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The Impact of Severe Covid-19 in Iraqi Patients on Serum Angiotensin-Converting Enzyme-2 Level and Other Various Diagnosis Biomarkers

Suzan Haleem Kamel[1], Fadhil Jawad Al-Tu'ma[1*], Riyadh Mohi Al-Saegh[2]

[1]Department of Chemistry and Biochemistry, College of Medicine, University of Kerbala, Kerbala, Iraq.
[2]Section of Nephrology, Department of Internal Medicine, College of Medicine, University of Kerbala, Kerbala, Iraq.
*Correspondence to: Fadhil Jawad Al-Tu'ma (E-mail: fadhil.jawad@uokerbala.edu.iq)
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Abstract

Objective: To study the effect of Covid-19 on the levels of some biomarker such as liver enzyme, ferritin, LDH, CRP and ACE-2 activity levels, and their relations with the severity of Covid-19 and the activity levels of angiotensin converting enzyme-2.

Methods: This case-control study was conducted on 176 male subjects who diagnosed by physician and were divided into three groups: 59 of them were infected with severe covid-19, 54 of them were infected with moderate covid-19 and 63 of them were checked and obtained as apparently healthy control. Severe and moderate patients were collected from Al-Hayat tertiary center at Al-Hussein Medical City, Kerbala Health Directorates, Kerbala – Iraq during April, 2020- June, 2021 with matched age ranged between (23-88) years. In this study, the levels of ACE-2 was measured through enzyme-linked immunosorbent assays (ELISA) in sera from healthy volunteers as a control group, and patients with moderate Covid-19, patients with severe Covid-19. Anthropometric, biochemical data were analyzed and then measuring the levels of some biomarker such as liver enzyme, ferritin, LDH, and CRP activity levels.

Results: The levels of ACE-2 were differing significantly among groups. However, the level of CRP, Ferritin and LDH were significantly higher in moderate Covid-19 and severe cases of Covid-19 groups compared to control indicating it to be an dependent predictor in the coronavirus disease and prognosis of disease. In contrast the severe infection was correlated with the age and chronic diseases such as pretention and T2DM.

Keywords: Covid-19, ACE 2, ferritin, LDH, CRP

Introduction

World Health Organization (WHO) reported several cases of pneumonia of unknown etiology in Wuhan City in Hubei Province in central China. The cases had been reported since December 8, 2019, and many patients worked at or lived.[1] On January 7, a novel coronavirus, originally abbreviated as 2019-nCoV by WHO, was identified from the throat swab sample of a patient.[2] This pathogen was later renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the coronavirus study group,[3] and the disease was named coronavirus disease 2019 (Covid-19) by the WHO. As of January 30,7736 confirmed and 12,167 suspected cases had been reported in China and 82 confirmed cases had been detected in 18 other countries. In the same day, WHO declared the SARS-CoV-2 outbreak as a Public Health Emergency of International Concern (PHEIC).[4] According to the National Health Commission of China, the mortality rate among confirmed cased in China was 2.1% as of February 4 and the mortality rate was 0.2% among cases outside China.[5] Among patients admitted to hospitals, the mortality rate ranged between 11% and 15%.[6,7] Covid-19 is moderately infectious with a relatively high mortality rate, but the information available in public reports and published literature is rapidly increasing.

Angiotensin-converting enzyme (EC 3.4.15.1), or ACE, is a central component of the renin–angiotensin system (RAS), which controls blood pressure by regulating the volume of fluids in the body, by converting the hormone angiotensin I to the active vasoconstrictor angiotensin II. Therefore, ACE indirectly increases blood pressure by constricting blood vessels. So, elderly individuals are at particular risk, since many of the co-morbidities are age-associated. Those with health conditions such as immune deficiencies, diabetes or cardiac disease will likely be at greater risk for more severe Covid-19 infections and ACE1/Ang II- mediated pathology. By contrast, children (who lack co-morbidities associated with ACE1/ACE2 imbalance) are predicted to have less morbidity and mortality from Covid-19.

The aim of the presented work is to determine the association between various biomarkers including angiotensin-converting activity, CRP, LDH, ferritin and liver enzyme activity levels (ALT, AST and ALP) with severity of Covid-19 infection in Iraqi pandemic of Kerbala Province.

Materials and Methods

This study was conducted on 176 subjects who diagnosed by physician and were divided into three groups: 59 of them were infected with severe covid-19, 54 of them were infected with moderate covid-19 and 63 of them were checked and obtained as apparently healthy control. Severe and moderate patients were collected from Al-Hayat tertiary center at Al-Hussein Medical City, Kerbala Health Directorates, Kerbala – Iraq during April, 2020- June, 2021 with matched age ranged between (23–88) years. They are diagnosed by quantitative by RT-PCR and chest X-ray or CT scan at the 7–12 day from symptoms on set, with age ranged between (30–67) years and it consisted of three categories Covid-19 patients were collected at admission and the disease severity was assessed using Murray scores.[8] The patients were considered to have severe/moderate Covid-19 depending upon fever, respiratory manifestations and radiological indicative of pneumonia. Patients

were considered to have severe Covid-19 if any of the following changes was present:

I. Respiratory distraction (≥ 30/min)
II. Resting oxygen saturated ≤ 90% or
III. Arterial oxygen (PaO2)/fraction of inspired oxygen ≤ 300 mmHg or
IV. Respiratory failure requiring mechanical ventilation and require intensive care unit.

Moreover, patient dead considered as Non-survived. This investigation was approved by local medical ethics and all participants, information consent before the onset of study. The patients were registered and handed over a file for recording their data such as name, age, gender, weight, height.

Control group were sixty three apparently healthy subjects were selected as control group. Their age and gender were matched to that of patients. None of them was anemic or has an obvious systemic disease or any chronic diseases.

Venous blood Samples Collection: five milliliters of venous blood were drawn from each the patients and control group by medical syringes was put into gel tubes and left at room temperature for nearly thirty minutes for clotting, then centrifuged at 3000 x g for 10 minutes to separate serum which was divided into two tubes, the first one was used to determine Ferritin, C-reactive protein concentration (CRP) and activity levels of each of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) on the cobas e601, and the second tube was stored at –20°C until using for Angiotensin - Converting Enzyme-2 (ACE-2) activity determination by ELISA Technique.

Data (represented as Mean ± SD) were analyzed by using the Statistical Package for the Social Sciences (SPSS) (version 23). Independent t-test was used to evaluate significant differences between healthy and patients groups. Pearson correlation coefficient test was applied to mention the statistical relationship (association) between any two variables in 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.

Results

The current study included 176 participants classified into (59 of them were severe infected with Covid-19, 54 participants were moderate infected with Covid-19 and the remaining 63 participants were apparently healthy control individuals). Some of anthropometric parameters including body mass index and age of the selected groups were illustrated in Table 1.

In this Table 1 a significant differences between each of severe and moderate Covid-19 group as compared with control group was observed with respect to the age ($P < 0.01$), while BMI data show a non-significant results ($P = 0.817$ and $P = 0.495$) respectively.

The biochemical and clinical feature of the moderate Covid-19 as compared with apparently healthy group were illustrated in Table 2. The three groups studied were found to be different with respect to ferritin, CRP levels, LDH, ACE-2, ALT, AST and ALP activity levels.

The mean ± SD values of the variables ferritin, LDH, CRP, ACE-2, ALT, AST and ALP are significantly higher in the severe and moderate Covid-19 as compared to that found in healthy control, Table 2. This table shows significant differences between moderate and control groups with respect to each of ferritin, LDH, CRP, ALT and AST, while ALP and ACE-2 activity levels were non-significant.

Table 3 show the significant correlation between moderate and severe Covid-19 as compared with control groups

Table 1. **Comparison of age and body mass index between moderate and severe Covid-19 groups as compared with control group**

Parameter	Moderate Covid-19 N = 54 Mean ± SD	Control group N = 63 Mean ± SD	P value	Control group N = 63 Mean ± SD	Severe Covid-19 N = 59 Mean ± SD	P value
Age, year	52.06 ± 14.35	40.03 ± 11.86	<0.001	40.03 ± 11.86	59.1 ± 12.64	<0.001
BMI, kg/m^2	32.59 ± 5.52	33.31 ± 5.83	0.495	33.31 ± 5.83	33.07 ± 5.72	0.817

BMI: Body mass index, *N*: Number, Significant $P < 0.05$, SD: Standard deviation.

Table 2. **The data obtained of various biochemical parameters in sera of moderate and severe Covid-19 as compared with healthy control group**

Parameter	Moderate Covid-19 N = 54 Mean ± SD	Healthy control N = 63 Mean ± SD	P value	Healthy control N = 63 Mean ± SD	Severe Covid-19 N = 59 Mean ± SD	P value
Ferritin, ng/ml	601.82 ± 168.52	75.65 ± 39.5	<0.001	75.65 ± 39.5	765.04 ± 259.37	<0.001
LDH activity, U/l	387.73 ± 129.64	135.79 ± 38.52	<0.001	135.79 ± 38.52	432.9 ± 144.86	<0.001
CRP, mg/dl	9.14 ± 3.58	0.35 ± 0.15	<0.001	0.35 ± 0.15	15.02 ± 6.53	<0.001
ACE-2 activity, ng/ml	3.83 ± 0.82	3.03 ± 0.82	0.721	3.03 ± 0.82	4.74 ± 0.85	<0.001
ALT activity, U/l	61.92 ± 27.52	27.63 ± 9.26	<0.001	27.63 ± 9.26	101.11 ± 34.69	<0.001
AST activity, U/l	40.86 ± 13.71	22.69 ± 8.65	<0.001	22.69 ± 8.65	51.6 ± 17.43	<0.001
ALP activity, U/l	90.11 ± 32.02	74.9 ± 23.82	0.006	74.9 ± 23.82	109.48 ± 36.14	<0.001

LDH: Lactate dehydrogenase, CRP: C-reactive protein, ACE-2: Angiotensin-converting enzyme, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, S.D: Standard deviation, *P* = prober value.

Table 3. **Hypertension, type-2 diabetes mellitus and smoking comparison between moderate and severe covid-19 as compared with control group**

Parameter		Moderate Covid-19 *N* = 54 (%)	Healthy control *N* = 63 (%)	*P* value	Healthy control *N* = 63 (%)	Severe Covid-19 *N* = 59 (%)	*P* value
Hypertension	With	30 (55.6%)	0 (0.0)	<0.001	0 (0.0)	26 (44.1%)	<0.001
	Without	24 (44.4%)	63 (100)		63 (100)	33 (55.9%)	
T2DM	With	20 (37.0%)	0 (0.0)	<0.001	0 (0.0)	28 (47.5%)	<0.001
	Without	34 (63.0%)	63 (100)		63 (100)	31 (52.5%)	
Smoking	Yes	4 (7.4%)	0 (0.0)	0.043	0 (0.0)	5 (8.5%)	0.024
	No	50 (92.6%)	63 (100)		63 (100)	54 (91.5%)	

according to the hypertension and T2DM ($P < 0.001$), but non-significant correlation was observed in smoking moderate and severe Covid-19 patients ($P = 0.043$ and $P = 0.024$) respectively.

These results showed that diabetic patients with Covid-19 had higher severe infection and case-fatality rates as compared with non-diabetic patients, and T2DM was associated with an increased risk of severe infection and mortality in patients with Covid-19.

Discussion

Various biochemical and genetic studies have been done recently on Iraqi patients infected with Covid-19 especially in Kerbala province.[9] Table 1 show a significant differences between each of severe and moderate Covid-19 group as compared with control group with respect to the age ($P < 0.01$), while BMI data show a non-significant results ($P = 0.817$ and $P = 0.495$) respectively.

The reason may be due to person ages and its relation with immunity decreases therefore chronic diseases increased due to lack of movement and lack of exercise.[10,11] Table 2 shows a biochemical and clinical feature of the moderate and severe Covid-19 as compared with apparently healthy group.

The three groups studied were found to be different with respect to ferritin, CRP levels, LDH, ACE-2, ALT, AST and ALP activity levels.

The mean ± SD values of the variables ferritin, LDH, CRP, ACE-2, ALT, AST and ALP activity levels are significantly higher in the severe and moderate Covid-19 as compared to that found in healthy control, Table 2. This table shows significant differences between moderate and control groups with respect to each of ferritin, LDH, CRP, ALT and AST, while ALP and ACE-2 activity levels were non-significant.

The elevation of ferritin may be due to that it is a key mediator of immune dys-regulation, especially under extreme hyper-ferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm. It has been reported that fatal outcomes by Covid-19 are accompanied by cytokine storm syndrome, thereby it has been suggested that disease severity is dependent of the cytokine storm syndrome.[12]

Many individuals with diabetes exhibit elevated serum ferritin levels, and it is known that they face a higher probability to experience serious complications from Covid-19. On this basis, we briefly review evidence supporting the hypothesis that ferritin levels might be a crucial factor influencing the severity of Covid-19.[12]

Notably, ferritin is not only the result of excessive inflammation, but also plays a pathogenic role in the inflammation process through its bind with the T-cell immunoglobulin and mucin domain 2 (TIM-2) by promoting the expression of multiple pro-inflammatory mediators.[13] The cytokine storm and the exaggerated host immune response (i.e, ferritin) participate in the development of ARDS, which is the leading cause of mortality if progresses to respiratory failure.[14] Hyper-ferritinemia caused by the excessive inflammation due to the infection is associated with the admission to the intensive care unit and high mortality, and represents an indication to recognize high-risk patients to guide the therapeutic intervention to control inflammation.[13] Serum ferritin, a feature of hemophagocytic 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.[10]

The ferritin levels in our study was significantly increase in severe more than that found in moderate group as compared with control and it was agreement with other report which indicate that Covid-19 patients with high levels of ferritin have greater proportions of severe and deceased cases ($P = 0.0016$).[15] Similarly, Sun et al revealed that severe patients and discharged patients have greater proportions of increased level of ferritin than non-severe patients and hospitalized patients (100% vs. 50%, 92.3% vs. 37.9% respectively, $P < 0.001$) and suggested that serum ferritin is a potential risk factor of poor prognosis in Covid-19 patients.[16] Ferritin levels greater than 800 g/l were found in 100% of patients with severe disease and 30% of those with non-severe disease.[17] Ferritin and IL-6 showed higher levels in non-survivors throughout the clinical course, and increased with disease deterioration.[10] Another meta-analysis also recommended serum ferritin as a candidate variable for risk stratification models that may serve as clinical predictors of severe and fatal Covid-19.[18]

Among inflammatory biomarkers, CRP levels was also increased significantly at the early stage of the patient studied, and is a positive correlation with the severity of Covid-19 as mentioned by other studies which described and has good diagnostic accuracy in early predicting severe Covid-19.[19-21] The present findings suggest that serum CRP levels could be used as an essential indicator of the progression and the severity of Covid-19. Also, suggests that patients with higher CRP levels should be carefully monitored throughout their disease course.[22] The obtained level of CRP in this studies was

increased in severe and moderate group without significant values when compared between them, but in others study CRP level could also be used in monitoring the progression and improvement of patients with Covid-19.[23] Tan et al. and other studies concluded that CRP was associated with disease progression and predicted early severe Covid-19.[21] CRP is a well-known biomarker of inflammation and is found elevated in 60.7% of patients with Covid-19. More severe cases demonstrated a more evident elevation in CRP levels as compared to non-severe cases (81.5% vs 56.4%, respectively).[24] Higher CRP levels are also linked to development of acute respiratory distress syndrome, higher troponin-T levels, and myocardial injury, which is observed in patients with severe Covid-19.[14] In response to infections, the liver synthesizes significant quantities of acute-phase proteins (APPs), such as CRP. This acute inflammatory protein is a highly sensitive biomarker for inflammation, tissue damage, and infection. It has been shown that CRP levels are correlated with levels of inflammation. CRP levels can promote phagocytosis and activate the complement system. In other words, CRP binds to microorganisms and promotes their removal through phagocytosis.[25]

As shown previously, this biomarker may be raised by viral or bacterial infections. The current study revealed significantly higher CRP levels in severe cases than in non-severe patients suggesting that the CRP level may be a biomarker of disease severity and progression in patients with Covid-19. Other reported indicate that more severe cases infected with Covid-19 expressed significantly higher levels of CRP than non-severe patients,[15] observed higher CRP levels in severe Covid-19 patients than in non-severe cases, suggesting that this biomarker can be monitored to evaluate disease progression[26] performed a meta-analysis to assess CRP levels as a potential biomarker of the Covid-19 prognosis. Their results indicated that CRP concentrations remain high in expired patients and could be a promising biomarker for assessing mortality.[27]

The most common patterns of liver enzyme abnormalities in patients with SARS-CoV-2 include elevated aminotransferases, with aspartate amino- transferase (AST) and alanine aminotransferase (ALT) typically 1–2 times more than the normal upper limit. There are many potential contributing etiologies to elevated liver enzymes in patients with SARS-CoV-2 including direct liver injury, associated inflammatory responses, congestive hepatopathy, hepatic ischemia, drug-induced liver injury (DILI), and muscle breakdown.[28,29] The alteration of liver enzyme activity levels are a common in sera of Covid-19 studied which related to liver dysfunction and could be the result of secondary liver damage due to the administration of hepatotoxic drugs, systemic inflammatory response, respiratory distress syndrome induced by increased levels of liver dysfunction biomarkers have been associated with severe Covid-19 and worse prognosis.[30]

The elevation in LDH activity level was also observed in sera of Covid-19 patients studied and may be due to that it is one of interest biomarkers, especially since elevated LDH levels have been associated with worse outcomes in patients with other viral infections. Early data in Covid-19 patients has suggested significant differences in LDH levels between patients without severe disease.[27] Severe infections may cause cytokine-mediated tissue damage and LDH enzyme release. Since LDH3 isoenzyme is present in lung tissue, patients with severe Covid-19 infections can be expected to release greater amounts of LDH3 in the circulation, as a severe form of interstitial pneumonia, often evolving into acute respiratory distress syndrome, is the hallmark of the disease. However, the contribution of the different LDH isoenzymes to the total LDH activity observation in Covid-19 has not been determined.[31]

Multiple studies have found LDH activity level act as a predictor of worse outcomes in hospitalized patients. Many of the prognosticators and therapies currently being studied for Covid-19 are based on experience with the previous coronavirus outbreak severe Acute Respiratory Syndrome (SARS), or with other viral respiratory infections. LDH levels were also found to be elevated in patients with Middle East Respiratory Syndrome (MERS). Elevated LDH levels seem to reflect that the multiple organ injury and failure may play a more prominent role in this pathology in influencing the clinical outcomes in patients with Covid-19.[32]

The activity of LDH levels could be considered for inclusion in future risk stratification models for Covid-19 severity and mortality. Larger studies are needed to confirm these findings.[30]

Chen et al. reported that CRP, ferritin, LDH, and ALT were significantly higher in severe cases as compared with mild cases.[7]

Table 3 show the significant correlation between moderate and severe Covid-19 as compared with control groups according to the hypertension and T2DM ($P < 0.001$), but non-significant correlation was observed in smoking moderate and severe Covid-19 patients ($P = 0.043$ and $P = 0.024$) respectively.

These results showed that diabetic patients with Covid-19 had higher severe infection and case-fatality rates as compared with non-diabetic patients, and T2DM was associated with an increased risk of severe infection and mortality in patients with Covid-19. T2DM may be related to the activation of the renin-angiotensin system, and patients with T2DM are often treated with angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs), which may both lead to the increased expression of ACE-2 in tissues, promoting virus absorption and increasing the risk of severe infection in patients with T2DM.[33]

Secondly, T2DM may induce the hypercoagulable state in patients with Covid-19, resulting in worse outcomes of these patients. Studies have reported that diabetic patients with Covid-19 had increased risk of hypercoagulability, and many severe and fatal patients with Covid-19 seemed to eventually die of small pulmonary embolism.[34]

Singh et al. have reported a prevalence of hypertension, diabetes and CVD in 21%, 11%, and 7% patients, respectively.[35] Similarly, in a meta-analysis of 8 trials that included 46,248 Covid-19 patients. Yang et al. reported a prevalence of 17%, 8%, and 5% for hypertension, diabetes and CVD respectively, in patients with Covid-19.[19] In contrast, an Italian study by Onder et al. found diabetes in nearly 36%, while CVD was associated in nearly 43% of 355 patients admitted with Covid-19.[36] Similarly, in a small study of 24 patients from United States, Bhatraju et al. reported diabetes to be associated with 58.0% patient with Covid-19.[37]

Moreover, this condition makes it difficult to control a SARS/CoV-2 infection. Older adults suffering from underlying systemic diseases are more prone to acute respiratory distress syndrome and cytokine storms.[38] The most common

comorbidities in one report were hypertension (30%), diabetes (19%), and coronary heart disease (8%).[10] Another report showed that the most frequent comorbidities in patients with Covid-19 who developed the acute respiratory distress syndrome were hypertension (27%), diabetes (19%), and cardiovascular disease (6%).[14]

In the early phase of the Covid-19 pandemic, it was proposed that antihypertensive treatment using ACE-2 inhibitors or angiotensin receptor blockers (ARBs) may contribute to adverse outcomes in patients with hypertension and Covid-19. Most of these studies have suggested that these antihypertensive drugs might increase tissue expression and/or activity of ACE-2 though some have reported no alternation or decrease of ACE-2 in response to the drug. Nevertheless, increased membrane expression of ACE-2 induced by these drugs can theoretically increase the chance of virus entry into organs.[39] The rates of T2DM in subjects affected by Covid-19 vary, depending on the median age, the severity of illness and the location of the study population. In general, people with diabetes are at higher risk of developing complications, because of viral infection. The differences in response are likely the result of the degree of viral loud, host immune response, age of the patient, and presence of comorbidities.[40]

According to various studies, the presented observed data found the effect of smoking nicotine on the renin-angiotensin system. Nicotine can impact the angiotensin-converting enzyme (ACE-2), which is relevant because coronaviruses bind to ACE-2. Current and past tobacco smoking is associated with changes in ACE-2 receptor expression. Through table (3) we found most of patients whether it is severe or moderate infection with Covid-19 nonsmokers, the reason is due to nicotine may bind with the ACE-2 receptor and decrease levels of ACE-2 in multiple organs.[41] Smoking is associated with increased susceptibility and mortality in MERS-CoV infection, potentially due to upregulation of dipeptidyl peptidase-IV, the host receptor for MERS-CoV, in smokers.[42] In addition, smoking increases severity and mortality of both bacterial and viral infections through the induction of mechanical and structural changes in the respiratory tract and alteration of cell and humoral-mediated immune responses.[43] In the context of respiratory viruses, smoking has been reported to cause increased hospital and ICU admissions with influenza infection, greater severity with respiratory syncytial virus bronchiolitis and increased mortality with viral pneumonia.[44]

In addition, a meta-analysis performed failed to find a relationship between active smoking and severe Covid-19 on Chinese patients, and another meta-analysis indicates that active smoking is not a predisposing factor for hospitalization.[45,46] The heterogeneity was low to moderate, and after sensitivity adjustments, the prevalence of a history of smoking was found to be 5.2% in no severe Covid-19 cases and 12.5% in severe cases. Furthermore, the prevalence of active smoking was 2.9% in no severe Covid-19 cases and 5.8% in severe cases. Therefore, severe Covid-19 was observed almost 1.5 to 2 times more frequently in history of smoking and current smoking groups.[27,47] In addition, a recent meta-analysis revealed that active smokers are at higher risk of mortality and serious complications.[48] Interestingly, this meta-analysis indicated that serious complications were observed in 48% of former smokers and 24% of current smokers during Covid-19 course.[48] In addition, a history of smoking has been reported to increase the progression of Covid-19 disease.[49] There is growing evidence to support WHO's statements that smokers are at a higher risk of developing severe Covid-19 and consequent death.[50,51] It seems very clear that the pandemic period is an opportunity to quit smoking due to the possibility of encountering worse clinical outcomes and complications in patients with smoking history.[52]

Conclusion

There is a positive correlation between the levels of both of parameters include ACE-2, CRP, Ferritin, LDH, ALT, AST and ALP levels in severe and moderate infection with Covid-19 as compared with control group. Type 2 diabetes and hypertension are important risk factors for severity and mortality in Covid-19 infected people and are targets that must be intensively addressed in the management of Covid-19 and most of infected patients were not smokers.

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