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Research Article

C-Reactive Protein (CRP) Medium and Severe Symptoms Levels of COVID-19

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Abstract

Coronavirus Disease 2019 (COVID-19) is a disease caused by SARS-CoV-2 and has caused a global pandemic. Patients with COVID-19 can experience symptoms such as fever, dry cough, headache, and shortness of breath which can lead to pneumonia. Excessive inflammation is considered a leading cause of critical illness and death in COVID-19 patients. C-Reactive Protein is a sensitive indicator as an early marker of infection and inflammation. This study presents an overview of the difference in the average CRP levels between patients with moderate and severe confirmed COVID-19 symptoms at UKI Hospital for June-September 2021. The study design was cross-sectional with descriptive and analytical data presentation obtained from medical record documents at UKI Hospital. The average CRP level of COVID-19 patients with moderate symptoms is 63,705 mg/L, totaling 139 patients. The average CRP level of COVID-19 patients with severe symptoms is 132,050 mg/L, totaling 57 patients. The results obtained from the Mann-Whitney test between groups of patients with moderate and severe COVID-19 showed a significant difference between CRP levels with moderate and severe symptoms with p <0.05.

Keywords: COVID-19, CRP levels, SARS-CoV-2

INTRODUCTION

A mysterious pneumonia case with unknown cause appeared in Wuhan City, China, in December 2019. The results of the study on samples of isolates, in that case, showed that there was a new type of Coronavirus infection named 2019 novel Coronavirus (2019-nCoV). On February 11, 2020, the World Health Organization (WHO) named the new virus, SARS-CoV-2 and the disease as Coronavirus Disease 2019 (COVID-19). This coronavirus is the main cause of respiratory disease outbreaks. The number of cases continues to grow over time. On March 11, 2020, WHO announced that COVID-19 had become a worldwide pandemic [1].

On March 2, 2020, two positive cases of COVID-19 were reported in Indonesia. As of March 31, 2020, 1,528 confirmed positive cases of COVID-19 and 136 cases of death due to COVID-19 in Indonesia. It has caused Indonesia to become the country with the highest mortality rate in Southeast Asia at 8.9% [2]. Since the COVID-19 pandemic, the Indonesian government has tried to overcome and facilitate COVID-19 patients by providing 90 COVID-19 referral hospitals in Jakarta to help treat Covid-19 patients properly and quickly.

Coronavirus is a positive single-stranded RNA virus. The glycoproteins on the envelope give the appearance of the coronavirus under the electron microscope like a crown. Coronaviruses belong to the order Nidovirales and the family Coronaviridae. Coronaviruses have four main structural proteins, namely: spike glycoprotein (S), membrane protein (M), envelope glycoprotein (E), and nucleocapsid protein (N). SARS-CoV-2 can be transmitted mainly through droplets both by direct contact and indirect contact [3].

In humans, SARS-CoV-2 primarily infects the respiratory tract cells that line the alveoli. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) will bind to the ACE-2 receptor in the human body, assisted by the TMPRSS2 enzyme, so it can enter cells and the part of the virus that binds to the ACE-2 receptor, the spike protein. Inside the cell, SARS-CoV-2 releases RNA genetic material, which then translates some of the RNA into proteins, and some of the viral proteins replicate to make more RNA. Next, viral proteins and RNA combine to create new viruses in the golgi bodies. In the final stage, vesicles containing viral particles will fuse with the plasma membrane to release new viral components [4].

The viral antigen will be presented to the APC, which will be processed to form peptides. Antigen presentation stimulates humoral and cellular immune responses mediated by virus-specific B and T cells. In the humoral immune response, IgM and IgG are formed against SARS-CoV-2. IgM against SARS-CoV-2 is produced early by the body, about 3-10 days after infection, and does not last long, and IgG appears later. The cellular immune response is mediated by cytotoxic T cells, which induce damage or apoptosis in infected cells by releasing many pro-inflammatory cytokines and chemokines. Then these pro-inflammatory cytokines and chemokines stimulate hepatocyte cells to form CRP. The cause of ARDS in SARS-CoV-2 infection is a cytokine storm, an uncontrolled systemic inflammatory response due to the release of large

amounts of pro-inflammatory cytokines and chemokines. ARDS is the leading cause of death in COVID-19 patients [4].

C-Reactive Protein (CRP) is an acute phase inflammatory protein that will increase during the inflammatory phase as occurs in infection with SARS-CoV-2 [5]. CRP levels rise rapidly within 6 to 8 hours and reached the highest peak within 48 hours of disease onset, and levels will decrease when the inflammatory stage ends and the patient recovers [6]. Increased levels of CRP indicate the infection severity and have been used as an indicator of COVID-19 severity. Induction of CRP gene transcription occurs mainly in hepatocytes in response to pro-inflammatory cytokines, particularly IL-6 [5]. C-Reactive Protein, an important marker markedly altered in severe COVID-19 patients. Significant increases in CRP were found with levels of 20 to 50 mg/L in patients with COVID-19. Patients with a severe course of COVID-19 had significantly higher CRP levels than patients with mild degrees [6].

RESEARCH METHODOLOGY

The research design in this study was cross-sectional, with descriptive and analytic data presentation. The study was conducted at UKI General Hospital in January 2022. The population of this study was the total number of patients confirmed positive for COVID-19 through RT-PCR treated at UKI General Hospital. The sample of this research was taken based on purposive sampling. Sampling was based on inclusion criteria: patients aged 18 years, patients confirmed positive for COVID-19 based on RT-PCR results, COVID-19 patients with moderate and severe symptoms, and patients who underwent CRP examination, so 196 samples were obtained. This research instrument is in the form of medical records of patients confirmed positive for COVID-19 at UKI Hospital in June-September 2021. All data was created in Microsoft Excel and processed further using SPSS.

RESULTS AND DISCUSSION

The sample in this study amounted to 196 people who met the inclusion criteria. The sample was divided into two groups, namely the group of moderately symptomatic COVID-19 patients and severe COVID-19 patients. The moderate symptom patient group consisted of 139 subjects, and the severe symptom patient group consisted of 57 subjects. Subjects consisted of 100 people (51%) women and 96 people (49%) men. The age range of the patients was 18-89 years. The characteristics of the research sample can be seen in Table 1, Table 2, and Table 3.

Table 1: Characteristics of Research Samples Based on Symptoms

No.	Symptom	Total (n)	Percentage (%)
1	Moderate Symptom	139	70,9
2	Severe Symptom	57	29,1
	Total	196	100

Table 2: Characteristics of Research Samples Based on Gender

Gender	Moderate Symptom		Severe Symptom		Total	
	Total (n)	Percentage (%)	Total (n)	Percentage (%)	Total (n)	Percentage (%)
Male	67	34,2	29	14,8	96	49
Female	72	36,7	28	14,3	100	51
Total	**139**	**70,9**	**57**	**29,1**	**196**	**100**

Table 3: Characteristics of Research Samples Based on Age

Age	Moderate Symptom		Severe Symptom		Total	
	Total (n)	Percentage (%)	Total (n)	Percentage (%)	Total (n)	Percentage (%)
18-25 years	13	6,63	0	0	13	6,63
26-45 years	53	27	12	6,12	65	33,12
46-65 years	68	34,7	23	11,73	91	46,43
>65 years	5	2,6	22	11,22	27	13,82
Total	**139**	**70,9**	**57**	**29,1**	**196**	**100**

The Mann-Whitney test was carried out to find the difference in the average CRP levels between the groups of patients with moderate and severe symptoms of COVID-19 because, in the normality test, the CRP levels of patients with moderate symptoms of COVID-19 were abnormal. The results of the Mann-Whitney test for CRP levels in each group are shown in Table 4.

Table 4: Hypothesis Test Results

	Median (Minimum-Maximum)	p Value
CRP levels of COVID-19 patients with moderate symptoms (n=139)	25 (2,5-332)	0,000
CRP levels of COVID-19 patients with severe symptoms (n=57)	144 (2,5-385)	

The results of the Mann-Whitney test between groups of patients with moderate and severe symptoms of COVID-19 showed a significant difference in average between CRP levels with moderate and severe symptoms with $p < 0.05$.

Table 5: Results of Examination of CRP Levels in COVID-19 Patients with Moderate Symptoms by Age

	CRP level					
Age Group	Increase		Normal		Total	
	N	%	n	%	n	%
18-25 years	11	9,2	2	10,0	13	9,4
26-45 years	46	38,7	7	35,0	53	38,1
46-65 years	58	48,7	10	50,0	68	48,9
>65 years	4	3,4	1	5,0	5	3,6
Total	119	85,6	20	14,4	139	100,0

Based on Table 5, 119 people (85.6%) had elevated CRP levels, and 20 (14.4%) had normal CRP levels. The increase in CRP levels was mostly experienced by the 46-56 year age group, as many as 58 people (48.7%).

Table 6: Results of Examination of CRP Levels in COVID-19 Patients Symptoms of Weight Based on Age

	CRP level					
Age Group	Increase		Normal		Total	
	N	%	n	%	n	%
18-25 years	0	0	0	0	0	0
26-45 years	11	20,0	1	50,0	12	21,05
46-65 years	23	41,8	0	0	23	40,35
>65 years	21	38,2	1	50,0	22	38,6
Total	55	96,5	2	3,5	57	100,0

Based on Table 6, as many as 55 people (96.5%) had elevated CRP levels, and two people (3.5%) had normal CRP levels. The highest increase in CRP levels was experienced by the 46-56 year age group, 23 people (41.8%).

Table 7: Average CRP Levels in COVID-19 Patients with Moderate and Severe Symptoms

Category	Total (n)	Average Level CRP (mg/L)
Moderate Symptom	139	63,705
- No Comorbid	68	53,054
- With Comorbid	71	73,905
Severe Symptom	57	132,050
- Not Died	23	134,282
- Died	34	130,532

Based on Table 7, the average CRP level of moderately symptomatic COVID-19 patients was 63,705 mg/L. The average CRP level of moderately symptomatic COVID-19 patients without comorbidities is 53,054 mg/L and with comorbidities is 73,905 mg/L. The average CRP level of patients with severe COVID-19 symptoms was 132,050 mg/L. The average CRP level of COVID-19 patients with severe symptoms who did not die was 134.282 mg/L, and those who died were 130,532 mg/L.

Table 8: Number of COVID-19 Patients with Moderate and Severe Symptoms who were examined for CRP Levels within 48 Hours

Category	Total	Checked Total	Percentage (%)
Moderate Symptom	139	95	68,34
Severe Symptom	57	38	66,66
Total	196	133	67,85

Based on Table 8, moderately symptomatic COVID-19 patients who were examined for CRP levels within 48 hours of the onset of the disease were 95 people (68.34%) out of a total of 139 people, while for COVID-19 patients with severe symptoms, there were 38 people (66, 66%) of the total 57 people.

A systemic inflammatory response occurs in COVID-19. C-Reactive Protein is a type of protein produced by the liver and is a marker of systemic inflammation and an early marker of infection/inflammation. The results of the Mann-Whitney test in this study showed a difference in the average CRP levels, which was a significant difference between moderate and severe symptoms of COVID-19. The average CRP level of patients with severe COVID-19 symptoms was higher, namely 132,050 mg/L, compared to the CRP level of patients with moderate symptoms of COVID-19, which was 63,705 mg/L. These results are consistent with several other studies examining CRP levels in COVID-19 patients. Research by Shang et al. [7] reported the mean CRP level in severe symptoms was 43.1 mg/L and ten mg/L in non-severe cases. In the study, Wang et al. [8] reported that the mean CRP level in patients with severe symptoms was 43.8 mg/L and 12.1 mg/L in non-severe patients. In the study, Young et al. [9] reported that the mean CRP level in patients with severe symptoms was 65.6 mg/L and 11.1 mg/L in non-severe cases. These studies found that the average CRP levels in severe COVID-19 symptoms were higher than those with moderate and mild symptoms.

In this study, the average increase in CRP levels in COVID-19 patients with moderate and severe symptoms was mostly experienced by the 46-65 year age group. It is in accordance with the research of Sumiati et al. [10], which showed that CRP levels increased the most at the age of 46-65, with a total of 40 people (57.14%). It is because, in that age group, the body's resistance or immunity has begun to decline. As a result, there is a decrease in the production of B and T cells in the bone marrow and thymus and a decrease in the function of mature lymphocytes in secondary lymphoid tissue, so the immune system is unable to respond properly [11]. In addition, at the age of 46-65 years, the geriatric syndrome can occur, namely, geriatric frailty, which is associated with increased inflammatory activity due to increased levels of several biomarkers such as TNF-, IL-6, cytokines, and acute phase proteins. C-Reactive Protein plays a key role in several disease processes, and elevated CRP levels increase susceptibility to other diseases and death in the elderly [12]. In a study by Aleksandara et al. [13], CRP levels were higher at age 65 compared to age <65. The healthy elderly showed low but higher levels of CRP and pro-inflammatory cytokines than the younger population. In addition, CRP levels are also influenced by the comorbid status of the patient. Conditions with comorbidities in the 196 COVID-19 patients studied were 71 people with hypertension (36.2%), 38 people with diabetes (19.4%), and 14 people with heart disease (7.1%). These results are in accordance with research by Fried et al. [14], which showed that 46.7% of patients with hypertension, 27.8% with diabetes, 18.6% had cardiovascular disease, 16.1% had obesity, 14.8% had lung disease, chronic kidney disease12.2%. C-Reactive Protein is one of the most widely recognized biomarkers of cardiovascular disease. In patients with hypertension, CRP levels are associated with end-organ damage such as left ventricular hypertrophy and albuminuria,

suggesting that inflammation may contribute to endothelial dysfunction in hypertension leading to heart and kidney damage [15]. In addition, inflammatory and metabolic factors associated with diabetes, such as high glucose levels, adipokines, lipoproteins, and free fatty acids, can trigger CRP production by endothelial cells, smooth muscle cells, and monocytes/macrophages [16].

In this study, the average CRP level of moderately symptomatic COVID-19 patients without comorbidities was 53.054 mg/L, while those with comorbidities were 73.905 mg/L. It shows that CRP levels in COVID-19 patients with comorbidities are higher than those without comorbidities. CRP levels in COVID-19 patients without comorbidities themselves are already very high. Therefore, when these patients have comorbidities, there will be a very high spike in CRP levels, leading to a cytokine storm.

Cytokine storm is an important mechanism of ARDS along with chronic systemic inflammatory stimulus resulting from releasing many pro-inflammatory markers and chemokines, such as effector cells. Cytokine storms stimulate attacks on the host body through the immune system causing multiple organ failures and ARDS, ultimately resulting in death [17]. In this study, 34 patients with severe symptoms of COVID-19 died with an average CRP level of 130,532 mg/L, and 26 experienced ARDS.

In this study, patients with severe symptoms of COVID-19 who died had a lower mean CRP level (130.532 mg/L) than those who did not die (134.282 mg/L). It contradicts the study of Luo et al. [18], who said that COVID-19 patients who died had CRP levels about ten times higher than those who recovered and contradicted the study of Chen et al. [19], who reported CRP levels in COVID-19 patients who died were higher than those who recovered. It happened because, in this study, the number of COVID-19 patients with severe symptoms who died was more (34 people) than those who did not die (23 people). So that when the average CRP level was calculated, it would be lower in the group of severe symptomatic COVID-19 patients with severe symptoms who died compared to those who did not die.

In this study, the number of COVID-19 patients who were examined for CRP levels on the first day of hospital admission moderate symptoms was 95 people (68.34%) out of a total of 139 people, while for COVID-19 patients with severe symptoms, 38 people (66, 66%) of the total 57 people. In this case, the authors have not found any research sources related to the rules for examining CRP levels in COVID-19 patients. However, a letter to the editor written by Ali [6] said CRP levels increased rapidly within 6 to 8 hours and reached the highest peak within 48 hours from the onset of the disease, and the levels will decrease when the inflammatory stage ends and the patient recovers. Therefore, patients confirmed positive for COVID-19 should have their CRP levels checked within 48 hours of disease onset so as not to miss the acute phase of COVID-19 inflammation.

CONCLUSIONS

After analyzing and discuss all of the data, it can be concluded that: a) The number of moderately symptomatic COVID-19 patients who underwent RT-PCR and CRP levels was 139 people consisting of 67 people (48%) men and 72 people (52%) women with an age range of 18-68 years; b) The number of COVID-19 patients with severe symptoms who underwent RT-PCR and CRP levels was 57, consisting of 29 people (51%) men and 28 (49%) women with an age range of 28-89 years; c) The average CRP level of COVID-19 patients with moderate symptoms is 63,705 mg/L; d) The average CRP level of COVID-19 patients with severe symptoms is 132,050 mg/L; and e) There is a difference in the mean CRP levels between the groups of moderate and severe COVID-19 patients. C-Reactive Protein is a sensitive indicator as an early marker of infection and inflammation. Therefore, patients confirmed positive for COVID-19 should have their CRP levels checked within 48 hours of disease onset so as not to miss the acute phase of COVID-19 inflammation. In addition, COVID-19 patients with elevated CRP levels require close monitoring so that they do not worsen into a cytokine storm that can cause death.

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