

Study the Association of Inflammatory Markers as CRP, LDH, D. Dimer and Ferritin with Severity of Covid19 Disease

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Abstract:

Background: coronavirus 19(covid19) spread as pandemic disease in all world from December 2019. The aim of this study to detect the association of biomarkers as C-reactive protein, ferritin, D. dimer and lactate dehydrogenase with severity of covid19 disease. **Methods and patients:** The patient's group includes 61 patients (30 moderate and 31 sever cases) and control group includes 30 healthy individuals. The inflammatory markers were measured by C4000 full automated instrument. **Results:** The results of this study showed the increased level of these biomarkers in patients group especially in severe cases of patients. In all detected biomarkers there are a significant differences between patients and control group. **Conclusion:** This study concludes that elevation of some biomarkers may be give a clue about the severity of covid19 disease.

Key words: covid19, ferritin, CRP, D. dimer, LDH

Introduction

The group of coronaviruses contain RNA nucleic acid with a positive strands and they are a large provided with an envelope. These viruses have projections like spikes consisting of glycoprotein on their surface, these spikes give the viruses a crown appearance under the electron microscope, therefore this group of viruses is called coronaviruses. These viruses are responsible for infection of a variety of mammalian and avian species (1).

The Coronavirus was classified by the international committee of Taxonomy under the coronaviridae family, subfamily called coronavirinae. Also, according to the

serological and genotyping features the coronavirus was classified into four genera that include Alpha, Beta, Gamma and Delta coronavirus (2).

The coronavirus has four major structural proteins. These protein include the spike (S), Membrane (M), envelope (E) and nucleocapside (N) protein. These proteins were encoded within the 3 ends of the virus genome. The S protein has 150 KDa and consists of homotrimers of the virus that make up the spikes distinctive on the viral surface (3).

The M protein with 25-30 KDa and three transmembrane domains which is the main structural proteins and define the viral envelope shape (4). The E protein is the smallest one of these proteins with a molecular weight of 8-12 KDa. The N protein is one of the fundamental proteins that bind to the RNA genome (5).

The D. dimer is produced during the coagulation of plasma and consider as a characteristic product of a degenerative and cross-linked fibrin. The elevated level of D. dimer represents the activation of coagulation following fibrinolytic process (6). The recent studies indicate a strong relation between D. dimer and the patients of covid19, these studies observed that increased level of D. dimer is correlated with severity and outcomes of covid19 infections (7).

Ferritin could be a key arbiter of resistant dysregulation, particularly beneath extraordinary hyperferritinemia, through coordinate immune-suppressive and pro-inflammatory impacts, paying to the cytokines storm (8). In one think about with twenty Covid19 patients, it was found that people with serious and exceptionally extreme covid19 uncovered increased serum ferritin level, being serum ferritin within the exceptionally serious covid19 gather essentially higher than within the serious covid19 gather (9).

Another study showed that many patients with high level of ferritin died during hospital admission and stay (10). Many laboratory findings data showed that severe covid19 patients who had cytokines storm also had elevated inflammatory mediators like ferritin, which is associated with serious and life- threatening disease (11).

C-reactive protein is one of the acute phase proteins and nonspecific markers of

inflammation and has been found to correlate with disease severity and treatment of many infectious and non-infectious conditions. C-reactive protein level have been reported in severe acute respiratory syndrome, Middle East respiratory syndrome, H1N1 influenza. Recent studies are showed that CRP level is at an increased in patients with covid19 and correlate with severity of disease (12).

Lactate dehydrogenase is present in the cytoplasm of all human tissues and increased level in the liver, heart and skeletal muscles, this enzyme catalyzes the reversible conversion of L-lactate and pyruvate in human cells. Elevation of LDH in covid19 patients is one of the abnormal diagnostic parameters with severe or fatal disease. The clinical and biological important of increased level of LDH are pulmonary injury and wide- spread organ damage (13).

Material and Methods

From July to November 2020, a total of 61 patients were admitted to the nursing home hospital in Baghdad. The patients group includes 31 moderate cases of covid19 disease and 30 patients severe cases of covid19, the patients group was classified as severe and moderate in this hospital according to the clinical criteria, physical examination as po2, CT scan results. the control group include 31 healthy individuals. The healthy individuals are not infected with covid19 and this is indicated by testing them with a rapid test for detecting IgM and IgG from the company of CTK (USA)

Five cubic centimeter of blood was drawn from all patients and control, then the samples was placed in gel tubes and centrifuged, then the serum was aspirated for analyzed by full automated instrument C4000 (abbott)

Results:

Sixty one patients infected with corona virus were included in this study. 31 were moderate (M) and 30 were severe cases (S), the patients group include 37 male (mean of age was 46.27) and 24 female (mean of age 42.21). The control group (C) include 31 with mean age (42.87).

The mean value of CRP, Ferritin, D. Dimer and LDH level in each group of

patients and control group was shown in the following table 1.

Table 1. show the number, mean value and standard deviation of patients and control groups.

Test name	M (moderate)	S (severe)	C (control)	T (total)
LDH (NO)	31	30	31	92
Mean	405.99	526.04	166.48	364.43
Std. Deviation	102.78	118.01	37.84	175.84
CRP (NO)	31	30	31	92
Mean	26.08	39.88	5.75	23.73
Std.Deviation	6.62	9.06	2.53	15.51
D.Dimer (NO)	31	30	31	92
Mean	488.40	1024.82	157.32	551.76
Std. Deviation	151.17	301.41	32.64	406.18
Ferritin	31	30	31	92
Mean	664.28	1470.53	187.10	766.40
Std. Deviation	174.81	380.01	40.89	581.35

There is a significant differences between patients and control group, also there is a significant differences between severe cases and moderate one of covid19 patients in all parameters that include CRP, D. Dimer, Ferritin and LDH. The P value less 0.05 (P. value is 0.000) as showed in the following figures 1, 2, 3, 4.

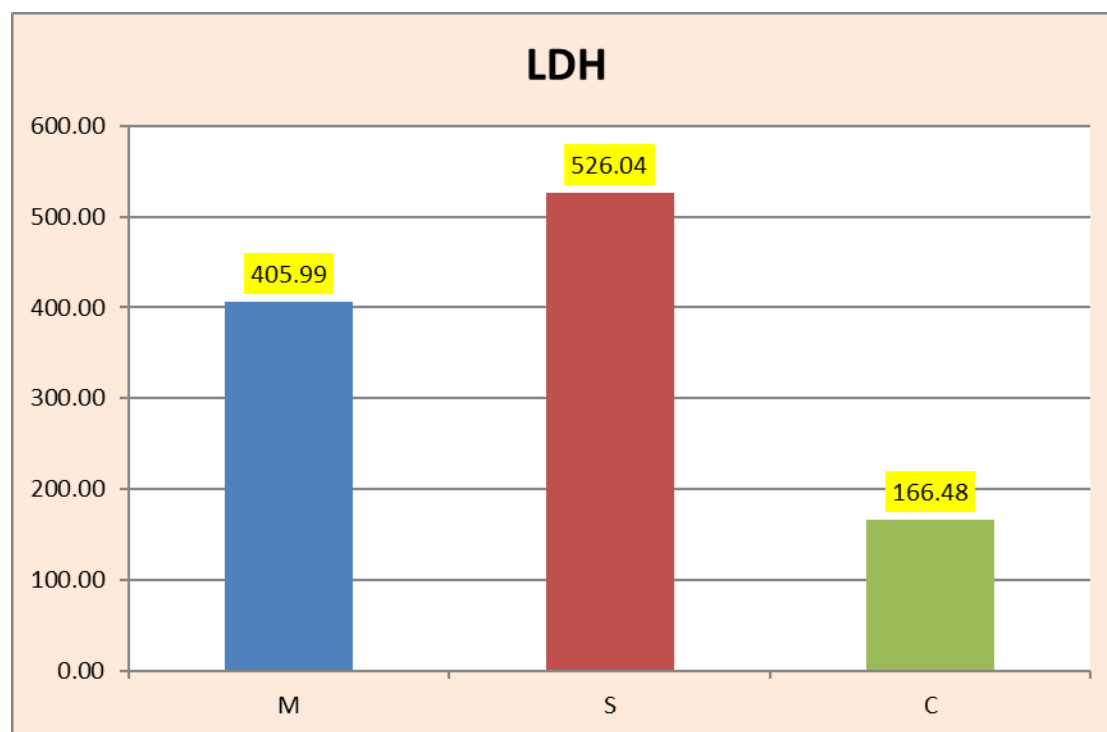


Figure 1. show the mean value of LDH in severe (S) , moderate (M) and control group.

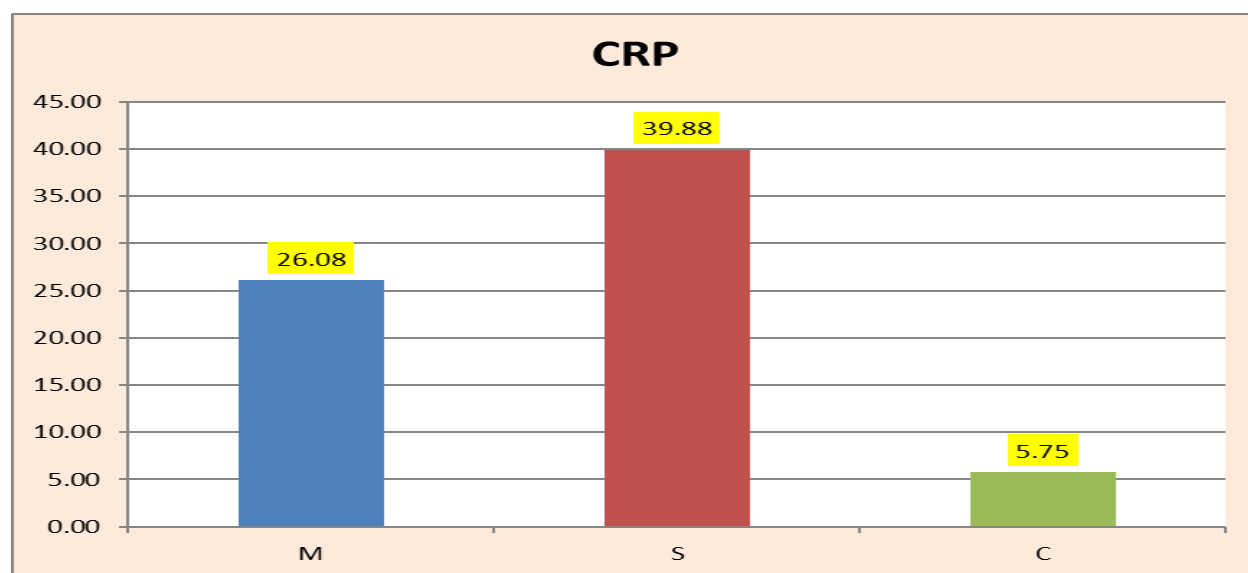


Figure 2. show the mean value of CRP (c-reactive protein) in severe, Moderate and control group.

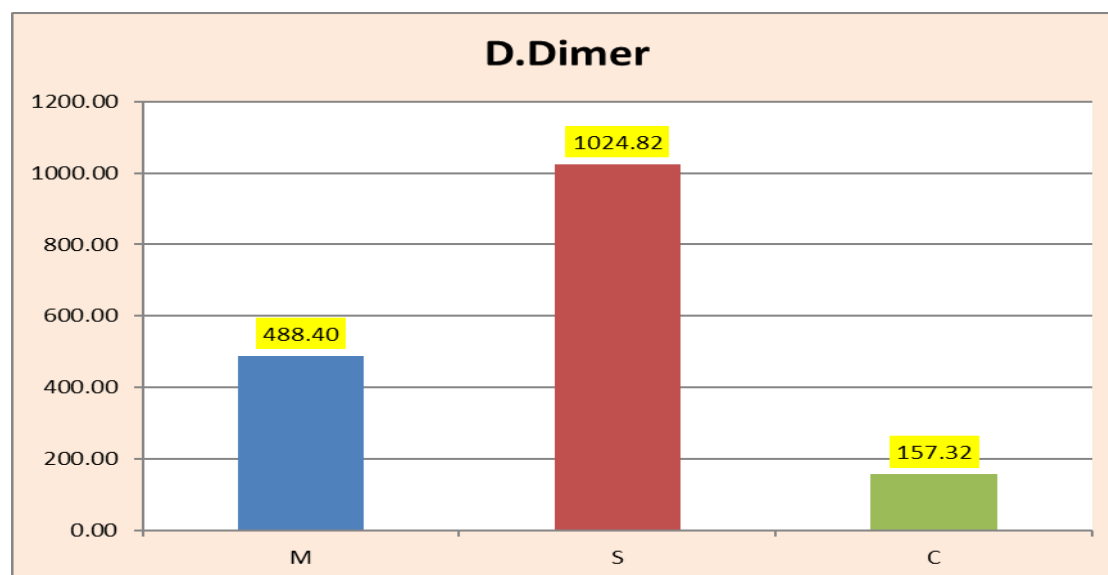


Figure 3. show the mean value of D.Dimer in severe, moderate and control group

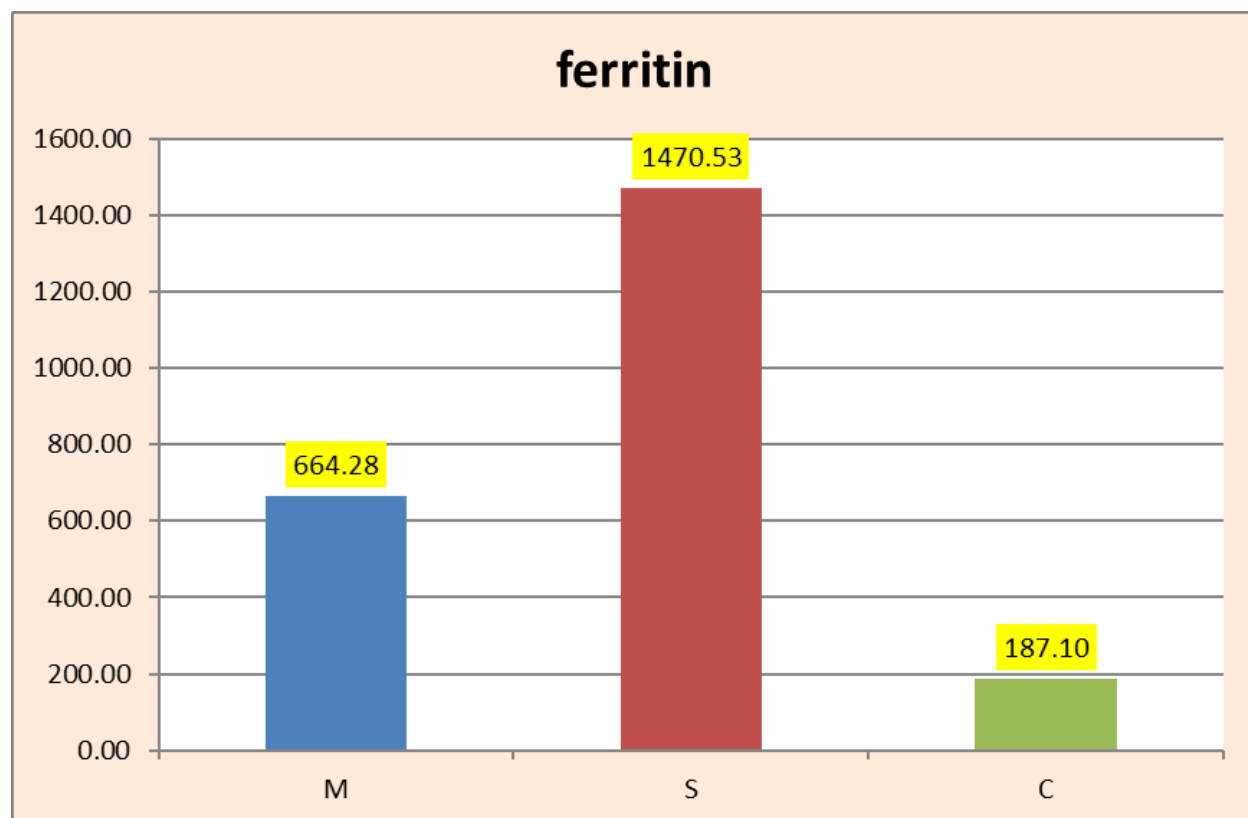


Figure 4. show the mean value of ferritin in severe, moderate and control

group

There is a significant differences between male and female patients in each of LDH and CRP (P value was (0.046, 0.039 consequently) while there is no significant differences between male and female patients in each of Ferritin and D.Dimer (P value were (0.073, 0.58 consequently). Also there is a significant differences between male and female in age (P value was 0.049). as shown in table 2.

Table 2. show the differences between male (M) and female (F) in LDH, CRP, D. Dimer, Ferritin and age).

		N	Mean	Std. Deviation	t	Sig. (2-tailed)
LDH	M	37	490.67	127.64	2.038*	0.046
	F	24	425.50	112.71		
CRP	M	37	35.08	10.70	2.111*	0.039
	F	24	29.44	9.35		
D.Dimer	M	37	818.50	358.46	1.828	0.073
	F	24	650.03	340.61		
Ferritin	M	37	1158.23	489.55	1.931	0.058
	F	24	910.60	488.77		
age	M	37	46.24	7.77	2.010*	0.049
	F	24	42.21	7.48		

* The mean difference is significant at the 0.05 level.

Discussion

After December 2019, the covid19 disease that caused by the coronavirus-2 that leads to severe acute respiratory syndrome. The rapid transmission of this virus from one individual to another one made the disease a pandemic disease (14).

This viral infection is not easy to controlled and the mortality rates is continue to increase if there is no vaccine and antiviral treatment is available (15).

Many studies around the world were investigate elevation of some blood markers that indicate the severity and mortality of infected patients with covid19. C-reactive protein is one of these important markers that change significantly in covid19 patients with severe syndromes (16).

The actual tasks for the clinicians are rapid investigate the covid19 patients that are at high risk for developing acute respiratory disease syndromes. Patients with chronic disease such hypertension, diabetes, old age patients, elevation of inflammatory markers such ferritin, C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase are considered as risk factors and more prone to severe covid19 patients (17).

Different biomarkers are investigated for their role in determination of scenario of covid19 patients. Lactate dehydrogenase is an important markers because elevation of this marker have relation with bad consequences in patients infected with other viral infections (18).

This study shows that LDH was elevated in the patients group and there are a significant differences between the patients and the control. Also, there is a significant differences between mild and severe cases of covid19 patients. LDH is a cytoplasmic glycolytic enzyme that is present in all tissues. The elevation in the level of this marker indicates the damage of the infected tissues. Many studies were found raise in the LDH in the initial stage of severe COVID-19 cases suggesting subclinical tissue damage (19).

In spite of using LDH as a sign of damage in the heart since the 1960s, diminished oxygenation and injury of multiple organs with up instruction of glycolytic pathway also because abnormal value of LDH. Elevation of lactate after infection leads to extracellular acidic PH that leads to activation of metalloproteases and increase macrophage interceded the angiogenesis (20).

The severe infection may produce cytokines- mediated damage and release of LDH into tissues. The LDH enzyme is found in the lung tissue as isoenzyme3, severe cases of Covid19 infections are probable to release a larger amount of quantities of this enzyme into circulation as a severe form of interstitial pneumonia, often progressing into acute respiratory distress syndrome, is the hallmark of the disease (20).

The result of our study was consistent with many studies as (19,20), the elevation of lactate in moderate and severe infection of patients group indicate the

occurrence of tissue harm of many organs and decreased oxygenation with upregulation of the glycolytic pathway (20).

The level of C- reactive protein have been used to differentiate between bacterial and viral infections, the level of this parameter in the viral infection is nominally to 20 µg/ml, while in the bacterial infections the level of this marker may be increase to 40 µg/ml (21).

This level of this protein was represent the amount of tissues that involved and can aid in the identifying the complications that may be produced. Other study found that CRP level was varied between 28.7 µg/ml in non-severe cases of Covid19 and 47.7 µg/ml in severe form of this disease (21).

This study showed the significance differences between the patients and the control group and also between moderate and severe cases of patients. This result was consistent with many studies as (22, 23). This study showed that CRP levels was high in two patient groups and more elevated in the severe group, this elevation indicates that covid19 disease is progressed and lung lesion of patients is large. The CRP levels were really interrelated with lung lesion and disease severity. This recommends that in the initial period of COVID-19, CRP levels may give the clinician first thought about severity of disease and size of lung lesions (21).

D-dimer is one of the proteins fragments and the main product of fibrin degradation by plasmin and is generated in the final phase of a clot formation; it is also known as fragment D-dimer and fibrin degradation fragment (24). All patients with severe forms of COVID-19 pneumonia usually undergo a series of laboratory studies that typically include the quantification of D-dimer, forming part of the «COVID-19 profile» (24).

This study showed elevation of D. Dimer in the patients group and a significant differences between moderate and severe cases of covid19 patients also be showed. D. Dimer level in moderate cases range (448.40) while in severe cases the level of this parameter is more than 1000 (1024.82), this result was consistent with many studies as (24, 25).

The SARS-COV-2 usually cause a significant thrombo-inflammatory response in

the Covid19 patients who suffer from severe pneumonic and progressive diffuse lung damage. The endothelial cells (ECs) play an important role in vasodilation control, thrombotic regulation, fibrinolysis with ant aggregation between other important functions with hypercoagulabl profile accompanied with severe disease and this indicating the active SARS-CoV-2 of ECs injury and dysfunction that may last for months in the survivors patients. The destruction that is produced on alveolar epithelial cells that start interstitial lung disease of diverse extent in the medium and long period, which could hit people in the future especially those with thousands of different cases of progressive pulmonary fibrosis (24).

This height of D. Dimer levels has been set up as being related with seriousness of malady and mortality in covid19 patients and ought to be considered to reflect enactment of the coagulation framework in this setting (26).

Serum ferritin, a feature of hemo-phagocytic lymphohistiocytosis, which is a known complication of viral infection, is closely related to poor recovery of COVID-19 patients, and those with impaired lung lesion are more likely to have increased ferritin levels (14).

The constructed study showed increased the level of ferritin in the patients group comparable to the control group. Also, the study showed increased concentration of this mediator in severe case above (1470.53), Ferritin, the major intracellular iron storage protein, is an acute phase reactant elevated in many inflammatory conditions, including acute infections (27). The elevation of ferritin that caused by extreme inflammatory processes due to different infections is related to the entrance to the intensive care unit and increased rate of mortality, and signifies a hints to identify the patients with high risk to monitor mediation to minimize inflammation. Increased level of ferritin in the Covid19 patients is associated with a cytokines storm, different inflammatory cytokines are increased that include IL-6, TNF- α , IL-12 and IFN- γ , these cytokines activate kupffer cells, hepatocytes and macrophage to release ferritin (14).

This study also showed that a significant difference between male and female only in C-reactive protein and LDH parameters, this may be due to the number of male

patients more than female in this study population.

Finally, this study was concluded that elevation of CRP, D. Dimer, LDH and Ferritin level increased in severe patients of covid19 more than in moderate cases, and the patients may be in a worse state of this disease.

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