

Estimation of some Inflammatory Markers in Covid-19 Patients in Erbil-City

Shayma Kh. Muhammed

Suhaila N. Darogha

Department of Biology/ College of Education/ Salahaddin University/ Erbil

p-ISSN: 1608-9391

e-ISSN: 2664-2786

Article information

Received: 24/12/2022

Revised: 20/ 2/ 2023

Accepted: 26/ 2/ 2023

DOI: 10.33899/rjs.2024.182821

corresponding author:

Shayma Kh. Muhammed

Shayma.muhammed@student.su.edu.krd

Suhaila N. Darogha

suhaila.darogha@su.edu.krd

ABSTRACT

The 2019 pandemic coronavirus disease has affected millions of individuals globally. The objective of the present study is to assess the possible predictors of CoV-2 severity and to identify the possible correlation between patients' parameters and disease severity. Consequently, we aimed to measure the serum levels of some inflammatory markers, including CRP, D-dimer, Ferritin, and Procalcitonin, as a biomarker for disease severity in CoV-2 patients. A total of 280 nasopharyngeal swabs and whole blood specimens were collected from healthy individuals and individuals suspected with CoV-2 between June 2021 and December 2021 of both sexes, categorized into four main groups: 70 healthy individuals with an age range (23-70), 210 CoV-2 patients in which their ages were between (21-75), (70 patients per mild, moderate and severe patients). According to our findings CoV-2 patients' groups had leukocytosis, with a significant increase in WBC and Granulocytes count, and a significant decrease in Lymphocyte and platelet. In regard to inflammatory parameters, CRP, D-dimer, ferritin and PCT showed significant differences between the CoV-2 patients groups compare to the control group, these inflammatory biomarkers were significantly elevated in CoV-2 patients group compared to healthy control group ($P < 0.005$). The optimal cut-off values for CRP, D-dimer, Ferritin, and PCT were determined by Receiver Operating Characteristic (ROC) Curve Analysis in CoV-2 patients. In conclusion, Inflammation biomarkers are the best predictors of severe CoV-2, and the combination of clinical signs can further predict severe CoV-2.

Keywords: COVID-19, SARS-CoV-2, CoV-2 Pandemic, Hematological parameter, Inflammatory biomarkers.

INTRODUCTION

The novel coronavirus (COVID-19) known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first appeared in Wuhan city, China, on 31 December 2019 and then rapidly spread throughout the world including Iraq (Mutlk *et al.*, 2021). A pandemic of SARS-CoV-2 was subsequently declared by the WHO (Boserup *et al.*, 2020). Globally, more than 528 million individuals (2,328,264 in Iraq) had contracted the disease as of the first of June 2022, and about 6.3 million people had died, counting 25,219 in Iraq (Organization, 2022). Patients are categorized into mild, moderate, severe, and critical cases based on their clinical symptoms and the results of laboratory tests (Sharma *et al.*, 2021; Wu and McGoogan, 2020).

The carry-out of biological markers enables a further certain interpretation of the disease's course. Leukocytes, CRP, ferritin, interleukin-6, and D-dimer are the primary indicators of inflammatory reactions (Lippi and Favaloro, 2020; Zheng *et al.*, 2020). The body may respond by creating an excessive number of cytokines as a consequence of the inflammatory response brought on by CoV-2, leading to the condition known as a cytokine storm (Grasseli *et al.*, 2020; Ji *et al.*, 2020).

C- reactive protein is a sensitive early indicator of tissue damage, infection, and inflammation that is generated by IL-6 in the liver. The amount of CRP expression rises considerably and quickly from its normal low level in acute inflammatory response (Mooiweer *et al.*, 2011; Hhan *et al.*, 2018). Treatment of severe CoV-2 patients benefits by monitoring the concentrations of inflammatory markers like CRP and IL-6 (Qin *et al.*, 2020).

D-dimer is discovered to be the fibrin breakdown product mediated by soluble plasmin and initiated by the start of the coagulation and fibrinolysis cascade (Zhou *et al.*, 2020). In individuals with CoV-2, it has been described as one of the most prevalent and quickly raised laboratory results linked with coagulopathy (Organization, 2022). In these patients, a striking relationship demonstrating the prognostic significance of D-dimer is the significant synergy between CoV-2 infection and venous thromboembolism (Kariyanna *et al.*, 2020).

As an "acute phase reactant," serum Ferritin reflects the severity of both chronic and acute inflammatory responses within the body. The direct immunosuppressive and pro-inflammatory consequences of a greater Ferritin level, which is a sign of an activated monocyte-macrophage system, could lead to a cytokine storm (Kernan and Carcillo, 2017; Vargas and Cortès-Rojo, 2020). Serum Ferritin is a protein that storage iron whose main function is to control cellular oxygen consumption (Chen *et al.*, 2022). In the situation of the development of CoV-2, serum ferritin has lately acquired significance as a biomarker for inflammation, as shown by earlier studies in this area (Kell and Pretorius, 2014; Cheong *et al.*, 2020).

Procalcitonin is a glycoprotein with non-hormonal activity produced by thyroid parafollicular C cells (Choi and McCarthy, 2018). It can also be produced after bacterial infection in a variety of extrathyroid tissues, which is mediated by elevated levels of TNF-alpha and IL-6 (Lippi and Cervellin, 2018). In healthy individuals, the serum PCT level is below detectable, but systemic inflammations, particularly those brought on by bacterial infections, cause the amount to rise (Floriańczyk, 2003). Recently, multiple investigations found an inverse relationship between high PCT and CoV-2 severity (Guan *et al.*, 2020; Zhang *et al.*, 2020). This study aimed to assess the value of some inflammatory biomarkers, including serum CRP, D-dimer, ferritin, and PCT in the early diagnosis and CoV-2 severity.

MATERIALS AND METHODS

Subjects

Two hundred and ten individuals who were tested positive for CoV-2 infection by reverse transcription-quantitative (RT-q) PCR of nasal or pharyngeal swab specimens in three hospitals (Rozhawa emergency, Emirati and lalav intensive care unit (ICU)) in Erbil city were comprised in this study. The patients were classified into three groups, 70 patients (35 female and 35 male) were complaining of mild symptoms and treated as outpatients, while another 140 patients were admitted

to the hospital, 70 of them (39 female and 31 male) complaining from moderate symptoms while 70 of them complaining from severe symptoms (38 female and 32 male) in which their ages were between (21-75), in addition to 70 healthy control (27 female and 43 male) with age range (23-70).

Blood Samples

After receiving written informed consent from all participants, a sample of venous blood (about 5 ml) was promptly taken from every CoV-2 patient and healthy persons' subject enrolled in this trial and placed into two separate laboratory tubes. Two ml of the blood in a test tube with EDTA was used for the measurement of a vital haematological parameter using an automated haematology analyser (Medonic mserries, sweden) to determine WBC, Granulocytes, Lymphocytes, Platelets, and Haemoglobin. The rest three ml of the whole blood was collected in a serum separating gel tube for 30 minutes to coagulate. The samples were centrifuged at 5,000 RPM for 5 minutes to collect serum for CRP and D-Dimer analysis using INDIKO PLUSE Instrument (Fenland), Ferritin levels were determined by Cobase 411 – Roche (Germany) and Procalcitonin (PCT) analysis using the enzyme-linked immunosorbent assay (ELISA) (Biotech, Germany).

Statistical Analysis

The data was analyzed using a (Graph Pad prism 9.0), variables with a normally distribution were appropriately reported as mean \pm SD. Statistical significance was defined as a P value 0.05. The data of haematological parameters and inflammatory markers presented of this study, the (ANOVA) and person correlation test was used to evaluate between-group comparisons for categorical variables, the predictive significance of the study determine severity via receiver operating characteristic (ROC) curve analyses and the results were expressed as area under curve (AUC), cut-off value, specificity and sensitivity. The symbol (*) refer to highly significantly difference between patient groups and healthy control; (ns) refer to non-significant between groups.

RESULTS AND DISCUSSION

The CoV-2 is characterized by acute respiratory distress syndrome, is brought on by the unique coronavirus SARS-COV-2, which is a multisystem disease caused by the incorporation of immunological, inflammatory, and coagulative cascades. The clinical appearance of CoV-2 ranges from asymptomatic to critical pneumonia, acute respiratory distress syndrome, and even death (Wiersinga *et al.*, 2020). During the worldwide CoV-2 pandemic, the role of laboratory medicine for clinical decision-making and evaluation of biomarkers for early prediction of the severity and mortality was markedly highlighted. In general, inflammatory markers as CRP, D-dimer, and PCT are accepted as important infection biomarkers of severe CoV-2 disease (Zhang *et al.*, 2020).

Evaluation of Hematological Parameters of SARS-CoV-19

Although we still know very little about the exact adaptive and innate immune response to SARS-CoV-2, the hematological changes might be a homeostatic defense against systemic inflammation that has been over activated (Allegra *et al.*, 2020; Li *et al.*, 2020). Sars-cov-2's progression and frequency depend on the relation between the viral cells and the immune cells of the organism (Younis and Fattah, 2021).

According to our findings CoV-2 patients' group had leukocytosis, WBC and Granulocyte count were elevated significantly with the severity of the disease, while Lymphocyte numbers decreased with severity in comparison with the control group. Regarding Monocyte cells, there was a non-significant difference between the CoV-2 groups compared to the control group, as shown in (Table 1).

The immune system in our bodies consists of two lines of defense against pathogens: the first line, known as WBC, which attacks foreign bodies within minutes to hours through direct ingestion via a process known as phagocytes; the second line, known as antibodies, and T lymphocytes, which produce chemicals that attack viruses, are the two lines of defense. (Marquez *et al.*, 2020).

Other studies that confirm our findings demonstrate that CoV-2 patients had greater WBC counts than the healthy group, particularly in the more severe cases (Lu *et al.*, 2021; Jalil *et al.*, 2022).

Our studies indicated lower lymphocyte counts and higher Granulocyte counts in CoV-2 groups compared to the healthy control group, which may be related to increased inflammation brought on by bacterial infection and immune system suppression brought on by CoV-2 infection (Waris *et al.*, 2021). According to several studies, Lymphopenia affects between 40% and 91.6% of CoV-2 patients, and it has been recommended that this condition may be used as a prognostic indicator (Zhao *et al.*, 2020). Our results are consistent with earlier research, which found that lymphocytopenia served like an efficient and dependable biomarker for the intensity of CoV-2 disease and was frequently associated with (SARS-CoV and MERS-CoV-2) infection (Elshazli *et al.*, 2020; Tang *et al.*, 2020). In accordance with our investigation, studies of Sánchez-Cerrillo *et al.* (2020) and Pirsalehi *et al.* (2021) revealed that CoV-2 patients had a marked decline in monocyte count.

In our immune system, platelets have an important function in blood clotting and are known to play a part. They are also a major controller of inflammatory illnesses (Aktaş *et al.*, 2013). Several proposed mechanisms for the thrombocytopenia brought on by CoV-2: Megakaryocyte and bone marrow suppression by a direct viral infection and inflammatory cytokines. CoV-2 patients' thrombocytopenia is brought on by lung damage because mature megakaryocytes, which are present in the lung, release platelets (Rizo-Téllez *et al.*, 2020; Wool and Miller, 2021). Studies Bashash *et al.* (2020), showed the predictive relevance of platelet count in this illness. They show in their meta-analysis of 19 studies that a lower count of platelet is linked to a higher danger of contracting serious disease. Our study found that the platelet there was a comparison of the results reveals that highly significant difference between CoV-2 cases compare to healthy cases, which was lower count of platelet especially in severe cases, that was similar to the other founding studies (Bashash *et al.*, 2020).

Table 1: Comparison of hematological parameters between healthy and COVID-19 cases

Parameters	Control	Category of COVID-19 cases			p. value
		Mild	Moderate	Severe	
WBC (10 ⁹ /l)	6.99±2.02a	9.59±5.02b	13.15±5.71cd	14.89±7.24d	0.000
Lym (10 ⁹ /l)	2.09±0.69a	1.02±0.54bc	0.94±0.55cd	0.81±0.51d	0.000
Mono (10 ⁹ /l)	0.57±1.03abcd	0.53±0.82bc	0.79±1.01c	0.31±0.22d	0.009
Gran (10 ⁹ /l)	4.29±1.62	8.08±4.78	11.41±5.30	13.82±6.83	0.000
HGB (g/dl)	14.05±1.65ab	13.71±1.55b	12.71±1.81c	11.87±1.74d	0.000
PLT (10 ⁹ /l)	219.48±59.89abd	247.51±96.84b	292.46±120.94c	203.20±100.21d	0.000
The mean difference is significant at the 0.05 level					
Combined letters: mean no significant differences between groups					

Evaluation of Inflammation Markers of Covid-19

CoV-2 reasons of a systemic inflammatory response leading to release of various inflammatory biomarkers in the body. Escalating levels of inflammatory biomarkers lead to increasing severity of CoV-2 illness (Huang *et al.*, 2020).

The current study found that the CRP level was highly significantly increase in severe patients compared to moderate and mild patients and the control group but there was a non-significant difference between mild and moderate. The optimal Cut-off values of CRP for predicting severity in CoV-2 patients were determined via (ROC) Curve analysis was for mild 6.100 mg/l (sensitivity= 75.71%; specificity=87.14%; (AUC) =0.847), moderate 7.535 mg/l (sensitivity=94.29%; specificity=97.14%; AUC=0.970) and sever 7.855 mg/l (sensitivity= 100%; specificity=97.14%; AUC=1.000) (Table 2) and Fig. (1).

The result of our study is consistent with those of Li *et al.* (2020) and Qin *et al.* (2020), who found that more severe instances of CoV-2 expressed larger CRP levels than non-severe patients, and suggestive of CRP level may be a biomarker of disease severity and progression in CoV-2

patients. Ji *et al.* (2020), suggested that one of the earliest biomarkers to represent physiological difficulties and the most significant biomarker for determining whether CoV-2 would advance was CRP levels.

Table 2: Comparison of inflammatory markers between healthy and COVID-19 cases

Parameters	Control	Category of COVID-19 cases			p. value
		Mild	Moderate	Severe	
CRP(mg/l)	3.74±2.33a	34.11±31.57bc	47.44±26.69c	79.83±63.59d	0.000
D-dimer (µg/ml)	0.92±0.20ab	2.18±1.60b	7.21±2.49c	14.49±9.21d	0.000
Ferritin (ng/ml)	96.96±72.98a	999.9±918.3bc	1071±648.4cd	1334±693.4d	0.000
PCT (pg/ml)	55.13±46.93	88.70±39.73	164.7±58.44	199.1±35.67	0.000

The mean difference is significant at the 0.05 level
 Combined letters: mean no significant differences between groups

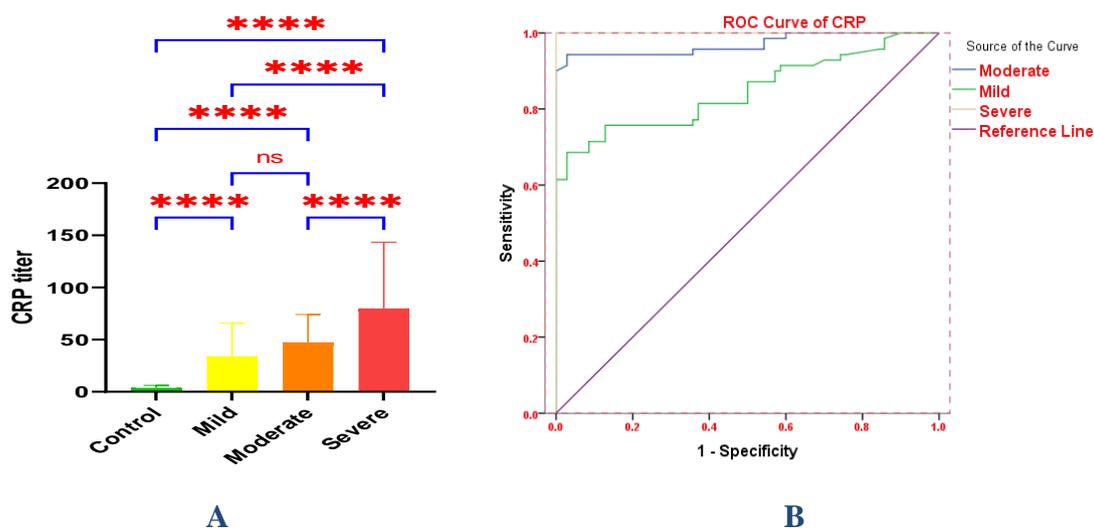


Fig. 1. A: Comparison of CRP level in patient group and healthy control. B: ROC curve of CRP level

Considering the markers of coagulation, the results showed D-dimer is the most significant marker of covid-19 patients, our results showed a highly increase significant in the level of D-dimer between severe patients compare to mild, moderate, and control groups, but there was a non-significant difference between mild and control group. The optimal Cut-off values of D-dimer for predicting severity in CoV-2 patients were determined via ROC Curve analysis were mild 0.74 µg/ml (sensitivity= 100%; specificity=97.14%; AUC=0.995), moderate 0.76 µg/ml (sensitivity=100%; specificity=97.14%; AUC=1.000) and sever 0.76 µg/ml (sensitivity= 100%; specificity=97.14%; AUC=1.000) p=0.000 (Table 2, 3) and Fig. (2).

Our study's findings are consistent with those of a number of other studies. Tang *et al.* (2020), reported that CoV-2 patients with a severe illness had D-dimer levels approximately 3.5 times higher than those with only mild or moderate illness. Wang *et al.* (2020) and Huang *et al.* (2020), who reported that CoV-2 patients with a severe level of illness had 2.5 times and 5 times higher levels of D-dimer than patients with only mild or moderate levels of illness, respectively. Because inflammatory cytokines may cause imbalances between coagulation and fibrinolysis in the alveoli, which may subsequently activate the fibrinolysis system and raise D-dimer levels, the

rise in D-dimer levels may be an indirect sign of an inflammatory response (Sharma *et al.*, 2021). Inflammatory storm activation and plasma release of proinflammatory cytokines like IL-7, IL-2, G-CSF, MCP-1, IP-10, MIP-1A, and TNF- may be the cause of the D-dimer level elevation. The endothelial dysfunction mechanism is triggered, resulting in damage to the microvascular system and activation of the coagulation system, which raises the D-dimer value. (He *et al.*, 2021).

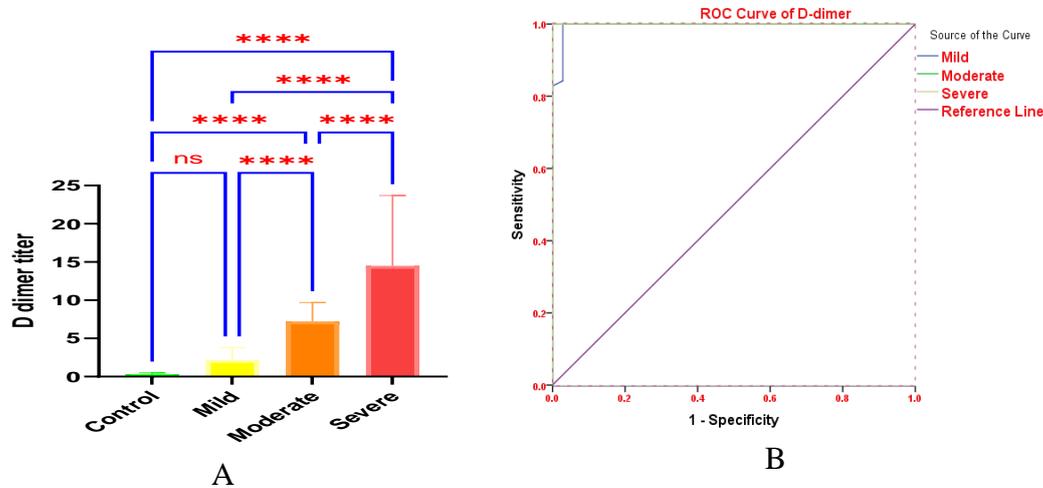


Fig. 2. A: Comparison of D-dimer level in patient group and healthy control. B: ROC curve of D-dimer level

The elevated ferritin level was a highly significant increase between (mild to moderate and severe) compared to the control group, but there was a high difference and non-significant difference between mild to moderate and moderate to severe that is showed in Fig. (3). The optimal Cut-off values of Ferritin for predicting severity in CoV-2 patients were determined via ROC Curve analysis were mild 162.1ng/ml (sensitivity=91.43%; specificity=87.14%; AUC=0.932), moderate 167.3 ng/ml (sensitivity = 90%; specificity = 92.86%; AUC=0.917) and severe 278.3 ng/ml (sensitivity = 92.86%; specificity = 97.14%; AUC=0.928) (Table 2, 3) and Fig. (3).

CoV-2 patients with serious illness exhibited higher ferritin levels compared to those with mild to moderate disease. This surplus could lead to a secondary bacterial infection and exacerbate CoV-2 illness. Our findings are consistent with evidence from other studies that have established a link between blood ferritin and the CoV-2 seriousness. Mohammed Saeed *et al.* (2020); Bozkurt *et al.* (2021); Maghfirah *et al.* (2020), in their research found that serum Ferritin levels and the severity of CoV-2 have a significant association with a strong positive correlation; this means that patients of CoV-2 experience more serious symptoms, which is greater than their serum ferritin levels. As an “acute-phase protein”, ferritin is frequently increased in many different inflammatory responses and could be a clear sign of cellular damage (Kell and Pretorius, 2014; Henry *et al.*, 2020). Several variables, including older age, sex, genetics, and iron consumption, influenced the CoV-2 case's ferritin rate (Mckinnon *et al.*, 2014). High ferritin serum levels are discovered during infection and may signify viral replication. In a severe case of CoV-2, an increase in ferritin rate brought on by a cytokine storm has been documented (Chen *et al.*, 2020).

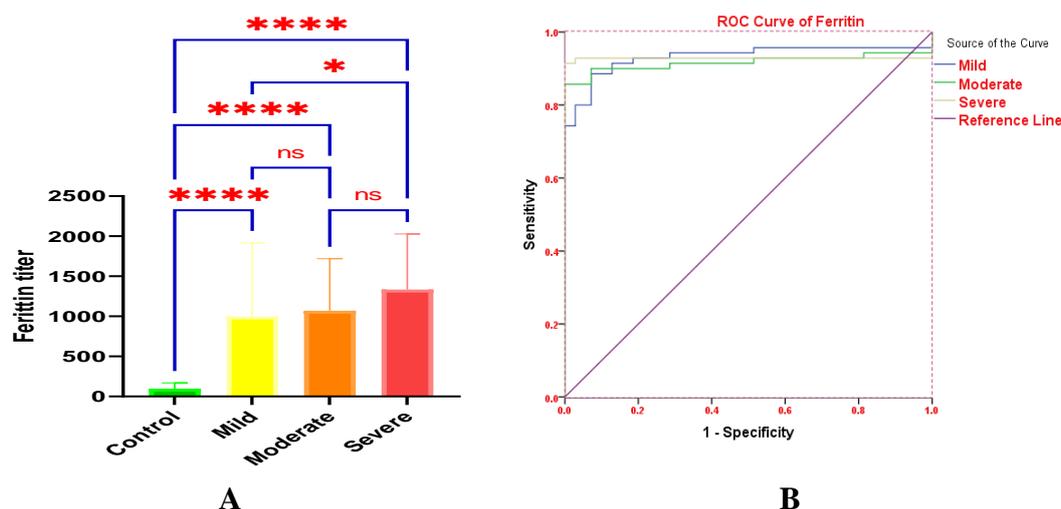


Fig. 3.A: Comparison of Ferritin level in patient group and healthy control. B: ROC curve of Ferritin level

Procalcitonin was a highly significant increase between the three groups of CoV-2 patients when compared with the group of control. The optimal Cut-off values of PCT for predicting severity in CoV-2 patients were determined via ROC Curve analysis for mild 66.09 pg/ml (sensitivity = 82.86%; specificity=78.57%; AUC = 0.832), moderate 97.13 pg/ml (sensitivity = 90%; specificity = 90%; AUC= 0.877), and severe 119.8 pg/ml (sensitivity = 100%; specificity = 92.86%; AUC = 0.963) (Table 2, 3) and Fig. (4).

As a consequence of our research, we determined that patients with severe cases had mean serum PCT levels that were about four times higher than those with moderate cases and eight times greater than those with light cases. PCT level may be a sign of how severe a condition is and may help assess how seriously CoV-2 patients are affected. All of our findings are consistent with previous research. Lippi and Plebani (2020), in their meta-analysis discovered that patients with CoV-2 had approximately 5-fold greater probability of developing the serious disease when their serum PCT levels were higher. Furthermore, the authors hypothesized that routine evaluation of the procalcitonin level would be useful in foretelling the development of CoV-2 to a more extreme condition. Vazzana *et al.* (2022), revealed that, on average, patients with a severe CoV-2 course had higher PCT levels than those with a non-severe course.

Along with CRP and interleukin IL-6, PCT is another inflammatory biomarker frequently checked in CoV-2 patients. Leukocytes and different parenchymal cells in the lungs, fat, and liver, in addition to leukocytes in reaction to proinflammatory cytokines and endotoxins, produce PCT (Meisner, 2014; Ponti *et al.*, 2020). Procalcitonin can be used to diagnose or predict certain diseases, because interferon-c prevents PCT production, serum concentrations in viral infections are thought to be consistently low, as well (Schuetz *et al.*, 2011). The PCT levels of most individuals with CoV-2 are very low at arrival, while increased inflammatory markers like WBC and CRP show that their lungs are inflamed (Guan *et al.*, 2020; Xu *et al.*, 2020).

However, as the condition progresses, the PCT levels rise, which may be associated to the prevalence of bacterial infections. In these patients, secondary bacterial pneumonia could develop due to the co-infection with bacteria and the viral illness (Rawson *et al.*, 2020). It has been established that co-infection with bacteria is a plausible cause for higher PCT in individuals with severe CoV-2 and dead patients with CoV-2 were more likely to experience multiple organ failure or co-infection (Wang *et al.*, 2020).

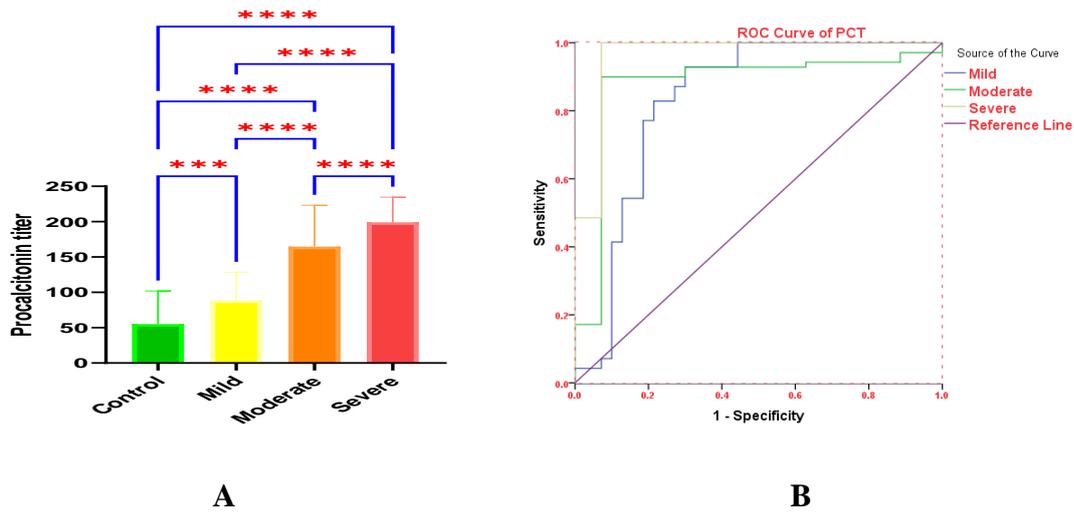


Fig. 4. A: Comparison of PCT of levels in the patient group and healthy control. B: ROC curve of PCT level.

Table 3: Regression of inflammatory markers Risk factor for severe covid-19

Inflammatory marker		Area under curve (AUROC)	Optimal cut off value	Sensitivity (%)	Specificity (%)	P. value
CRP (mg/l)	Mild	0.847	6.100	75.71	87.14	0.000
	Moderate	0.970	7.535	94.29	97.14	0.000
	Severe	1.000	7.855	100	97.14	0.000
D-dimer(µg/ml)	Mild	0.995	0.74	100	97.14	0.000
	Moderate	1.000	0.76	100	97.14	0.000
	Severe	1.000	0.76	100	97.14	0.000
Ferritin(ng/ml)	Mild	0.932	162.1	91.43	87.14	0.000
	Moderate	0.917	167.3	90	92.86	0.000
	Severe	0.928	278.3	92.86	97.14	0.000
PCT (pg/ml)	Mild	0.832	66.09	82.86	78.57	0.000
	Moderate	0.877	97.13	90	90	0.000
	Severe	0.963	119.8	100	92.86	0.000

To correlate PCT values with other inflammatory biomarkers, the Pearson correlation coefficient was calculated, and the results are shown in (Table 4). PCT displayed a highly significant positive correlation with hemoglobin in the mild group and a highly significant negative correlation with platelet, Lymphocyte, and CRP ($P < 0.01$), while PCT displayed a highly significant positive correlation with Lymphocyte and a significant negative correlation with platelet and Ferritin in moderate group. In the severe group, there was a highly negative correlation with D-dimer and a positive correlation with hemoglobin ($p < 0.01$ and $p < 0.05$) respectively.

Table 4: Correlation of PCT with hematological and inflammatory markers among Covid- 19 patients

Parameters	Patients' categories					
	Mild		Moderate		Severe	
	Pearson correlation	P. value	Pearson correlation	P. value	Pearson correlation	P. value
Age (year)	0.039	0.748	0.005	0.965	-0.041	0.738
WBC (10 ⁹ /l)	-0.116	0.337	-0.066	0.585	-0.145	0.230
Lym (10 ⁹ /l)	-0.243*	0.042	0.342**	0.004	0.011	0.930
Mono (10 ⁹ /l)	-0.014	0.911	-0.072	0.551	-0.036	0.770
Gran (10 ⁹ /l)	-0.090	0.457	-0.094	0.441	-0.151	0.212
HGB (g/dl)	0.396**	0.001	-0.151	0.213	0.275*	0.021
PLT (10 ⁹ /l)	-0.357**	0.002	0.282*	0.018	0.163	0.178
CRP (mg/l)	-0.246*	0.040	0.039	0.746	-0.144	0.235
D-dimer (µg/ml)	0.066	0.585	-0.014	0.907	-0.584**	0.000
Ferritin (ng/ml)	-0.158	0.192	-0.254*	0.034	-0.007	0.955
** : Correlation is significant at the 0.01 level (2-tailed).						
* : Correlation is significant at the 0.05 level (2-tailed).						

CONCLUSION

In conclusion, CRP, D-dimer, Ferritin, PCT and platelets can efficiently assess the severity of CoV-2, It is the most effective forecaster of severe Covid-19, and the combination of the clinical markers can further predict severe CoV-2. Therefore, it is suggested that these markers be utilized to quickly detect severe disease in CoV-2 patients in order to assist the early start of effective treatment. Additionally, the dynamics of inflammatory markers in CoV-2 patients might be serve as a helpful marker for the change from a mild to a severe infection.

REFERENCES

- Aktaş, G.; Çakıroğlu, B.; Şit, M.; Üyetürk, U.; Alçelik, A.; Savlı, H.; Kemahlı, E. (2013). Mean platelet volume: a simple indicator of chronic prostatitis. *Acta Med. Mediterr.*, **29**(3).
- Allegra, A.; Di Gioacchino, M.; Tonacci, A.; Musolino, C.; Gangemi, S. (2020). Immunopathology of SARS-CoV-2 Infection: Immune Cells and Mediators, Prognostic Factors, and Immune-Therapeutic Implications. *Int. J. Mol. Sci.*, **21**(13). Doi: 0.3390/ijms21134782
- Bashash, D.; Hosseini-Baharanchi, F.S.; Rezaie-Tavirani, M.; Safa, M.; Akbari Dilmaghani, N.; Faranoush, M.; Abolghasemi, H. (2020). The Prognostic Value of Thrombocytopenia in COVID-19 Patients; a Systematic Review and Meta-Analysis. *Arch. Acad. Emerg. Med.*, **8**(1), e75.
- Boserup, B.; McKenney, M.; Elkbuli, A. (2020). The impact of the COVID-19 pandemic on emergency department visits and patient safety in the United States. *The American J. Emerg. Med.*, **38**(9), 1732-1736. Doi: 10.1016/j.ajem.2020.06.007
- Bozkurt, F.T.; Tercan, M.; Patmano, G.; Bingol Tanriverdi, T.; Demir, H. A.; Yurekli, U. F. (2021). Can ferritin levels predict the severity of illness in patients with COVID-19? *Cureus*, **13**(1), e12832. Doi:10.7759/cureus.12832
- Chen, J.; He, Z.-X.; Wang, F.K. (2022). Evaluation of ferritin level in COVID-19 patients and its inflammatory response. *Appl. Nanosci.*, 1-7. Doi:10.1007/s13204-021-02115-9
- Chen, R.; Sang, L.; Jiang, M.; Yang, Z.; Jia, N.; Fu, W.; Zhong, N. (2020). Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. *J. Allergy Clin. Immunol.*, **146**(1), 89-100. Doi: 10.1016/j.jaci.2020.05.003
- Cheong, M.; Chew, S.T.H.; Oliver, J.; Baggs, G.; Low, Y.L.; How, C.H.; Tey, S.L. (2020). Nutritional biomarkers and associated factors in community-dwelling older adults:

- Findings from the SHIELD study. *Nutrients*, **12**(11), 3329. <https://doi.org/10.3390/nu12113329>
- Choi, J.J.; McCarthy, M.W. (2018). Novel applications for serum procalcitonin testing in clinical practice. *Expert Rev. Molec. Diagnost.*, **18**(1), 27-34. <https://doi.org/10.1080/14737159.2018.1407244>
- Elshazli, R.M.; Toraih, E.A.; Elgaml, A.; El-Mowafy, M.; El-Mesery, M.; Amin, M.N.; Kandil, E. (2020). Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: A meta-analysis of 6320 patients. *PLoS One*, **15**(8), e0238160. Doi: 10.1371/journal.pone.0238160
- Floriańczyk, B. (2003). Structure and diagnostic value of procalcitonin. Paper presented at the Annales Universitatis Mariae Curie-Skłodowska. *Sectio D: Medicina.*, **58**(1), 338-42.
- Grasselli, G.; Zangrillo, A.; Zanella, A.; Antonelli, M.; Cabrini, L.; Castelli, A.; Network, C. L. I. (2020). Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region. *Italy. Jama.*, **323**(16), 1574-1581. Doi:10.1001/jama.2020.5394
- Guan, W.J.; Ni, Z.Y.; Hu, Y.; Liang, W.H.; Ou, C.Q.; He, J.X.; Hui, D.S. (2020). Clinical characteristics of coronavirus disease 2019 in China. *New England J. Med.*, **382**(18), 1708-1720. Doi:10.1056/NEJMoa2002032
- Hahn, W.H.; Song, J.H.; Kim, H.; Park, S. (2018). Is procalcitonin to C-reactive protein ratio useful for the detection of late onset neonatal sepsis? *The J. Maternal-Fetal Neonatal Med.*, **31**(6), 822-826. <https://doi.org/10.1080/14767058.2017.1297410>
- He, X.; Yao, F.; Chen, J.; Wang, Y.; Fang, X.; Lin, X.; Wu, Q. (2021). The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. *Scientific Reports*, **11**(1), 1830. Doi: 10.1038/s41598-021-81300-w
- Henry, B. M.; de Oliveira, M.H.S.; Benoit, S.; Plebani, M.; Lippi, G. (2020). Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin. Chem. Lab. Med.*, **58**(7), 1021-1028. Doi: 10.1515/cclm-2020-0369
- Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*, **395**(10223), 497-506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
- Jalil, A.T.; Shanshool, M.T.; Dilyf, S.H.; Saleh, M.M.; Suleiman, A.A. (2022). Hematological and serological parameters for detection of COVID-19. *J. Microbiol., Biotechnol. Food Sci.*, **11**(4), e4229-e4229. <https://doi.org/10.55251/jmbfs.4229>
- Ji, Q.; Zhang, D.; Zhao, Y. (2020). Searching for safe-haven assets during the COVID-19 pandemic. *International Rev. Financ. Analysis*, **71**, 101526.
- Kariyanna, P.T.; Aurora, L.; Jayarangaiah, A.; Yadav, V.; Hossain, N.A.; Akter, N.; McFarlane, I. M. (2020). Utility of D-dimer as a Prognostic Factor in SARS CoV2 Infection: A Review. *Am. J. Med. Case Rep.*, **8**(10), 337-340.
- Kell, D.B.; Pretorius, E. (2014). Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. *Metallomics*, **6**(4), 748-773. Doi: 10.1039/c3mt00347g
- Kernan, K. F.; Carcillo, J. A. (2017). Hyperferritinemia and inflammation. *International Immunol.*, **29**(9), 401-409. Doi:10.1093/intimm/dxx031
- Li, Q.; Cao, Y.; Chen, L.; Wu, D.; Yu, J.; Wang, H.; Hu, Y. (2020). Hematological features of persons with COVID-19. *Leukemia*, **34**(8), 2163-2172. Doi: 10.1038/s41375-020-0910-1
- Lippi, G.; Cervellin, G. (2018). Procalcitonin for diagnosing and monitoring bacterial infections: for or against? *Clin. Chem. and Laboratory Med. (CCLM)*, **56**(8), 1193-1195. <https://doi.org/10.1515/cclm-2018-0312>

- Lippi, G.; Favaloro, E. J. (2020). D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. *Thrombosis and Haemostasis*, **120**(05), 876-878. Doi: 10.1016/j.thromres.2020.09.040
- Lippi, G.; Plebani, M. (2020). Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. *Clin. Chim. Acta.*, **505**, 190-191. Doi:10.1055/s-0040-1709650
- Lu, Y.; Huang, Z.; Wang, M.; Tang, K.; Wang, S.; Gao, P.; Zhao, J. (2021). Clinical characteristics and predictors of mortality in young adults with severe COVID-19: a retrospective observational study. *Ann. Clin. Microbiol. Antimicrob.*, **20**(1), 3. Doi: 10.1186/S12941-020-00412-9
- Maghfirah, A.I.; Esa, T.; Widaningsih, Y.; Bahrnun, U. (2022). Correlation of serum ferritin levels and COVID-19 severity in Makassar. *J. Microbiol. Immunol.*, **4**(1), 1-5.
- Marques, E. S.; Moraes, C.L.D.; Hasselmann, M.H.; Deslandes, S.F.; Reichenheim, M.E. (2020). Violence against women, children, and adolescents during the COVID-19 pandemic: overview, contributing factors, and mitigating measures. *Cadernos de Saude Publica*, **36**, e00074420. Doi: 10.1590/0102-311X00074420
- McKinnon, E.J.; Rossi, E.; Beilby, J.P.; Trinder, D.; Olynyk, J.K. (2014). Factors that affect serum levels of ferritin in Australian adults and implications for follow-up. *Clin. Gastroenterol. Hepatol.*, **12**(1), 101-108. e104. Doi: 10.1016/j.cgh.2013.07.019
- Meisner, M. (2014). Update on procalcitonin measurements. *Ann. Lab. Med.*, **34**(4), 263-273. Doi: 10.3343/alm.2014.34.4.263
- Mohammedsaeed, W.; Surrati, A.M.; Alnakhli, H.Q.; Alharbi, M.; Syeed, N. (2020). Alteration of ferritin levels and lymphocytes counts in saudi patients with COVID-19 infection in Al Madinah Al Munawarah. *International J. Diabetes and Endocrinol.*, **4**(5), 61-66. Doi: 10.11648/j.ijde.20200504.12
- Mooiweer, E.; Luijk, B.; Bonten, M.J.; Ekkelenkamp, M.B. (2011). C-Reactive protein levels but not CRP dynamics predict mortality in patients with pneumococcal pneumonia. *J. Infection*, **62**(4), 314-316. <https://doi.org/10.1016/j.jinf.2011.01.012>
- Mutlk, S.T.; Abdulsattar, B.O.; Jones, I.M. (2021). The Pandemic of COVID-19: Current Scheme of Iraq (24 February- 8 August 2020). *Raf. J. Sci.*, **30**(1),11-17. <https://doi.org/10.33899/rjs.2021.167678>
- Organization, W.H. (2022). "COVID-19 Weekly Epidemiological Update". 115th ed., 26 October 2022.
- Pirsalehi, A.; Salari, S.; Baghestani, A.; Sanadgol, G.; Shirini, D.; Baerz, M. M.; Bashash, D. (2021). Differential alteration trend of white blood cells (WBCs) and monocytes count in severe and non-severe COVID-19 patients within a 7-day follow-up. *Iran. J. Microbiol.*, **13**(1), 8-16. <https://doi.org/10.18502/2Fijm.v13i1.5486>
- Ponti, G.; Maccaferri, M.; Ruini, C.; Tomasi, A.; Ozben, T. (2020). Biomarkers associated with COVID-19 disease progression. *Crit. Rev. Clin. Lab. Sci.*, **57**(6), 389-399.
- Qin, C.; Zhou, L.; Hu, Z.; Zhang, S.; Yang, S.; Tao, Y.; Tian, D.S. (2020). Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan. *China. Clin. Infect. Dis.*, **71**(15), 762-768. Doi: 10.18502/ijm.v13i1.5486
- Rawson, T.M.; Moore, L.S.P.; Zhu, N.; Ranganathan, N.; Skolimowska, K.; Gilchrist, M.; Holmes, A. (2020). Bacterial and fungal coinfection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. *Clin. Infect. Dis.*, **71**(9), 2459-2468. Doi: 10.1093/cid/ciaa530
- Rizo-Téllez, S.A.; Méndez-García, L.A.; Flores-Rebollo, C.; Alba-Flores, F.; Alcántara-Suárez, R.; Manjarrez-Reyna, A.N.; Escobedo, G. (2020). The Neutrophil-to-Monocyte ratio and lymphocyte-to-neutrophil ratio at admission predict in-hospital mortality in Mexican patients with severe SARS-CoV-2 infection (Covid-19). *Microorganisms*, **8**(10). Doi: 10.3390/microorganisms8101560

- Sánchez-Cerrillo, I.; Landete, P.; Aldave, B.; Sánchez-Alonso, S.; Azofra, A.S.; Marcos-Jiménez, A.; Martín-Gayo, E. (2020). Differential redistribution of activated monocyte and dendritic cell subsets to the lung associates with severity of COVID-19. *MedRxiv.*, 2020. 2005.2013.20100925. Doi: 10.1101/2020.05.13.20100925
- Schuetz, P.; Albrich, W.; Mueller, B. (2011). Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. *BMC Med.*, **9**(1), 1-9. Doi: 10.1186/1741-7015-9-107
- Sharma, A.; Ahmad Farouk, I.; Lal, S.K. (2021). COVID-19: A Review on the novel coronavirus disease evolution, transmission, detection. *Control and Prevention. Viruses*, **13**(2). Doi: 10.3390/v13020202
- Tang, N.; Li, D.; Wang, X.; Sun, Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J. Thromb. Haemost.*, **18**(4), 844-847. Doi: 10.1111/jth.14768
- Younis, K.M.; Fattah, S.A. (2021). A brief review of novel coronavirus. *Raf. J. Sci.*, **30**(1), 21-29.
- Vargas-Vargas, M.; Cortés-Rojo, C. (2020). Ferritin levels and COVID-19. *Revista. Panamericana. de Salud Pública.*, **44**, e72. Doi:10.26633/rpsp.2020.72
- Vazzana, N.; Dipaola, F.; Ognibene, S. (2022). Procalcitonin and secondary bacterial infections in COVID-19: association with disease severity and outcomes. *Acta. Clin. Belg.*, **77**(2), 268-272. Doi: 10.1080/17843286.2020.1824749
- Wang, Y.; Lu, X., Li, Y.; Chen, H.; Chen, T.; Su, N.; Wang, J. (2020). Clinical course and outcomes of 344 intensive care patients with COVID-19. *Am. J. Respir. Crit. Care. Med.*, **201**(11), 1430-1434. Doi: 10.1164/rccm.202003-0736LE
- Waris, A.; Din, M.; Khalid, A.; Abbas Lail, R.; Shaheen, A., Khan, N.; Ali, M. (2021). Evaluation of hematological parameters as an indicator of disease severity in Covid-19 patients: Pakistan's experience. *J. Clin. Lab. Anal.*, **35**(6), e23809. <https://doi.org/10.1002/jcla.23809>
- Wiersinga, W.J.; Rhodes, A.; Cheng, A. C.; Peacock, S. J.; Prescott, H. C. (2020). Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A Review. *Jama.*, **324**(8), 782-793. Doi: 10.1001/jama.2020.12839
- Wool, G.D.; Miller, J.L. (2021). The impact of COVID-19 disease on platelets and coagulation. *Pathobiol.*, **88**(1), 15-27. Doi: 10.1159/000512007
- Wu, Z.; McGoogan, J. M. (2020). Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for disease control and prevention. *Jama.*, **323**(13), 1239-1242. Doi: 10.1001/jama.2020.2648
- Xu, J.B.; Xu, C.; Zhang, R.B.; Wu, M.; Pan, C.K.; Li, X.J.; Zhu, S. (2020). Associations of procalcitonin, C-reaction protein and neutrophil-to-lymphocyte ratio with mortality in hospitalized COVID-19 patients in China. *Sci. Rep.*, **10**(1), 15058. Doi: 10.1038/s41598-020-72164-7
- Zhang, J. J.; Dong, X.; Cao, Y.Y.; Yuan, Y.D.; Yang, Y.B.; Yan, Y.Q.; Gao, Y.D. (2020). Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan. *China. Allergy.*, **75**(7), 1730-1741. Doi: 10.1111/all.14238
- Zhang, X.; Cai, H.; Hu, J.; Lian, J.; Gu, J.; Zhang, S.; Yu, G. (2020). Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. *Internat. J. Infectious Dise.*, **94**, 81-87. <https://doi.org/10.1016/j.ijid.2020.03.040>
- Zhao, Q.; Meng, M.; Kumar, R.; Wu, Y.; Huang, J.; Deng, Y.; Yang, L. (2020). Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A systemic review and meta-analysis. *Int. J. Infect. Dis.*, **96**, 131-135. <https://doi.org/10.1016/j.ijid.2020.03.040>
- Zheng, S.; Fan, J.; Yu, F.; Feng, B.; Lou, B.; Zou, Q.; Yang, X. (2020). Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China,

January-March 2020: retrospective cohort study. *Bmj.*,
369. <https://doi.org/10.1136/bmj.m1443>

Zhou, Z.; Ren, L.; Zhang, L.; Zhong, J.; Xiao, Y.; Jia, Z.; Jiang, S. (2020). Heightened innate immune responses in the respiratory tract of COVID-19 patients. *Cell. Host. Microb.*, 27(6), 883-890. e882. <https://doi.org/10.1016/j.chom.2020.04.017>

تقدير بعض المعلمات الالتهابية لدى مرضى كوفيد-19 في مدينة أربيل

سهيلة نافع داروغه

شيماء خليل محمد

قسم علوم الحياة/ كلية التربية/ جامعة صلاح الدين/ أربيل

الملخص

أثر مرض فيروس كورونا الوبائي لعام 2019 على ملايين الأفراد على مستوى العالم. كان الهدف من الدراسة الحالية هو تقييم المتنبات المحتملة لشدة مرض Cov-2 وتحديد العلاقة المحتملة بين معلمات المرضى وشدة المرض، وبالتالي، كنا نهدف إلى قياس مستويات مصل بعض علامات الالتهاب، بما في ذلك CRP و D-Dimer و Ferritin و Procalcitonin، كمؤشر حيوي لشدة المرض لدى مرضى CoV-2. تم جمع 280 مسحة من البلعوم الأنفي وعينات دم كاملة من الأفراد الأصحاء والأفراد المشتبه في إصابتهم بفيروس CoV-2 بين حزيران 2021 و كانون الأول 2021 من كلا الجنسين، مصنفة إلى أربع مجموعات رئيسية: 70 فردا سليما تتراوح أعمارهم بين (23-70)، 210 مريضا ب CoV-2 كانت أعمارهم بين (21-75)، (70 فرد لكل إصابة خفيفة، إصابة معتدلة وإصابة شديدة). وفقا للنتائج التي توصلنا إليها، كانت هناك ارتفاع معنوي في عدد الكريات الدم البيضاء وعدد الخلايا المحببة وانخفاض معنوي في عدد الخلايا اللمفاوية والصفائح الدموية لدى مجموعات مرضى CoV-2 مقارنة بمجموعة التحكم الصحية. فيما يتعلق بالمعلمات الالتهابية، أظهر CRP و D-dimer و Ferritin و PCT أظهرت النتائج اختلافات معنوية في مستوى هذه المعلمات بين مجموعات مرضى CoV-2 مقارنة بالمجموعة التحكم الصحية. حيث ارتفعت مستوى هذه المعلمات معنويا لدى مرضى CoV-2 مقارنة بمجموعة التحكم الصحية. ($P < 0.005$). تم تحديد قيم القطع المثلى ل CRP و D-dimer و Ferritin و PCT من خلال تحليل منحني خصائص تشغيل جهاز الاستقبال (ROC) في CoV-2، و أخيرا فان المؤشرات الحيوية للالتهابات تعتبر هي افضل للتنبؤ للإصابة ب CoV-2 الشديد، ويمكن أن يؤدي الجمع بين العلامات السريرية إلى التنبؤ بشكل أكبر ب Covid-19 الشديد. ويمكن للمؤشرات الحيوية للالتهابات تقييم شدة CoV-2 بدقة.

الكلمات الدالة: SARS-CoV-2، جائحة CoV-2، معلمة أمراض الدم، المؤشرات الحيوية الالتهابية .