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Determination of C-reactive protein concentration by the turbidimetric method in diagnostics of viral and bacterial infections

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ABSTRACT

During the flu season that can impair human health, it is difficult to determine whether a patient has a bacterial or viral infection. The C-Reactive Protein marker is one of the markers in laboratory diagnostics that shows inflammatory processes in the body. The purpose of this study was to prove that the CRP marker is an indicator of bacterial infections and that it is presented in higher concentration in patients with bacterial infection than in patients with a viral infection. Therefore it is helpful in the differentiating bacterial infections from viral infections.

Keywords: C-reactive protein, Inflammation, Bacterial infections, Viral infections, Infections

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1. Introduction

1.1. Inflammation

The body's response to injury or infection is inflammation. As a part of that response, the liver produces a substance called C-reactive protein (CRP) that is released into the bloodstream. Infectious diseases are a significant cause of death, injury and social and economic distress for millions of citizens around the globe. Poverty, inadequate access to health services, human displacement, evolving infections and antibiotic resistance all lead to the increasing severity of infectious diseases [1].

An inflammatory reaction is a defensive dynamic process of the organism. It is present in patients with viral, bacterial, fungal or parasitic infections. To initiate appropriate diagnosis as soon as possible and to avoid unnecessary antibiotic therapies, it would be helpful for the doctor to learn as soon as possible whether the infection is bacterial or viral.

1.2. Characteristics of C-reactive protein

CRP belongs to the family of pentameric proteins known as pentraxins. Its structure has been determined in 1996 by X-ray crystallography at 3 Å resolution **[2]**. The human CRP molecule is composed of five identical nonglycosylated polypeptide subunits, each containing 206 amino acid residues **[3]**. In the case of an acute process, such as trauma, plasma CRP concentrations rise within 6 hours, peak after 48 hours and CRP

concentration then decreases with a half-life of approximately 19 hours **[4]**. According to Štraus **[5],** the serum of healthy adults and adolescents contains less than 5 mg/L of CRP. The 10-50 mg/L concentration range of CRP is associated with moderate inflammation, such as local infection, surgery, deep vein thrombosis and most viral infections **[6]**. A concentration of CRP up to 100 mg/L is a condition that indicates the involvement of a higher degree of the inflammatory process **[7]**. Determination of CRP is a good laboratory analysis tool to distinguish bacterial from viral infections. CRP is determined by immunonephelometric, immunoturbidimetric, or radial immunodiffusion **[5]**.

1.3. Infections

Even today, despite the great advances in laboratory diagnostics and modern devices available, it is difficult to distinguish bacterial infection or sepsis from possible other non-infectious causes based on the clinical picture [8]. CRP has been used for a long time as a sensitive indicator of bacterial infection and many studies are underway to determine its effectiveness as a predictor of infection. Given that there is a lag in time i.e. the need to take some time from the beginning of infection to an increase in the value of CRP, this inflammatory marker is often used in combination with other biomarkers in the serum (leukocytes, fibrinogen, erythrocyte sedimentation rate, procalcitonin) [9]. Respiratory infections are the most common reason to visit a doctor and the main reason for prescribing antibiotics in the world. Primary health care and respiratory diseases are at the forefront of healthcare costs with an 18% share, with acute respiratory infections leading the way [10]. The most common bacterial agents of respiratory infections of the upper respiratory tract are *Streptococcus pneumoniae, Streptococcus pyogenes* (*beta-hemolytic streptococcus group A*, BHS-A), *Haemophilus influenzae* and *Moraxella catarrhalis* [11].

Furthermore, research from 2001 which included 30 patients out of which 15 had bacterial infections (*beta-hemolytic streptococcus group A*) and 15, viral infections (measles, rubella, rotavirus enteritis), proves that CRP values were highly increased in patients with bacterial infections compared to viral infections. In patients with bacterial infections, the differential index (DI) ranged from 3.9 to 50, while in viral infections, DI ranged from 0 to 0.9) [12].

The presence of viruses is obvious in the host organism when the virus is pathogenic, however, many healthy organisms are a host to non-pathogenic virus infections, and those viruses can be active or inactive. Viruses are agents of many diseases that affect humans, from the common cold to those diseases that can be lethal (e.g. rabies) [13]. Although bacteria [14], as well as fungi [15] can cause acute respiratory infections (ARIs), the most common cause of those are respiratory viruses (rhinoviruses, coronaviruses, parainfluenza viruses, influenza viruses, adenoviruses, human metapneumovirus and respiratory syncytial) are responsible for more than 85% of all infections [16]. Research in 2013 [17] uses C-reactive protein as a predictor of bacterial infection among patients with an influenza-like illness. They prove that C-reactive protein (CRP) levels among patients with influenza-like illnesses diagnosed with a bacterial infection will be higher than patients diagnosed with influenza or other viral infection.

Researchers that compare bacterial and viral infections in an acute phase by measuring inflammatory markers including C reactive-protein (CRP), serum amyloid A (SAA), and 2'-5'-oligoadenylate synthetase (2-5A synthetase) concluded that in the acute phase of bacterial infections, CRP values were highly increased while 2-5A were normal. In a viral infection, CRP values were normal or slightly increased compared to the 2-5A synthetase where levels were increased. Also, they concluded that CRP values and SAA paralleled each other [12].

A study from 2007 [18] shows that CRP values during respiratory virus infections, including co-infection with multiple viruses, did not increase significantly. However, when an individually analyzed respiratory virus (RV), during specific RV infections, a significant increase in CRP level was observed with more prominent increases in elderly patients (61.9%, 2,855 of 4,610 cases).

Previous studies [19] have shown that, if not treated, influenza virus infections can increase susceptibility to secondary bacterial infections, such as pneumococcal pneumonia. Also, several different studies have shown

that the respiratory syncytial virus (RSV) induces the attachment of *S. pneumoniae*, *Pseudomonas aeruginosa* and *Haemophilus influenzae* to respiratory epithelial cells which can cause lung diseases [20] [21].
Furthermore, adenovirus and rhinovirus have also been shown to promote adhesion of *S. pneumoniae* to the airway epithelium [22].
A 2004 study [23] shows that moderately elevated CRP (10–60 m /l) is a common finding in upper respiratory tract infection (influenza A, influenza B, rhinovirus, and other agents) and cannot support a diagnosis of bacterial infection when the disease lasts less than seven days. However, after a week, certain values can suggest a viral infection complication.

2. Materials and methods

The inclusion of the subjects in this research was made based on the medical history taken by the doctor at the patient's arrival at the Polyclinic Atrijum, located in Džemala Bijedića St 185, Sarajevo, Bosnia and Herzegovina.
After taking the anamnesis and examination, as well as a certain diagnosis determined by an independent and randomly selected physician who is not actively participating in this study, based on symptoms suggestive of bacterial or viral infection, further laboratory tests were suggested, including a marker C reactive protein.

2.1. Demographic characteristics of patients

The study included 60 patients (female and male) who came to do their laboratory analysis in Polyclinic Atrijum. The serum CRP concentration was determined in 60 subjects divided into three groups:

- Group I - Patients with a bacterial infection
- Group II - Patients with a viral infection
- Group III - Control group of subjects

30 respondents were female and 30 males, and the inclusion of the subjects in the research was made based on the medical history taken by the doctor at the patient's arrival at the Polyclinic Atrijum.

Group I consists of patients who have sought out a physician after the onset of the first symptoms of bacterial inflammation (body temperature was 38°C or above, patients often feel languor, muscle pain, sore and painful throat, swelling, redness, chest pain, headache, sore throat with purulent deposits, etc.). After a physical examination by a physician, laboratory tests, with the focus on CRP examination were induced and antibiotic therapy (for high CRP values) was initiated. After the antibiotic therapy (7-12 days), patients returned for a follow-up examination and were re-tested for CRP.

Group II consists of patients who have sought out a physician after experienced symptoms of viral infection (mild fever, nasal congestion, red pharynx with exudate, cough, mild cough, enlarged lymph nodes, sore throat). After a physical examination by a physician, laboratory determination of the CRP concentration was prescribed and symptomatic therapy was performed according to the obtained values (medicines against fever and pain, nasal congestion, sore throat or mild dry cough, vitamin C, various vitamins and mineral supplements, zinc).

Group III consists of patients who came to the Polyclinic Atrijum for preventative checkups. Part of the arrivals was due to a legal obligation that requires every employee to undergo a systematic review once a year. While another part of the patients come on their own initiative.
Individuals who went through a routine check-up by an internist, were those who needed systematic preventive checkups to assess their ability to do work-related tasks. Subsequently, those patients were examined using electrocardiography, abdominal ultrasound, ultrasound of the thyroid gland and laboratory analyses

(Sedimentation, CBC, RBC, ALT, AST, tPSA, PSA, HDL, LDL, K, Mg, Na, Trig, TSH and CRP). This group consists of completely healthy subjects with no symptoms of inflammation.

The use of antibiotics without medical guidelines is inappropriate because the use of unnecessary and inaccurate drugs and the wrong doses of the same and inappropriate duration of therapy increases the risk of developing resistant bacteria. Moreover, it can affect the first sample in bacterial infection cases of the CRP marker. Accordingly, patients who used antibiotic therapy before coming to the Polyclinic Atrijum were excluded from the study.

2.2. Blood sampling and preparation

Patient samples were taken in a standard way to collect samples for biochemical analysis and treatment. Blood from the cubital vein was used as the sample for analysis. Using separator gel tubes and centrifuging (3500 rpm for 15 min) these samples yielded transparent serum samples that were used for analysis on automatic analyzers. Interferences in serum samples such as hemolysis, lipemia, or ictericity were not used for analysis because they would give inadequate results.

2.3. Analytical methods

C-reactive protein was determined in serum by a quantitative, highly sensitive immunoturbidimetric method on a Mindray BS 480 analyzer. The principle of the method is based on the formation of a complex between specific antibodies bound to latex particles, which is in suspension in the reagent and human CRP in the serum sample. The resulting content of insoluble aggregates, measured spectrophotometrically at a wavelength of 340 nm, is proportional to the concentration of CRP in the serum tested. The measuring range of the method is 0-300 mg/L. This means that the lower limit of detection (lowest measurable concentration) is 0 mg/L and the linearity is up to 300 mg/L.

2.4. Statistical Analyses

The preparation and storage of data for statistical analysis were done in Excel (Microsoft). The software package used when processing the data is IBM-SPSS Statistics 20.0. The following statistical procedures were used:

1. Descriptive statistics for calculating mean, median, and standard deviation.
2. Kolmogorov-Smirnov and Shapiro-Wilk test for normality of distributions.
3. Mann-Whitney U for examining statistically significant differences between study groups.
4. Spearman's coefficient for correlation testing.

3. Results and discussion

3.1. Control of the precision and specificity of the test

Prior to the start of the research, quality control for the CRP biochemical marker was established. Ten control serums were administered for Control Normal and Control Pathological. The results of the control are shown in Table 1.

Table 1. The accuracy of determination method for CRP

CRP	Control Normal	Control Pathological
$\acute{X}$ (mg/L)	2.,56	37.,6
SD	0.,085	1.,091
CV %	3.,32	2.,90

The mean control value for CRP was 2.56 mg/L for control normal serum and 37.6 mg/L for control pathological (Table 1). The precision of the method itself is significant since the coefficient of variation is in the range of 2.90% to 3.32%.

Fig. 1 and Fig. 2 show Levey-Jennings control charts for our CRP value of controls. All controls were in the range of 2 standard deviations (2 SD), which implies that the methods were reliable.

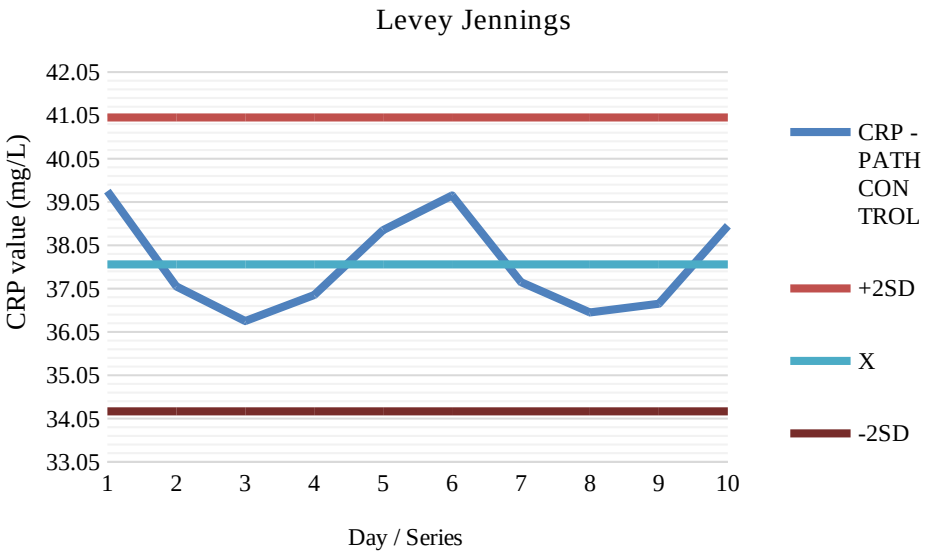

Figure 1. Levey-Jennings Control Card for the CRP – Normal Control

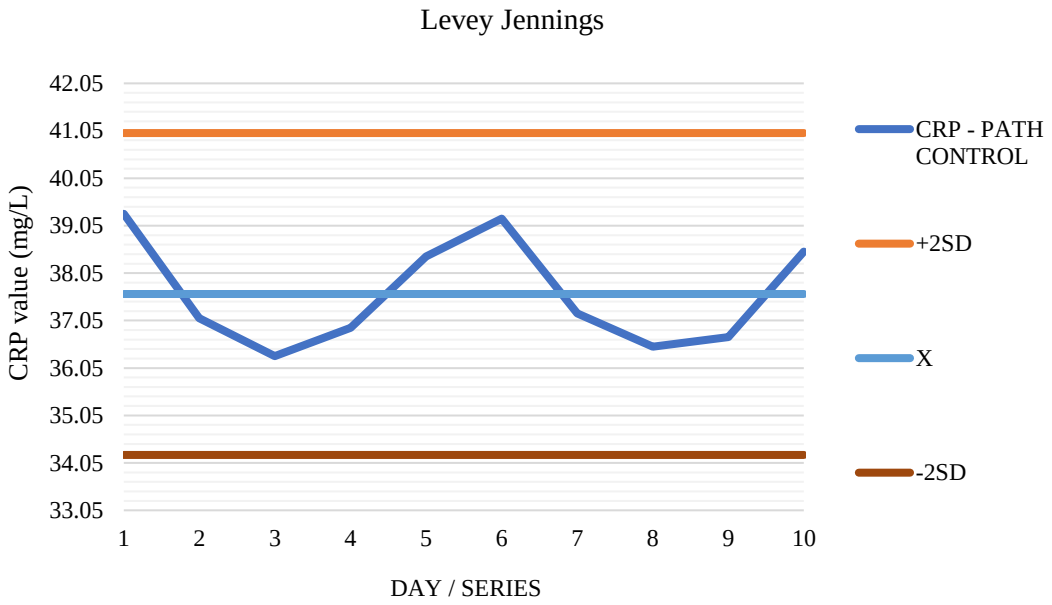

Figure 2. Levey-Jennings Control Card for CRP – Pathological Control

3.2. Descriptive statistics for calculating mean, median, and standard deviation

For subjects with higher value of the CRP marker (Group I), two measurements were performed: upon arrival at the Polyclinic Atrijum and on their second arrival after using the prescribed antibiotics, which were for 7-10 days. Group I subjects included a total of 20 patients, of which 10 were male and 10 were female. The study

showed that the mean age of the subjects in the first group of patients with bacterial infection was 43.85. The youngest respondent was 14 years old, while the oldest was 79 (Table 2).

The mean CRP before taking therapy was 73.63, while the lowest CRP before taking therapy was 12.50 and the highest was 167.20. The mean value for days of treatment in subjects with bacterial infection is 9.15, while the minimum value was 7.00. The maximum value for days of therapy is 10 days. Mean CRP of subjects with bacterial infection after therapy was 5.97. The minimum CRP value of subjects with bacterial infection after therapy was 1.37, while the maximum value was 14.00 (Table 2, Fig. 3). A significant difference between the values of CRP markers upon arrival of patients in the clinic and after taking antibiotic therapy was observed. CRP marker values before taking therapy are significantly higher.

Table 2. Group I - Patients with a bacterial infection

BACTERIAL INFECTION						
	No	Mean	Min	Max	Median	SD
Age	20.00	43.85	14.00	79.00	46.50	19.34
Male	10.00	47.25	19.00	79.00	49.50	22.42
Female	10.00	41.58	14.00	67.00	41.50	17.67
TD	20.00	9.15	7.00	10.00	10.00	1.35
CRP $_1$	20.00	73.63	12.50	167.20	52.10	49.08
CRP $_2$	20.00	5.97	1.37	14.00	6.45	3.55

No-Number of patients; SD – Standard deviations; TD-Therapy Duration; CRP1-Before therapy; CRP2-After therapy

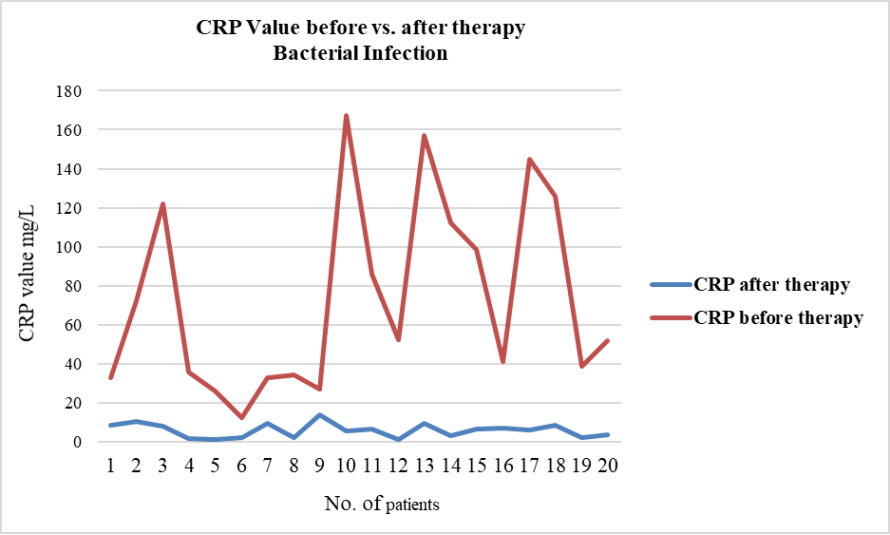

Figure 3. Graphical representation of CRP value in Group I before and after therapy

Table 3 refers to Group II that included 20 total patients, of which 10 were male and 10 were female. The mean age of the subjects was 43.25, while the youngest patient was 14 years old and the oldest was 71. The mean value of CRP was 10.34, with a minimum value of 5.64. and the maximum value of 16.20. The standard deviation for CRP in the second group of subjects was 3.03 (Table 3). Fig. 4 graphically represents CRP values for Group II.

Table 3. Group II - Patients with viral infections

VIRAL INFECTION						
	No	Mean	Min	Max	Median	SD
Age	20.00	43.25	14.00	71.00	42.50	17.92
Male	10.00	45.80	18.00	69.00	44.00	18.72
Female	10.00	40.70	14.00	71.00	43.00	17.68
CRP	20.00	10.34	5.64	16.20	10.70	3.03

No-Number of patients; SD-Standard deviations

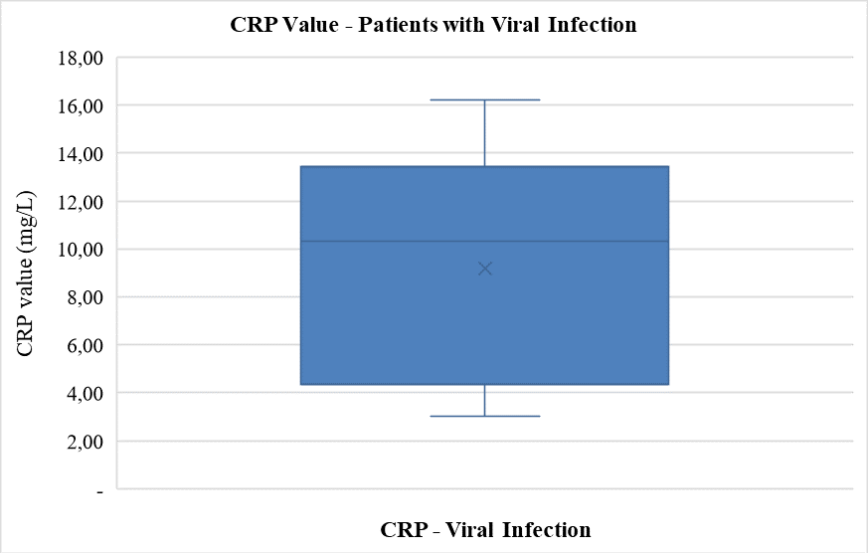

Figure 4. Graphical representation of CRP value in Group II

The third group (Table 4, Fig.5) consists of healthy, asymptomatic subjects (control group) which included 20 total patients, of which 10 were female and 10, male. The mean age of the subjects in the control group was 43.45, while the youngest was 14 years old and the oldest was 64. CRP Concentration mean value was 1.16, with a minimum value of 0.08 and a maximum value of 3.82. The standard deviation for CRP in the third group of subjects was 1.14.

According to the results of our research, it has been shown that the CRP value in healthy subjects or control group is significantly lower compared to bacterial infection.

An early study from 2013 also has established that CRP mean values in healthy patients compared to patients with bacterial infections were noted to be decreasing [24].

Table 4. Group III – Healthy patients

CONTROL GROUP						
	No	Mean	Min	Max	Median	SD
Age	20.00	43.45	18.00	64.00	42.50	13.66
Male	10.00	42.10	18.00	58.00	44.00	11.33
Female	10.00	44.80	18.00	64.00	41.00	16.17
CRP	20.00	1.16	0.08	3.82	0.85	1.14

No-Number of patients; SD-Standard deviation

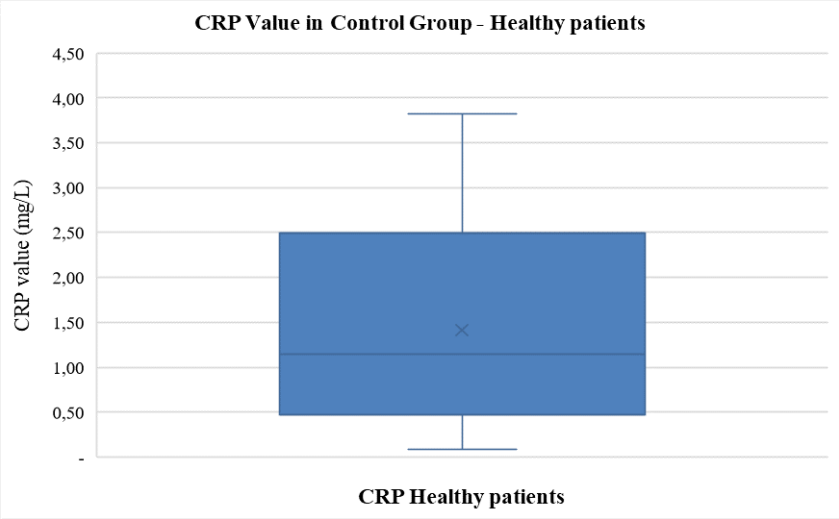

Figure 5. Graphical representation of CRP value in Group III

In many previous studies, it has been firmly established that determining the serum concentration of C-reactive protein (CRP) is a quick, simple, and inexpensive procedure for evaluating treatment progression [25] [26] [27]. Fig. 6 graphically represents the differences between mean values in all three groups.

The mean value of the CRP parameter tested was found to be highest in Group I – Patients with bacterial infection (mean 73.63 mg/L). The mean of the CRP test parameter was also higher in subjects with Group II – Patients with a viral infection (mean 10.34 mg/L), while the mean value of the CRP test parameter was lowest in Group III – Control Group with the concentration of 1.16 mg/L.

Research by Hansson, *et al*. [28] compared sera of erythrocyte sedimentation rate (ESR) and CRP in 607 patients, and concluded that both sera were comparably increased in patients that had upper respiratory tract infections. They concluded that CRP patients were more elevated than ESR in infectious diseases (tonsillitis, sinusitis, pneumonia, and cystitis). A similarity can be observed when comparing conducted analysis with patients having a bacterial infection.

Also, research from 2018 [29] showed that there are differences in laboratory findings between patients with chronic obstructive pulmonary disease (COPD), pneumonia and patients with exacerbations. In this study, higher values of C-reactive protein (CRP), procalcitonin (PCT), TNF-α were found in pneumonia, as well as interleukin (IL-6, IL-1, and IL-8) and lower values of the partial pressure of oxygen (PaO_2), while in patients with exacerbations higher values of the partial pressure of carbon dioxide ($PaCO_2$) were found.

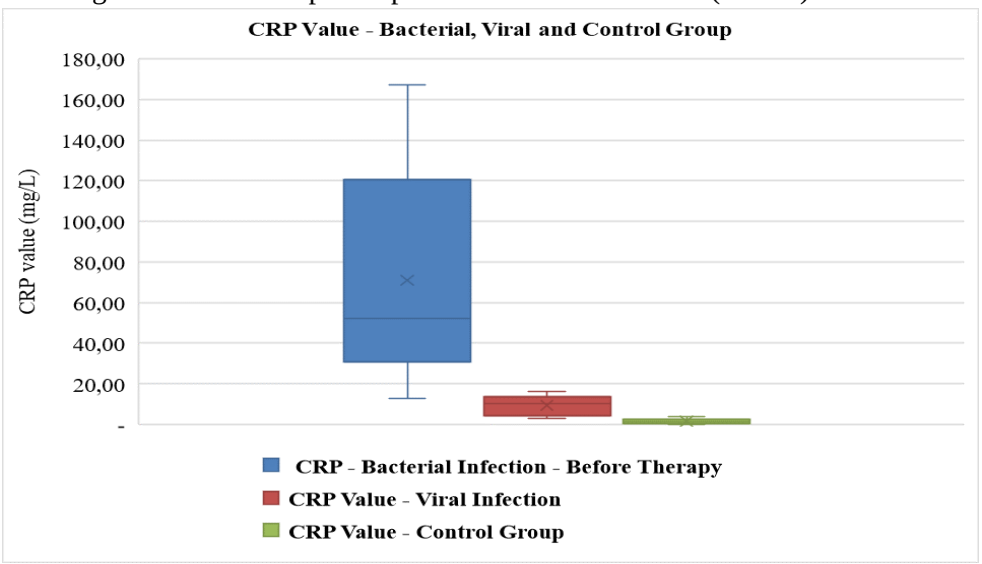

Figure 6. Graphical representation of CRP value in all three groups

3.3. Kolmogorov-Smirnov and Shapiro-Wilk test for normality of distributions

To test the differences between used parameters, the normality of the distributions of the results obtained with three parameters was checked. This was done by applying the Kolmogorov-Smirnov test and the Shapiro-Wilk test. If statistical significance is presented, we conclude that the distribution of results is statistically significantly different from the normal distribution, in which case the use of non-parametric statistics is applied. Table 5 represents the test of normality for three parameters. Figure 7 is a histogram for CRP value in the control group – healthy patients. It shows that the value of CRP was not normally distributed because values of Skewness and Kurtosis tests are not close to zero. Parameter values are presented on the abscissa, while frequency values are presented on the ordinate.

Figure 8 depicts the histogram of CRP values in patients with viral infection. It shows that the value of CRP was not normally distributed because values of Skewness and Kurtosis are not close to zero. Parameter values are presented on the abscissa, while frequency values are presented on the ordinate.

Figure 9 shows the histogram of CRP value in patients with a bacterial infection. It shows that the value of CRP was not normally distributed because values of Skewness and Kurtosis are not close to zero. Parameter values are presented on the abscissa, while frequency values are presented on the ordinate.

Table 5. Test of normality

TEST OF NORMALITY						
Groups	**Kolmogorov-Smirnov[a]**			**Shapiro-Wilk**		
	Statistic	df	Sig.	Statistic	df	Sig.
CRP Control group	.192	20	.051	.851	20	.006
CRP Bacterial Infection	.219	20	.013	.886	20	.022
CRP Viral Infection	.137	20	.200*	.963	20	.603
*. This is a lower bound of the true significance.						
a. Lilliefors Significance Correction						

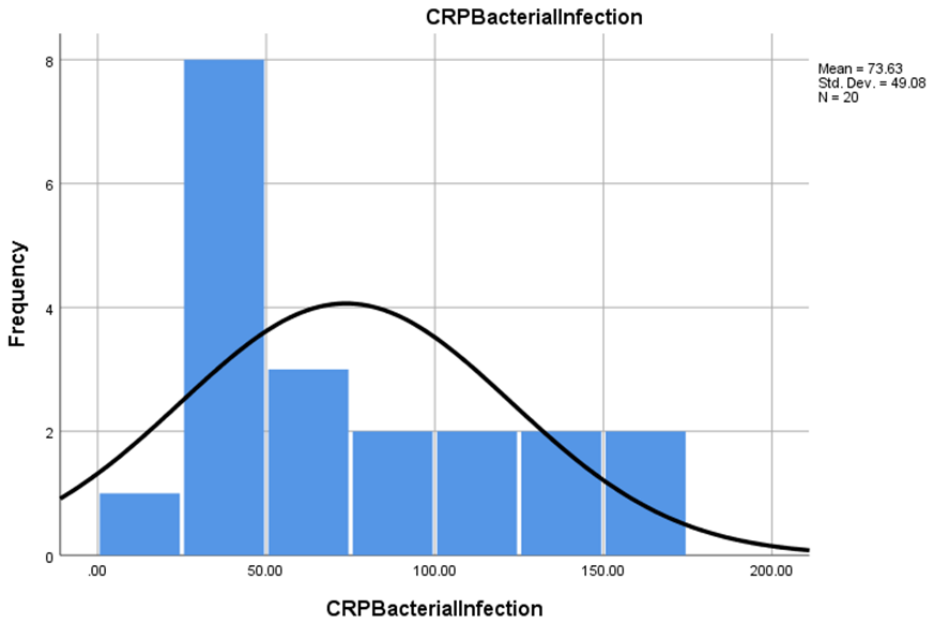

Figure 7. Histogram of CRP value in the Group I-Bacterial infection

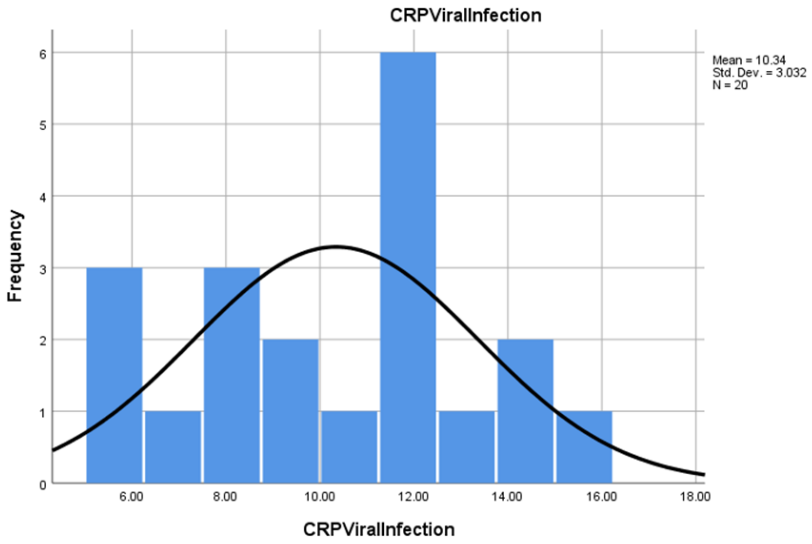

Figure 8. Histogram of CRP value in Group II-Viral infection

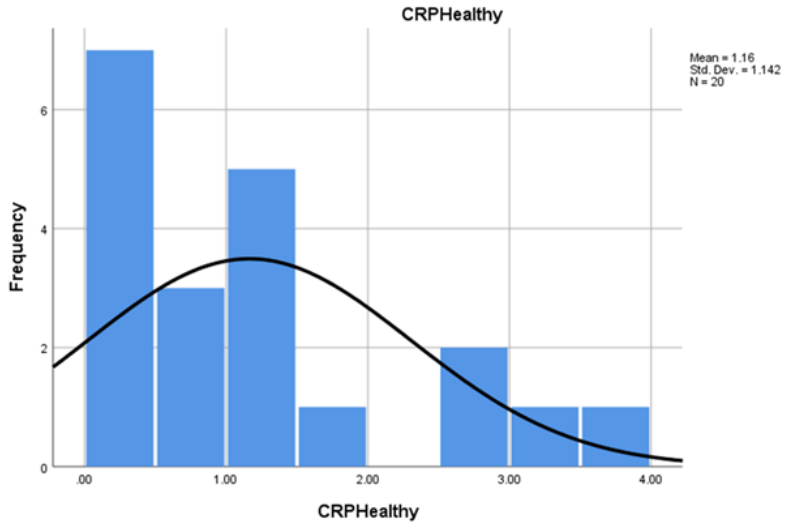

Figure 9. Histogram of CRP value in Group III-Control group

3.4. Mann-Whitney U test for examining statistically significant differences between study groups

Mann-Whitney U test represented in Table 7 shows that there was a statistically significant difference in the value of CRP values between the patients with bacterial infection and patients with viral infection ($p<0.001$) with a mean rank of CRP value of 30.30 for the patient with bacterial infection and 10.70 for the patients with the viral infection.

Research from 2013 [24] and a report from 2004 [25] are consistent with these findings and suggest that there is a certain relationship between the level of infection and the concentration of serum CRP.

Örtqvist *et al.* [30] and, Almirall *et al.* [25] strongly supported these findings as well. In research from 1995, it was shown that bacterial pneumonia in laboratory findings gives a high IL-6 (Interleukin-6), and also a higher value of CRP marker. According to this research, the level of IL-6 and CRP markers represents a promising diagnostic tool in the laboratory when used in differentiating and diagnosis of lung diseases. Furthermore, in the research from 2004, researchers studied the usefulness of C-reactive protein as a marker in laboratory diagnostics and concluded that CRP could be an additional support to physicians in diagnosing lung disease or other bacterial infections [25].

In a study by Meisner *et al.* [31] it has been shown that in the diagnosis of severe pneumonia, CRP values greater than 50.0 mg/L show high sensitivity and low specificity, while CRP values greater than 100 mg/L show a sensitivity of 86% and a specificity of 33%.

Table 6. Test of statistics for parameters in viral infection and bacterial infection

	Group	N	Mean	SD	SD Error
CRP	**Viral Infection**	20	10.3405	3.03172	0.67791
	Bacterial Infection	20	73.6330	49.07988	10.97460

N-Number of patients; SD-Standard deviation; SD Error-Standard deviation error mean

Table 7. Test of ranks in bacterial and viral infections

RANKS				
	Group	**N**	**Mean Rank**	**Sum of Ranks**
CRP	**Viral Infection**	20	10.70	214.00
	Bacterial Infection	20	30.30	606.00
	Total	40		

Table 8. Statistical test

Mann-Whitney U	4.000
Wilcoxon W	214.000
Z	-5.303
Asymp. Sig. (2-tailed)	.000
Exact Sig. [2*(1-tailed Sig.)]	.000[b]
a. Grouping Variable: Group	
b. Not corrected for ties.	

After examining the normality of the distribution of the three parameters measured in the subjects, it could be concluded that there is no evidence to support the normal distribution of parameters.
Due to these results, correlations shown in Table 6 for the two parameters used (bacterial and viral infection) were made. According to the previous tests, in Table 8 the parameter difference between the two groups of subjects (CRP value in patients with bacterial and viral infection) with Mann-Whitney U tests was examined.

3.5. Spearman's coefficient for correlation testing

To verify differences between CRP value of patients with bacterial infection and patients with a viral infection, Spearman's coefficient test was applied (Table 9). Results show low positive correlations between CRP value of patients with a bacterial infection and viral infection. The correlation between those two parameters was not statistically significant (r=0.060, p=0.801).

Baig *et al.* [24] included 162 patients with symptoms of bacterial infection and 30 healthy patients, prove that patients with bacterial pneumonia had significantly higher CRP markers (76.50 ± 11.60 to 101.25 ± 15.65 mg/L) than in patients who had a viral infection (60.45 ± 9.10 mg/L) or another pathogen in their body (65.15 ± 12.25

mg/L) that was the cause of the disease. This work has significantly contributed to researchers in discovering how important a CRP marker is in diagnosing respiratory infections.

Research in 2013, conducted by J.P. Haran *et al.* in which 131 patients were included, and divided into three groups comprising patients with influenza, patients with other viral infections, and patients with bacterial infections significantly proved that the CRP marker can help in differentiating bacterial from viral infections. This study showed that the CRP marker in the group of subjects with influenza was 25.65 mg/L, the height of the CRP marker in patients with viral infections was 18.73 mg/L and for bacterial infection, it was significantly higher value 135.96 mg/L. From above mentioned results we can conclude that values of the CRP marker were similar with patients having viral infection and influenza, but also that CRP value in patients with bacterial infection was significantly higher. This research proved once again that the CRP marker is very important in the differentiation of the diseases in patients, especially when during the influenza season [17].

Table 9. Correlations

			CRP - Bacterial Infection	**CRP - Viral Infection**
Spearman's rho	**CRP - Bacterial Infection**	**Correlation Coefficient**	1.000	.060
		Sig. (2-tailed)	.	.801
		N	20	20
	CRP - Viral Infection	**Correlation Coefficient**	.060	1.000
		Sig. (2-tailed)	.801	.
		N	20	20

N=Number of patients

4. Conclusion

Biomarkers have an important and indispensable place in the laboratory diagnosis of many diseases, especially infections. They help differentiate bacterial from viral or fungal infection and contribute to an objective assessment of the severity of the disease, such as distinguishing sepsis from a milder local infection. Despite great advances in laboratory diagnostics and modern devices, it is difficult to distinguish bacterial infection or sepsis from possible other non-infectious causes of systemic inflammatory response syndrome (SIRS) based on the clinical picture [8].

C-reactive protein (CRP) is an acute-phase reactant, a protein produced in the liver triggered by inflammatory cytokines in a variety of clinical conditions, such as infection, inflammation, ischemia and injury. It owes its name to the fact that it reacts with the C-polysaccharide of the cell wall of the bacterium *Streptococcus pneumonia* [32]. Due to the simple determination of serum concentrations, the best clinical and epidemiological correlation and the differentiation currently used to define infections, CRP is a special marker that allows the discovery of new ways to prevent and treat many common diseases and reduce motility and mortality. That was the reason for choosing it in this study.

According to the results of our research, it has been shown that the CRP value in healthy subjects or those with viral infection is significantly lower compared to those with bacterial infections which is in the line with the previous research conducted in this area [24], [28], [33].

In summary, our results suggest that CRP marker is a very effective and specific marker that could aid in distinguishing bacterial from viral infection in patients. CRP marker potentially can be useful to reduce the usage of unnecessary antibiotic therapies as well it can prevent misdiagnosis of bacterial infection when a viral infection is present.

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