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C reactive protein, Procalcitonin, Ferritin Levels in Mild, Severe and Critically Ill Patients with Coronavirus Disease 2019 (COVID-19)

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Abstract – The severe acute respiratory syndrome coronavirus-2 has infected millions of people worldwide, causing the COVID-19 pandemic. The pathogenic mechanism of infection is still under investigation.
Due to lack of appropriate treatment, it is important to determine specific biomarkers to help clinicians identify patients at high risk of death, especially among those with severe COVID-19. These inflammatory factors may be prognostic biomarkers for predicting severe COVID-19 infection, therefore early identification of patients with COVID-19 with possible adverse prognostic factors is important for treatment and limiting severe outcomes and death.
In the study we investigated the potential interdependence of some laboratory parameters - C reactive protein, procalcitonin, ferritin in different clinical severity COVID-19 patients. Study results indicate that average values of these biomarkers vary in accordance with severity of COVID-19 infection. These values are explicitly higher in critically ill patients in comparison with mild and severe forms of disease.

Keywords – Severe Acute Respiratory Syndrome Coronavirus-2, Procalcitonin, C-Reactive Protein, Ferritin.

The coronavirus disease 2019 (COVID-19) has become an urgent public health problem due to the increasing number of infections worldwide. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread rapidly abroad and remains a serious issue globally, posing numerous challenges [1].

COVID-19 is a complex multisystem disease and pathogenesis is still under study. Judging by clinical data and data presented in the current literature, most patients with COVID-19 develop an abnormal inflammatory response to the viral infection, leading to failure of different organs and death [2]. The majority of COVID-19 patients have mild to moderate symptoms including fever, dry cough, and fatigue, but a sub-cohort will develop severe disease, which often presents with acute respiratory distress syndrome, coagulation dysfunction, septic shock, and multiple organ failure [3]. Older age, comorbid conditions, lymphopenia, higher levels of lactat dehydrogenase (LDH), and D-dimer have been correlated with a greater risk of intensive care unit admission and death [3,4,5]. The inflammatory process caused by infection may play a major role in the pathogenesis of multiple organ damage and be responsible for the severe outcome of COVID-19 patients. Inflammatory markers include leukocyte count, LDH, C-reactive protein (CRP), fibrinogen, and D-dimer, which are commonly used in clinical practice to monitor the septic process [6,7].

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Studies on COVID-19 patients have reported changes in the levels of some inflammatory markers such as procalcitonin, CRP, erythrocyte sedimentation rate and serum amyloid A. However, little attention has been paid to ferritin, even though hyperferritinemia has been shown to be associated with complications in other viral diseases [8,9]. Although ferritin is reported as an acute-phase protein, there is a lack of data is available in the literature reporting its particular modified levels, leading also to misunderstanding regarding its interpretation [10,20]. The role of iron metabolism is considered to be directly involved in COVID infection [16,17]. Many individuals with diabetes exhibit elevated serum ferritin levels [14], and it is known that they face a higher probability to experience serious complications from COVID-19 [19]. The current studies on COVID-19 were comprehensively investigated to determine the potential relationship of ferritin with severe condition, mortality, and other critical clinical features of COVID-19 patients [11].

Recent literature advocates hyperferritinemic syndrome as one of the main modifications in COVID-19 infection suggesting evaluation of ferritin levels as a parameter of infection [17]. Hyperferritinemia 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 [12,13,14].

Serum ferritin, a feature of hemophagocytic lymphohistiocytosis, as the 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 [3,15]. Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm [16].

Ferritin production occurs when intracellular iron concentration augments, with iron being stored in the form of ferritin and subsequently expelled from the cell [17]. 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 [18]. Laboratory findings in patients with severe COVID-19 showed data consistent with cytokine storm involving elevated inflammatory markers, including ferritin, which has been associated with critical and life-threatening illness [15,21].

Inflammatory parameters such as lymphocyte count, neutrophils, and CRP, cellular enzymes such as LDH, creatine kinase (CK), and the biomarker combination scores such as neutrophil-lymphocyte ratio (NLR), CRP-lymphocyte ratio (CLR) could be prognostic biomarkers for predicting the prognosis of severe COVID-19. Elevation of CRP and LDH, lymphopenia, and leukocytopenia are common laboratory changes seen in COVID-19 [22]. The CRP may become a helpful clinical tool to stratify patients with systemic inflammatory response syndrome according to disease severity [23].

CRP is not an independent risk factor for prognosis, and the lack of specificity of inflammatory parameters including CRP and neutrophil count has been regarded as a disadvantage. Inflammation has been linked to coagulation abnormalities, and this is a common pathological manifestation in severe COVID-19 patients [24]. Systemic inflammation and host immune response play an important role in COVID-19. The decrease in the lymphocyte count observed in COVID-19 suggests that the immune system comes under attack. Subsequently, excessive inflammation and uncontrolled immune activation result in organ or tissue injury [25].

Procalcitonin (PCT) is a 116-amino-acid precursor peptide from the hormone calcitonin and is part of the inflammatory cascade in sepsis [26]. Elevated levels are strongly correlated with systemic bacterial infection [27]. Procalcitonin levels tend to be elevated in bacterial infections whereas they are depressed in viral infections [26,30]. Procalcitonin is almost undetectable under physiological conditions (pg/ml range), but rises to very high values in response to bacteraemia or fungaemia, and appears to be related to the severity of infection. This response can be duplicated by in vivo endotoxin administration, which results in a rapid rise in procalcitonin, paralleling that of tumor necrosis factor and interleukin - 6 [28,29]. Studies have revealed that procalcitonin levels are elevated in Gram-positive and, to a greater extent, Gram-negative bacterial sepsis but not in viral infections [31].

The aim of our study was to determine some of above mentioned laboratory parameters due to their potential diagnostic and prognostic roles in different severity COVID-19 patients.

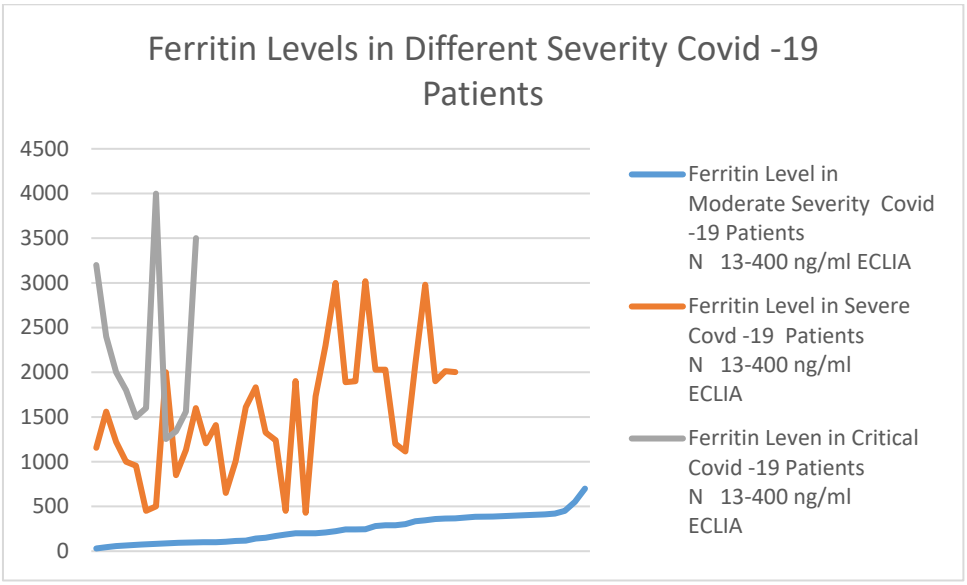
The patients admitted to the First University Clinic and undergoing treatment for a new coronavirus infection were included in the study. In all patients the novel SARSCoV 2 was confirmed by polymerase chain reaction using GeneXpert analyzer (USA) (reagents - Xpert Xpress SARS-CoV-2 (Cepheid, USA). Upon admission to the hospital, various laboratory routine tests were also conducted. Despite laboratory parameters analyses, computed tomography of the patients' chest was performed on an Aquilion 16-

slice CT scanner (Toshiba, Japan), and chest radiography was performed on a RADspeed fit Plus X-ray machine (Schimadzu, Japan).411 ဓ

As study results (diagram #1) show in 50 moderate severity Covid-19 patients ferritin levels are mainly in norm - from 13 -400 ng/ml ECLIA, only 12% (6 patients) reveal slight increase above norm –from 400 to 700 ng/ml ECLIA. Ferritin levels in all severe Covid-19 patients (37) are increased and vary between 400 to 3000 ng/ml ECLIA. In critically ill Covid-19 patients ferritin levels are extremely high – between 1255 to 4000 ng/ml ECLIA.

Ferritin Levels in Different Severity Covid -19 Patients.

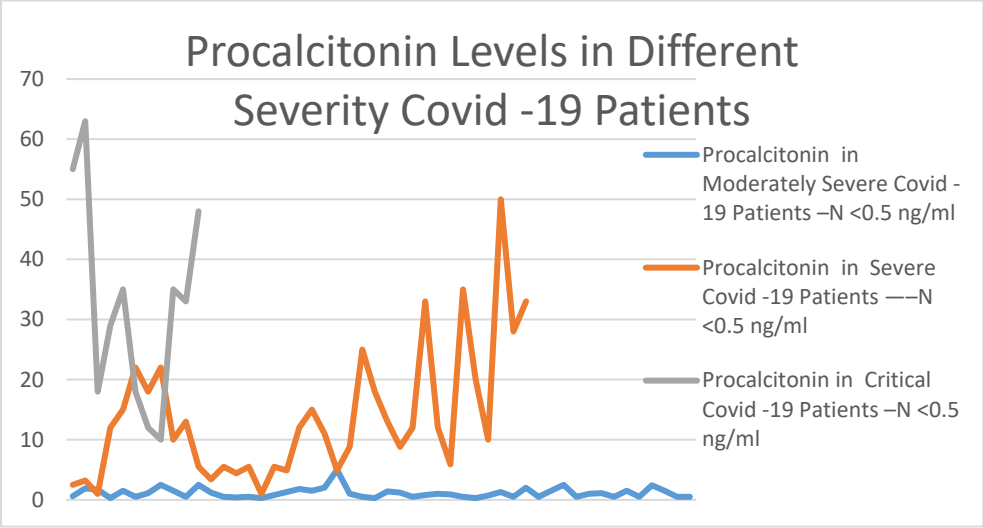
Diagram #1



In 62% moderate severity patients procalcitonin levels are increased slightly, averagely reaching 1.6 ng/ml (n=<0.5ng/ml). In severe Covid-19 patients procalcitonin levels range from 1 peaking till 50ng/ml, average value is 37 ng/ml. In critically ill Covid-19 patients procalcitonin levels are from 10 till 63 ng/ml, average value is 33 ng/ml.

Diagram #2.

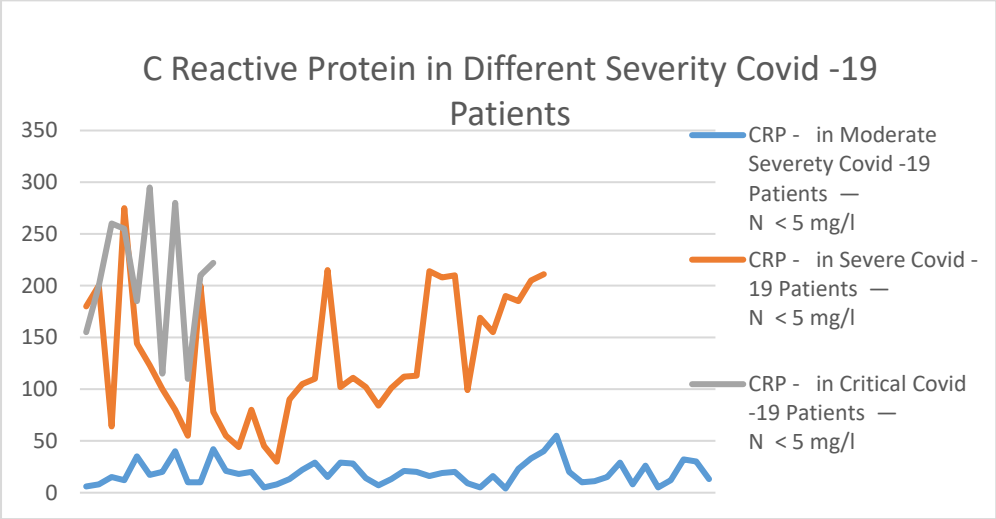
Procalcitonin Levels in Different Severity Covid -19 Patients



C reactive protein value in moderate severity Covid 19 patients varies from 4 till 55 mg/l, average value is 19 mg/l. In severe Covid-19 patients the average value is 131 mg/l - from 30 - 275mg/l. As regarding of critically ill Covid-19 patients average value is much higher -208mg/l and varies between 110-295 mg/l.

Diagram #3

C Reactive Protein Levels in Different Severity Covid -19 Patients



Study results indicate that average values of CRP, procalcitonin and ferritin varies depend on severity of COVID-19 infection and these values are significantly higher critically ill patients.

Laboratory tests accompanied by clinical evaluation can provide a rapid assessment of the disease state and provide adequate treatment for COVID-19 infection. The identification of effective laboratory biomarkers in order to classify patients based on their risk is a prerequisite for providing adequate treatment.

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