Evaluation of Some Biomarkers and Interleukin-29 as Predictor Early diagnosis and Severity Stratification of Patients with COVID-19

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Abstract

Background: Coronavirus disease- 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Interferon- λ1 (IFN-λ1), also named Interleukin-29 (IL-29), is a new member of the IFN- family or Type III IFN. IL-29 is mainly produced by macrophages and maturing dendritic cells and involved in many immunological responses and indicates antiviral activity similar to type I interferons (T1IFNs). Accordingly, this study aims to evaluate some biomarkers and IL-29 levels among COVID-19 patients. Methods: A case- control study, that included (30) patients diagnosed with Covid-19 (19 males and 11 females), who attended to Merjan Teaching Hospital, Babylon, Iraq; and (30) apparently healthy subjects as a control group. Standard methods were used to measure the investigations. Results: The results revealed that there were highly significant increases (P value < 0.05) of fasting blood glucose, HbA1c, total cholesterol, triglyceride, LDL-C, VLDL, ALT, AST, ALP, ferritin, D-Dimer and IL-29; while, revealed highly significant decreases of zinc, copper and vitamin D levels (P value < 0.01) in COVID-19 patients when compared with control. The presented study also showed high odd ratio, sensitivity and specificity values for most biomarkers. Conclusion: It was concluded that there were significant increases in levels of IL- 29, ferritin, liver enzymes, D dimer, CRP and LDH; while, decrease of Vitamin and trace elements in patients with COVID-19. Elevated levels of IL-29 and ferritin were signified worsening of COVID-19 infection. To monitor the progression of COVID-19, IL-29 and ferritin should be considered as potential biomarkers for severity in COVID-19.

Key words: COVID-19, SARS-CoV-2, Interferon -λ1, interleukin- 29

1. Introduction

Coronavirus disease 2019 or COVID-19 is a viral infection cause by the severe acute respiratory syndrome coronavirus 2 (SARSCoV-2), (Li Q *et al.*, 2020; Gorbalenya AE *et al.*, 2020). This novel disease spread rapidly to other regions of the world. According to WHO statistics, there are 581,182,629 (until July 30, 2022) confirmed cases and 6,418,043 deaths in 219 countries caused by the high transmission capacity of SARS-CoV- 2, (Keynaz K, *et al.*, 2022).

The pathophysiology of COVID-19 has not been fully understood (Li G. *et al.*, 2020), it is clear now, its pathology arises from a primary deficit in type I interferon production (Schultze, J.L. 2021). Viral infection leads to rapid activation of innate immune cells, especially in patients who develop severe disease (Schett, G., 2020; Qin, C., 2020). Some biomarkers are related to moderate and severe COVID 19 infection like increased levels of serum C-reactive protein (CRP), alanine aminotransferase, lactate dehydrogenase, hypoalbuminemia, ferritin, D-dimer (Chen, G.,2020; Ruan, Q., 2020; Haider N *et al.*, 2021); or like low lymphocytes absolute numbers (Li, Y.X. *et al.*, 2020). The patients display increased levels of proinflammatory cytokines in serum like IL-1B, IL-6, IL-12, IFN-γ (Bizzarri, M. *et al.*, 2021). The more severe patients display higher plasma levels of these biomarkers suggesting an association with the severity degree (Chen, L., 2020; Wan, S., 2020; Huang, C., 2020). Due to limited studies attending the role of Interleukin-29 (Interferon- λ1) in covid-19; therefore, it couldn't decide whether IL-29 affect the prognosis of covid-19 or not. So, this study, would investigate IL-29 in patients with covid-19, and changes in levels of the biomarkers that associated with the condition.

2. Material and Methods

A case control study, that included (30) patients diagnosed with Covid-19 (19 males and 11 females),

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who visited Merjan Teaching Hospital, Babylon, Iraq; and (30) apparently healthy subjects as a control group. All patients were examined by specialist physicians and diagnosis by quantitative RT-PCR, throughout the period from October 2020 to February 2021. Patients with other chronic diseases or smoker were excluded. Biochemical and immune markers were measured by standard methods.

3. Statistical Analysis

Data were expressed as means ± standard deviation (SD). All statistical analyses were performed using SPSS for windows (version 26, USA). A value of $P < 0.05$ was considered statistically significant.

4. Results

The results revealed that fasting blood glucose, HbA1c, total cholesterol, triglyceride, LDL-C, VLDL, ALT, AST, ALP, ferritin, D-Dimer and IL-29 were significantly higher ($p < 0.05$); while, zinc, copper and vitamin D were significantly lower ($p < 0.01$) in patients in comparison with control. Details of clinical and laboratory data were shown in table 1.

Table (1). Clinical and biochemical characteristics of patients and healthy control

Variables		Patients (n=30)	Controls (n=30)	P .Value
Age (years)		59.17±7.64	58.27±5.76	0.609
Gender	Males	19 (63.3%)	14 (46.7%)	0.194
	Females	11 (36.66%)	16 (53.33%)	
BMI (kg/m^2)		27.12±3.25	25.15±2.32	0.09
SBP (mm/Hg)		134.57±21.96	132.82±6.52	0.68
DBP (mm/Hg)		79.27±16.38	80.83±5.1	0.619
Fasting blood glucose (mg/dL)		277.2±100.5	78.21±13.1	<0.001
HbA1c (%)		7.67±1.53	4.78±0.53	<0.001
Total cholesterol (mg/dL)		170.77±20.97	149.97±21.38	<0.001
Triglyceride (mg/dL)		216.3±81.74	163.9±43.36	0.003
HDL-C (mg/dL)		36.3±10.93	40.73±9.3	0.096
LDL-C (mg/dL)		88.66±19.5	76.43±18.94	0.017
VLDL-C (mg/dL)		44.07±15.77	32.78±8.67	0.001
ALT (U/L)		29.23±20.76	19.53±3.76	0.015
AST (U/L)		44.4±22.09	23.8±4.9	<0.001
ALP		141.63+93.74	106.17+17.89	0.046
Zinc (µg/dl)		22.63±11.93	78.7±10.15	<0.001
Cu (µg/dl)		62.43+6.1	85.77±10.87	<0.001
Vitamin D (ng/ml)		19.16±11.01	47.22±18.73	<0.001
Ferritin		914.6±608.0	83.5±24.64	<0.001
D-Dimer		2574.6±2533.63	266.77±83.98	<0.001
IL-29 (pg/mL)		1521.0±49.36	147.0±6.7	<0.001
Non-significant at P>0.05, SD: standard deviation				

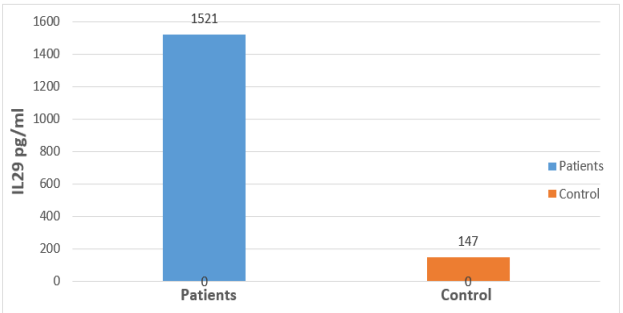

Figure (1) IL-29 concentration in healthy controls (HC) and COVID Patients.

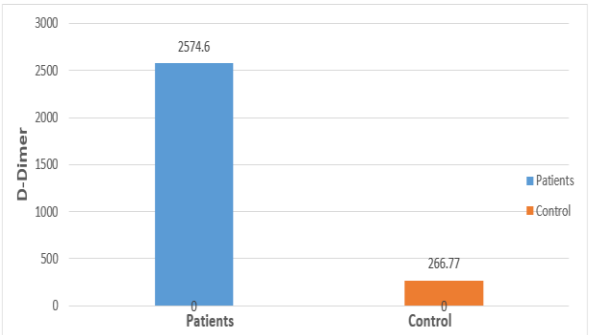

Figure (2) D-Dimer concentration in healthy controls (HC) and COVID Patients.

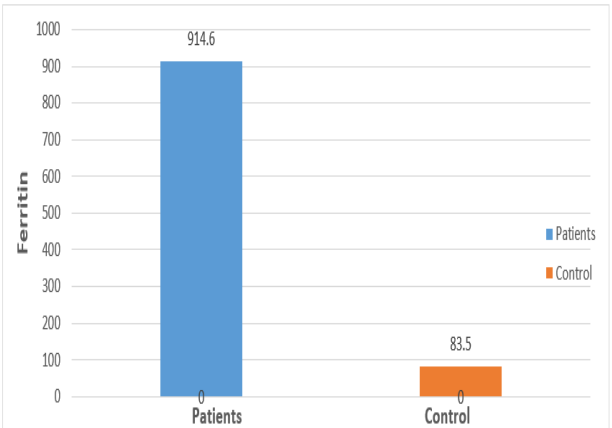

Figure (3) Ferritin concentration in healthy controls (HC) and COVID Patients.

The diagnostic value and the cut-off of the biochemical and inflammatory markers (IL-29) have been evaluated by AUC (area under the curve) and ROC (receiving operative curve) analysis, as shown in table 2. The ROC curves could evaluate the diagnostic efficacy of a diagnostic test by measuring the area under the ROC curve (AUC). In clinical practice, a diagnostic test is considered acceptable if its AUC is ≥ 0.8 and good if it is ≥ 0.9.

Table 2. AUC (area under the curve) of ROC (receiving operating curve) and cut-off of biochemicals and IL-29.						
Variables	ROC area	Sensitivity %	Specificity %	Cut-off	P-Value	95% Confidence limits
FBG (mg/dL)	1.0	100%	100%	120.3	<0.001	1.0-1.0
HbA1c (%)	0.998	100%	93.3%	5.6	<0.001	0.994-1.0
TC (mg/dL)	0.788	90%	80%	166.5	<0.001	0.67-0.905
TG (mg/dL)	0.668	86.7%	76.8%	161	0.025	0.529-0.808
HDL-C (mg/dL)	0.389	91%	80%	49	0.139	0.244-0.534
LDL-C (mg/dL)	0.697	83.3%	73.3%	93.5	0.009	0.564-0.83
VLDL-C (mg/dL)	0.704	90%	80%	34	0.007	0.572-0.836
Cu (µg/dl)	0.981	96.7%	83.3%	69.5	<0.001	0.956-1.0
Zinc (µg/dl)	0.002	96.7%	83.3%	71.5	<0.001	0.0-0.08
Vitamin D (ng/ml)	0.096	96.7%	87.1%	20.95	<0.001	0.022-0.17
D-Dimer	0.983	93.3%	96.7%	416	<0.001	0.959-1.0
Ferritin	0.998	96.7%	100%	167	<0.001	0.992-1.0
IL-29 (pg/mL)	0.097	96.7%	89.4%	789.5	<0.001	1.0-1.0
AUC: area under the curve; CI: confidence interval, significant at p < 0.05.						

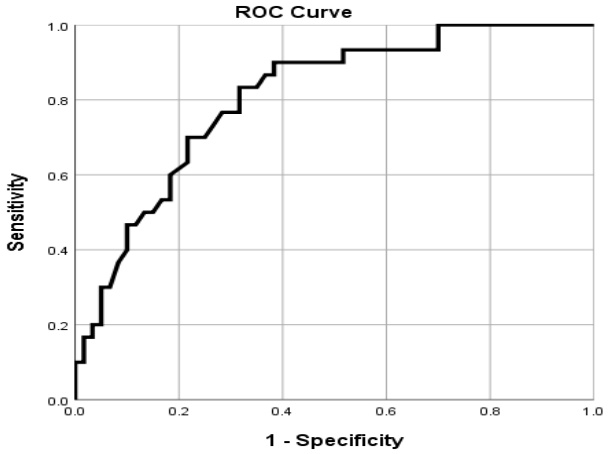

Figure (4): Receiver- Operating characteristic (ROC) curve analysis for the IL29 in the COVID patients

The odds ratios (ORs) were shown in table 3. The OR represented the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure.

Table 3: Predictors of unfavorable outcome in multivariable logistic regression analysis.			
Variables	OR	95 % CI	P. Value
Age (years)	1.727	0.61-4.84	0.297
BMI (kg/m^2)	2.667	0.92-7.69	0.067
FBG (mg/dL)	0.091	0.03-0.26	<0.001
HbA1c (%)	0.333	0.22-0.50	<0.001
TC (mg/dL)	0.483	0.37-0.63	0.15
TG (mg/dL)	5.688	1.59-20.33	0.005
HDL-C (mg/dL)	0.609	0.19-1.89	0.39
LDL-C (mg/dL)	2.75	0.934-8.1	0.063
VLDL-C (mg/dL)	5.688	1.59-20.33	0.005
Cu (µg/dl)	9.10	1.535-53.925	<0.001
Zinc (µg/dl)	3.10	0.45-21.3.26	<0.001
Vitamin D (ng/ml)	0.04	0.01-0.156	<0.001
D-Dimer	0.118	0.047-0.295	<0.001
Ferritin	40.60	34.82-473.30	<0.001
IL-29 (pg/mL)	45.0	9.73-208.07	<0.001

In order to correlate inflammatory markers (IL-29) values in COVID-19 patients with other biochemical markers and clinical characteristics, the Pearson correlation coefficient (r^2) was calculated. IL-29 displayed no significant positive or negative correlation ($p > 0.05$) with biochemical markers and clinical characteristics, as shown in table 4.

Table 4. Correlations of serum IL-29 levels with biochemical and clinical characteristics.		
Variable	r- Value	P-Value
Age (years)	0.152	0.422
Gender	0.103	0.588
BMI (kg/m^2)	-0.129	0.495
SBP (mm/Hg)	-0.154	0.417
DBP (mm/Hg)	-0.194	0.305
FBG (mg⁄dL)	0.171	0.366
HbA1c (%)	0.168	0.375
Total cholesterol (mg/dL)	-0.06	0.753
Triglyceride (mg/dL)	-0.007	0.970
HDL-C (mg/dL)	-0.153	0.419
LDL-C (mg/dL)	0.119	0.532
VLDL-C (mg/dL)	-0.034	0.859
ALT (U/l)	-0.151	0.426
AST(U/l)	-0.131	0.489
ALP	0.294	0.141
Cu (µg/dl)	-0.179	0.345
Vitamin D (ng/ml)	-0.215	0.254
Zinc (µg/dl)	-0.062	0.743
D-Dimer	-0.003	0.987
Ferritin	-0.041	0.828

5. Discussion

The illness course of SARS-CoV-2 infection (COVID-19 is ranging from asymptomatic to severely ill, with complications of acute respiratory failure (the main pathologic changes), this makes it crucial to collect strong evidence to determine the patient's condition in a timely manner and predict complications. Biochemical and immune markers are quantitative measurements that reflect the pathophysiology of disease and thus help clinicians in recognizing the severity of medical illness, also aid in the development of clinical care management algorithms that have the potential to improve patient outcomes, will be helpful in differentiating severely ill patients, allow for the appropriate allocation of healthcare resources, help to prevent virus-induced acute inflammatory response complications such as acute hypoxemic respiratory failure and multiorgan

dysfunction including hepatic, renal injury and acute cardiac in affected patients (Mennechet FJ *et al.*, 2006; Gad HH *et al.*, 2009; Haider N *et al.*, 2021). The recent discovery of interleukin- 29 has ushered in a new era of cytokines research. IL-29 has been the focus of intense study in the fields of immunotherapy and antiviral research, and instantly has been suggested the potential antiviral, antiproliferative, and immunomodulatory capabilities of IL-29 (Vandamme *et al.*, 2015). In the current study, the concentrations of IL-29 were significantly higher in patients than control. This data suggests the protective role of IL-29 in patients with COVID-19 and decreased levels of this cytokine could predict the severe condition in the COVID-19. IL-29 appears to have immune-regulating functions because IL-29 stimulates human cell-derived DCs that proliferate FOXP3-expressing suppressor T cells (Mennechet FJ *et al.*, 2006; Gad HH *et al.*, 2009). IFN-λ was appeared to have antiviral activity, tissue-protective and anti-inflammatory properties, previous studies have examined the role of IFN-λ at epithelial levels and reported that IFN-λ have similar roles in epithelial tissue against viral and bacterial infections (Galani IE, *et al.*, 2017; Lazear HM, *et al.*, 2017).

Also, this study was revealed a significant decrease of vitamin D level in patient group; that mean, the insufficiency of vitamin D could be linked with more serious consequences related to the infection of COVID-19 (Mutaz S A, et al., 2022). Previous studies were demonstrated, that vitamin D starts the adaptive immunity to reduce many of the pro-inflammatory cytokines and it will lead to opposing COVID-19 outcomes; also, vitamin D encourages the immune response and epithelial cells of the respiratory system to discharge materials, such as cathelicidin, which is considered as an anti-microbial peptide (B.Z. Reis, et al., 2021). There direct relations between vitamin D insufficiency and the severity of COVID-19 infection., Also, (B.Z. Reis, et al., 2021) reported that about 82.2% of patients who were hospitalized or vitamin D deficiency (<10 mg/mL) in patients hospitalized for COVID-19 (moderate-to-severe), were prone to be longer stay in the hospital. This study examined serum Zn, and Cu concentrations that might be new targets for diagnosis COVID-19. Zn is involved in the development and maturation of immune cells and the inflammatory response (Read SA et al., 2019). In infected cells, the processing of coronavirus replicase polyproteins has been shown to be inhibited by Zn through inhibitory proteolytic mechanisms (Omer F K et al., 2020). According to Sattar et al. 2020, zinc intake with azithromycin and chloroquine accelerated the recovery rate in COVID-19 patients. Also, in another previous study, modulation of ACE-2 receptor levels with Zn therapy was considered a potential therapeutic strategy in the treatment of COVID-19 (Zhang H et al., 2020).

Serum Cu level was showed a statistically significant difference between the healthy and patient groups. Impairment of the immune system and increased infection rate have been associated with copper deficiency (Taheri M, *et al.* 2020).

Elevation of D-dimer in this study has to be one of common laboratory findings noted in covid-19 patients requiring hospitalization, that agreed with (Mansouritorghabeh, 2020; and Haider N *et al.*, 2021). Although increased D-dimer concentrations might be driven by inflammatory mechanisms and dead-space ventilation might be due to mechanisms other than micro- clots, previous studies suggest that intravascular pathology plays a major role increasing dead space and causing hypoxemia in COVID-19-related ARDS (Grasselli *et al.*, 2020). Malik *et al.*, 2021; have found that elevated D-dimer values are associated with nearly threefold higher risk of poor outcomes in COVID-19 patients. Previous studies showed that CRP, LDH, D-dimer, liver enzymes and ferritin levels were positively correlated with lung injury Murray scores (Liu *et al.*, 2020; B.Z. Reis, *et al.*, 2021). Therefore, the combinations of these parameters in COVID-19 infected patients upon hospital admission may predict severe acute lung injury.

Serum trace element concentrations of the patients, and was significantly negatively correlated with RP, LDH, D-dimer, liver enzymes and ferritin levels, while positively with. Vitamin D; this finding agreed with (Omer F K *et al.*, 2020).

6. Conclusion

Since the beginning of COVID-19 outbreak, the capacity of biochemical and immunological factors to predict patients with severe or fatal forms of COVID-19 has been of great scientific importance. It is critical to obtain a full profile of the laboratory analysis. According to the reviewed literature immunological and biochemical parameters are associated with COVID-19 patients and can thus be used as predictive factors. Interleukin-29 is a newly discovered cytokine, that have the important role in inflammation, this issue especially can be facilitated by evaluation of IL-29 and other biochemical markers. Serum IL-29 and ferritin were the best predictor for risks in patients with COVID-19. More researches are needed to explore if IL-29 measures could be help in strategy for treatment and/or prognosis for outcome or an indicator of disease stage.

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References

B.Z. Reis, A.L. Fernandes, L.P. Sales, M.D. Santos, C.C. Santos, A.J. Pinto, K.F. Goessler, A. S.

Franco, C.S.C. Duran, C.B.R. Silva, M.B. Macêdo, H.H.H. Dalmolin, J. Baggio, G.G.M. Balbi, L. Antonangelo, V.F. Caparbo, B. Gualano, I.H. Murai, R.M.R. Pereira, *Am. J. Clin. Nutr.*, 2021; 114(2): 598-604, 08 02.

Bizzarri, M.; Laganà, A.S.; Aragona, D.; Unfer, V. Inositol and Pulmonary Function. Could Myo-Inositol Treatment Downregulate Inflammation and Cytokine Release Syndrome in SARS-CoV-2? *Eur. Rev. Med. Pharmacol. Sci.* 2020, *24*, 3426–3432.

Chen, G.; Wu, D.; Guo, W.; Cao, Y.; Huang, D.; Wang, H.; Wang, T.; Zhang, X.; Chen, H.; Yu, H.; et al. Clinical and Immunological Features of Severe and Moderate Coronavirus Disease 2019. *J. Clin. Investig.* 2020.

Chen, L.; Liu, H.G.; Liu, W.; Liu, J.; Liu, K.; Shang, J.; Deng, Y.; Wei, S. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* 2020, *43*, E005.

Gad HH, Dellgren C, Hamming OJ, Vends S, Paludan SR, Hartmann R. Interferon-λ is functionally an interferon but structurally related to the interleukin-10 family. *J Biol Chem*. 2009; 284(31):20869-20875.

Galani IE, Triantafyllia V, Eleminiadou E-E, et al. Interferon-λ mediates non-redundant front-line antiviral protection against influenza virus infection without compromising host fitness. *Immunity*. 2017; 46(5):875-890.e6.

Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, *et al*. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* (2020).

Haider N, Mahdi T, Hamed J. Evaluation of Some Biomarkers in the Diagnosis and Severity Identification of Patients with COVID-19. *IMDC-IST* 2021, September 07-09.

Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; *et al.* Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. *Lancet* 2020, *395*, 497–506.

Keynaz K, Fahimeh N, Nooshin A.; *et al.* A Review of Routine Laboratory Biomarkers for the Detection of Severe COVID-19 Disease. *Hindawi. International Journal of Analytical Chemistry*. Volume 2022, Article ID 9006487, 14 pages.

Lazear HM, Schoggins JW, Diamond MS. Shared and distinct functions of type I and type III interferons. Immunity. 2019;50(4):907-923.

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med.* (2020) 382:1199–207.

Li, G.; Fan, Y.; Lai, Y.; Han, T.; Li, Z.; Zhou, P.; Pan, P.; Wang, W.; Hu, D.; Liu, X.; et al. Coronavirus Infections and Immune Responses. J. Med. Virol. 2020, 92, 424–432.

Li, Y.X.; Wu, W.; Yang, T.; Zhou, W.; Fu, Y.M.; Feng, Q.M.; Ye, J.M. Characteristics of peripheral blood leukocyte differential counts in patients with COVID-19. *Zhonghua Nei Ke Za Zhi* 2020, *59*, E003.

Liu Y., Yang Y., Zhang C., et al. (2020). Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Science China. Life sciences. 63(3): 364–374.

Malik P., Patel U., Mehta D., *et al.* (2021). Biomarkers and outcomes of COVID-19 hospitalizations: systematic review and meta-analysis. *BMJ evidence-based medicine*. 26(3): 107–108.

Mansouritorghabeh, H & Rostami, M. (2020): D-dimer level in COVID-19 infection: a systematic review, *Expert Review of Hematology*.

Mennechet FJ, Uzé G. Interferon-λ–treated dendritic cells specifically induce proliferation of FOXP3-expressing suppressor T cells. *Blood*. 2006;107(11):4417-4423.

Mohamadian, M., Chiti, H., Shoghli, A., Biglari, S., Parsamanesh, N., & Esmaeilzadeh, A. (2021). COVID-19: Virology, biology and novel laboratory diagnosis. *The journal of gene medicine*, 23(2), e3303.

Mutaz S A, Sinan B E, Essa R J. Evaluating the level of vitamin D in Iraqi covid-19 patients and its association with biochemical parameters, *Eurasian Chem. Commun*. 5, 2022,126-135.

Omer F K, · Fatma B O, · Emine P, Yucel K, Neslihan Y, Mehmet E Y, Ebubekir B. Evaluation of Serum Trace Element Levels and Biochemical Parameters of COVID-19 Patients According to Disease Severity. *Biological Trace Element Research, part of Springer Nature.* (2022) 200:3138–3146.

Qin, C.; Zhou, L.; Hu, Z.; Zhang, S.; Yang, S.; Tao, Y.; Xie, C.; Ma, K.; Shang, K.; Wang, W.; et al. Dysregulation of Immune Response in Patients with COVID-19 in Wuhan, China. *Clin. Infect. Dis.* 2020.

Read SA *et al* (2019), The role of zinc in antiviral immunity. *Adv Nutr* 10(4):696–710.

Ruan, Q.; Yang, K.; Wang, W.; Jiang, L.; Song, J. Clinical Predictors of Mortality Due to COVID-19 Based on an Analysis of Data of 150 Patients from Wuhan, China. *Intensive Care Med.* 2020, 1–3.

Sattar Y *et al.*, Three cases of COVID-19 disease with colonic manifestations. *Am J Gastroenterol.* (2020).

Schett, G.; Sticherling, M.; Neurath, M.F. COVID-19: Risk for Cytokine Targeting in Chronic Inflammatory Diseases? *Nat. Rev. Immunol.* 2020.

Schultze, J.L.; Aschenbrenner, A.C. COVID-19 and the Human Innate Immune System. *Cell* 2021, 184, 1671–1692.

Taheri M, *et al.*, A review on the serum electrolytes and trace element's role in the pathophysiology of COVID-19. *Biol Trace Element Res.* 2020, 1–7.

Vandamme, T., Peeters, M., Dogan, F., Pauwels,

P., Van Assche, E., Beyens, M., Mortier, G., Vandeweyer, G., de Herder, W., Van Camp, G., 2015. Whole-exome characterization of pancreatic neuroendocrine tumor cell lines BON-1 and QGP-1. *J. Mol. Endocrinol.* 54, 137–147.

Wan, S.; Yi, Q.; Fan, S.; Lv, J.; Zhang, X.; Guo, L.; Lang, C.; Xiao, Q.; Xiao, K.; Yi, Z.; et al. Relationships among Lymphocyte Subsets, Cytokines, and the Pulmonary Inflammation Index in Coronavirus (COVID-19) Infected Patients. *Br. J. Haematol.* 2020.

Zhang H *et al* (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive. *Care Med,* 46(4):586–590.