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Correlation of C-Reactive Protein and Erythrocyte Sedimentation Rate in Covid-19 Cases

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

In December 2019, a mysterious pneumonia case was first reported in Wuhan, Hubei Province known as COVID-19, and its etiologic agent, SARS-Cov-2 virus. C-Reactive Protein (CRP) is a homopentameric protein that appears in inflammatory conditions. Erythrocyte sedimentation rate (ESR) increases in both acute and chronic inflammations. This study aimed to determine the correlation between CRP and ESR concentrations with the status of PCR diagnostic test results in patients. It was a correlation study with a cross-sectional approach. The data was taken from results from the first PCR and laboratory examination of the patients for COVID-19. The population of this study was patients under monitoring (PDP) for COVID-19 who were treated at a hospital in East Bekasi, West Java. The sample for this study was 65 people, consisting of 28 (43.1%)

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negative COVID-19 patients and 37 (56.9%) positive COVID-19 patients. The results showed that at the start of the PCR test for COVID-19, there was a weakly significant increase in CRP (r=0.311), and there was a significant relationship between the COVID-19 PCR results and the patient's CRP levels (p=0.040) in the age group 1-40 years. In addition, there was an increase in the respiratory rate in patients with high CRP with a weak significance (r=0.366), and a significant relationship between the CRP test results and the patients' respiratory rate (p=0.026). In addition, there was a strong relationship between CRP increase and LED increase (p=0.000).

Keywords: COVID-19; SARS-CoV-2; CRP; LED; respiratory frequency.

1. INTRODUCTION

In December 2019, a mysterious pneumonia case was first reported in Wuhan, Hubei Province. The source of infection for this case is not yet known, but the first case is suspected to be related to a fish market in Wuhan [1]. Researchers from the Institute of Virology in Wuhan conducted a metagenomic analysis to identify the etiology of the pneumonia incident, which was finally identified as a strain from the coronaviridae family; they called it nCoV-2019 [2]. On 11 February 2020, WHO announced the official name of the disease and virus causing the current pandemic with the disease COVID-19 along with the new etiological name, SARS-Cov-2 [3]. The SARS-Cov-2 virus belongs to the betacoronavirus genus. The results of the phylogenetic analysis shows that this virus belongs to the same subgenus as the coronavirus that caused the SARS outbreak in 2002- 2004, namely Sarbecovirus. The spread of SARS-CoV-2 between humans through droplets that comes out during coughing or sneezing is the main source of transmission that makes this virus very infectious [3]. Case fatality in COVID-19 patients is very high in critically ill patients with severe pneumonia [4].

C-Reactive Protein is a homopentameric protein that appears in inflammatory conditions. It was discovered in 1930 by Tillet and Francis, who studied sera from patients with acute pneumococcal infections. This protein is named based on its reaction with the capsule (C)-polysaccharide of Pneumococcus [5,6]. C-Reactive Protein levels are increased in inflammatory conditions such as rheumatoid arthritis, cardiovascular disease, and infections. As a protein that occurs in acute conditions, its concentration in plasma can increase by at least 25% of its normal level during inflammation [7]. Viral infections can increase CRP concentrations but are not as high as bacterial infections. Substantively elevated CRP values are frequently found in patients with pneumonia, and high CRP levels are a strong predictor of disease in general practice [8].

Erythrocyte sedimentation rate is an examination method developed by R. S. Fåhræus and A.V.A. Westergren in 1921 [9]. This method is widely used as a benchmark for analyzing laboratory results of disease activity in clinical medicine, especially for inflammation-related diseases [10]. In acute, chronic inflammation, malignancy, and necrosis or tissue infarction, there will be an increase in plasma proteins which causes red blood cells to tend to stick to one another. It will increase the weight of the red blood cells and precipitate faster so that the value of the ESR will increase [11]. Knowing this, researchers wanted to know the correlation between CRP and ESR in patients with COVID-19 infection and if CRP and ESR examinations are good for screening tests for COVID-19 disease. The formulation of the problem in this study is "What is the profile and correlation between the results of the CRP examination and the results of the status of the COVID-19 PCR diagnostic examination? The aim of the research, is to determine the etiology, pathophysiology, and clinical manifestations of COVID-19 and their effect on CRP and ESR examinations.

2. LITERATURE REVIEW

Coronavirus is a single-enveloped RNA virus belonging to the subfamily Orthocoronavirinae which has a "crown-like" characteristic in the form of sharp protrusions on its surface [12]. It is an RNA virus with the largest genome material, around 26.4 – 31.7 kb, accompanied by guanine-cytosine bonds (G-C Content) as much as 32% - 43%. Most coronaviruses have 6 ORFs in one conserved gene (ORF1ab, spike, capsule, membrane, and nucleocapsid). The genome of the coronavirus structural proteins is arranged with directionality in the form of 5' – 3' consisting of S, E, M, and N. [13] The four main proteins of this virus are Spike (S), Membrane (M), Envelope (E) and Nucleocapsid (N). Encoded by

ORFs 10 and 11. Apart from the four main proteins, some CoVs also encode special structural and accessory proteins such as Hemagglutinin-esterase (HE), 3a/b protein, and 4a/b protein. All of these proteins have important responsibilities for viral replication and survival. Genotypically and serotypically, coronaviruses can be divided into four subfamilies, including α, β, γ, and δ-CoVs. Infection in humans is caused by α- and β-CoVs [12]. The SARS-CoV and MERS-CoV viruses belong to the β-CoVs subfamily [12]. From a phylogenetic examination of the ORF1ab (RNA-dependent RNA polymerase) protein sequence, a 90% similarity was found between the SARS-CoV-2 virus and other SARS-CoV, and 90% sequence similarity with other β-CoV viruses. This theory explains that the SARS-CoV-2 virus belongs to the Sarbecovirus subgenus of the β-CoV subfamily [14]. SARS-CoV, MERS-CoV, and 2019-nCoV can cause human disease but have slightly different biological characteristics and virulence [14].

Research conducted by Benevuto et al. proved that SARS-CoV-2 has a similar genome sequence to a coronavirus isolated from a chrysanthemum bat in 2015. Their research supports the statement that COVID-19 is a zoonosis with the transmission of infection from bats to humans [14]. Apart from being zoonotic, COVID-19 infection can also be transmitted through droplets from patients who are positively infected with SARS-CoV-2. Spreading through fellow humans through droplets that come out when coughing or sneezing is the main source of transmission that makes this virus very infectious [1]. Recent studies have also proven that SARS-CoV-2 can be detected in infected patients' urine and feces, indicating a risk of fecal-oral transmission. However, it is not yet certain whether food contaminated with the virus can be a transmission route. Apart from transmitting the virus through droplets between humans directly, the spread of the SARS-CoV-2 virus can also be through objects exposed to the virus. If an object is exposed to the virus, and someone comes in contact with the object and touches the nose, eyes, or mouth, then that can be a route of transmission of the COVID-19 disease [15]. The stability of SARS-CoV-2 in inanimate objects is not much different from that of SARS-CoV. Experiments conducted by van Doremalen et al. showed that SARSCoV-2 was more stable on plastic and stainless steel (>72 hours) than on copper (4 hours) and cardboard (24 hours) [1].

Transmission of the SARS-CoV-2 virus can be through zoonotic routes and human contact [15]. If someone inhales a virus particle, the virus will bind to its receptor, namely ACE2, which is a functional receptor that SARS-CoV-2 binds for virus penetration into cells, similar to SARS-CoV, but ACE2's affinity for SARS-CoV- 2 10-20 times higher than SARS-CoV [16]. Human angiotensin-converting-enzyme-2 is a type I membrane protein that crosses the membrane only once (single transmembrane), with enzymatically active sites present on the surface of cells in the lung and other tissues [17]. According to a study by Yuan Li et al., who examined GTEx on human tissue, ACE2 had high concentrations in the small intestine, testes, kidney, heart, thyroid, and adipose tissue. It proves that there is a possibility that COVID-19 does not only attack the respiratory system [18]. The Cryo-EM structure owned by the viral S protein will become a ligand of its receptor on ACE2, then fusion of the virus will occur into the cell through the plasma membrane [19]. After the virus enters the host cell, the RNA genome of the virus will be released and enter the cytoplasm of the cell. The viral RNA will translate from the large ORF codes, rep1a, and rep1b, which are then translated into two polyproteins (pp1a and pp1ab) and structural proteins [20].

PP1a polyprotein contains nsp 1-11, and pp1b contains nsp 1-16. Each polyprotein will be cut into individual nsp by protease enzymes, namely PLpro, coded from nsp3, and Mpro, coded from nsp5. Then, these nsp will gather in the replicase-transcriptase complex to create a suitable environment for the replication and synthesis of new RNA and help in the virus's resistance against the immune system [21]. Newly synthesized structural glycoproteins (M, S, N, and E) penetrate the endoplasmic reticulum membranes and the Golgi apparatus [20]. This protein will travel along the ERGIC, a tubulovesicular membrane collection that becomes the bridge between the endoplasmic reticulum and the golgi [22]. At that location, the viral genome encapsulated by protein N (nucleoprotein) will develop and become a mature virion [21]. Primary viral replication occurs mostly in the epithelial tissue of the upper respiratory tract (nasal cavity and pharynx), with further multiplication in the lower respiratory tract and the gastrointestinal mucosa [23]. The lungs are particularly vulnerable to SARS-CoV-2 infection due to their large surface area, and it appears that type 2 epithelial cells in the lungs act as the best reservoir for viral replication [24].

When the virus enters the host cell, the antigen peptide from the virus will be presented by MHC class 1 on the surface of APC cells. APC cells are central to the body's immunity against viruses [20]. The respiratory system consists of three main components: epithelial cells, alveolar macrophages, and DCs. DC cells are under the epithelial cells, while macrophages are on the apical side of the epithelium. DC cells and macrophages function as innate immune cells to fight viruses until adaptive immunity is involved [25]. In addition, the function of APC is for antigen presentation, which will stimulate cellular and humoral immunity mediated by specific B and T cells against viruses [20].

Antigen-presenting cells can present viral antigens through several pathways, namely phagocytosis from epithelial cells that undergo apoptosis, and then they will be synthesized into peptide antigens, and viruses can infect APC directly. It is already known that the functional receptor of SARS-CoV-2 is ACE2 [24]. Based on data published in The Human Protein Atlas regarding the distribution of ACE2 in body tissues, there are ACE2 receptors in lymphatic tissue but in limited numbers [26]. This theory supports the possibility that SARS-CoV-2 could infect APCs directly.

Antigen-presenting cells that carry antigen particles will enter the lymph nodes and make non-covalent bonds between the ligands (antigens) and receptors on the surface of naive T cells, namely TcR [27]. The TcR receptor associates with either a CD4 or CD8 co-receptor, depending on the type of T cell. This molecule attaches to the MHC (class I for CD8 and class II for CD4) to stabilize the interaction between T cells and APCs [28]. T cells are active and work depending on the cell type. CD8+ cells are cytotoxic and can lyse virus-infected cells, while CD4+ T cells are often known as a T helper population because they proliferate productively and can induce the activation and maturation of B cells [29].

B cells activated by CD4+ T cells will produce IgG and IgM antibodies. The antibody profile against the SARS-CoV virus is similar to that of other acute viral infections. The SARS-specific IgM antibody disappeared within 12 weeks, whereas the SARS-specific IgG antibody persisted for a longer time, indicating IgG has a protective responsibility. [20] The functions of antibodies or often referred to as immunoglobulins in fighting infection include; (1) Neutralization of pathogens especially for viral infections, (2) Opsonization for phagocytosis of foreign bodies, (3) Activating the complement system by increasing chemotaxis. Apart from functioning as an immune reaction component, antibodies can also be biomarkers for diagnosing COVID-19 infection, especially for IgG and IgM [30].

It is believed that cytokines play an important role in the immunopathological process during viral infection. A rapid and well-coordinated innate immune response. However, if the immune response is irregular or excessive, it can exacerbate the infection [31]. Based on laboratory tests, it was found that most COVID-19 patients had lymphopenia and increased concentrations of biomarkers related to infection. There are conditions of neutrophilia and lymphopenia, which make the increase from a higher NLR found in severe COVID-19 sufferers compared to mild ones. The total concentration of B, T, and NK cells also significantly decreased. Based on the data, it is suspected that COVID-19 can attack lymphocytes, especially T lymphocytes, which causes the immune system to become dysregulated during illness [32]. A study conducted by Huang et al. concluded that patients infected with SARS-CoV-2 had increased concentrations of IL1B, IFNγ, IP10, and MCP1, which may be the cause of Th1 cell activation. Moreover, patients requiring ICU admission had increased concentrations of GCSF, IP10, MCP1, MIP1A, and TNFα, suggesting that increased stocks are related to the severity of COVID-19 patients. Increased concentrations of excessive proinflammatory cytokines create a cytokine storm condition in patients [12].

The cytokine storm can attract many inflammatory cells, such as neutrophils and monocytes, resulting in heavy infiltration of inflammatory cells in the lung tissue and causing fatal damage [31]. The most serious complication of cytokine storms is the occurrence of ARDS [33]. Acute Respiratory Distress Syndrome is a lethal syndrome caused by severe pneumonia [33]. In this condition, there is increased permeability to fluids and proteins across the lung endothelium, leading to edema in the lung interstitium. Furthermore, the edema fluid will move towards the alveoli, which generally occurs due to damage to the endothelium, which is physiologically tight and impermeable. Increasing the permeability of the alveoli capillaries to fluids, proteins, neutrophils, and even erythrocytes will

lead to the accumulation of excess fluid in the alveolar spaces. It is the hallmark of ARDS [34]. Acute Respiratory Distress Syndrome is the most serious complication caused by COVID-19 and has a higher objection rate than other ARDS etiologies. The mortality rate for ARDS ranges from 26% to 61.5% if ever admitted to a critical care setting. In patients receiving mechanical ventilation, mortality can range from 65.7% to 94% [33].

The World Health Organization reports that the incubation period for COVID-19 is between 2 and 10 days. However, some other literature states that the incubation period can be more than two weeks, and there is a possibility that a very long incubation period can cause multiple infections [4]. Clinical and epidemiological data from the Chinese CDC regarding 72,314 case records (confirmed, suspected, diagnosed, and asymptomatic cases) shared in JAMA (24 February 2020) divided COVID-19 patients into three categories including a) Symptomatic patients, mild and moderate, with pneumonia and/or non-pneumonia symptoms; b) Patients with moderate symptoms, with symptoms Respiratory rate of 30 breaths/minute and blood oxygen saturation of 93%; c) Critically symptomatic patients, with symptoms of respiratory failure, septic shock, and multiorgan dysfunction [34].

The severity of the patient's clinical picture seems to correlate with age, where patients over 70 generally have more severe symptoms. In addition, there are also comorbid factors such as COPD, hypertension, and obesity, but currently, no scientifically valid explanation has been developed [35]. The clinical manifestations in non-severe COVID-19 patients are asymptomatic and symptomatic. Asymptomatic patients did not show any clinical manifestations, and no pathological radiographic findings were found, but laboratory tests had a positive interpretation of infection. Symptomatic patients generally have acute upper respiratory tract infection symptoms, and pneumonia is found on chest radiographs [36].

Currently, the main diagnosis of COVID-19 cases is by detecting viral RNA through NAAT, such as rRT-PCR. The target viral genes include the N, E, S, ORF, and RdRp genes [37]. In addition, several studies have carried out examinations using samples in the form of serum, feces, and eye secretions [38]. The rRT-PCR assay begins with converting the viral RNA genome to DNA by RNA-dependent DNA polymerase (reverse transcriptase). This reaction relies on a small DNA primer sequence tailored to specifically recognize the viral RNA genome sequence and reverse transcriptase to make short complementary DNA (cDNA) from viral RNA. The amplification of this DNA is monitored directly as the PCR reaction progresses [38]. If the NAAT laboratory examination is conducted in an area not exposed to SARS-CoV-2. A positive indication of infection must meet one of the following conditions; a) Positive NAAT results for at least two different targets on the SARS-CoV-2 virus genome, where at least one target is more specific for the SARS-CoV-2 virus using validated assays; and b) One NAAT result is positive for the presence of betacoronavirus, and the SARS-CoV-2 virus is further identified by sequencing part or all of the viral genome as long as the target sequence is greater than or different from the amplicon examined in the NAAT test used. If the NAAT laboratory examination is carried out in an area exposed to SARS-CoV-2, the indication of infection becomes easier. It is enough to have a positive result in one of the viral RNA genes [39].

Erythrocyte sedimentation rate (ESR) is an examination method developed by R. S. Fåhræus and A.V.A. Westergren in 1921 [9]. Although they were credited with the discovery of ESR and its clinical implications, Biernacki and Poland had already described the finding of red blood cell sedimentation several decades earlier. A researcher named Edmund Faustyn Biernacki found that blood from anemic patients precipitates faster than from normal people. There are 3 phases in the red blood deposition process, including; (1) aggregation, (2) precipitation, and (3) collection. Aggregation is the most important factor in determining the results of this test. Two factors can affect aggregation, including the high molecular weight of the plasma component and the structure of the red blood cells. Normally, erythrocytes have a negative charge and repel each other, whereas plasma proteins (fibrinogen, beta-globulin, alpha-globulin, gamma-globulin, and albumin) have a positive charge and can neutralize the negative charge on the surface of the erythrocytes. Therefore, an increase in plasma protein is strongly associated with an increase in ESR. In addition, the ESR is also influenced by the size of the erythrocyte cells, and macrocytes precipitate faster than microcytes [40].

Erythrocyte sedimentation rate is an easy and often performed test in the laboratory. The

International Council for Standardization in Haematology recommends the Westergren method as the best ESR examination [41].

In acute, chronic inflammation, malignancy, and necrosis or tissue infarction, there will be an increase in plasma proteins which causes the erythrocytes to tend to stick to one another. It will increase the weight of the erythrocytes and settle down faster so that the ESR value will increase [11]. Based on laboratory tests, patients positively infected with COVID-19 experience increased ESR levels. Based on research conducted by researchers in China on COVID-19 patients, almost all studies showed an increase in ESR with a percentage of 85% of the patients sampled. This study supports the theory that ESR increases in patients with infection and inflammation [10,11].

3. RESEARCH METHOD

This type of research used a retrospective analytic design with a history of patient examination at a private hospital in East Bekasi. This study aimed to determine if CRP and ESR examinations could be used as screening tests in patients with COVID-19. This research wacarried out from May to November 2020 in a private hospital laboratory in East Bekasi. The population of this study was all patients in a private hospital in the East Bekasi area, while the sample was patients who had rRT-PCR tests for COVID-19 diagnostics. The research instruments used were a) the results of the COVID-19 diagnostic rRT-PCR examination, b) patient medical records, and c) the Laboratory coat. This study used secondary data from the results of rRT-PCR, CRP, and complete blood count (including ESR). These data was processed using SPSS for Windows 24.0. The data obtained from the data collection process will be converted into tables, and then the data will be processed using the SPSS computer application.

4. RESULTS AND DISCUSSION

This study used secondary data, which was conducted at a private hospital located in East Bekasi. Data collection was carried out from May 2020 to July 2020. There are no specific specifications for this data regarding the time of the patient's disease phase because this study only uses the results of data from a complete blood check from the first time the patient had a PCR examination. In addition, researchers cannot confirm how long and since when the patient has been infected with COVID-19. In this study, the number of samples obtained was 65 people. From the data obtained, there were 28 (43.1%) negative COVID-19 patients and 37 (56.9%) positive COVID-19 patients. The data that has been collected was then analyzed to determine the profile of the CRP and LED examination results. There are several limitations. The first is that this study only uses data from PCR and complete blood counts when the patient arrives at the hospital for an examination, so the researcher cannot monitor the progress of the patient's disease. Second, the data does not attach the results of the patient's radiographs, so researchers cannot know the phase of the disease and the severity of the patient's disease. Third, the data does not include the possibility of other co-morbidities or comorbid diseases from the patient. Meanwhile, CRP and ESR are markers of non-specific inflammation. This means, the results of CRP and LED examinations still have a bias and are not specific to COVID-19 disease.

Table 1. Characteristics of the sample by age

Age	Negative COVID-19	Positive COVID-19	Total
≤ 10 years old	1 (1.5%)	0 (0%)	1 (1.5%)
11-20 years old	1 (1.5%)	0 (0%)	1 (1.5%)
21-30 years old	2 (3.1%)	3 (4.6%)	5 (7.7%)
31-40 years old	6 (9.2 %)	8 (12.3%)	14 (21.5%)
41-50 years old	9 (13.8%)	11 (16.9%)	22 (30.8%)
51-60 years old	7 (9.2%)	8 (12.3%)	15 (21.5%)
61-70 years old	1 (1.5%)	6 (9.2%)	7 (10.8%)
71-80 years old	1 (1.5%)	1 (1.5%)	2 (3.1%)
81-90 years old	1 (1.5%)	0 (0%)	1 (1.5%)
Total	28 (43.1%)	37 (56.9%)	65 (100%)

Table 1 shows that the age group between 41-50 years is the most vulnerable group to being infected with COVID-19, with a total percentage of 16.9%. Furthermore, in the age group between 21-30 years, 31-40 years, 41-50 years, 51-60 years, and 61-70 years, there were more positive samples of COVID-19 than negative samples COVID-19.

Table 2 shows that the age group between 31-40 years is the group with the highest number of samples and a positive rate of COVID-19 in the age group 1 to 40 years, with a total sample percentage of 66.7% and a positive rate of 38.1%.

Table 3 shows that the highest number of samples in the age group over 40 years is 41-50, with a sample size of 20 patients (25%). The highest number of positive COVID-19 patients was also found in this age group, with a percentage of 45.5%.

Table 4 shows that in the age group 1-40 years, there are more male samples than female samples, where the male sample amounted to 11 patients out of a total of 21 patients. But the number difference is very small, only amounting to 1 sample.

Table 5 shows that in the age group of 40-90 years, there were more male patients than women; besides that, the number of positive patients was also found more in men, with a total percentage of 34.1%.

Bivariate analysis was conducted to see the relationship between the independent and dependent variables. The independent variables in this study were the results of blood sedimentation rate and c-reactive protein. The dependent variable in this study was the results of the patient's PCR examination. Researchers also examined the relationship between ESR and CRP with symptoms of inflammation, namely respiratory frequency.

In Table 6, the results of the Kolmogorov-Smirnov normality test for this data are 0.000, indicating that the distribution of the data is not normal, so the statistical calculation used is the Spearman statistical test to test the correlation coefficient. More were found with normal CRP concentrations in the 1-40 years group, with 14 out of 21 samples, 66.7%. In addition, four patients were also found with high CRP and positive for COVID-19. Found a value of p = 0.682 and a value of r = -0.095

Table 2. Characteristics of the sample by age in the 1-40 year group

Age	Negative COVID-19	Positive COVID-19	Total
≤ 10 years old	1 (4.8%)	0 (0%)	1 (4.8%)
11-20 years old	1 (4.8%)	0 (0%)	1 (4.8%)
21-30 years old	2 (9.5%)	3 (14.3%)	5 (23.8%)
31-40 years old	6 (28.6%)	8 (38.1%)	14 (66.7%)
Total	10 (47.6%)	11 (52.4)	21 (100%)

Table 3. Characteristics of the sample by age in the age group 41-90 years

Age	Negative COVID-19	Positive COVID-19	Total
41-50 years old	9 (20.5%)	11 (25%)	20 (45.5%)
51-60 years old	6 (13.6%)	8 (18.2%)	14 (31.8%)
61-70 years old	1 (2.3%)	6 (13.6%)	7 (15.9%)
71-80 years old	1 (2.3%)	1 (2.3%)	2 (4.5%)
81-90 years old	1 (2.3%)	0 (0.0%)	1 (2.3%)
Total	18 (40.9%)	26 (59.1%)	44 (100%)

Table 4. Characteristics of the sample based on sex in the age group 1-40 years

Gender	Negative COVID-19	Positive COVID-19	Total
Male	6 (28,6%)	5 (23.8%)	11 (52.4%)
Female	4 (19.0%)	6 (28.6%)	10 (47.6%)
Total	10 (44%)	11 (56%)	21 (100%)

Table 5. Characteristics of the sample based on sex in the age group 41-90 years

Gender	Negative COVID-19	Positive COVID-19	Total
Male	8 (18.2%)	15 (34.1%)	23 (52.3%)
Female	10 (22.7%)	11 (25.0%)	21 (47.7%)
Total	18 (40.9%)	26 (59.1%)	44 (100%)

Table 6. Results of statistical calculations between PCR and CRP in the 1-40 year group

CRP	Negative Covid-19	Positive Covid-19	Total	p Value	r Value
Normal	7 (33.3%)	7 (33.3%)	14 (66.7%)	0.682	-0.095
High	3 (14.3%)	4 (19.0%)	7 (33.3%)		
Total	10 (47.6%)	11 (52.4%)	21 (100%)		

Table 7. Results of statistical calculations between PCR and CRP in the 41-90 year group

CRP	Negative Covid-19	Positive Covid-19	Total	p Value	r Value
Normal	8 (18.2%)	7 (15.9%)	15 (34.1%)	0.040	0.311
High	10 (22.7%)	19 (43.2%)	29 (65.9%)		
Total	18 (40.9%)	26 (59.1%)	44 (100%)		

In Table 7, the results of the Kolmogorov-Smirnov normality test for this data are 0.000, indicating that the distribution of the data is not normal, so the statistical calculation used is the Spearman statistical test to test the correlation coefficient. In the age group of 41-90 years, more patients with high CRP than normal. High CRP values were also higher in patients with positive status for COVID-19, with 19 out of 29 patients and a percentage of 43.2% obtaining a p-value of 0.040 and an r-value of 0.311.

In Table 8, The Kolmogorov-Smirnov normality test results for this data are 0.000, indicating that the data distribution is normal, so the statistical calculation used is the Spearman statistical test. In the 1-40 years group, there were more patients with normal ESR concentration than those with high ESR. Only three patients (14.3%) were positive for COVID-19 with high ESR, while positive patients for COVID-19 with normal ESR were eight patients (38.1%). In COVID-19 patients, there are more patients with normal ESR than those with high ESR. Obtained value of p = 0.224 and value of r = -0.277.

Table 9 the Kolmogorov-Smirnov normality test results for this data are 0.044, indicating that the data distribution is normal, so the statistical calculation used is the Pearson statistical test. The data showed that in the 40-90-year-old group, there were more patients with high ESR. Besides that, it was also found that more patients with positive COVID-19 status had high ESR concentrations, with a total of 36 out of 44 patients (81.8%). Obtained value of p = 0.180 and value of r = 0.206.

Table 8. Results of statistical calculations between PCR and LED in the age group 1-40 years

LED	Negative Covid-19	Positive Covid-19	Total	p Value	r Value
Normal	4 (19.0%)	8 (38.1%)	12 (57.1%)	0.224	-0.277
High	6 (28.6%)	3 (14.3%)	9 (42.6%)		
Total	10 (47.6%)	11 (52.4%)	21 (100%)		

Table 9. Results of statistical calculations between PCR and LED in the age group 41-90 years

LED	Negative Covid-19	Positive Covid-19	Total	Value p	Value r
Normal	4 (9.1%)	4 (9.1%)	8 (18.2%)	0.180	0.206
High	14 (31.8%)	22 (50.0%)	36 (81.8%)		
Total	18 (40.9%)	26 (59.1%)	44 (100%)		

Infection by microorganisms in the host is known as infection and can trigger inflammation. High CRP concentrations are commonly found in patients with inflammatory conditions. Patients with inflammatory conditions may experience respiratory frequency. Against this background, bivariate statistical calculations were also carried out to look for a stronger correlation between CRP concentrations and ESR in positive COVID-19 patients with increased respiratory rates. From a total of 65 positive and negative samples, in this statistical calculation, we only used samples with a positive COVID-19 status with 37 patients. The normal value of respiratory frequency in this statistical calculation is 12-20 times per minute, and if the sample exceeds this number, it will be referred to as high respiratory frequency.

In Table 10, the Kolmogorov-Smirnov normality test obtained a value of 0.000 which indicates the data is not normally distributed, so the Spearman correlation test is used. The patient's respiratory rate was found to be more normal than high, with a total of 26 patients and a percentage of 70.3%. However, in patients with high CRP, more patients with high respiratory rates were found than those with low respiratory rates, with ten patients (27%). Obtained value of p = 0.026 and value of r = 0.366.

In Table 11, the Kolmogorov-Smirnov normality test obtained a value of 0.000 which indicates the data is not normally distributed, so the Spearman correlation test is used. It was found that patients with high ESR were more likely to have normal respiratory rates, with a total sample of 18 patients and a percentage of 48.6%. Meanwhile, there were seven patients with high ESR and high respiratory rates. The value of p = 0.744 and the value of r = 0.055.

From a total of 65 positive and negative samples, in this statistical calculation, we only used samples with a positive COVID-19 status with 37 patients. The normal value of respiratory frequency in this statistical calculation is 35-37 degrees Celsius; if the sample exceeds this amount, it will be referred to as high respiratory frequency. Calculations were made using Spearman bivariate analysis because the result of the normality test from the patient was 0.002, which indicated that the data distribution was not normal.

Table 12 shows that there were more patients with normal temperature than with high temperature, with 22 out of 37 patients; the percentage was 59.5%. Then, high temperatures are also more common in patients with high CRP concentrations with per obtained value of p = 0.918 and value of r = 0.018.

In Table 13, the examination and bivariate analysis results between the concentrations of the sedimentation rate showed that high temperatures were found more in patients with high ESR concentrations, with a percentage of 27.0%. The p-value was found to be 0.032, and the r-value was -0.354. The normal pulse frequency humans use is 60-100 bpm; above this value, it is considered a high pulse frequency. The Kolmogorov-Smirnov normality test obtained a value of 0.200, indicating that the data was normally distributed, so the Pearson correlation test was used.

Table 10. Results of statistical calculations between CRP and respiratory frequency

Breathing Frequency	Normal CRP	High CRP	Total	p Value	r Value
Normal	13 (35.1%)	13 (35.1%)	26 (70.3%)	0.026	0.366
High	1 (2.7%)	10 (27%)	11 (29.7%)		
Total	14 (37.8%)	23 (62.2%)	37 (100%)		

Table 11. Results of statistical calculations between LEDs and respiratory frequency

Breathing Frequency	Normal LED	High LED	Total	p Value	r Value
Normal	8 (21.6%)	18 (48.6%)	26 (70.3%)		
High	4 (10.8%)	7 (18.9%)	11 (29.7%)	0.744	0.055
Total	12 (32.4%)	25 (67.6%)	37 (100%)		

Table 12. Results of examination and bivariate analysis between the concentration of c-reactive protein and temperature

Temperature	Normal CRP	High CRP	Total	p Value	r Value
Normal	9 (24.3%)	13 (35.1%)	22 (59.5%)		
High	5 (21.6%)	10 (27.0%)	15 (40.5%)	0.918	0.018
Total	14 (37.8%)	23 (62.2%)	37 (100%)		

Table 13. Results of examination and bivariate analysis between the concentration of the sedimentation rate and temperature

Temperature	Normal LED	High LED	Total	p Value	r Value
Normal	7 (18.9%)	15 (40.5%)	22 (59.5%)		
High	5 (13.5%)	10 (27.0%)	15 (40.5%)	0.032	-0.354
Total	20 (54.1%)	17 (45.9%)	37 (100%)		

Table 14. Results of examination and bivariate analysis between c-reactive protein and pulse frequency

Pulse Frequency	Normal CRP	High CRP	Total	p Value	r Value
Normal	10 (27.0%)	14 (37.8%)	24 (64.9%)		
High	4 (10.8%)	9 (24.3%)	13 (35.1%)	0.721	-0.610
Total	14 (37.8%)	17 (62.2%)	37 (100%)		

Table 15. Results of examination and bivariate analysis between c-reactive protein and pulse frequency

Pulse Frequency	Normal LED	High LED	Total	p Value	r Value
Normal	8 (21.6%)	16 (43.2%)	24 (64.9%)		
High	4 (10.8%)	9 (24.3%)	13 (35.1%)	0.563	-0.980
Total	12 (32.4%)	25 (67.5%)	37 (100%)		

Table 16. Results of examination and bivariate analysis between c-reactive protein and pulse frequency

CRP	Normal LED	High LED	Total	p Value	r Value
Normal	8 (21.6%)	4 (10.8%)	12 (32.4%)		
High	6 (16.2%)	19 (51.4%)	13 (67.6%)	0.000	0.557
Total	14 (37.8%)	23 (62.2%)	37 (100%)		

Table 14 shows that in COVID-19 patients, there are more patients with a normal pulse rate than those with a high pulse rate, where patients with a high pulse rate account for 24 out of 37 patients (64.9%) of the total positive COVID-19 patients. High pulse rates are also more common in patients with high CRP concentrations. Obtained value of p = 0.721 and value of r = -0.610.

Table 15 shows that a high pulse frequency is found more in patients with high ESR concentrations, with a percentage of 24.3%. The p-value was found to be 0.563, and the value of r = -0.980. From a total of all positive samples with a total of 37 patients, bivariate analysis calculations were also carried out between CRP and ESR. Normal CRP values range from 0-6 mg/L, and normal ESR values are 0-10 mm/h for men and 0-15 mm/h for women.

Table 16 shows that the descriptive calculation between CRP and ESR found that patients with high ESR values with high CRP totaled 13 samples (67.6%). Found a value of p = 0.000 and a value of r = 0.577.

From the study results in all age groups, statistical calculations show that there were more positive patients with COVID-19 in the age group

of 41-50 years, namely 12 out of 38 positive patients with COVID-19, with a percentage of 31.5%. If divided into two age groups which include the age group 1-40 years and 41-90 years, the highest rates are found in the age group 31-40 years and 41-50 years. It can be caused because age is a risk factor for COVID-19 disease. As we age, the immune system declines, which has a major impact on health and survival. This decline in immunity predisposes older people to a higher risk of viral and bacterial infections. In addition, the mortality rate from infectious diseases is also three times higher in elderly patients compared to young adult patients. In addition, based on demographic research conducted by Deni Hidayati with the title "Profile of Residents Confirmed Positive for COVID-19 and Death: Cases of Indonesia and DKI Jakarta," which examined the profile of residents infected with COVID-19 from 2 March 2020 to 28 May 2020. He proved that in Indonesia, the age group that is vulnerable to being infected with COVID-19 is the age group 31-40. He concluded that this age group is a time when a person is very productive, so they are more likely to leave the house. It can increase the risk of exposure to the virus [42].

In addition, he also concluded that the COVID-19 infection rate was higher in men than women. It can be caused by the lifestyle of men who smoke more, so they are more susceptible to suffering from respiratory tract diseases [42]. Men are also more often exposed to outside air, which may be contaminated with SARS-CoV-2 because they are more likely to be outside the home for work and other interests. Then, according to Elena Ortona et al., women also have stronger innate and adaptive immune systems than men. Factors that influence this include biological factors (genetic and sex hormones) and psychosocial factors [43]. The research above supports the results of the research obtained on this data, where it was found that there were more positive samples for COVID-19 with male sex, with a total of 34 out of 65 patients, and the percentage was 52.5%. The same thing was also found in the division of the age group into 1-40 years and 41-90 years, where there were more male samples than female samples.

In this study, two statistical calculations were performed in the bivariate and descriptive analysis between CRP and PCR, namely the sample age group 1-40 years and the sample age group 41-90 years. In the data for the age group 1-40 years, more samples were found with normal CRP concentrations in positive COVID-19 patients. The number of positive COVID-19 patients who experienced increased CRP concentrations was only four patients out of a total of 21 patients, with a percentage of 19.0%. In the age group of 41-90 years, it was found that there were more COVID-19 patients with high CRP concentrations, with a total sample of 19 patients out of 29 positive patients, and the percentage was 65.9%

The components used are the results of the CRP examination as the dependent variable and the results of the PCR examination as the independent variable. The bivariate analysis research conducted on the two age groups is the correlation coefficient using Spearman statistical calculations, which is a statistical calculation for data that is not normally distributed because it is based on the Kolmogorov Smirnov normality test performed on the three data showing a result of 0.000 where new data can be called normally distributed if the resulting number is above 0.05. In statistical calculations, two components are assessed: the value of r and the value of p. The value of r is a symbol of one of the components of bivariate statistics, namely the Spearman correlation, which is useful for knowing whether the two variables studied are directly proportional or vice versa. Directly proportional means that the higher the dependent variable, the higher the independent variable associated with this calculation. Data can be directly proportional if the value of r is positive, and data can be inversely proportional if the value of r is negative. The p-value is a symbol of the 2-tailed Sigma calculation results, which is useful for knowing whether or not the correlation is strong. Data can be said to be correlated with a p-value <0.05. Because Spearman correlation calculations can only be done with nominal data, the researchers changed the PCR results to number 1 for negative and number 2 for positive.

The normal value of CRP in the human body ranges from 1.0 mg – 6.0 mg [6]. CRP was significantly increased in bacterial and viral infections, although not as prominent as in bacterial infections. The concentration of CRP in patients is thought to be the key to the severity of COVID-19 patients. [4] During the patient in the infectious phase or inflammatory disease status, CRP levels increase rapidly in the first 6-8 hours and peak at levels up to 350-400 mg/L after 48 hours [44].

This study conducted a bivariate analysis between CRP and LED with temperature. The normal temperature value is 35-37 degrees

Celsius. The research was carried out using statistical and analytical calculations. In the descriptive calculation of CRP with temperature, it was found that there were more patients with normal temperature, with a total of 22 patients (59.5%). Then, patients with high CRP and high temperature were found in 10 people (27%). The analytic calculation found a value of p = 0.918 which means that there is no significant relationship between the two variables and a value of r = 0.018 which means that there are more patients with a high temperature with high CRP. In the descriptive calculation between ESR and temperature, it was found that 15 patients (40.5%) had high ESR with high temperature. With a value of p = 0.032 which means that there is a significant relationship between the two variables, then the value of r = -0.354 means that there are more patients with normal temperatures at high ESR.

In this study, statistical calculations were carried out between CRP and LED, with the normal value of the normal pulse frequency being 60-100 bpm. Descriptive calculation between CRP and pulse frequency found more samples with normal pulse frequency with 13 patients (35.1%). Patients with high CRP and pulse frequency totaled nine (24.3%). The analytical calculation was p=0.721, meaning there is no relationship between the two variables. Besides that, it was found to be r=-0.610, which means there are more patients with normal pulse frequency at high CRP concentrations. In the descriptive calculation between ESR and pulse frequency, nine patients with high CRP values and high pulse frequency were found (24.3%). Analytical calculations found a value of p = 0.563, meaning there was no significant relationship between the two variables, then found a value of r = -0.980 means that there are more patients with normal pulse frequency values at high ESR concentrations.

In this study, bivariate analysis was also calculated between the two dependent variables, namely CRP and LED. Calculation of descriptive analysis found that patients with high ESR values and high CRP values were 24 patients (67.6%). Then in the calculation of the normality test, it was found that the Kolmogorov-Smirnov value was 0.000, which means that the data was not normally distributed. Therefore, the Spearman correlation coefficient test was carried out in the analytical and statistical calculations. The value of p = 0.000 was found, which means a significant relationship exists between the CRP value and the LED. In addition, a value of r = 0.557 was found, which means that more patients were found with high CRP concentrations and high ESR. Based on the theory we know, CRP and ESR values generally increase in inflammatory conditions.

Please note that this research has several limitations. Some have been described previously. The first is that this study only uses data from PCR and complete blood counts when the patient arrives at the hospital for an examination, so the researcher cannot monitor the progress of the patient's disease. Second, the data does not attach the results of the patient's radiographs, so researchers cannot know the phase of the disease and the severity of the patient's disease. Third, the data does not include the possibility of other co-morbidities or comorbid diseases from the patient. Meanwhile, CRP and ESR are markers of non-specific inflammation. So that the results of CRP and LED examinations still have a bias and are not specific to COVID-19 disease [44,45]. Thus, an increase in CRP and LED must have a strong relationship.

5. CONCLUSION

CRP examination was only significant in the 41-90 age group; there was a significant relationship between increased CRP and respiratory rate in COVID-19 patients, and there was a significant relationship between increased CRP and ESR in COVID-19 patients. Thus, currently, the disease COVID-19 is still a pandemic and is a disease that is quite life-threatening. Therefore, health workers should provide good and well-understood education to the public about properly preventing and dealing with COVID-19 in the hope of reducing the positive number of COVID-19 patients in the future. COVID-19 is a disease that is quite dangerous and is a disease with droplet transmission, so this disease is very infectious. COVID-19 patients are encouraged to self-isolate to avoid further transmission of the disease. In addition, it is also recommended for patients to immediately come to the hospital and do an examination if the patient's symptoms worsen.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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