*Academy of Romanian Scientists* *Volume 9, No. 2, 2020, pp. 88 - 99*
*Annals Series on Biological Sciences* ISSN 2285 – 4177

ORIGINAL PAPERS

# Significance of Hematological Parameters and Biochemical Markers in Severe Forms of Covid-19

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**Abstract**

SARS-CoV-2 is a new virus that affects the human population, about which not all the details are known, and for which the research is ongoing. Several common in vitro diagnostic tests have been implicated in the unfavorable progression of COVID-19, providing potentially important prognostic information.

According to some synthesis studies, the progressively low values of the lymphocyte / leukocyte ratio, and progressively increased of the neutrophil / lymphocyte and neutrophil / platelets ratios, correlate with the more severe evolution of COVID-19. The existence of a number of lymphocytes <20% on day 10-12 indicates a pre-severe condition, and a number of <5% on days 17-19 indicates a critical one.

D-dimers are the most important prognostic element in monitoring patients with severe forms of COVID-19. Elevated levels of D-dimers compared to the reference biological interval observed at hospitalization of patients with COVID-19 and their marked increase, up to 3-4 times the initial value, were associated with increased mortality, which probably reflects the activation of coagulation in infection / sepsis, cytokine storm and imminent organ failure.

Increasing ALT values by more than 5 times the reference biological interval increased the risk of mortality of patients with COVID-19 by seven times. High levels of AST compared to the biological reference range were observed in both patients with non-severe COVID-19 disease as well as in a double the number of patients with severe disease.

The value of serum creatinine at hospitalization is a predictor of the death of hospitalized patients for COVID-19. More frequent measurements of serum creatinine are recommended in the management of COVID-19 to improve the early detection of renal lesions in patients with COVID-19.

At patients confirmed with COVID19, elevated levels of highly sensitive troponin I (hs-cTnI) were observed during hospitalization, and more than 50% of those who died had a significantly higher concentration of hs-cTnI compared to the biological interval of reference.

Hyperferritinemia has been associated with an increased severity of COVID-19 disease, because of elevated ferritin levels compared to the reference biological range, the so-called "cytokine storm" is developed which can be fatal for half of COVID-19 patients, especially for the elderly.
Lactate dehydrogenase (LDH) has been associated with altered outcomes in patients with viral infections. In an American study (n = 1532 COVID-19 patients), the association between elevated LDH levels (that were measured as soon as possible after hospitalization) and the severity of the disease in patients with COVID-19 was assessed. Elevated LDH levels were associated with a 6 fold increase in the chance of developing severe symptoms and a 16 fold increase in mortality in patients with COVID-19. C-reactive protein (CRP) is part of the acute phase plasma proteins. COVID-19 increases CRP. This seems to correlate the severity and prognosis of the disease. Studies have found low levels of PCR in patients who do not require oxygen therapy (mean 11 mg / L,) compared to patients who have become hypoxemic (mean 66 mg / L).

**Keywords:** hematological parameters, biochemical markers, severe evolution of COVID-19

DOI https://doi.org/10.56082/annalsarscibio.2020.2.88

## Introduction

SARS-CoV-2 is a new virus that has appeared in the human population, not all the details about it are known, and research is ongoing. Therefore, because SARS-CoV-2 behaves similarly to SARS and MERS, certain details during the infectious process are deduced from the study of those viruses. Coronaviruses belong to the family Coronaviridae, order Nidovirales. Coronaviruses have dimensions of 65–125 nm in diameter and contain as nucleus material isolated RNA, with dimensions of 26 - 32kbs in length. The subgroups of the coronavirus family are alpha (a), beta (b), gamma (c) and delta (d) coronavirus.

SARS-CoV-2 is a virus that is transmitted through contact with the respiratory fluids of an infected patient: when he coughs, sneezes or speaks, he releases small drops of fluid, which contain the virus. They form aerosols and deposit on various surrounding surfaces. Subsequently, if another person inhales air containing aerosols or touches contaminated surfaces and then touch their face, eyes, mouth or nose, the virus enters the airways.

The virus is composed of an RNA molecule, surrounded by a series of structural and functional proteins. Known structural proteins are protein S (or spike - which leads to the characteristic appearance), protein M (membrane), protein E (envelope), protein N (nucleocapsid). The S protein has the role of attaching to receptors in human cells and facilitates the fusion of viral content with the cell. In the case of SARS-CoV-2, the receptor is the angiotensin converting enzyme (ACE2), which is found in large quantities in the respiratory

tract and lung parenchyma. In the case of SARS and SARS-CoV-2, the initial infection occurs in the ciliated epithelial cells of the bronchi.

The binding of S protein to ACE2 is greatly favored by the existence of the polybasic cleavage site - a protein fragment cleaved by the enzyme furin (commonly found in the human body), which allows the S protein fragments (S1, S2 and S3) to fulfill their function. In addition to the fusion of the viral envelope with the cell membrane, the virus also infects the human cell by endocytosis (the cell membrane around the portion that binds to the virus forms a vesicle inside the cell, detaches from the membrane and introduces the virus into the cell through that vesicle) . Through the process of entering the cell, the virus loses its envelope (which fuses with the cell membrane) and the viral RNA is free in the cytoplasm, performing two processes: replication and transcription. First, the cellular components responsible for RNA transcription produce viral proteins, and the RNA is copied. Subsequently, these proteins and copies of the initial RNA are "packaged" into new virions, released by the cell to spread the infection (Fig. 1).

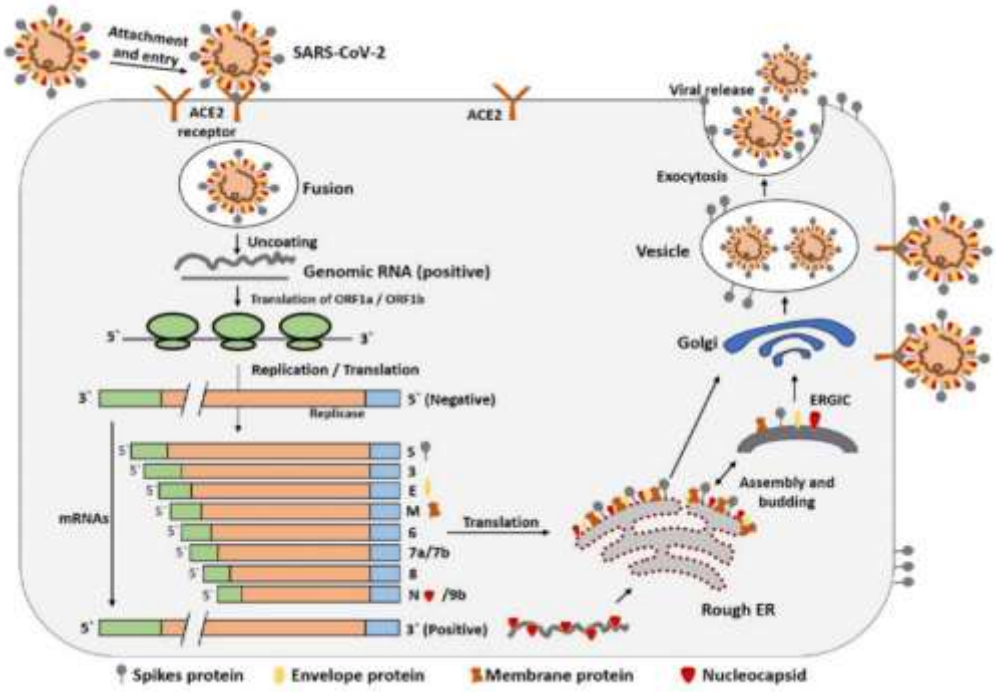


**Fig 1.** The structure of the SARS-CoV-2 virus and the interaction with the cells of the human body, through the ACE2 receptor (from Shereen 2020)

## The body's immune response

As with other viruses, bacteria or parasites that invade the body, the immune system is activated and performs a series of processes when it encounters the SARS-CoV-2 virus. First, antigen presenting cells (APCs) incorporate the virus, digest it, and than the proteins fragment it to obtain only the specific portions of SARS-CoV-2, which thus act as antigens. The APC subsequently presents these antigens to cytotoxic T lymphocytes. Thus, the immune cells are informed about the profile of the virus they need to attack (they recognize it by the antigen presented). There are two types of immune responses to this antigenic presentation: humoral and cellular. Details of these processes are largely extrapolated from knowledge of the SARS virus.

Humoral immunity consists of the production of specific antibodies against these antigens, antibodies that appear rapidly during infection and disappear rapidly (IgM) and antibodies that appear more slowly and persist in the body for a long time, even after the infection has healed (IgG).

Cellular immunity is the training of certain immune cells in recognizing and destroying the virus. It has been observed in SARS-CoV-2 infection that the number of CD4 + and CD8 + T lymphocytes is low in the peripheral blood (because they are destroyed in the process of eliminating the virus), but has high concentrations of activation markers. Regarding the SARS virus, memory cells, that are able to recognize the virus, were identified in the blood of patients cured several years after infection. The persistence of memory cells is an important element to consider in the development of the SARS-CoV-2 vaccine. Cases have been reported in which SARS-CoV-2 infection recurs after it was considered cured. This indicates an impediment of the immune system in effectively eliminating the virus, in which case a potential vaccine would have limited efficacy.

On the other hand, there is evidence that coronaviruses are equipped with mechanisms by which they can evade immune attack. Firstly, after infection of the cell, the vesicles in which the virus is located lack the receptors that could recognize the virus as an "invader" of the body. Secondly, the synthesis of interferon (with antiviral function) is inhibited by coronaviruses, and the presentation of viral antigens by APC is low in infected patients.

## Severe forms of COVID-19: what happens in the body?

First of all, it is important to remember that SARS-CoV-2 does not lead to a high proportion of severe cases of pneumonia, nor to an increased mortality, compared to seasonal flu. Specifically, 80% of cases are mild, 15% are severe and only 5% are very severe, requiring ventilatory support. In terms of mortality, to date, 3.4% of WHO reported cases have progressed to death. This value is higher

than in the case of seasonal flu, which has a maximum mortality of 0.15% (according to CDC estimates for winter 2019-2020), but significantly lower than the mortality caused by coronaviruses that have led to epidemics in the past, SARS and, respectively, MERS, with mortality of 9.6% and 34%, respectively.

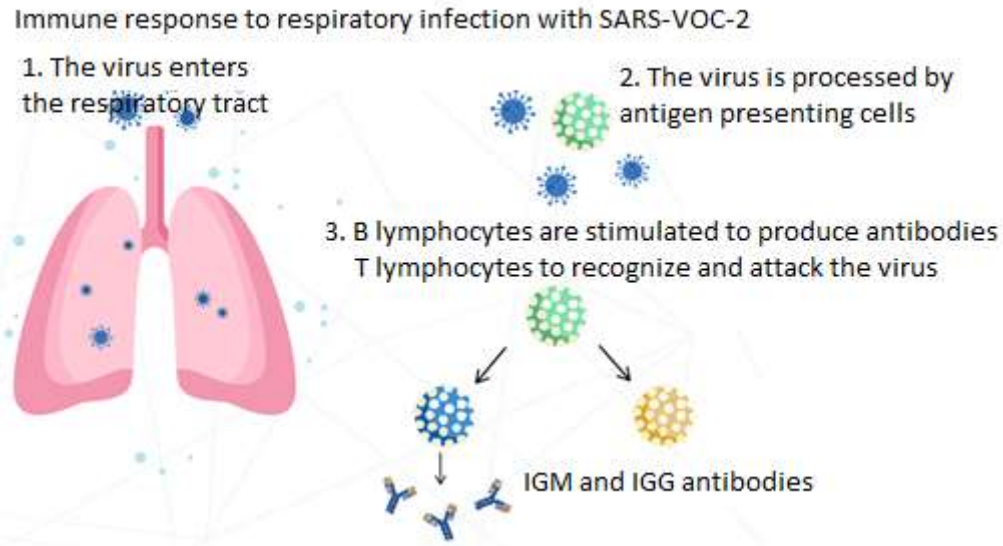


**Fig 2.** The process by which the immune response helps the body to respond to the SARS-CoV-2 virus

From symptomatology point of view, three stages of the infection are described:

Incubation period - the patient is asymptomatic, may or may not present the virus in respiratory secretions;

Symptomatic period - the patient has non-severe symptoms and the virus can be detected;

Severe period - the patient has a severe form of infection, and the virus is present in large quantities in respiratory secretions.

The immune response plays an important role in the evolution of the disease and in the appearance of severe forms. Thus, in asymptomatic and mild forms, the immune system has an appropriate far-reaching action: it attacks the virus and protects the body. At this stage, immune stimulation therapies could be beneficial (such as interferon, which stimulates the antiviral response).

If this initial immune response is insufficient, the virus spreads in the body, especially in tissues that are rich in the ACE2 receptor (eg intestines or kidneys). There, the virus multiplies, destroying the cells from which it is released. The intracellular components thus released stimulate an exaggerated immune response, leading to lung inflammation and ARDS - at this stage of severe

infection, the immune response is harmful, not beneficial, and treatment may include specific anti-inflammatory therapies (such as tocilizumab or other cytokine inhibitors, used in rheumatology).

Acute respiratory distress syndrome (ARDS) is, according to studies to date, a leading cause of mortality in COVID-19. This syndrome consists of acute inflammation of the lungs, which leads to acute respiratory failure and, consequently, lack of oxygenation of the whole body. In COVID-19 (similar to SARS and MERS), the exaggerated immune response is a major component in the occurrence of ARDS. Thus, immune cells respond to infection by releasing excessive amounts of proinflammatory cytokines and chemokines: interferon, TNF alpha, interleukins 1beta, 6, 12, 18, 33, and others, which activate a violent immune response against the lungs (producing ARDS), and on other organs (leading to multiple organ failure), which progresses rapidly to death.

Several common in vitro diagnostic tests have been implicated in the unfavorable progression of COVID-19, providing potentially important prognostic information (Table 1). Monitoring the biochemical parameters of patients with COVID-19 by in vitro diagnostic tests is essential for assessing the severity and progression of the disease, as well as for monitoring the therapeutic intervention. In addition to more frequent laboratory tests, new evidence suggests that patients with severe COVID-19 may be at risk for cytokine storm syndrome. Cytokine testing, especially IL-61, should be used, if possible, to assess severe patients suspected of hyperinflammation..

**Table 1.** Laboratory analyzes in adult patients with a severe prognosis in the evolution of COVID-19

| Laboratory test | Abnormal values | Potential clinical significance |
|---|---|---|
| Hemoleucograma | Leukocyte growth | Bacterial superinfection |
| | Neutrophil growth | Bacterial superinfection |
| | Decrease in lymphocytes | Decreased immune response to the virus |
| | Decreased platelet count | Coagulopathy |
| Albumin | Decrease | Impaired liver function |
| LDH | Growth | Lung damage or generalized organ damage |
| ALT | Growth | Liver damage and / or organ damage |
| AST | Growth | Liver damage and / or organ damage |
| Total bilirubin | Growth | Liver damage |
| Creatinine | Growth | Kidney damage |
| Urea | Estimated growth | Kidney damage |
| Procalcitonin | Growth | (Supra) bacterial infection |
| C-reactive protein | Growth | Severe viral infection / sepsis |
| Ferritin | Growth | Severe inflammation |
| Cytokine (IL-6) | Growth | Cytokine storm |

**Hematological parameters with changes**

Changes in quantitative and qualitative hematological cytomorphological parameters are located in an important place in the biological picture of the patient with COVID-19 with severe evolution. Without being specific to this condition and absent at its debut, they appear obviously with the progression of the disease, their magnitude correlating with the transition to more severe stages of evolution.

The determination of haemoglobin values, the number of leukocytes and their differentiated number, the number of platelets, as well as the examination of the peripheral blood smear are useful investigations to evaluate the prognosis of the patient with COVID-19 and to monitor its evolution under treatment (Gologan , 2020).

Patients infected with the new coronavirus (SARS-CoV-2) tend to have a higher neutrophil / lymphocyte ratio in favor of neutrophils (NLR). NLR is an independent risk factor for hospital mortality for patients with COVID-19, especially for men. NLR assessment can help identify individuals at high risk of COVID-19.

Patients with the new coronavirus infection (COVID-19) have higher blood levels of neutrophils, which have the potential of spreading the inflammation and microvascular thrombosis - including in the lungs of patients with acute respiratory distress syndrome.

Lymphocytes play a crucial role in maintaining the immune homeostasis and inflammatory response throughout the body. Four potential mechanisms leading to a decrease in lymphocyte counts have been speculated.

(1) The virus can directly infect lymphocytes, resulting in the death of lymphocytes. Lymphocytes express the ACE2 coronavirus receptor and may be a direct target of viruses.

(2) The virus can directly destroy the lymphatic organs. Decreased lymphocyte counts may be related to lymphocyte dysfunction and direct damage to organs such as the thymus and spleen.

(3) The activity of inflammatory cytokines may lead to apoptosis of lymphocytes. Research has confirmed that tumor necrosis factor (TNF) α, interleukin (il) -6 and other pro-inflammatory cytokines could induce a decrease in lymphocyte counts.

(4) Inhibition of lymphocytes by metabolic molecules produced by metabolic disorders, such as hyperlactic acidemia. Severe type COVID-19 patients have elevated lactic acid levels in their blood, which could suppress lymphocyte proliferation.

In conclusion, lymphopenia is an effective indicator of the severity of COVID-19.

Elevated levels of D-dimer and thrombocytopenia have also been reported at patients with severe COVID-19, suggesting that a state of hypercoagulability may contribute to disease severity and mortality.

According to synthesis studies, leukocytosis, lymphopenia (considered at values <1,500 / mm3 and present in about 85% of critically ill patients) and thrombocytopenia (considered at values <150,000 / mm3 and present in about 36% of them) are associated with a higher severity of COVID-19 and a higher risk of death. The existence of a number of lymphocytes <20% on day 10-12 indicates a pre-severe condition, and a number of <5% on days 17-19 indicates a critical one.

D-dimers are the most important prognostic element in monitoring patients with severe forms of COVID-19. Elevated levels of D-dimers compared to the biological reference interval observed at hospitalization of patients with COVID-19 and their marked increase, up to 3-4 times the initial value, were associated with increased mortality, which probably reflects the activation of coagulation in infection / sepsis, cytokine storm and imminent organ failure. The continuous increase in the value of D-dimers compared to the biological reference range indicates a progressive severity of infection in COVID-19.

Some patients with severe COVID-19 infection may develop coagulopathy (according to the criteria of ISTH - The International Society of Thrombosis and Haemostasis) with fulminant activation of coagulation and consumption of coagulation factors leading to a marked increase in D-dimers.

D-dimers result from the degradation of stabilized fibrin (cross-polymerized) under the action of plasmin, which proves a fibrinolysis secondary to coagulation. This test has a higher diagnostic value than PDF (fibrin degradation products), especially for Disseminated Intravascular Coagulation (DIC) and thrombotic manifestations, including those caused by COVID-19.

**Variation of biochemical markers**

Consecutive data on 55 laboratory parameters and cytokines from 642 patients with COVID-19 were profiled throughout the course of the disease determined 3 clinical stages (acute stage, days 1-9; critical stage, days 10-15, and the stage of convalescence, day 15 until the end of the observation). Laboratory results based on 75 deaths and 357 discharged patients showed that, in the acute stage, fatality can be predicted by older age and abnormal lactate dehydrogenase (LDH), urea, lymphocyte count and procalcitonin (PCT). At the critical stage, fatal outcome could be predicted by age and abnormal PCT, LDH, cholinesterase, lymphocyte count, and monocyte percentage.

**Lactate dehydrogenase (LDH)** is an intracellular enzyme found in almost all organs, which catalyzes the interconversion of pyruvate and lactate, with the concomitant interconversion of NADH and NAD +. The enzyme is composed of

two major subunits (A and B) and is present in five separate isoenzymes (LDH-1 in cardiomyocytes, LDH-2 in the reticuloendothelial system, LDH-3 in pneumocytes, LDH-4 in the kidneys and pancreas, and LDH -5 in the liver and striated muscles). Although LDH has traditionally been used as a marker of heart damage since the 1960s, abnormal values can result from multiple organ damage and decreased oxygenation. Extracellular pH is acidic due to infection and tissue damage and it triggers activation of metalloproteases and increased macrophage-mediated angiogenesis.

Lactate dehydrogenase (LDH) has been associated with altered outcomes in patients with viral infections. In an American study (Brandon Sept 2020) (n = 1532 COVID-19 patients), the association between elevated LDH levels measured in the shortest time after hospitalization and disease severity in patients with COVID-19 was evaluated. Elevated LDH levels were associated with a ~ 6-fold increase in the chance of developing severe symptoms and a ~ 16-fold increase in mortality in patients with COVID-19.

Severe infections can cause cytokine-mediated tissue damage and LDH release. Because LDH is present in lung tissue (isoenzyme 3), patients with severe COVID-19 infections are expected to release higher amounts of circulating LDH, as a severe form of interstitial pneumonia, which often progresses to acute respiratory distress syndrome, being, the distinctive sign of the disease. LDH levels are elevated in thrombotic microangiopathy, which is associated with renal failure and myocardial injury.

**C-reactive protein (PCR)** is part of the acute phase plasma proteins. It is secreted by hepatocytes and macrophages at the action of IL-1, IL-6, TNF-α. It binds to neutrophil, macrophage and T lymphocyte receptors with their activation. Like antibodies, with the participation of Ca ions, it binds specifically to bacteria, fungi (phosphorylcholine, phosphotidylcholine, unshielded galactans), and the complex formed activates the complement in a classical way. Consequently, microbes are lysed or opsonized by the activation and appearance on their membrane of complement components (C3b, etc.), which contribute to phagocytosis, due to receptors for these components.

COVID-19 increases CRP. This seems to correlate the severity and prognosis of the disease. Other etiologies (such as heart failure) are considered in a patient with severe respiratory failure and normal PCR.

• Young et al. 3/3 found low levels of PCR in patients who did not require oxygen therapy (mean 11 mg / L, interquartile range 1-20 mg / L) compared to patients who became hypoxemic (mean 66 mg / L, interquartile range 48-98 mg / L).

• Ruan et al. 3/3 found that PCR levels correlated with the risk of mortality (surviving patients had a median PCR of ~ 40 mg / L, with an interquartile range of ~ 10-60 mg / L, while patients who had died had an average of 125 mg / L, with an interquartile range of ~ 60-160 mg / L)

Fibrinogen is a laboratory test used to monitor COVID-19 patients. At the debut of the infection, increased fibrinogen values were found compared to the biological reference range. During the disease, especially in patients who develop severe CID-type coagulopathies, associated with COVID-19, the value of fibrinogen can decrease dramatically, 100 mg / dl.

A common pattern of coagulopathy characterized by increased levels of D-dimers and fibrinogen was observed in patients with COVID-19. This correlates with the growth in parallel of another inflammatory marker (CRP-C Reactive Protein).

Monitoring of COVID-19 patients who develop coagulopathies associated with the disease is also performed by determining PT- prothrombin time / Quick time, which explores extrinsic coagulation (factors II, V, VII, X - dependent on vitamin K) but also fibrinogen.

Excessive amounts of proinflammatory cytokines and chemokines: interferon, TNF alpha, interleukins 1beta, 6, 12, 18, 33, and others are released by immune cells that respond to SARS-CoV-2 infection by activating a violent immune response against the lungs (producing ARDS) and other organs (leading to multiple organ failure), which progress rapidly to death. Associated biological markers may include increases in C-reactive protein and ferritin, which appear to correlate with disease severity and mortality (Rouen 3/3/20).

Interleukins have been known in biology and medicine as activating or inhibiting factors of various cell types.

The types of interleukins are proteinaceous in nature, and the number and sequence of amino acids in each peptide chain is different. It is known that the result of such a primary structure is reflected in different spatial configurations of proteins.

Interleukin 6 (IL-6) is a 26 KDa protein and is also known as B cell stimulating factor (BSF-2) or interferon β2. It is produced by fibroblasts, monocytes and T-line cells and some non-lymphoid tumor cells. It is active in stimulating the proliferation of B cells and hepatocytes and T cells as well as hematopoietic stem cells. It has strong antiviral activity which is why they have also been called interferon β2 (IFβ2).

Interleukin 6 (IL-6) was remarkably elevated, with fatal cases having more robust production than cases discharged over the entire observation period. LDH, PCT, lymphocytes and IL-6 were considered very important prognostic factors for COVID-19-related death. The cytokine IL-6 stimulates humoral and cellular immune responses by acting on both B lymphocytes and T lymphocytes. IL-6 acts as an important factor in the growth and differentiation of B cells and stimulates their production of immunoglobulins. It also promotes T cell activation, growth and differentiation.

Some patients who develop severe forms of COVID-19 experience dangerous and systemic inflammation, triggered by an overactive immune response, called a "cytokine storm."

Hyperferitinemia has been associated with an increased severity of COVID-19 disease because at elevated ferritin levels compared to the reference biological range develops the so-called "cytokine storm" which can be fatal for half of COVID-19 patients, for the elderly. The increase in ferritin (values> 400 ng / mL) occurs in the case of excessive exogenous iron intake.

Increasing ALT values by more than 5-fold over the reference biological interval increased the risk of mortality in patients with COVID-19 sevenfold. In most patients who had elevated ALT levels during COVID-19, it was observed that after recovery ALT returned to the biological reference range.

High levels of AST compared to the biological reference range were observed at both patients with non-severe COVID-19 disease as well as in a double number of patients with severe disease.

Patients diagnosed with COVID-19 by CT scan in the subclinical phase had a significantly lower level of AST than patients diagnosed after the onset of symptoms.

The value of serum creatinine at hospitalization is a predictor of the death of hospitalized patients for COVID-19. More frequent measurements of serum creatinine are recommended in the management of COVID-19 to improve the early detection of renal lesions in patients with COVID-19.

Mortality in patients with COVID-19 was significantly associated with elevated levels of proteinuria, hematuria, urea-derived blood nitrogen (BUN), serum creatinine, uric acid, D-dimers.

In patients confirmed with COVID19, elevated levels of highly sensitive troponin I (hs-cTnI) were observed during hospitalization, and more than 50% of those who died had a significantly higher concentration of hs-cTnI compared to the biological interval of reference.

Elevated NT-proBNP (> 88.64 pg / mL) may be an independent predictor of mortality in COVID-19 confirmed patients.

As measuring troponin levels is useful in the diagnosis of myocardial infarction, the change in cTn concentration in patients confirmed with SARS-CoV-2 infection should be interpreted in the clinical context.

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