

## STUDY ON THE MONITORING OF INFLAMMATORY MARKERS IN SARS-COV2 INFECTION

**Tatiana Ciurea, Daniela Tiță, Maria Prisecaru, Ionuț Stoica, Diana Ioana Tiță**

**Key words:** Sars-Cov2, marker, IL-6 (Interleukin-6), CRP (C Reactive Protein), Ferritin, D-dimers, acute respiratory distress syndrome (ARDS), hyper cytokinic syndrome, cytokine storm

### INTRODUCTION

Coronavirus disease (CoV-19), which is caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), has created a global crisis affecting various aspects of human life. The lung is a major target organ of the virus, but other organs can be infected. (Dasgupta A. et al. 2020).

CoV-19 may present asymptotically, as a mild, influenza-like illness with mild inflammation of the upper respiratory tract or severe illness characterized by sudden inflammation, systemic coagulopathy and severe damage to the lungs, cardiovascular system, multi-organ failure and even death. There is also evidence that SARS-CoV-2 infection can occasionally cause long-term and sometimes debilitating symptoms, including fatigue, shortness of breath, joint pain, and chest pain. (Chen N, et al. 2020). CoV-19 infection usually has a gradual onset with low-grade fever, fever, fatigue, headache in the first days of illness. In general, the most common clinical signs of SARS CoV-2 infection are fever (83-99 %), dry cough (59-82 %), fatigue (44-70 %).

About 1/3 of patients have general malaise, dyspnea, anorexia. (Pranata R, et al. 2020). Every 5th patient has cough with sputum, myalgia, low back pain, pharyngeal pain. The initially mild progression of CoV-19 infection may progress rapidly over the course of a week, especially in the 2<sup>nd</sup> week of illness, so patients with pneumonia may experience a second febrile wave and dyspnea 5-14 days after the onset of symptoms. The cough may last 7-10 days before symptoms worsen. (Pranata R, et al. 2020; Huang I, Lim MA, Pranata R. 2020; Huang I, Pranata R. 2020).

Pulmonary exam shows signs of pneumonia in both lungs when the virus has already affected the lungs. Some patients may have pulmonary imaging changes (especially on CT) without other classic clinical signs specific to pneumonia. (Wu C. et al. 2019; Xu Z. et al. 2020).

Clinical worsening on day 5-14 of the disease is explained by a disproportionate cytokine response ("cytokine storm"/hyper cytokine syndrome). The general condition of patients can worsen rapidly (in

hours) with the development of acute respiratory distress, refractory metabolic acidosis, coagulation dysfunction, renal failure, heart failure, septic shock, multi organ dysfunction, etc. The level of hypoxemia is not directly related to changes. (Ridker, Paul M., et al. 2010; Clerkin KJ. Et al. 2020; Li Y. et al. 2019; Chen N. et al. 2020; Han H. et al. 2020).

Laboratory comorbidities and markers have been proposed for risk assessment, diseases severity, conduct (preparation of respiratory support) and prognosis. There is growing evidence that critically ill patients experience hyper inflammation characterized by elevated serum values for: IL-6, CRP, D-dimer, ferritin, etc. (Wu C, et al. 2020; Chen G, et al. 2020; Qin C, et al. 2020).

Interleukin-6 (IL-6) is a cytokine with many functions, acting on B and T cell, hematopoietic stem cells, hepatocytes, and neurons. Specialist studies have shown that patients with acute respiratory distress have elevated IL-6 levels. (Mehta P. et al. 2020; Han H, et al. 2020; Miguel-Bayarri V. et al. 2012; Song J, et al. 2020).

Studies have shown that levels of IL-6, the most common type of cytokine released by activated macrophages, rise sharply in severe CoV-19 manifestations. (Chen N. et al. 2020).

C-Reactive Protein is produced by the liver, being a sensitive marker of general inflammation and tissue damage in the body; an increase in serum levels is associated with the severity of the disease. (Gong J. et al. 2020).

Studies have shown that CRP levels were significantly higher in the early periods of severe cases and have been shown to be a more sensitive biomarker in reflecting disease development, are more reliable for early identification of case severity. (Sproston NR, Ashworth JJ. 2018; Tan C. et al. 2020).

D-dimers are degradation products of fibrin, a substance that forms part of fibrin clots. D-dimers act as a marker of increased coagulation and fibrinolysis (degradation of clots under the action of plasmin), with increased values in patients with vascular thrombosis. (Zhang L. et al. 2018).

Monitoring of D-dimers is also useful in the case of recurrent deep vein thrombosis, values above

the permissible upper limit of this compound in people with a history of venous thrombosis who have stopped taking the anticoagulant, being representative of the risk of a new acute venous obstruction, or arterial. (Tang N. et al. 2020).

Intravascular coagulation disseminated by various etiologies (infections, neuro trauma, systemic inflammatory syndrome) is another condition in which the determination of d-dimers is diagnostic, the test being used to monitor the patient's progress during treatment. (Zhang L. et al. 2020).

Ferritin is a protein that forms as a complex between ferrous hydroxide and another protein called apoferritin. Ferritin is the form of storage of iron in the body, its concentration highlighting the iron deposits present in the human body.

Ferritin can be used as an acute phase protein, with elevated levels of ferritin being correlated with the activity of the inflammatory response. Furthermore, studies have reported elevated CoV-19 values in elderly and hypertensive patients, diabetes, cancer. (Cheng L, et al. 2020; Taneri PE. Et al. 2020).

The present study aims to evaluate inflammatory markers in the context of worsening health of patients diagnosed with Covid disease19.

## MATERIALS AND METHODS

The study group included 100 patients aged 54 to 85 years, diagnosed with Covid-19, who had blood samples taken for venous testing for biochemical and immunological analysis. The harvesting containers used were 0.105M (1/9) sodium citrate for D-Dimer and vacutainer without anticoagulant for ferritin, interleukin 6 and C-reactive protein.

The method of determination used was chemiluminescence immunochemistry for fertility, interleukin, D-dimers and the latex-immunoturbidimetry method for CRP.

Causes of rejection of the sample - intense lipemic or intensely hemolyzed specimen.

## RESULTS AND DISCUSSION

The patients studied were divided into genders and age groups. Of the 100 patients diagnosed with CoV disease -19, 43% were female and 57% male, the sex ratio being M/F = 1.32. (Fig. 1).

Analyzing Fig. 1, shows a higher number of male patients investigated compared to female patients. The age group of patients was as follows (Fig. 2).

Fig. 2 found that the highest number of patients was in the 66-77 age group, with the severity of CoV disease increasing with age.

Following serological testing, the following results were obtained in female patients.

All female patients had values outside the reference range for all inflammatory markers investigated. (Fig. 3). If the ferritin whose reference range according to the insert of the kit is 13-150 ng/mL and the C-reactive protein (reference range values lower than 5mg/L) showed the highest values in the age group 78-89 years, interleukin -6 (reference range 2.7 -4.4 pg/mL) recorded the highest values in the age group 66-77 years, followed by the age group 54-65 years. D-dimers showed the highest values in the age group 54-65 years, followed by the age group 78-89 years (reference range 0-0.5 µg/mL).

The following results were obtained in male patients following serological determinations.

In the case of male patients as well, the values of the investigated analytes were outside the recommended reference range (Fig. 4). The highest values were for C-reactive protein in the age group 78-89 years, for interleukin-6 in the age group 54-65 years, D-dimers in the age group 66-77 years and ferritin in the age group age 78-89 years.

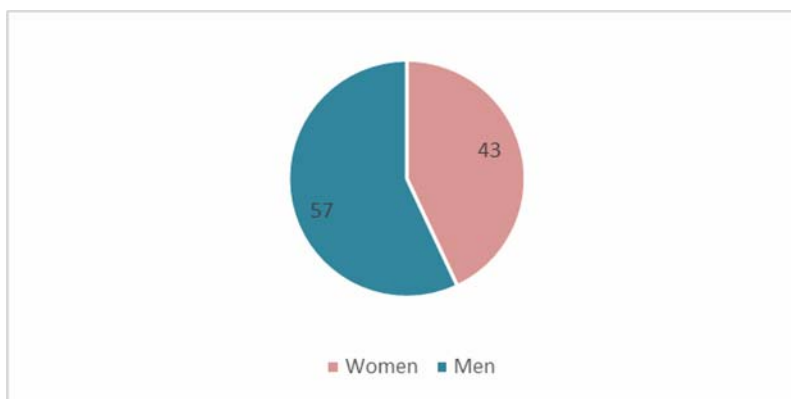


Fig. 1. Distribution by sex of the investigated patients

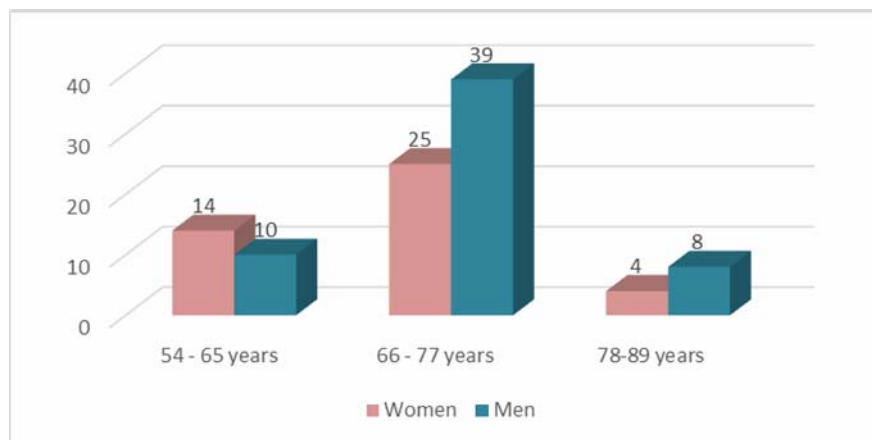


Fig. 2. Distribution by age groups of the investigated patients

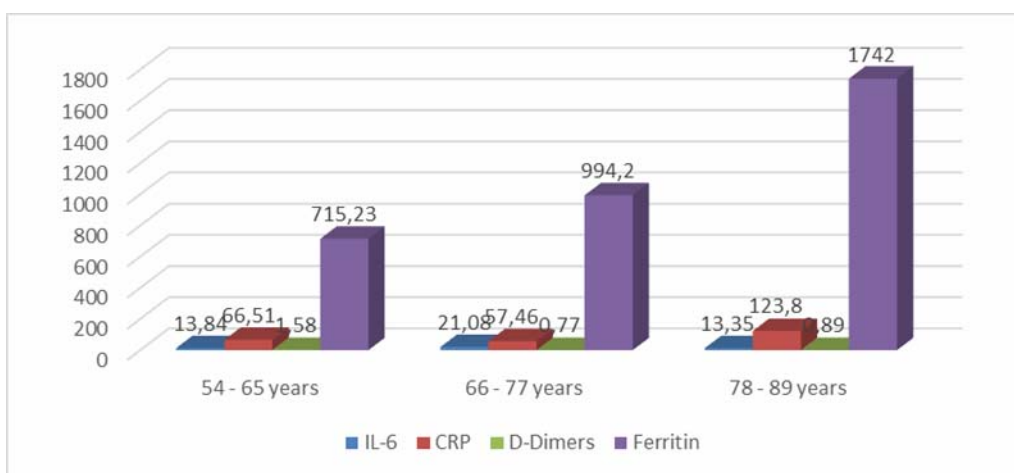


Fig. 3. Graphical representation of the average values of the analytes investigated in female patients

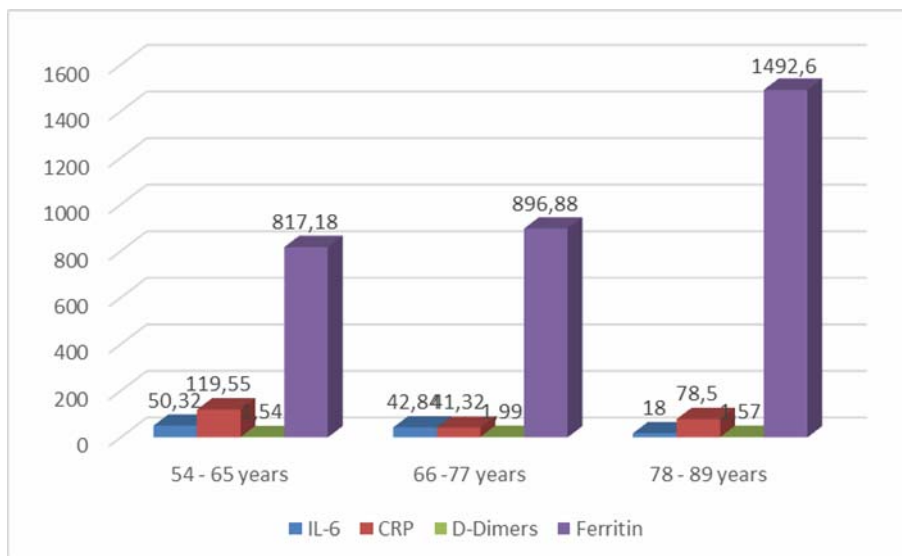


Fig. 4. Graphical representation of the average values of the analyzed analytes in male patients

SARS CoV-2 is an RNA virus that enters human cells by attaching a type 2 conversion enzyme (ACE 2) that is significantly expressed in alveolar cells, cardiac myocytes, vascular endothelium, and other cells. Like other zoonotic viral infections, it can the ability to cause a severe form of the disease through a severe systemic inflammatory response, acute respiratory distress, multiple organ failure, and shock. According to the literature, inflammation is a defense reaction of vascularized tissues against local aggression. It primarily involves a local inflammatory reaction, which may be accompanied by many numbers of systemic and metabolic changes known as the acute phase response. In the case of the acute inflammatory reaction, the increase in the concentration of acute phase proteins (C-reactive protein, ferritin) is correlated with the activity of the inflammatory response. In inflammation-free organ dysfunction, this increase in acute phase protein is not present. Therefore, the determination of acute phase proteins is an important criterion for differentiating between inflammatory and functional damage to an organ. (Bullard J. *et al.* 2020; Chen W. *et al.* 2020; Dasgupta A. *et al.* 2020).

CoV-19 disease is associated with a severe inflammatory response of the body; According to the clinical evaluation, elderly patients with a previous condition (cardiovascular disease, obesity, type II diabetes) have an increased risk of severe pathological response to SARS-CoV2 exposure. The most common abnormality associated with Covid 19 disease is a decrease in platelets and an increase in D-dimer levels, which is associated with an increased risk of requiring ventilatory support, admission to the intensive care unit, and death. Also, according to published data, 71% of patients who developed severe forms of the disease had typical changes in laboratory tests for disseminated intravascular coagulation. All these changes indicate a form of coagulopathy (a blood clotting abnormality) that can predispose to thrombotic events. (Tan C. *et al.* 2020; Zhang L. *et al.* 2020).

Interleukin-6 (IL-6) is a multifunctional protein that regulates the immune response, acute phase reactions and hematopoiesis and is produced by lymphatic and non-lymphatic cells and by normal and transformed cells, including T cells, B cells, monocytes, fibroblasts, vascular endothelial cells, cardiac myxomas, bladder cell carcinomas, myelomas, astrocytoma, and glioblastomas, (Han H. *et al.* 2020; Song J. *et al.* 2020; Wu C. *et al.* 2020).

Elevated serum values obtained in the present study for all age categories investigated confirmed that IL-6 is an ideal marker in monitoring patients with CoV-19. Elevated level for IL-6 correlates directly with disease severity and pro coagulant profile.

Monitoring of inflammatory markers such as CRP, D-dimers, ferritin, and IL-6 allows the adoption

of the best therapeutic behavior in the treatment of patients with CoV-19.

## CONCLUSIONS

- SARS-CoV 2 infection can lead to a severe form of the disease through a severe systemic inflammatory response, acute respiratory distress, multiple organ failure and shock.
- Inflammatory markers in Covid-19 disease provide information about the severity of infection and tissue inflammation.
- Inflammatory markers in Covid-19 disease provide information about the severity of infection and tissue inflammation.
- Increased values for inflammatory markers are associated with an aggravating potential, with an unfavorable prognosis.

## ABSTRACT

COVID-19 may present as a silent asymptomatic infection, a mild upper respiratory tract disease or a severe illness characterized by fulminant inflammation, systemic coagulopathy and severe damage to the lungs and cardiovascular system and other organs. Acute respiratory distress syndrome (ARDS) and multiple organ dysfunctions are among the leading causes of death and severe forms in patients diagnosed with CoV-19. Severely ill patients (CoV-19) have hyper inflammation and associated biomarkers provide useful information for risk assessment. Moreover, the serum levels of inflammatory markers such as: IL-6, ferritin, CRP, D-dimers are closely related to the severity of the disease.

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#### AUTHORS' ADDRESS

CIUREA TATIANA - Bagdasar-Arseni  
Emergency Clinical Hospital, Bucharest, e-mail:  
[ciurea\\_t@yahoo.com](mailto:ciurea_t@yahoo.com);  
TIȚĂ DANIELA- Bacau Emergency County  
Hospital, Romania; e-mail:  
[danielatita2007@yahoo.com](mailto:danielatita2007@yahoo.com);  
PRISECARU MARIA, STOICA IONUȚ -  
„Vasile Alecsandri” University of Bacau, Faculty of  
Science, Department of Biology, Bacau, Romania, e-  
mail: [prisecaru\\_maria@yahoo.com](mailto:prisecaru_maria@yahoo.com);  
[ionut\\_stoica23@yahoo.com](mailto:ionut_stoica23@yahoo.com);  
TIȚĂ DIANA IOANA - University  
Dunarea de Jos Galati, Faculty of Medicine and  
Pharmacy, e-mail: [dianaioana2525@yahoo.com](mailto:dianaioana2525@yahoo.com).