytokines. The aim of this study is to evaluate the levels of Ghrelin and IL-6 in obese patients infected with COVID-19 as early predictor markers of COVID-19 severity. In this case-control study, 60 obese subjects, included 30 obese volunteers without any chronic disease or COVID-19 and 30 obese patients infected with COVID-19 and admitted to Al-Sader Medical City and Al-Amal hospital in Najaf, Iraq, divided into three cases according to the severity (13 mild/moderate), (10 severe) and (7 dead) with the age ranged between (25-60) years. Thirty (20 male and 10 female) apparently healthy subjects were selected as control group, their age and sex were comparable to the patients. The enzyme linked immunosorbent assay (ELISA) kits used to measure serum Ghrelin and IL-6 levels. The serum level of Ghrelin was significantly decreased, while serum level of IL-6 increased in non-survived and sever cases than the mild/moderate cases. Ghrelin negatively correlated with serum level of IL-6 in obese patients infected with COVID-19. IL-6 and Ghrelin levels in the obese patients can be a useful prognostic tool associated with COVID-19 to predicts the SARS-COV-2 severity in the obese patients with COVID-19.

KEYWORDS: Ghrelin, interleukin 6, SARS CoV 2 (COVID-19)

1. INTRODUCTION

The coronavirus infection 2019 (COVID-19), a pandemic responsible for high confirmed cases and deaths according to the WHO (December2021) [16]. COVID-19 can cause a wide range of severe conditions, including acute respiratory failure, bacterial super infections, thromboembolic events and viral sepsis and may causes renal impairment, neurological abnormalities, as well as an extensive inflammatory response overall [1]. Patients with COVID-19 exhibit largely the symptoms of pneumonia, as well as particular radiologic ground-glass pulmonary opacities and hematologic alterations, including neutrophilia, thrombocytopenia and lymphopenia [21]. The progression and outcomes of a disease are extremely varied. Some of these patients deteriorate rapidly and acquire (ARDS) and multiple-organ failure, leading to mortality risk within a short of time [9]. Cytokine storms have a crucial role in the disease progression and are considered as one of the leading causes of ARDS and liver and renal failure. Therefore, a deeper knowledge of the characteristics of cytokine storms and the identification of major indicators that drive illness progression in COVID-19 patients may have substantial implications for the clinical management of

these patients [26].

Ghrelin is a peptide principally released in the stomach that induces appetite and growth hormone (GH) secretion [15]. Ghrelin is a peptide principally released in the stomach that induces appetite and growth hormone (GH) secretion. Cells that produce Ghrelin are found in multiorgan in the body, such as the gastrointestinal, but in smaller quantities. Ghrelin has many effects, such as stomach secretion, stimulation of growth hormone production and gastrointestinal motility as well as increasing food intake, regulation of glucose homeostasis and tissue regeneration and control inflammatory processes [8].

It is generally agreed upon that interleukin 6 is one of the most important cytokines that contributes to inflammation. It is generated by a diverse collection of cell types. The expression of IL-6 can be triggered by TNF and IL-1, which are the two most important factors [11], [13]. It is generated by a broad variety of cells, including T and B cells, lymphocytes and monocytes, fibroblasts, endothelial cells, mesangial and adipose tissues, as well as certain cancer cells that are activated by Toll-like receptors. Additionally, it is produced by various tissues. TNF and IL-1, which are the two most critical factors, are able to stimulate the production of IL-6 by acting as a transcription factor [13].

2. Materials and Methods

This case control study involved 60 Obese patients, 30 (20 males and 10 females) without COVID-19 infection, and 30 (20 males and 10 females) obese patients ,and collected within 7–12 days of diagnosis COVID-19 symptoms which confirmed by reverse transcriptase-PCR (RT-PCR) and (CXR) chest X-ray or CT scan, with age ranged between (25-60) years, were recruited from Al-Sader Medical City and Al-Amal Hospital in Najaf-Iraq, within the period from October 2021 to April 2022 and 30 (10 females and 20 males) with normal weight healthy as control group are comparable with patients in sex and age. The patients were categorized into three groups according to Murray scores system [18]: Group I (n = 7 dead), Group II (n = 10 Severe) and Group III (n = 13 mild – moderate). Subjects having a history of alcoholism, liver illness, or smoking were not included in this study to eliminate these confounding variables. This study was approved by local medical ethics committee and all subjects gave informed consent before the onset of study. Five ml of blood sample were collected from patients and control groups. Blood sample were divided into two tubes, 3 ml allowed to clot for 10-15 minutes at room temperature and then centrifuged for 10 minutes (3000 x g) in order to get serum. Serum samples were divided into tubes and stored at -80 °C until time of biochemical assay. The remaining 2 ml of blood was prepared to measure Complete Blood Count (CBC) by using auto hematology analyzer (linear, Spain). The concentration of serum ferritin, and D-dimer levels were measured by fluorescence immunoassay (ichromaTM). The levels of Ghrelin and IL-6 were measured through enzyme-linked immunosorbent assays (ELISA) (Melsin ELISA Kits, China).

3. Statistical Analysis

Using the Statistical Analysis Software for the Social Sciences, we evaluated the observed data supplied in the form of mean ± SD (SPSS). Statistically significant differences between the healthy and sick groups were analyzed using the independent t-test. In this analysis, we used the Pearson correlation coefficient to mention the statistical relationship between any two variables in the present study. The levels of significance of 5% ($P \leq 0.05$) and 1% ($P \leq 0.01$) were obtained to represent the strength of evidence in support of significant differences between variables.

4. Results and discussion

This study involved 60 obese individuals, 30 of whom were infected with COVID-19 and 30 obese

individuals without COVID-19 and 30 healthy subjects. As indicated in the table 1, there were no significant differences in age or sex among the groups.

The results of study were revealed significant increase in the levels of Ferritin, D-dimer, neutrophils and Neutrophils to lymphocytes ratio (NLR) and Cu levels in obese infected with COVID-19 patients than the obese group and healthy group especially in critical and severe cases in the obese patients with COVID-19 than the mild/moderate cases as shown in table 2. The study also, found significant decrease in the levels of Ghrelin, Zn and monocyte to lymphocytes ratio (MLR) in the obese patients with COVID-19 compared with obese without COVID-19, and normal weight as healthy control groups.

In table 2 shown a significant decrease in the level of Ghrelin and increased level of IL-6 in non-survived and severe cases. The common biochemical parameters were correlated with the levels of Ghrelin and IL-6 In the obese infected with COVID-19 patient group as shown in table 3. The Age, BMI, lymphocyte and monocyte levels have positive correlation with Ghrelin levels and negative correlation with IL-6, ferritin, D-dimer, MLR, NLR and neutrophil in COVID-19 patient group.

Table 1. Demographic and General Characteristics in patients and control groups

Parameters	Groups			*P* value
	Obese with COVID-19 Mean±SD	Obese without COVID-19 Mean±SD	Healthy group Mean±SD	
Total number	30	30	30	----
Male/Female	20/10	20/10	20/10	----
Age (Year)	49.54±10.17	48.03±7.20	48.13±7.93	A:0.682 B:0.625 C:0.913
BMI (kg/m²)	33.44±4.76	34.09±3.27	22.52±2.03	A:0.001 B:0.001 C:0.001
SBP (mmHg)	144.49±10.10	147.13±10.02	120.35±5.74	A:0.05 B:0.05 C:0.05
DBP (mmHg)	8.13±1.06	8.20±1.11	7.91±0.63	A:0.891 B:0.617 C:0.701
SpO_2	90.64±3.71	97.13±3.34	98.50±0.69	A:0.01 B:0.0001 C:0.05
Neutrophil x 10^3/ ml Mean±SD Median	12.94±4.90 7.32	4.48±0.76 4.55	4.07±0.88 4.14	A < 0.01 B: 0.763 C < 0.01
Lymphocyte x 10^3/ ml Mean±SD Median	0.91±0.69 0.64	2.52±0.62 2.48	2.40±0.51 2.38	A <0.001 B : 0.626 C :0.001
Monocyte x 10^3/ ml Mean±SD Median	0.56±0.50 0.42	0.48±0.17 0.47	0.43±0.082 0.44	A :0.683 B :0.803 C :0.729
NLR Mean±SD Median	14.22±0.62 12.66	1.77±0.56 1.79	1.69±0.53 1.54	A< 0.001 B:0.753 C:0.001
MLR Mean±SD Median	0.62±0.61 0.57	0.21±0.05 0.20	0.181±0.32 0.19	A :0.01 B :0.05

				C :0.001
D-dimer (ng/ml) Mean±SD Median	1178.17±1120.10 516	75.34±20.82 73.31	60.12±22.15 69.91	A:0.0001 B :0.05 C:0.0001
Ferritin (ng/ml) Mean±SD Median	897.73±12.3 882.15	89.24±37.83 73.64	72.17±40.28 96.42	A:0.0001 B :0.03 C:0.0001
Ghrelin (Pg/mL)	47.30±15.14	79.13±16.96	50.01±17.43	A: 0.268 B: 0.001 C: 0.001
IL-6 Pg/mL	344.23±70.13	790.34±194.29	138.89±46.36	A: 0.0001 B: 0.0001 C: 0.0001

Data represented as Mean±SD,SD: standard deviation, BMI: body mass index, SBP: Systolic blood presser, DBP diastolic blood pressure , SpO_2 : Oxygen saturation
A= p value (Obese with COVID+Obese), B=p value (Obese with COVID + Healthy), C= p value (Obese+ Healthy), NLR: neutrophil lymphocyte ratio, MLR monocyte lymphocyte ratio

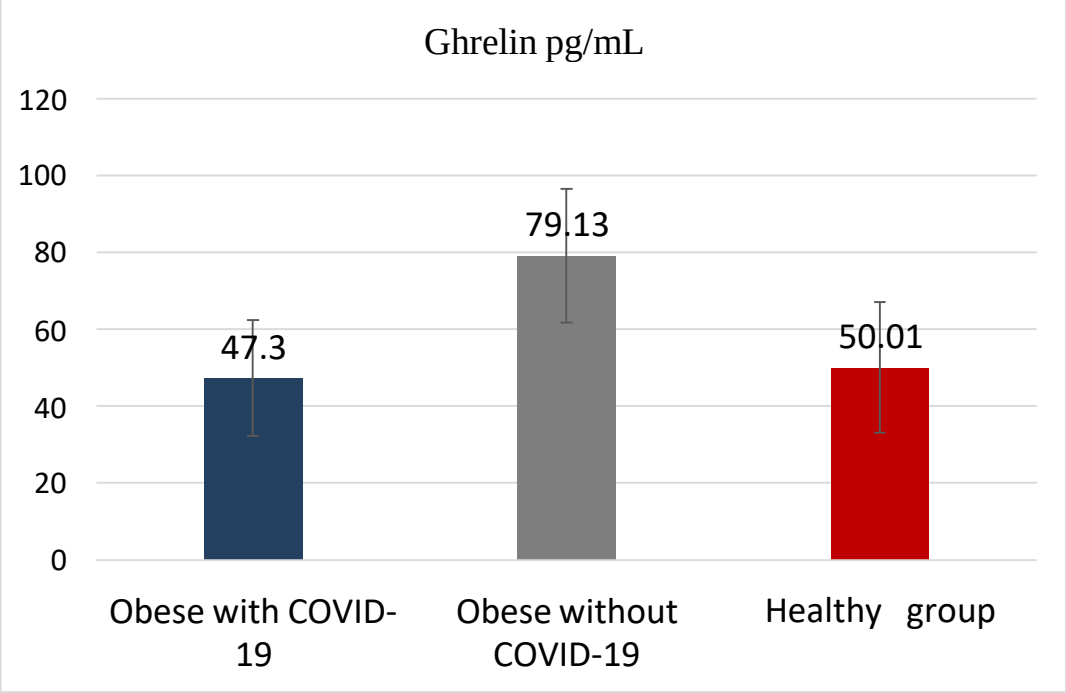

Figure 1. Comparisons of Ghrelin levels among patient groups and healthy group

ISSN: 1343-4292
Volume 140, Issue 06, September, 2022

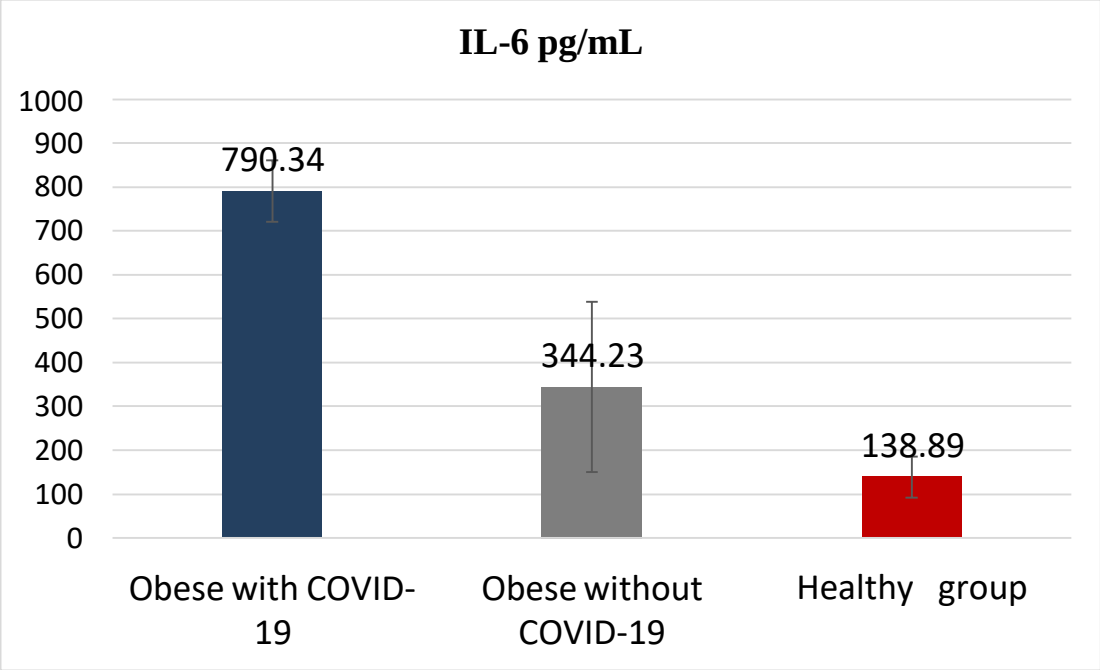

Figure 2. Comparisons of serum IL-6 levels in obese groups with and without COVID-19 infection and Healthy group

Table 2. Demographic and General characteristics in COVID-19 patient's categories

Parameters	Case of COVID-19 patients			*P* value
	Dead Mean±SD	Sever Mean±SD	Mild/Moderate Mean±SD	
%	24%	33.33%	43.33%	----
Age (Year)	56.03±3.10	52.13±4.24	40.37±10.16	A:0.178 B:0.05 C:0.05
BMI (kg/m²)	37.12±2.08	33.11±3.90	30.07±2.34	A:0.182 B:0.06 C:0.175
SBP (mmHg)	142.1±3.18	144.6±6.39	146.76±8.01	A:0.186 B:0.200 C:0.187
DBP (mmHg	70.03±10.36	70.11±9.78	75.12±10.18	A:0.662 B:0.05 C:0.05
SpO_2	85.70±6.10	88.35±4.38	94.88±2.80	A:0.06 B:0.04 C:0.04
Neutrophil x10³/ ml	13.87±5.01	12.24±3.45	10.83±2.36	A:0.633 B :0.04 C:0.04
Lymphocyte x10³/ ml	0.82±0.43	0.90±0.56	0.93±0.58	A:0.762 B:0.624 C:0.785
Monocyte x10³/ ml	0.43±0.31	0.60±.47	0.58±0.53	A:0.03 B :0.05 C:0.677

NLR	16.91±11.65	13.6±6.16	11.645±4.068	A:0.01 B :0.01 C:0.05
MLR	0.52±0.72	0.66±0.723	0.623±0.913	A:0.239 B :0.651 C:0.925
D-dimer (ng/ml)	1182.10±1046	1011±976.43	602.04±204.90	A:0.03 B:0.0001 C:0.0001
Ferritin (ng/ml)	1217.4±409.33	1082±310.21	461.50±52.62	A:0.01 B:0.0001 C:0.001
Ghrelin (Pg/mL)	42.47±8.68	43.28±9.43	48.02±6.26	A :NS B:0.021 C< 0.049
IL-6 Pg/mL	1002.17±228.13	961.42±158.36	389.28±101.38	A:0.001 B:0.0001 C: 0.001

Data represented as Mean ± SD, SD: standard deviation, BMI: body mass index, SBP: Systolic blood presser, DBP diastolic blood pressure , SpO_2 : Oxygen saturation
A= p value (Deadx sever), B=p value (Deadx moderate) C= p value (sever x moderate), LR: neutrophil lymphocyte ratio, MLR monocyte lymphocyte ratio

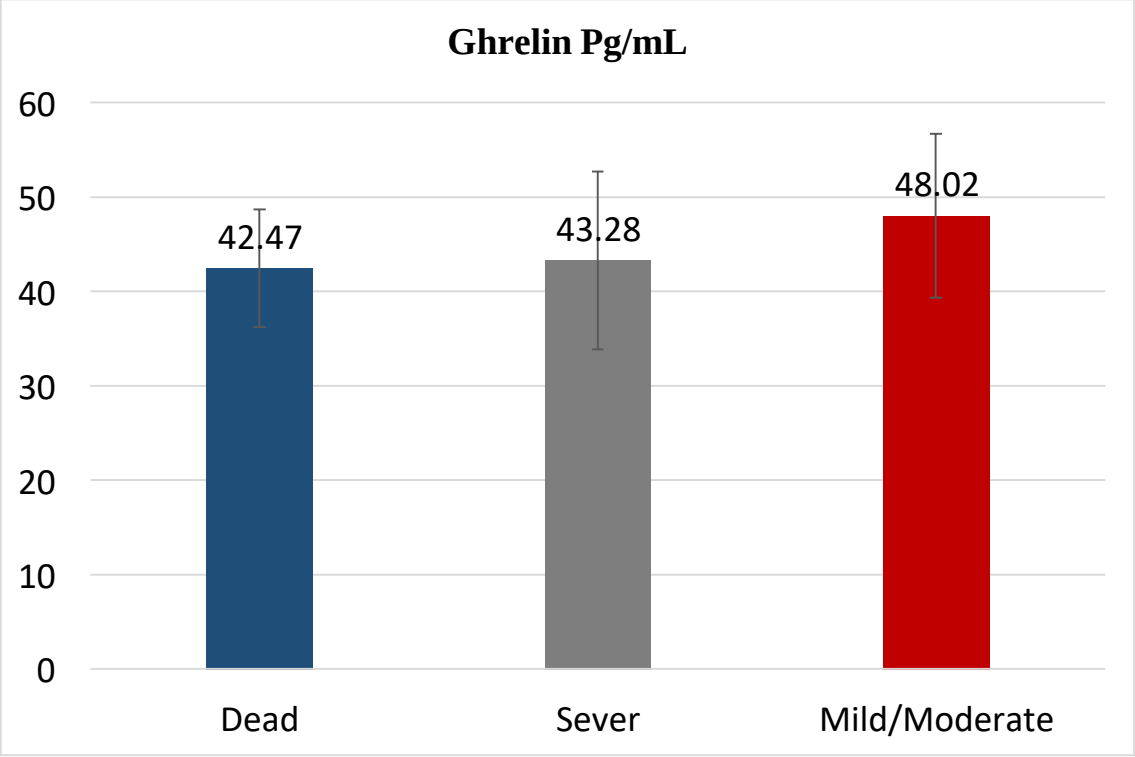

Figure 3. Comparisons of serum Ghrelin levels in COVID-19 patient categories

ISSN: 1343-4292
Volume 140, Issue 06, September, 2022

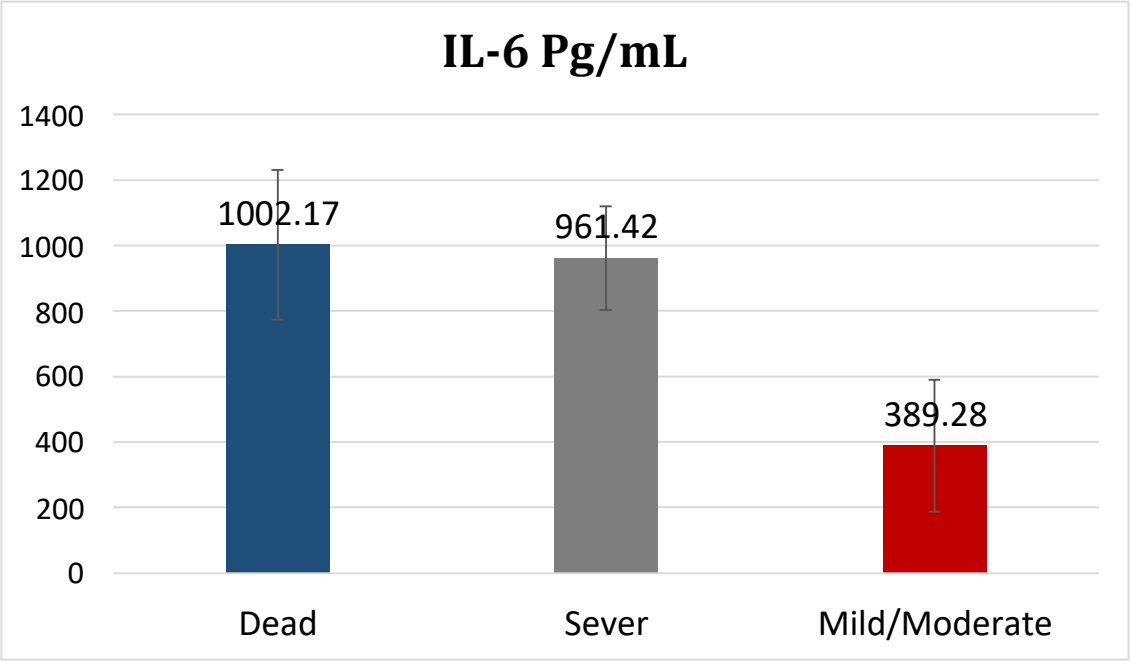

Figure 4. Comparisons of IL-6 levels in COVID-19 patient categories

Table 3. Correlation analysis between serum ghrelin and IL-6 levels with biochemical parameters in patients infected with COVID-19

Parameters	Ghrelin ng/mL		IL-6 Pg/mL	
	r	*p* value	r	*p* value
Age (years)	0.147	0.126	0.162	0.070
BMI (kg/m^2)	0.410	0.01	0.436	0.001
Lymphocyte x 10^3/ ml	0.143	0.083	-0.536	0.0001
Neutrophil. x 10^3/ ml	-0.197	0.050	0.581	0.0001
Monocyte x 10^3/ ml	0.164	0.063	0.306	0.001
NLR	-0.231	0.05	0.562	0.0001
MLR	-0.184	0.076	-0.347	0.01
D-dimer (ng/ml)	-0.27	0.041	0.566	0.0001
Ferritin (ng/ml)	-0.250	0.05	0.493	0.0001
IL-6 (Pg/ml)	-0.398	0.01	-	-
Ghrelin (ng/mL)	-	-	-0.398	0.01

BMI: Body mass index, r: Pearson correlation coefficient, NLR: neutrophil / lymphocyte ratio, MLR: monocyte lymphocyte ratio

The best of our knowledge, this is the first study to evaluate the levels of IL-6 and Ghrelin in Iraqi obese patients infected with COVID-19 as a potential markers for COVID-19 severity.

The SARS-CoV-2 sickness is more severe in individuals with a higher body mass index, and that extreme obesity may raise the risk of heart disease and kidney failure, necessitating dialysis and mechanical ventilation [4].

Several hematological markers, including white blood cell total count, lymphocytes and neutrophils have been linked to COVID-19 infection and its severity. Reduced lymphocyte, basophil and eosinophil counts, as well as increased neutrophil and neutrophil-lymphocyte counts, have been linked to COVID-19 infection and an even worse clinical prognosis [20].

Ghrelin is a peptide hormone mostly produced by the stomach. Ghrelin's interesting antioxidant, anti-inflammatory, and antiviral activities make it a prospective drug for mitigating SARS-side CoV-2's effects. Ghrelin also upregulates PPAR and downregulates NF-kappaB expression, which have anti-inflammatory actions and can reduce the unchecked cytokine production that causes lung injury [12].

In addition to their roles in stimulating appetite and maintaining energy balance, ghrelin and its receptor, GHS-R1a, have direct effects on the cardiovascular system. These effects include inhibition of sympathetic nerve activation, anti-inflammation, anti-apoptosis, endothelial dysfunction and regulation of autophagy. These effects are in addition to the roles that they play in stimulating appetite [22].

Previous research linked ghrelin levels to COVID-19 prognosis, indicating a role for ghrelin insufficiency in the metabolic abnormalities associated with this disease. Several pathways, such as increased body fat [3], insulin resistance [3] and hyperleptinemia [6] can lead to development of the disease. The accumulation of excess fat is a major contributor to the metabolic disorders [24].

Ghrelin levels are decreased in human obesity [23]. Low ghrelin levels in obese people may be caused by a lack of leptin or insulin. Recent research suggests that decreased serum ghrelin in metabolic syndrome may just represent the obese status since adiposity drives the other aspects of the illness [7].

Multifunctional cytokine interleukin 6 (IL-6) is highly active in persons with (SARS) severe acute respiratory syndrome caused by coronavirus 2. Overactive host immune system and autoimmune damage may contribute to elevated levels of this pleiotropic cytokine, which causes inflammation and cytokine storm and is linked to multiorgan failure [17].

Interleukin 6 (IL-6) has a function in health and in certain illness conditions like sepsis, where it interacts with both immune and non-immune system cells and often shows hormone-like features that impact homeostatic processes. COVID-19 [2].

Disease prognosis may be improved by measuring IL6 levels. Increased levels of IL-6 amplify viral infection by dampening the CD8+ T-cell response, interacting favorably with IL-17, and promoting the expression of the programmed cell death factors PD-1 and PDL-1 [19]. Rapid SARS-CoV-2 replication can result in respiratory infection and subsequent elevation of IL-6 levels [25]. Previous research indicated that the risk of respiratory failure was 22 times higher in individuals with increased IL-6 levels compared to those with lower IL-6 levels [10].

When IL-6 attaches to alveolar epithelial cells, it triggers a cascade of cytokine production, including IL-6, which in turn activates the innate immune responses and adaptive immune responses. In addition, because of the nature of these proinflammatory substances, vascular permeability increases, leading to an increase in fluid and blood cell infiltration into the alveoli and a subsequent decrease in alveolar oxygen tension and the development of dyspnea or ARDS [14].

Prior study found that severely sick individuals with clearly elevated IL-6 concentrations had a much higher mortality rate (72.7%). Moreover, the IL-6 levels were much higher in dead than sever and moderate groups. These findings indicate that increases in the IL-6 concentration may be an useful indicator of COVID-19 prognosis [5].

5. Conclusion

The current results found that the serum levels of Ghrelin decreased in the obese patients with COVID-19. Also found elevated serum level IL-6 in the obese patients with COVID-19 than the obses subjects without COVID-19 and with healthy normal weight group. IL-6 and ghrelin levels in obese COVID-19 patients can be used as good prognostic tools to predict the severity of COVID-19.

Acknowledgements
The authors thank the patients for their cooperation and the medical staffs in the laboratories of the Al-Sader Medical City of Najaf and Al-Amal hospital in Najaf

DECLARATION OF INTERESTS
The authors declare no conflict of interests

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6. References

[1] Anderberg, S. B., Luther, T., Berglund, M., Larsson, R., Rubertsson, S., Lipcsey, M., Larsson, A., Frithiof, R., & Hultström, M. (2021). Increased levels of plasma cytokines and correlations to organ failure and 30-day mortality in critically ill Covid-19 patients. Cytokine, 138, 155389.

[2] Belaid, B., Lamara Mahammad, L., Mihi, B., Rahali, S. Y., Djidjeli, A., Larab, Z., Berkani, L., Berkane, I., Sayah, W., & Merah, F. (2022). T cell counts and IL-6 concentration in blood of North African COVID-19 patients are two independent prognostic factors for severe disease and death. Journal of Leukocyte Biology, 111(1), 269–281.

[3] Bergman, R. N., & Mittelman, S. D. (1998). Central role of the adipocyte in insulin resistance. Journal of Basic and Clinical Physiology and Pharmacology, 9(2–4), 205–222.

[4] Caci, G., Albini, A., Malerba, M., Noonan, D. M., Pochetti, P., & Polosa, R. (2020). COVID-19 and obesity: dangerous liaisons. Journal of Clinical Medicine, 9(8), 2511.

[5] Chen, X., Zhou, J., Chen, C., Hou, B., Ali, A., Li, F., Hua, Z., Wu, Y., Yang, Q., & Chen, M. (2021). Consecutive Monitoring of Interleukin-6 Is Needed for COVID-19 Patients. Virologica Sinica, 36(5), 1093–1096.

[6] de Courten, M., Zimmet, P., Hodge, A., Collins, V., Nicolson, M., Staten, M., Dowse, G., & Alberti, K. (1997). Hyperleptinaemia: the missing link in the metabolic syndrome? Diabetic Medicine, 14(3), 200–208.

[7] Fagerberg, B., Hultén, L. M., & Hulthe, J. (2003). Plasma ghrelin, body fat, insulin resistance, and smoking in clinically healthy men: the atherosclerosis and insulin resistance study. Metabolism, 52(11), 1460–1463.

[8] Ginter, G., Ceranowicz, P., & Warzecha, Z. (2021). Protective and Healing Effects of Ghrelin and Risk of Cancer in the Digestive System. In International Journal of Molecular Sciences (Vol. 22, Issue 19). https://doi.org/10.3390/ijms221910571

[9] Goh, K. J., Choong, M. C., Cheong, E. H., Kalimuddin, S., Wen, S. D., Phua, G. C., Chan, K. S., & Mohideen, S. H. (2020). Rapid progression to acute respiratory distress syndrome: review of current understanding of critical illness from coronavirus disease 2019 (COVID-19) infection. Ann Acad Med Singapore, 49(3), 108–118.

[10] Herold, T., Jurinovic, V., Arnreich, C., Lipworth, B. J., Hellmuth, J. C., von Bergwelt-Baildon, M., Klein, M., & Weinberger, T. (2020). Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. Journal of Allergy and Clinical Immunology, 146(1), 128–136.

[11] Hunter, C. A., & Jones, S. A. (2015). IL-6 as a keystone cytokine in health and disease. Nature Immunology, 16(5), 448–457.

[12] Jafari, A., Sadeghpour, S., Ghasemnejad-Berenji, H., Pashapour, S., & Ghasemnejad-Berenji, M. (2021). Potential Antioxidative, Anti-inflammatory and Immunomodulatory Effects of Ghrelin, an Endogenous Peptide from the Stomach in SARS-CoV2 Infection. International Journal of Peptide Research and Therapeutics, 27(3), 1875–1883. https://doi.org/10.1007/s10989-021-10217-9

[13] Kang, S., Narazaki, M., Metwally, H., & Kishimoto, T. (2020). Historical overview of the interleukin-6 family cytokine. Journal of Experimental Medicine, 217(5).

[14] Knudsen, L., & Ochs, M. (2018). The micromechanics of lung alveoli: structure and function of surfactant and tissue components. Histochemistry and Cell Biology, 150(6), 661–676.

[15] Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H., & Kangawa, K. (1999). Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature, 402(6762), 656–660.

[16] Larsson, A., Lipcsey, M., Hultström, M., Frithiof, R., & Eriksson, M. (2021). Plasma Leptin Is Increased in Intensive Care Patients with COVID-19—An Investigation Performed in the PronMed-Cohort. Biomedicines, 10(1), 4.

[17] Majidpoor, J., & Mortezaee, K. (2022). Interleukin-6 in SARS-CoV-2 induced disease: Interactions and therapeutic applications. Biomedicine & Pharmacotherapy, 145, 112419. https://doi.org/https://doi.org/10.1016/j.biopha.2021.112419

[18] Murray, J. F., Matthay, M. A., Luce, J. M., & Flick, M. R. (1988). An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis, 138(3), 720–723.

[19] Nguyen, N., Nguyen, H., Ukoha, C., Hoang, L., Patel, C., Ikram, F. G., Acharya, P., Dhillon, A., & Sidhu, M. (2022). Relation of interleukin-6 levels in COVID-19 patients with major adverse cardiac events. Baylor University Medical Center Proceedings, 35(1), 6–9.

[20] Palladino, M. (2021). Complete blood count alterations in COVID-19 patients: A narrative review. Biochemia Medica, 31(3), 0.

[21] Tang, D., Comish, P., & Kang, R. (2020). The hallmarks of COVID-19 disease. PLoS Pathogens, 16(5), e1008536.

[22] Tokudome, T., & Kangawa, K. (2019). Physiological significance of ghrelin in the cardiovascular system. Proceedings of the Japan Academy, Series B, 95(8), 459–467.

[23] Tschop, M., Weyer, C., Tataranni, P. A., Devanarayan, V., Ravussin, E., & Heiman, M. L. (2001). Circulating ghrelin levels are decreased in human obesity. Diabetes, 50(4), 707–709.

[24] Ukkola, O., & Bouchard, C. (2001). Clustering of metabolic abnormalities in obese individuals: the role of genetic factors. Annals of Medicine, 33(2), 79–90.

[25] Ulhaq, Z. S., & Soraya, G. V. (2020). Interleukin-6 as a potential biomarker of COVID-19 progression. Medecine et Maladies Infectieuses, 50(4), 382.

[26] Ye, Q., Wang, B., & Mao, J. (2020). The pathogenesis and treatment of theCytokine Storm'in COVID-19. Journal of Infection, 80(6), 607–613.