

ALTERATIONS IN CRP, D-DIMER AND LDH LEVELS IN PATIENTS WITH COVID 19

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ABSTRACT

The previously unknown coronavirus type called SARS-CoV-2 first appeared during December 2019 in Wuhan, Hubei Province in China, whereas it was isolated in January 2020. During February 2020 in the Republic of Northern Macedonia was confirmed the first case of COVID 19. It was a patient born in 1970, whom had stayed in Italy for some time. Alternations in biochemical parameters have been observed in various researches conducted in different countries. The aim of this study is to evaluate the alternations in the biochemical parameters CRP, D-dimer and LDH levels, as important markers in a group of patients diagnosed with COVID 19 in the Polog region. The study included 118 patients with COVID-19, whose analysis were performed in the Laboratory of the Clinical Hospital of Tetovo. Levels of biochemical parameters, such as D-dimers, CRP and LDH were increased in patients infected with SARS-CoV-2 (2019), these parameters can be used as important biomarkers which help healthcares to detect these patients in early stages, for adequate treatment, follow the treatment and prognosis of the disorder.

KEYWORDS: Covid-19, D-dimers, CRP, LDH

INTRODUCTION

SARS-CoV-2 is the seventh detected coronavirus that causes infection in humans [1]. The three types of viruses SARS-CoV, MERS CoV and SARS-CoV-2 can cause severe infections, while HKU1, NL63 and 229E are associated with mild symptoms [2]. The previously unknown coronavirus type called SARS-CoV-2 first appeared during December 2019 in Wuhan, Hubei Province in China, after that it was isolated in January 2020 [3]. During February 2020, at the Republic of Northern Macedonia was confirmed the first case infected with COVID 19. It was a patient born in 1970, whom had stayed in Italy for some time [4].

COVID 19 presents with different clinical features and patients symptoms are different in both frequency and severity. Symptoms that are absent early in the disease may develop as the disease progresses [5, 6]. The following symptoms are most commonly reported in patients: fever, shortness of breath, fatigue, loss of appetite, loss of smell and / or taste [7, 8].

COVID 19 is reported as a multisystemic disease. The most common and serious occurrence of infection is pneumonia but unfortunately there are no specific clinical features that distinguish COVID 19 from other viral respiratory diseases [9]. Patients with pre-existing cardiovascular disease are at greater risk of suffering from COVID 19 with severe symptomatology and poor prognosis [7], while acute renal disease during COVID 19 is associated with sepsis, multiorgan

failure and shock, suggesting that the cause of acute renal disease are acute tubular necrosis, although the exact pathogenesis of renal involvement in COVID 19 infection are still unclear [10].

Several studies have reported clinical manifestations and biochemical characteristics of blood in patients with COVID 19, but there have been differences in results due to different study designs and insufficient number of samples [11]. Blood biochemical changes play an essential role in assessing patients condition, prognosis, treatment as well as curative effect [12].

C-reactive protein (CRP) is a protein produced by the liver and serves as an early marker of infection and inflammation [13]. When inflammation or tissue damage passes, the CRP concentration decreases making it an important parameter for monitoring disease. From various studies was conducted increase at the CRP level up to 86% of infected patients with COVID 19 with a severe condition. A significant correlation was observed between CRP concentrations and the deterioration of the condition of infected patients, but not at patients with severe symptoms, which is why the researchers proposed CRP as a suitable marker for predicting the probability of worsening of non-severely ill patients with COVID 19, with a threshold of CRP values of 26.9 mg / L [14].

D-dimer is a fibrin degradation product, used as a biomarker for thrombotic disorders. Following the outbreak of the COVID-19 pandemic, D-dimer has been identified as a potential indicator for disease prognosis and management [15]. Increased D-dimer values in patients with COVID19 may occur as a consequence of infection which causes release of proinflammatory cytokines; inflammation can also lead to thrombosis and acute inflammation caused by sepsis can affect blood clotting [16].

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme which in the absence of oxygen converts pyruvate to lactate, which enters the bloodstream after cell death [17]. Various studies report that its values increase in a range of diseases such as acute respiratory syndrome (SARS), diabetes and cancers. Elevated LDH levels in patients with COVID 19 are highly pronounced, especially in patients with severe and critical condition [18]. Serum LDH level determinations can be used as an important marker in disease exacerbation and mortality of infected patients. The association between LDH levels and the severity of COVID 19 may reflect direct lung damage and the spread of tissue damage [19].

THE AIM OF THIS SURVEY

The aim of this survey was to evaluate the alternations at the biochemical parameters, such as: CRP, D-dimers and LDH levels, as important markers in a group of patients diagnosed with COVID 19 in the Polog region.

MATERIAL AND METHODS

This study was conducted in the period between March-April 2020. During this study were analyzed the clinical results of 118 adult patients with a mean age of 64.3 years old, of which 69 were male patients and 49 were female patients, whose blood samples were tasted at the Laboratory of Clinic Hospital in Tetovo. Diagnosis of SARS-CoV-2 infection was confirmed by PCR (RT-PCR) test on the throat or nasopharyngeal swab. The patients included in the study belong to both genders and various age groups.

Serum CRP assays were analyzed by turbidimetric method, whereas LDH was determined by enzymatic method in Dimension RXL apparatus. In other hand D-dimer levels were determined by the hemiluminescence method in the Immulite 2000 apparatus. The data obtained were distributed based on gender and specific marker determination and then

expressed in maximum, minimum and mean value, standard deviation, relative percentage and statistical significance. Values of $p < 0.05$ were obtained statistically reliable.

Table 1: Presentation of Reference Values of Biochemical Parameters: D-dimers, CRP and LDH Levels

Reference Values	
D - dimers	< 885 ngFeu/ml
CRP	< 3 mg/L
LDH	81-234 U/L

RESULTS

The study was performed on 118 patients, whose samples were collected according to the strict rules of anti-COVID measures. The average age of study participants was $64.3 (\pm 12.84)$ years old. From the total number of patients, 41.5% (49 patients) belong to the female gender and 58.4% (69 patients) belong to the male gender.

The distribution of patients taken in the study based on age is presented in figure no.1.

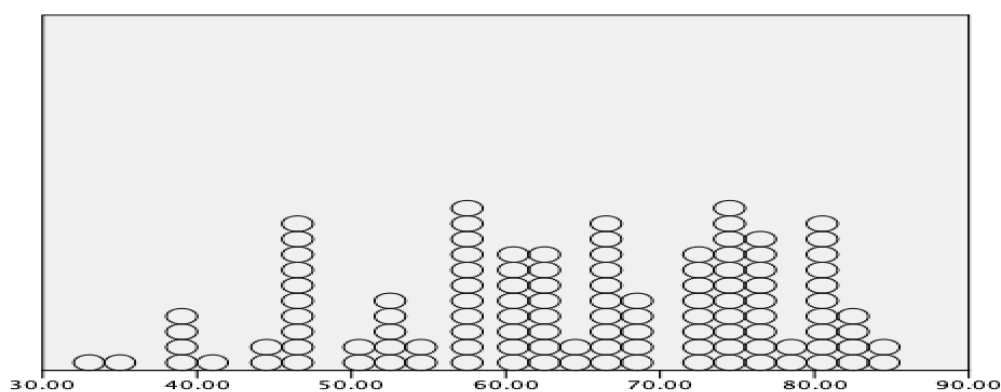


Figure 1: Distribution of Patients by Age.

The minimal age of patient was 33 years old, while the maximum age was 84 years old.

From the statistical processing of the parameters obtained in the study we obtained the following results.

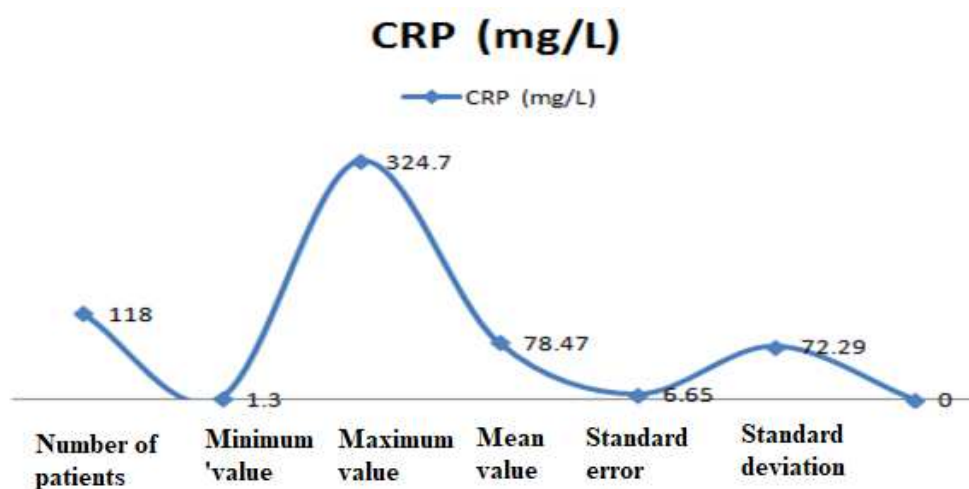


Figure 2: Descriptive Variable of C-Reactive Protein.

From figure 2 in which the data are presented after processing the CRP parameter, results that the mean value obtained in patients with COVID 19 was 78.47 (\pm 72.29). The minimum value encountered was within the limits of the reference values 1.3 mg / L, while the maximum value was 324.7 mg / L.

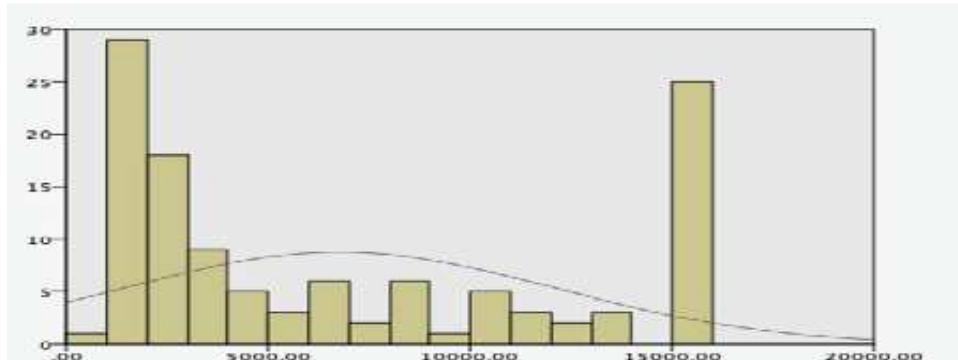


Figure 3: Distribution of D-Dimers Results Expressed in ng / mlFeu.

Significant alternations were presented in the values of the D-dimers analyzed in patients with COVID 19. In none of the patients taken in the study was found a normal value of this parameter. Values higher than 15000 ngFeu / ml were encountered in 21.18% of cases, while in 78.82% of cases the value of D-dimers were between 981 <15000 ngFeu / ml. The minimum value obtained in this study group was 981 ngFeu / ml, while the average was 6758.4 (\pm 5381.2).

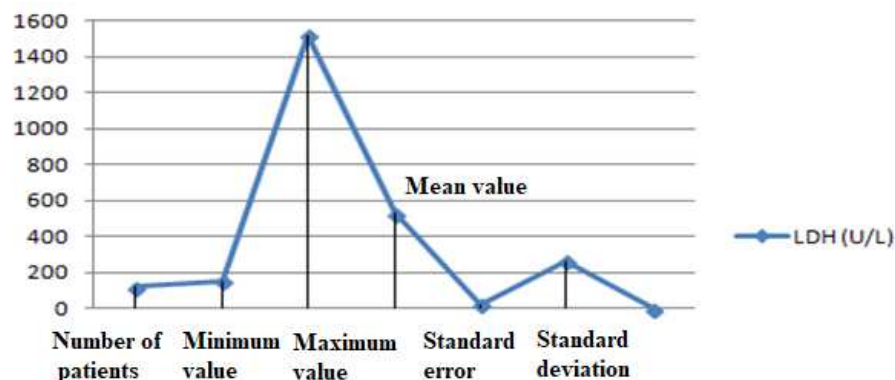


Figure 4: Graphic Presentation of LDH Values Obtained in Patients with COVID 19 Expressed in U / L.

From the statistical processing of the results obtained in patients with COVID 19 results that the average value of LDH was 529.33 (\pm 264.02). From the total number of patients, 9.32% have normal LDH values, while 90.68% have increased values of this parameter. The highest value encountered was 1365 U / L.

Table 2: Correlation between D-dimers, CRP and LDH Levels in Patients with Covid 19

		ddimeri	LDH
ddimeri	Pearson Correlation	1	.581**
	Sig. (1-tailed)		.000
	N	118	118
LDH	Pearson Correlation	.581**	1
	Sig. (1-tailed)	.000	
	N	118	118

		ddimeri	CRP
ddimeri	Pearson Correlation	1	.145
	Sig. (2-tailed)		.118
	N	118	118
CRP	Pearson Correlation	.145	1
	Sig. (2-tailed)	.118	
	N	118	118

		CRP	LDH
CRP	Pearson Correlation	1	.332**
	Sig. (2-tailed)		.000
	N	118	118
LDH	Pearson Correlation	.332**	1
	Sig. (2-tailed)	.000	
	N	118	118

From table number 2 it can be seen that there is a positive correlation with statistically reliable values between the parameters of D-dimers vs LDH level, and CRP vs LDH levels, while between the parameters D-dimers and CRP level there is a non-significant positive correlation, where $p = 0.118$.

DISCUSSION

D-dimers is a fibrin degradation product and its main use is in the diagnosis and management of thrombotic disorders. Prior to the COVID-19 pandemic, D-dimers was not considered a useful biomarker for bacterial or viral pneumonia although there is some evidence to the contrary [20]. Several studies have shown that D-dimers levels are associated with pneumonia severity and clinical outcome [21]. In a study conducted by Zhou et al. D-dimers levels higher than $1\mu\text{g} / \text{ml}$ ($2000 \text{ ng Feu} / \text{ml}$) are reported to pose a high risk of mortality [22].

Elevated CRP levels indicate more severe disease condition and this is associated with lung damage and poor prognosis. Elevated CRP values correlate with symptomatic severity in patients with COVID-19, and these increased values may be associated with overproduction of inflammatory cytokines that fight microbes. But when the immune system becomes hyperactive, it can damage lung tissue and thus stimulate the production of CRP by inflammatory cytokines and by tissue destruction in patients with COVID-19 [14].

LDH is an intracellular enzyme which is found in the cells of almost all organs [23]. Severe infections can cause cytokine-mediated tissue damage and LDH release [24], and since LDH is found in lung tissue, patients with severe COVID-19 infections may release amounts largest LDH in the blood [25].

Several studies have shown that elevated serum LDH values correlate with lung damage and disease severity [27] and respiratory failure [26] in patients with COVID-19, which coincides with the results obtained in our study.

CONCLUSION

Levels of biochemical parameters such as D-dimers, CRP and LDH levels are increased in patients infected with SARS-CoV-2 (2019) and these parameters can be used as important biomarkers which help healthcares to detect these patients in stages early, for adequate treatment, condition monitoring and prognosis.

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