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Biochemical and immunological insights into COVID-19 multi system involvement in Iraqi patients

A. J. Akmakji*, Z. N. M. Albarzanji**, A. N. F. Alsulaiman***

*Prime Minister Health Services, Kirkuk, Iraq
**University of Kirkuk, Kirkuk, Iraq
***Directorate General of Education, Kirkuk, Iraq

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Prime Minister Health Services, Kirkuk, Iraq. E-mail: ghassanalubaidy1961@ntu.edu.iq

College of Dentistry, University of Kirkuk, Kirkuk, Iraq. E-mail: yuosra_amer@unmosul.edu.iq

Directorate General of Education, Kirkuk, Iraq. E-mail: ha.a.aljawadi@ntu.edu.iq

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The emergence of COVID-19 has created a serious and pressing international public health emergency. In cases of COVID-19 infection, biomarkers may be employed to detect severity of the disease as reflected by the level of some inflammatory mediators such as; IL-6, IL-8 and CRP. This case control study was performed to examine the demographic characteristics, biochemical and level of inflammatory meditators in Iraqi patients diagnosed with COVID-19 who were admitted to Al-Sheffa 14 Hospital, Kirkuk, Iraq for management. The study included a cohort of 100 patients who were diagnosed with COVID-19 infection diagnosed depending on clinical features , which was confirmed by PCR testing. Those patients were admitted to the hospital during the period from November 2021 to March 2022. Demographic data such as age and gender of the patients were gathered and a control group of 30 sex and age matched healthy persons were also included. The following serum biochemical (ALT, AST, ALP, urea, creatinine, vitamin D and LDH), inflammatory (CRP, D dimer and ferritin) and immunological mediators (Il-6 and Il-8) were measured and compared with those of the control group. The age range of the patients' group was 31–81 years, which is statistically not different from that of the control group (31–90 years). The patients (54% female, 46% male) and the control (53.3% females, 46.7% males) groups have similar sex distribution. Among the patients' group, the greater incidence of infection was among individuals aged 61–70 years while the lowest incidence was in the 31–40 years age group. These observations indicate a statistically higher level of all the above biochemical abnormalities in the COVID-19 patients relative to the control. Correlation analyses showed significant connections between D-dimer and vitamin D levels, as well as D-dimer and IL-6 and IL-8 levels in patients with COVID-19. COVID-19 patients displayed clear demographic traits and notable abnormalities in biochemical, and immunological indicators when compared to healthy persons. This work highlights the significance of integrating these discoveries into risk assessment models and patient care methods for COVID-19.

Keywords: COVID-19; vitamin D; D-dimer; disease severity.

Introduction

COVID-19 is an illness that is triggered by SARS-CoV-2, a new strain of coronavirus that is similar to the virus responsible for causing SARS (severe acute respiratory distress syndrome (Hejran et al., 2025). Similar to SARS and MERS, COVID-19 is associated with severe consequences including ARDS (acute respiratory distress syndrome), severe pneumonia, acute respiratory failure, acute cardiac events, and ischemic events caused by a prothrombotic condition, as reported from China (Hamadalla et al., 2023). Milder symptoms include a sore throat, cough, mild fevers, and a general feeling of discomfort. While the symptom complex is still being assessed, it is important to have a strong suspicion of COVID-19 in individuals who experience muscle pain, headache, and a recent onset of loss of taste or smell (Santos et al., 2021).

The characteristics of the patient population and their presentation, including symptoms and laboratory findings, are constantly changing. This is due to the increasing number of publications, initially from China and now from Europe and the USA (Rodriguez-Morales et al., 2020). While the primary symptoms of COVID-19 are typically respiratory, there is a growing number of reports indicating symptoms related to the gastrointestinal (GI) tract (Al-Azzawy et al., 2021; Spadaro et al., 2021). Additionally, there have been reports of venous and arterial thrombotic complications associated with the infection, such as ischemic strokes, myocardial infarction, deep vein thrombosis (DVT), and pulmonary emboli (Cronin et al., 2022; Singh et al., 2023). Vasculitis is a condition that causes damage to organs in seriously ill patients. This damage is caused by the activation of inflammatory cascades, complement activation, and pro-inflammatory cytokines such as interleukin-6 (Quinaglia et al., 2021). Unfortunately, the severity of vasculitis cannot be easily predicted using current laboratory biomarkers like D-dimer or prothrombin time/activated partial thromboplastin time. As a result, it is difficult to categorize patients into risk groups for appropriate early anticoagulant or fibrinolytic therapy (Osoro et al., 2023).

The Diagnosis and Treatment Program for 2019 New Coronavirus Pneumonia (trial version seven) (Chow et al., 2023) categorizes COVID-19 patients into four groups based on the severity of their condition: mild, moderate, severe, and critical. Several hematological measures, including white blood cell (WBC) count, lymphopenia, C-reactive protein (CRP), and certain biochemical parameters like lactate dehydrogenase (LDH), creatine kinase (CK), and troponin have been found to be linked to the severity of COVID-19 (Singh et al., 2023; Wang et al., 2023). This study emphasizes how demographic variables determine the susceptibility to the disease. It also investigates how the virus affects other organs and acts as a multisystem disease not limited to the respiratory system. The results indicate that these criteria may be used to evaluate the severity of illnesses in an efficient manner, offering insightful information that can enhance treatment plans and patient outcomes.

Materials and methods

Study subjects and design and data collection. A case-control study involved 100 patients who had been diagnosed with COVID-19 infections and referred to Al Shefaa Hospital, Kirkuk, Iraq for in-patient management between November 2021 and March 2022. The diagnosis was performed in accordance with the Iraqi National Guidelines and interim WHO guidelines for the diagnosis and treatment of COVID-19 (Merza et al., 2020). Typical symptoms comprised of vertigo dyspnea, rhinorrhea, pharyngitis, diarrhea, and reduced appetite. The study obtained permission from the Ethics Committee of the Ministry of Health and the Ministry of Higher Education and Scientific Research in Iraq. Prior to data and sample collection, all participating patients provided informed consent. Age and sex matched 30 healthy subjects were included in the study as the control group and dealt with in a similar way to the patients' group regarding laboratory investigations.

Laboratory investigation. Covid-19 RNA extraction and Real-time PCR: Using the EXM3000® semi-automated equipment (Zybio®, China) and the viral genomic extraction kit (DNA/RNA viral extraction kit), nucleic acid was extracted from a nasal swab in accordance with the manufacturer's instructions.

The Zybio SARS-CoV-2 Nucleic Acid Detection Kit was used in accordance with the manufacturer's instructions for viral genomic detection. Using the 2019-nCoV Real-time PCR kit (Sacace Biotechnologies® Ltd, Italy), a one-step viral amplification was carried out in the SaCycler-96 Real-time PCR Detection System (Sacace®, Italy). Our thermocycling conditions were as follows: cDNA synthesis was carried out for 45 cycles at 37 °C for 1 minute, 50 °C for 5 minutes, 95 °C for 2 minutes, 95 °C for 5 seconds, and 60 °C for 30 seconds.

COVID-19 biochemical, inflammatory and immunological markers. Patients reclining in the isolation ward employing a 10 cc syringe. The specimens were gathered in EDTA tubes for hematological analyses. In addition, serum samples were acquired from the collected venous blood samples. Following the collection process, the blood samples underwent centrifugation in order to isolate the serum component. The biochemical laboratory used Sysmex (Japan) to analyze serum samples for biochemical parameters (liver markers{ALT, AST and LDH} and renal markers (urea and creatinine), serum ferritin, D-dimer and CRP. The levels of 25-dihydroxy vitamin D3 (vitamin D) and Interleukin-6 (IL-6 and IL8) were assessed using the sandwich-ELISA method (Sunlong Biotech Co®, China).

Statistical analysis. Quantitative data analysis was conducted using Minitab program version 17, employing T-test, Chi-Square, and a significance level (P-value) of 0.01–0.05. The enumeration statistics were represented as a percentage. The T-test was utilized to quantify characteristics. Quantitative measurement refers to the process of obtaining numerical data in order to assess or compare different variables. Chi-Square, on the other hand, is a statistical test used to determine the significance of the relationship between categorical variables. Quantification of quantitative attributes involved the count of individuals who are ill or in good health, etc.

Results

Sociodemographic characteristics of the study population. The study comprised a cohort of 100 patients who tested PCR positive for COVID-19 and had indications for admission to AL-Sheffa 14 Hospital/Kirkuk/Iraq for management.

Out of the total number of patients, 56% were female, in contrast males represented only 44% . The control group included of 16 females (53.3%) and 14 males (46.6%) who were clinically normal and tested negative for PCR. as shown Table 1.

The study included patients aged between 31 and 68 years, with a mean age of 61–70 years being the most common age group. This was followed by the age group of 71–80 years. Infected individuals were also found in the age groups of 51–60 and 41–50 years. Statistically, there was a highly significant difference (P < 0.001) as clarified in Table 2.

Table 1
COVID infection according to gender sex distribution among patients with Covid-19

Sex	Infected patients, n (%)	Control group, n (%)
Females	54 (54%)	14 (53.3%)
Males	46 (46%)	16 (46.6%)
Total	100 (100%)	30 (100.0%)

Note: $\chi^2 = 0.459$; P = 0.498.

Table 3 demonstrates a significant increase in COVID-19 infections as age increases. The data indicates that there is gender equality across all age groups. The table clearly shows that understanding and explaining the differences in COVID-19 transmission and infection relies on the specific patterns of infections based on age and sex, as well as the age and sex distribution within the community.

Table 2
Distribution of COVID-19 patients by gender among age groups

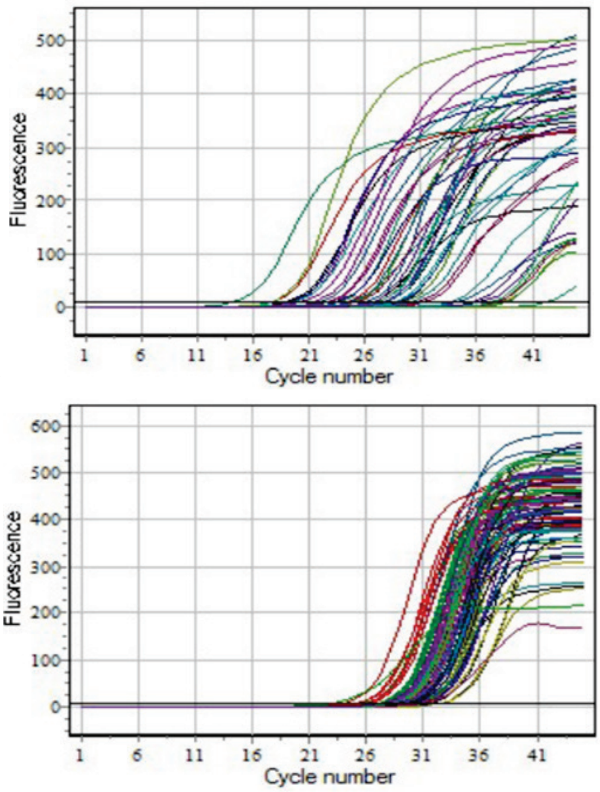
Age group, years	Number of patients	%
31–40	5	5
41–50	15	15
51–60	16	16
61–70	32	32
71–80	24	24
81–99	8	8
Total	100	100

Table 3
Distribution of COVID-19 patients by gender among age groups

Age group, years	Patients			Controls		
	male	female	%	Male	female	%
31–40	4	1	5	2	2	13.3
41–50	6	10	16	3	5	26.7
51–60	7	9	16	4	4	26.7
61–70	13	18	31	1	1	6.7
71–80	10	14	24	2	2	13.3
81–99	4	4	8	2	2	13.3
Total	44	56	100	14	16	30

Note: $\chi^2 = 3.128$, P = 0.680.

Molecular diagnosis of COVID19. In order to identify the presence of the viral genome in the nasal swabs for the purpose of molecular COVID-19 detection, real-time PCR was utilized. In order to amplify the OPFa1b region in the COVID-19 genome on the FAM channel (Fig. 1a), the kit uses specially designed primers and probes.



a

b

Fig. 1. Amplification of the target gene using the RT-PCR method using the Log graph type: a – HEX channel (internal control); b – FAM channel (ORFa1b target gene)

Additionally, an internal control on the HEX channel is used to evaluate the quality of the extraction and amplification process

(Fig. 1b). As seen in Figures 1a and 1b, our samples are clear of contamination as non template control (NTC) was used and nothing complicated happened. It is evident that the tested samples had varying virus loads.

Biochemical, inflammatory, and immunological marker analysis. One of the biochemical factors examined in Covid-19 patients was alanine transaminase (ALT). The average ALT value for the COVID-19 patients was 41.6 ± 6.8 U/L, while AST value in the healthy control group 14.1 ± 2.2 U/L was significantly lower (P = 0.0003). The average LDH of the healthy control sample was 364 ± 30 U/L. In contrast, the average of the lactic dehydrogenase enzyme (LDH) of the infected group was 1069 ± 35 U/L. The albumin mean in Covid-19 patients showed a significant decrease (3.47 ± 0.68 g/dL) compared to the mean of healthy controls (5.06 ± 0.28 g/dL). The average serum ferritin and D-dimer values of Covid-19 patients were 345.0 and 2803 ng/mL, respectively, while the average values of the healthy group were 83.1 and 302 ng/mL. The mean vitamin D value observed in Covid-19 patients was 0.458 ± 0.063, while the mean value in the healthy control group for vitamin D was 0.493 ± 0.056.

The average CRP of Covid-19 patients was 103.7 ± 12.8, while the control group comprised of healthy persons had an average of 2.47 ± 1.25. In addition, the severe group had significantly higher levels of IL-6 and IL-8 compared to the moderate group. The mean levels of IL-6 in Covid-19 patients were (0.554 ± 0.089) and (0.629 ± 0.137) in the severe group, while in the mild group they were (0.615 ± 0.063) and (0.651 ± 0.045) for IL-8, respectively.

The D-dimer and vitamin D levels show a strong positive correlation of 0.065. Additionally, the D-dimer levels have a significant negative correlation of 0.101 with IL6 in COVID-19 patients. Furthermore, D-dimer levels have a significant positive correlation of +0.003 with IL8 concentration in infected patients (Fig. 2).

Table 4
Biochemical and immunological biomarker abnormalities in COVID-19 patients in compared with the healthy group

Bio-markers	Variables	Infected group		Control group		P-value
		mean	SD	mean	SD	
Biochemical	ALT, U/L	41.6	6.8	22.5	4.0	0.0002
	LDH, U/L	1069	35	364	30	0.0006
	AST, U/L	38.6	4.6	14.1	2.2	0.0003
	ALP, g/dL	3.47	0.68	5.07	0.28	0.0005
	Urea, mg/dL	57.7	6.5	24.3	4.6	0.0004
	Creatinine, mg/dL	0.958	0.133	0.772	0.069	0.0080
	Vitamin D	0.458	0.063	0.494	0.056	0.0480
Inflammatory	CRP, mg/dL	103.7	12.8	2.5	1.3	0.0005
	D-dimer, ng/mL	2803	38	302	20	0.0002
Immunological	Serum ferritin, ng/mL	345.0	28.7	83.1	18.9	0.0004
	IL6	0.554	0.089	0.615	0.063	0.0060
	IL8	0.629	0.137	0.651	0.045	0.3570

Notes: SD = standard deviation; P-value measured using ANOVA.

Discussion

People with COVID-19 may suffer serious effects of the disease due to immune system dysfunction associated with increased cytokine storm (Pober & Sessa, 2007). Most severe instances were linked to overactivation of cytokine storm, which accelerated the development of acute lung injury and the acute respiratory distress syndrome (ARDS) that followed (Albarzanji et al., 2020).

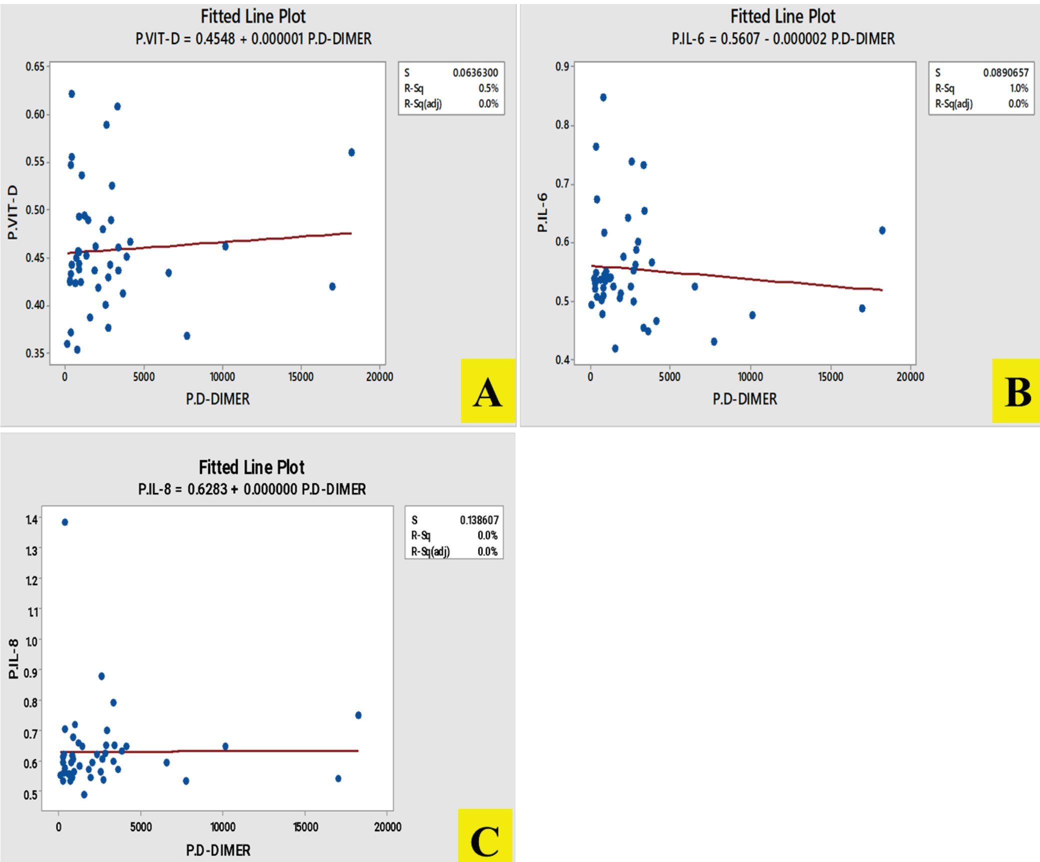


Fig. 2. The correlation between D-dimer and measured parameters: *A* – correlation between D-dimer and vitamin D_3 blood serum levels in Covid-19 patients; *B* – correlation between D-dimer and IL-6 blood serum levels in covid-19 patients; *C* – correlation between D-dimer and IL-8 blood serum levels in covid-19 patients

Understanding changes in morbidity requires an understanding of age (Abbas et al., 2023). Age is a measure of how much lasting damage has been inflicted over the course of a person's life and is thus highly correlated with the occurrence of long-term illnesses and disabilities (Abbas et al., 2023). The age-specific case-fatality rates of COVID-19 from Italy were applied to populations that are somewhat younger and less healthy by Pijls et al. (2021). However, according to another study, the majority of people were between the ages of 20 and

30. The mean age was 25.2 ± 5.7, and 51% of the participants were men (Dowd et al., 2020).

A examination of COVID-19 data from Norway, Italy, Spain, Germany, Switzerland, Belgium, and other countries revealed that men die at a greater rate than women in all age groups older than 20 (Piemonti & Marina, 2020). On the other hand, age-related differences exist between genders in terms of confirmed SARS-CoV-2 infections in every country; females between the ages of 10 and 50 have a greater rate than males under the age of 10 and over 50. Age-related differences in SARS-CoV-2 infections between males and females are comparable to seasonal and pandemic influenza A virus infections that have been documented in Japan and Australia (Eshima et al., 2011; Wong et al., 2019). In accordance with our findings, the most infected group consisted of females and older age groups (61–70), followed by (71–80) and (41–50).

Although gender-related exposure risk may have a different effect on male and female infection rates, data interpretation suggests biological sex differences as a component in male-biased mortality (Scully et al., 2020). Women presented more confirmed COVID-19 cases than males did in our research. This may be due to the fact that women may have been hospitalized at a higher rate than males during the period of the sampling. Older women (60–90 years) may be more likely to be hospitalized with COVID-19 because postmenopausal decreases in estradiol cause ACE2 activity to rise and make them more vulnerable to serious infection. In addition to immunological aging, comorbidity prevalence, and longer life expectancy, these variables make them more vulnerable than males in the same age range (Farshbafnadi et al., 2021).

In our study, indicators of liver cell injury such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and AST were found to be elevated in COVID-19 patients. This might be due to the high expression of ACE2 receptors in cholangiocytes, which is comparable to type 2 alveolar cells in the lungs, which makes the liver become a major target for SARS-CoV-2, and its involvement plays a crucial role in the pathophysiology of COVID-19. Upon exposure to the virus, the liver cytosolic enzymes, coupled with lactate dehydrogenase (LDH), are released into the circulation after hepatic damage and might be crucial diagnostic indicators for determining the extent of liver involvement in COVID-19 (Albarzanji et al., 2020). In severe COVID-19 instances, albumin (ALB) levels, a measure of liver function, frequently drop, indicating the effect of the infection on liver synthesis capability (Lebbe et al., 2024).

Furthermore, our work shows that there is evidence of kidney involvement in COVID-19 individuals due to noticeably higher levels of renal function indicators such as creatinine and urea. This is probably because kidney tissues have high levels of ACE2 receptor expression, which promotes viral entry and consequent renal damage.

Research demonstrates that COVID-19 patients have much higher levels of urea and creatinine than healthy controls do, underscoring the crucial role renal impairment plays in the course of the disease (Chu et al., 2005; Albarzanji et al., 2020).

Systemic inflammation , commonly measured by C-reactive protein (CRP), has been closely linked to the severity of COVID-19. The mean CRP in our study was 103.7 ± 12.8 mg/dL, which was significantly higher (P = 0.0005) than the mean CRP for the control group, which was 2.47 ± 1.25 mg/dL. Elevated CRP levels, a sign of an acute phase response mediated by the pro-inflammatory cytokine IL-6, are linked to severe cases. This link highlights the significance of CRP as a marker for determining the severity of the disease and guiding treatment (Shi et al., 2020).

D-dimer is one fibrin breakdown product that has become well-known as a sign of coagulation issues in COVID-19. Elevated D-dimer levels have long been associated with a poor prognosis, particularly in those with cardiovascular issues (d-dimer debate). In this study, the infected group's D-dimer value was 2803 ± 38 ng/mL, while the control group's was 302 ± 20 ng/mL (P = 0.0002). It has been demonstrated that this biomarker is helpful in the early diagnosis and ongoing care of COVID-19 patients (Thachil et al., 2022). In severe cases of the virus, it is also linked to pulmonary thrombosis and aids in the diagnosis of deep vein thrombosis (Wang et al., 2011; Giannitsis et al., 2017; Chen et al., 2020). Because of the correlation between its levels and clinical outcomes, D-dimer is a valuable diagnostic tool for assessing the risk of thromboembolic events and guiding anticoagulant medication in COVID-19 patients.

Since vitamin D possesses immunomodulatory properties, it has been a focus of COVID-19 study. Our results show that, in comparison to healthy persons, COVID-19 patients frequently have lower mean levels of vitamin D. This deficit can worsen the course of the disease and have serious consequences since it is linked to compromised immune responses and an increased chance of a cytokine storm. According to Sharifi et al. (2019), adequate levels of vitamin D seem to reduce these risks, indicating that vitamin D supplementation may help improve patient outcomes.

A key component of the cytokine storm seen in severe COVID-19 patients is interleukin-6 (IL-6). This pro-inflammatory cytokine is involved in the hyperinflammatory state that typifies severe illness in addition to inducing the development of acute-phase proteins like CRP. The significance of IL-6 as a prognostic indicator and possible therapeutic target is highlighted by the substantial association seen between its levels and the severity of the disease (Tanaka et al., 2014; Gupta et al., 2020).

Another important cytokine in COVID-19 is interleukin-8 (IL-8), which is especially important since it acts as a chemoattractant for neutrophils. In extreme situations, elevated IL-8 levels have been noted, and this helps draw immune cells to inflammatory areas. Particularly through processes like Netosis, which has been connected to organ damage and higher mortality in COVID-19 patients, this can result in tissue damage (Zuo et al., 2020). The relevance of IL-8 as a measure of illness severity and a possible target for management is highlighted by the continuous rise of this marker in severe cases.

Conclusions

Our research validates the assumption that COVID-19 patients have dramatically changed biochemical indicators associated with hepatic and renal function (ALT, AST, LDH, ALB, urea, and creatinine), inflammatory markers (CRP and D-dimer), and immunological markers (vitamin D, IL-6, and IL-8) reflecting the multisystemic nature of the disease.

These indicators can be useful tools for early diagnosis and prognosis since they are strongly correlated with the severity of the disease. Comprehending their functions within the pathophysiology of COVID-19 is crucial in order to formulate focused therapy approaches and enhance patient results.

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