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ASSESSING THE RELATIONSHIP BETWEEN ORGAN FUNCTION TEST RESULTS AND COVID-19 SEVERITY

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A number of recent reports have indicated the association of COVID-19 with multiple organ failure and the need to clarify the relationship between organ testing parameters and disease progression. Therefore, this study aimed to determine the degree of abnormal organ function test parameters and its correlation with COVID-19 severity. A cross-sectional study was conducted among COVID-19 patients admitted at Sanaka hospital, India, from August to September 2020. A total of 100 qRT-PCR-confirmed COVID-19 patients divided into groups with mild or severe cases were enrolled. The data from venous blood samples for liver, renal, cardiac and inflammatory test parameters were included from the Sanaka hospital laboratory database. Biochemical prognostic tests were carried out using a clinical automated ERBA analyzer, cardiac markers were estimated with Enzyme Linked Fluorescent Assay. The Pearson correlation analysis was used to analyze the data. Aspartate/Alanine aminotransferases and alkaline phosphatase activity, creatinine, urea and troponin levels were higher in the confirmed positive cases of COVID-19. Significantly higher levels of troponin, D-dimer and C reactive protein (CRP) were found in patients with severe COVID form compared to a mild one. A strong positive correlation between elevated D-dimer and Ferritin with CRP level was revealed in this group of patients. It was concluded that the positive relationship between serum D-dimer, ferritin levels and CRP level in patients can be considered a stable indicator of disease severity.

K e y w o r d s: COVID-19, liver function test, renal function test, D-dimer, ferritin, CRP.

Coronaviruses are a family of viruses that are known to cause both respiratory and intestinal diseases in various animal species and humans. These viruses tend to target the upper respiratory tract, causing anywhere from moderate to severe illnesses [1]. Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), is widely spread around the world and has caused significant pressure on the society and impacted human health. SARS-CoV-2 primarily causes pneumonia and the disease was named novel coronavirus acute respiratory distress (ARS) (COVID-19). SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor to enter the lungs leading to severe lung fibrosis resulting in high mortality in severity of cases [2, 3].

The coronavirus pandemic is a global health crisis of our time and the greatest challenge ever faced since its emergence in Wuhan, China. It has become a pandemic that has heavily affected the global population.

As of 20 August 2023, over 769 million confirmed cases and over 6.9 million deaths have been reported globally. Similarly, there have been 5.7 million confirmed cases of COVID-19 with 4.7 million deaths both directly and indirectly in India. Compared to the general population, healthcare workers and their families have been identified to be at a higher risk of getting infected with COVID-19. Even though healthcare workers represent less than 2–3% of the population, 14–35% of COVID-19 cases have been reported by WHO to be among health workers [4].

Recently, there has been some insight into the impact of COVID-19 on other organs, as a number of reports have indicated that more than half of patients with COVID-19 showed damaging effects on liver

and kidney, since ACE2 is also expressed in both organs [5].

Liver cell injury had elevated neutrophils, decreased lymphocytes, and decreased albumin. This result may be explained by the fact that SARS-CoV-2 can damage hepatocytes by binding to the ACE2 receptors of hepatocytes, which leads to liver enzyme abnormalities. An increased level of total bilirubin, aspartate transferase (AST),) alanine aminotransferase (ALT) and Alkaline phosphatase (ALP) in blood indicates hepatocyte damage causes liver failure [6].

COVID-19 is characterized by acute respiratory failure and diffuse alveolar damage in lung. After SARS-CoV-2 infects the lung, the virus may migrate to the blood, accumulate in kidney, and cause damage to resident renal cells. The pathophysiological understanding of COVID-19-related kidney injury is yet to be elucidated. There are several mechanisms involved in kidney injury during SARS-CoV-2 infection, including direct invasion of SARS-CoV-2 into the renal parenchyma, an imbalanced Renin Angiotensin Aldosterone System (RAAS), micro thrombosis and hemodynamic instability. Major possible mechanism of kidney injury in COVID-19 patients: SARS-CoV-2 enters kidney cells through human ACE2, resulting in degeneration and necrosis of kidney cells (Fig. 1) [6, 7].

Initial coagulopathy in COVID-19 patients presents with hypercoagulable state is seen due to several coagulation abnormalities from elevated circulating prothrombotic factors such as elevated von Willebrand factor (vWF), factor VIII, D-dimer, fibrinogen, neutrophil extracellular traps, prothrombotic microparticles, and anionic phospholipids. While D-dimer is a marker for detecting thromboembolic processes and is sensitive to the high risk of thromboembolism [9].

Enormous information has been provided on COVID-19 clinical features, but limited information has been depicted on liver and kidney biomarker derangement, especially, on the association of disease severity and organ function test parameters in the Indian population. Therefore, the aim of the present study was to determine the magnitude of abnormal organ function test parameters and inflammatory markers in hospitalized patients with confirmed SARS-CoV-2 infection in the Bardhaman district of the Bengali Indian population.

Materials and Methods

The present study is an analytical type of study among the recruited patients of Sanaka hospital, Durgapur, West Bengal. This study was carried out in the Department of Biochemistry at Shri Ramakrishna Institute of Medical Sciences and Sanaka hospital, Durgapur, in August/September 2020. A confirmed case of COVID-19 patients of either sex with 25-65 age groups was included in this study. A total of 100 qRT-PCR confirmed COVID-19 patients were enrolled in this study from a Sanaka hospital laboratory database. Most of the study participants were older than 40 years. The mean age was significantly higher in severe group than that of mild. The duration of symptoms before admission was also higher in severe groups (Table 1).

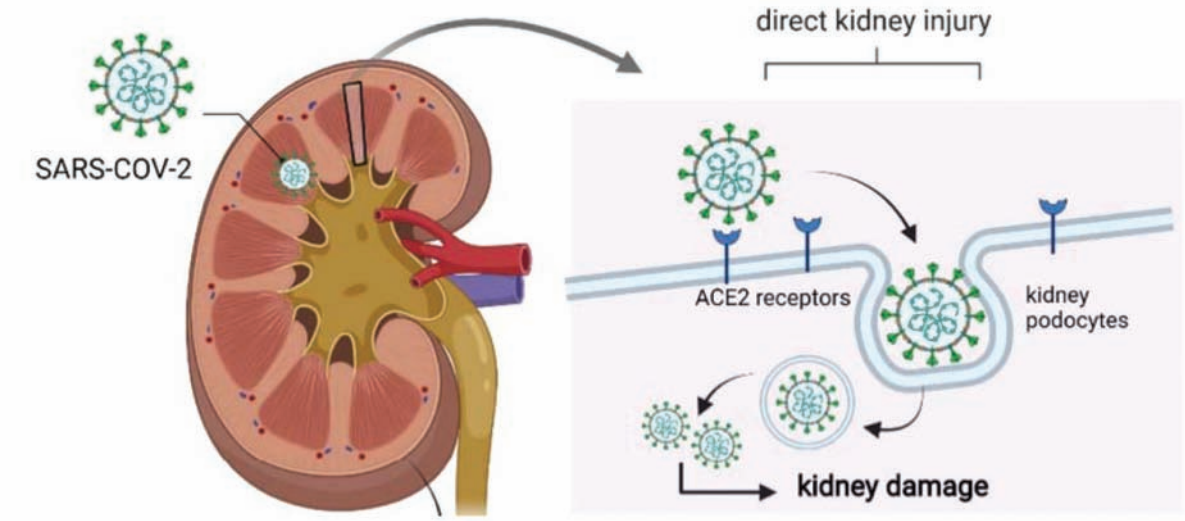

Fig. 1. Degeneration of Nephron cells by SARS-CoV-2 through ACE2 receptor [8]

The present study was approved by institutional ethical committee (Approval No. SET/SRIMS&SH/EC/MED/47/17). Patients with hepatic disease, cardivascular disease, renal disease, pulmonary tuberculosis, HIV, pregnant women, muscular disorder and subjects who were not willing to give consent were excluded from the study. The diagnosis of patients based on the WHO interim guidance [10]. A signed informed written and verbal consent was taken from each subject or their relatives, prior to study. It was not promising to involve patients or the public in the design, conduct, or reporting of our research work. The present study recruited total 100 participant information on convenient basis from laboratory database of Central clinical laboratory from Sanaka hospital from August to September 2020. Requests to the laboratory are generated online, and the laboratory results are sent electronically from the laboratory information management system (LIMS) to the patient's electronic medical record.

Sample collection for clinical chemistry test analysis. Subjects who have been tested for liver, renal and cardiac parameters and also for coagulation profile and inflammatory marker were included from laboratory-based clinical data reports from the patient test requisition form. For this purpose, 5 ml of venous blood samples were collected by serum separating tubes (SST) for biochemical analysis and 3 ml venous blood samples were collected in sodium citrate (blue top) tube for coagulation parameters screening. The liver function tests, renal function and inflammatory markers were analyzed by ERBA EM 400. Cardiac markers were analyzed using MINI VIDAS - automated immunoassay system based on the Enzyme Linked Fluorescent Assay (ELFA) principles. Whereas coagulation parameters were analyzed by ERBA ECL 105 is a single channel semi-automated coagulation analyzer. All central clinical laboratory tests and their interpretation were done with the manufacturer's recommendation and standard operating procedure.

Nasopharyngeal swab collection and confirmation of SARS-CoV-2. Confirmation of COVID-19 cases or the presence of SARS-CoV-2 was detected by real-time reverse transcription polymerase chain reaction (qRT-PCR) test. As per the standard safety rules and standard protocol of Sanaka hospital Swab samples were collected from every individual for SARS-CoV-2 confirmation. The RNA was extracted from the collected nasopharyngeal swab sample by using QIAamp viral RNA mini kit (Qiagen #52,906); RNeasy Mini kit (Qiagen #74106) according to the standard kit protocol instructions.

Nasopharyngeal swabs were collected from every individual and kept M6 transport media till further procedure. Samples were mixed with viral RNA extraction diluent lysis buffer (Sample diluent+ lysis buffer; diluent for virus inactivation) and added into RT-qPCR plates. Then, the master mix was prepared and pipetted into the RT-qPCR plate followed by 7 µl of the pooled patient sample. The plate was sealed inside the biosafety cabinet and then removed for RT-qPCR. All the procedure was done in a Class II Biosafety Cabinet using BSL-2 precautions. The extracted RNA was used as a new material for one-step reverse transcription quantitative PCR (RT-qPCR) by using Takara Bio Inc. (#RR064B). One-step RT-qPCR allows cDNA synthesis from RNA using Prime script Reverse Transcriptase, followed by PCR amplification. So fourth, PCR amplification products are detected and monitored in real time with either probe- or TB Green-based detection. The primer-probe sequences from oligonucleotides primers targeting the open reading frame 1ab (ORF1ab) were 5'-GGGAGCCTTGAATACACCAAAA-3' (Forward primer) 5'-TGTAGCACGATTGCAGCATTG-3' (reverse primer) and the probe for the corresponding primer sequence was 5'-FAM-AY CACATTG-GCACCCGCAATCCTG-BHQ1-3'.

Table 1. General characteristics and clinical features among COVID-19 confirmed cases, n = 100

Variables	Frequency	Percentage, %
Mean Age	48.62 ± 12.39	
Gender:		
Male	38	38%
Female	62	62%
Diseases diversity:		
Mild	42	42%
Severe	58	58%
Comorbidities:		
Diabetes	32	32%
Hypertension	46	46%
Cardiac	22	22%
Patient outcome:		
Improvement	52	52%
Death	38	38%

Statistical analysis. Quantitative data were expressed as mean and standard deviation (SD). For the variables, paired test was employed to analyse the difference. A correlation analysis was done by using Pearson correlation analysis. All statistical analyses were performed using the SPSS 20.0 (SPSS Inc) software package. A (*P* value of < 0.05) was considered statistically significant.

Results and Discussion

COVID-19 has become a serious public health intimidation across the world. It is one of the viral infections having high mortality risk. Beyond the health of human beings, COVID-19 is notably identified pandemic which triggered the most serious economic crisis. Which have created a radical of uncertainty (health, economic and social challenges) around the world. New disease-related findings are being revealed day by day and the treatment-related algorithms are continuously being updated [11].

In terms of biochemical parameters, D-dimer, LDH, CRP levels determined the risk of Intensive care unit (ICU) admission while D-dimer, LDH, urea, creatinine, CK-MB, troponin and ferritin predicted the risk of mortality. Higher CK-MB levels signify disease severity and mortality (Table 2).

The present study investigated biochemical tests including liver, renal and cardiac parameters screening of COVID-19 qRT-PCR confirmed cases using a routine clinical chemistry automated analyzer and compared with patients with mild liver and renal tests and had highly abnormal liver and renal test results at the time of admission.

The biochemical parameters i.e., ALT, AST and ALP, Renal function tests, like Creatinine and Urea and Cardiac Function tests, Troponin (TnT) and ALP levels were found to be significantly higher in the confirmed positive cases of COVID-19.

The present study data have shown that infection rates of COVID-19 are higher in females than in males (Table 1), where 38% were male and 62% were female. This may be due to more chances of transmission of diseases among females in this region, because of a lack of awareness and illiteracy among the females of this region.

Abnormal liver function test results were seen in up to more than half of patients. A number of studies have shown that COVID-19 stratification

Table 2. Blood glucose, renal, liver and cardiac function test parameters among COVID-19 confirmed cases (*n* = 100)

Biochemical parameters	Severe (*n* = 60)	Mild (*n* = 40)	*P* value
Glucose, mg/dl	179.9 ± 69.3	96.72 ± 9.51	<0.0001
Urea, mg/dl	115.90 ± 82.69	27.55 ± 6.91	<0.0001
Creatinine, mg/dl	4.06 ± 3.87	0.78 ± 0.15	<0.001
Na^{+}, mEq/ml	173.00 ± 32.61	133.2 ± 18.17	<0.0001
K^{2+}, mEq/ml	37.0 ± 0.0	4.09 ± 0.59	<0.001
SGOT, IU/l	84.35 ± 52.86	28.10 ± 14.17	<0.0001
SGPT, IU/l	94.86 ± 30.69	29.53 ± 10.85	<0.0001
ALP, IU/l	120.20 ± 27.44	69.21 ± 13.05	<0.0001
Protein, gm/dl	8.86 ± 0.80	6.92 ± 0.52	<0.0001
Globulin, gm/dl	3.95 ± 1.10	3.01 ± 0.30	<0.0001
CRP, ng/ml	55.32 ± 6.36	12.07 ± 1.59	<0.0001
Ferritin, ng/ml	641.2 ± 293.3	148.90 ± 64.95	<0.0001
D-Dimer, ng/ml	1173.0 ±708.4	389.50 ± 93.08	<0.0001
Troponin, pg/ml	58.23 ± 123.50	20.0 ± 5.5	0.003
CK-MB, U/l	3.65 ± 2.93	38.00 ± 08.23	0.002

Note. SGOT – serum glutamate oxaloacetate transaminase, SGPT – serum glutamate oxaloacetate pyruvate transaminase, ALP – alkaline phosphatase, CK-MB – creatine kinase-MB, (Mean ± SD)

based on disease severity, including the need for ICU admission and the extent of respiratory distress, indicated that serum AST and ALT were elevated in patients with critical COVID-19 compared to those with severe and moderate disease [12].

The present study suggested the evidence for the liver enzyme derangement especially ALP which is significantly higher in severe cases in comparison with mild case [13]. The prognostic value of liver enzymes derangement is not well defined but there are few studies reported that particularly elevated AST total bilirubin and ALT, are associated with increased disease severity, whereas other studies report as there is no association with disease severity and progression in COVID-19 cases [14, 15].

Various reports across the world regarding the primary mechanism suggested that SARS-CoV-2 passing through blood, intestine and may infect the liver and damage hepatocytes resulting in elevation in the AST, bilirubin and ALT values [16]. However, secondary mechanism is due to administration of various hepatotoxic drugs leading to respiratory distress syndrome-induced hypoxia results in systemic inflammatory response, which is believed to be associated with the risk of COVID-19-related liver dysfunction [17].

Among renal function tests, serum urea and creatinine levels are significantly higher in severe cases compared with mild ones. Gupta N. et al., evidenced the increased levels of serum urea and creatinine in COVID-19 cases [18]. This is due to the presence of ACE2 receptor on the tubular cell surface, which could be directly infected, which further interacts with circulating mediators resulting in microcirculatory derangement, endothelial dysfunction, and finally tubular injury [19].

Cardiac injury is a common clinical feature of COVID-19 patients; this could result from SARS-CoV-2 infection as a result of direct and indirect effects on cardiomyocytes, including acute myocardial infarction, heart failure, arrhythmias, myocarditis, sepsis, septic shock, cardiac arrest and pulmonary embolism [20].

The results of the current study showed significantly higher troponin levels in severe group (58.23 ± 123.5 pg/ml) compared with mild group (20.0 ± 5.5 pg/ml) COVID-19 cases. A greater frequency and magnitude of increased troponin in hospitalized patients shows the association with more severe disease. Guo et al. studied 187 COVID-19 patients and reported that 52 (27.8%) had a myocardial injury as determined by elevated levels of troponin [21].

D-dimer is the main fibrin disintegration fragment and is used in the synthesis and degradation of fibrin as a biomarker. Healthy people have modest levels of d-dimer in circulation, while high levels are detected in thrombosis-related diseases. D-dimer comes from cross-linked fibrin synthesis and lysis and is responsible for coagulation activation and fibrinolysis. It is believed that coagulation function abnormality, including D-dimer, has role in the progression of COVID-19 diseases [22].

Zhang et al. [23] reported that D-dimer value ≥2000 μg/l at hospital admission was a predictor of mortality in COVID-19 patients.

In the study from Wuhan, China, Zhou et al. [24] reported that D-dimer is an independent risk factor for disease course and is significantly increased in severe pneumonia cases. A group of researchers have reported that clinicians should be alert in the early period when D-dimer is >1 μg/ml [24].

Release of an acute phase protein ferritin and CRP in results of destroyed hepatocytes. Ferritin is a systemic inflammatory marker that can be used to predict the severity and mortality of SARS-COV-2 disease [25].

In this study, we have estimated the levels of D-dimer and ferritin in the severity of COVID-19 cases. The mean levels of D-dimer (1173.0 ± 708.4 ng/ml) and ferritin (641.2 ± 293.3 ng/ml) were significantly higher (<0.001) in severe COVID-19 cases when compared with the mild cases. The D-dimer and ferritin mean levels in mild cases were 389.5 ± 93.08 and 148.9 ± 64.95 ng/ml, respectively (Table 2).

The present study also analyzed non-specific inflammatory marker i.e., CRP is an acute phase reactant elevated generally upon infection or inflammation. An increased level specifies the severity of the infection and has also been used as an indicator of COVID-19 disease severity [26]. In this study, patients with severe disease courses had significantly higher CRP levels in severe (55.32 ±6.36 ng/ml) than in mild (12.07 ± 1.59 ng/ml) cases of COVID-19.

Gao Y et al. [27] reported in CRP levels 39.4 mg/l in patients with severe symptoms and patients with mild symptoms, CRP concentration of 18.8 mg/l.

A similar study was conducted by Mo P. et al. [28] and concluded that the mean concentration of CRP was significantly higher in severe patients

(46 mg/l) than that of non-severe patients (23 mg/l). In this study, we also analyzed the relationship between elevated D-dimer and ferritin with CRP in disease severity of COVID-19. The Pearson correlation analysis for elevated D-dimer and ferritin with CRP was found to be positive association for both D-dimer ($r = 0.60$, $P < 0.001$) (Fig. 2). An increase in D-dimer levels and CRP in blood levels and its positive association may be used as a predictor marker to predict pulmonary embolism in COVID-19 patients. Ferritin levels are elevated in various systemic inflammation as well as in various infectious diseases, whereas CRP is an inflammatory marker. So, the present study evaluated the relationship between ferritin and CRP and found significant positive correlation ($r = 0.50$, $P < 0.001$) (Fig. 3). Ferritin is a key mediator of immune deregulation and an increased level of ferritin is important in diseases characterzed by inflammatory and infectious processes and its positive relation with CRP might be useful to prevent tissue damage and its leading comorbidities.

Conclusion. Abnormality in organ function biomarkers could be helpful for risk stratification and for predicting COVID-19 disease severity. Among all, AST, ALT, creatinine, urea, troponin represent the most predictive parameters of organ failures among severe COVID-19 patients, whereas elevated CK-MB levels indicated severity of diseases, specially with MI comorbidity. Liver, renal biomarkers Would be used for COVID-19 disease management especially in severe cases. Nevertheless, this study also demonstrated the D-dimer and inflammatory

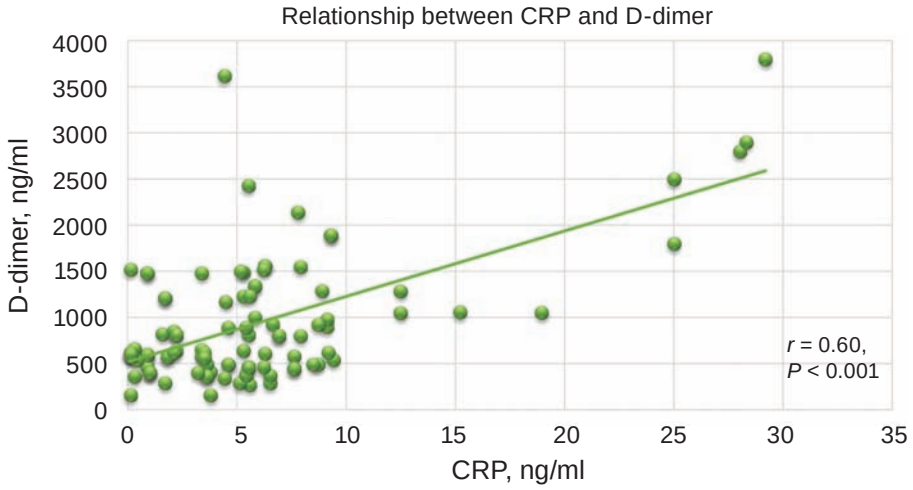

Fig. 2. Correlation analysis between CRP and D-dimer in confirmed cases of COVID-19

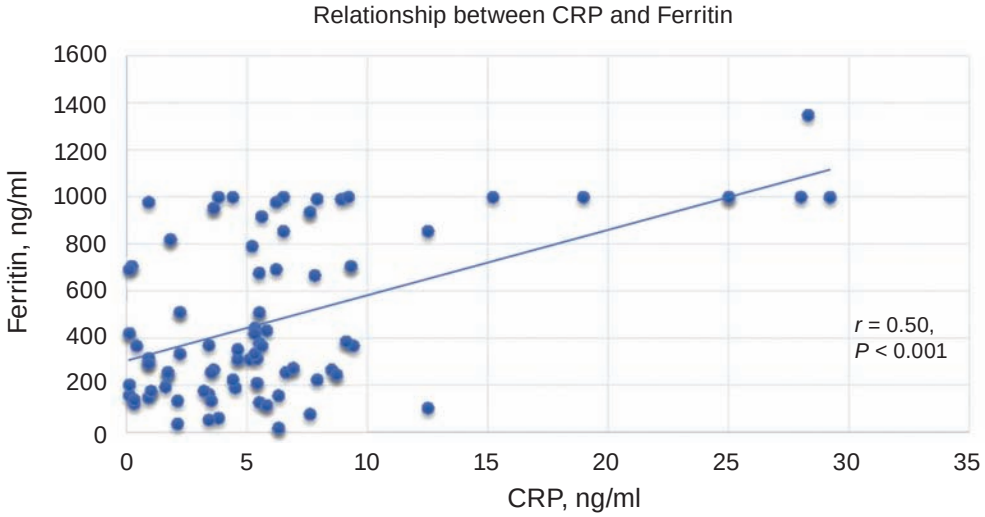

Fig. 3. Correlation analysis between CRP and ferritin in confirmed cases of COVID-19

markers (i.e., ferritin and CRP) levels were higher in patients with severe group COVID-19 than that of mild group COVID-19 cases. Thus, it is evident that patients with higher levels of D-dimer and inflammatory markers might have a risk for severe infection and it can also provide a timely reminder to clinicians. This study also revealed the positive association of serum D-dimer and ferritin levels with CRP in COVID-19 patients, including disease severity. Positive association of serum D-dimer and ferritin levels with CRP on hospital admission could be seen as a steady pointer for disease severity and increased risk of death. Thus, this apparent help physicians to mark prime decisions about critical care and enhancement of care planning. Future clinical studies should be performed with large sample size to further clarify its prognostic role in severity of COVID-19 patients.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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ОЦІНКА ЗВ'ЯЗКУ МІЖ ПОКАЗНИКАМИ ТЕСТІВ ФУНКЦІОНУВАННЯ ОРГАНІВ ТА ТЯЖКІСТЮ ПЕРЕБІГУ COVID-19

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Дані останніх публікацій свідчать про взаємозв'язок COVID-19 із поліорганною недостатністю, що вказує на необхідність досліджень залежності між показниками тестування функцій органів та перебігом захворювання. Метою цієї роботи було визначити ступінь відхилень параметрів тестів функціонування органів та їхню кореляцію з тяжкістю перебігу COVID-19. Проведено поперечне дослідження серед пацієнтів із COVID-19, госпіталізованих до лікарні Санака (Індія) з серпня по вересень 2020 року. Загалом, 100 пацієнтів із підтвердженим за допомогою qRT-PCR діагнозом COVID-19 було розподілено на групи з легким та важким перебігом захворювання. Зразки венозної крові для тестів отримано з бази даних лабораторії лікарні Санака. Біохімічні тести проводили за допомогою клінічного автоматизованого аналізатора ERBA, кардіологічні маркери оцінювали за допомогою ензимзв'язаного флуоресцентного аналізу. Для статистичної обробки даних використовували кореляційний аналіз Пірсона. Активність аспартатамінотрансферази/аланінамінотрансферази та лужної фосфатази, рівень креатиніну, сечовини та тропоніну були вищими у пацієнтів із підтвердженим COVID-19. Значно вищі рівні тропоніну, D-димеру та С-реактивного протеїну виявлені у пацієнтів із тяжкою формою COVID-19. У цій групі пацієнтів спостерігали виражену позитивну кореляціюя між підвищеними рівнями D-димеру і феритину та рівнем С-реактивного протеїну. Зроблено висновок, що позитивний зв'язок між рівнями D-димеру, феритину та рівнем С-реактивного протеїну у пацієнтів можна розглядати як стабільний показник тяжкості перебігу COVID-19.

Ключові слова: COVID-19, печінкові проби, ниркові проби, D-димер, феритин, С-реактивний протеїн.

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