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Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) in COVID-19 patients at the RSPTN UNHAS, Makassar

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ABSTRACT

Background: Coronavirus Disease-19 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) as part of the novel coronavirus. Clinical monitoring and appropriate treatment strategies are essential to reduce case fatality. Various examination parameters to support diagnosis such as ESR and CRP in assessing the response of a systemic inflammatory process. C-reactive protein (CRP) levels can be used in the initial diagnosis of pneumonia and patients with severe pneumonia have high CRP levels. Erythrocyte Sedimentation Rate (ESR) as a non-specific inflammatory response examination which has increased in various physiological disorders such as infection and inflammation
Objective:. The purpose of this study was to determine the levels of ESR and CRP as biomarkers of inflammation in patients with COVID-19 at RSPTN UNHAS, Makassar.
Methods: This study involved 32 subjects who met the inclusion criteria for positive RT-PCR COVID-19, age 21-70 years and signed of informed concent. Erythrocyte Sedimentation Rate Check by Auto ESR Analyzer using the Westergreen method and C-reactive protein Check by qualitative test.
Results: The result of this research that the average age of the subjects was 51 years consisting of 14 (56.2%) female subjects and 18 (43.8%) male subjects. The median value of CRP examination is 48.00 mg/dL and the median value of ESR is 63.00 mm/hour.
Conclusion: There is a significant difference between the CRP values in male and female subjects. There is a significant relationship between CRP and ESR values with a strong correlation

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1. Introduction

Obstructive sleep apnea syndrome (OSA), a December 2019, a number of cases of pneumonia with no known cause emerged in Wuhan, Hubei, China. The causative pathogen was identified as a novel coronavirus caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) [1]. Initially, the disease was tentatively named by the World Health Organization (WHO) as the 2019 novel coronavirus (2019-nCoV) and announced under the new name Coronavirus Disease (COVID-19) in February [2]

A number of cases have been reported and based on the latest updated data from the for handling COVID-19 on August 2, 2020, it was reported that COVID-19 cases spread to 216 countries with a total of 17,660,523 confirmed cases and 680,894 deaths. In Indonesia, the last updated report on October 17, 2020 reported that there were 357,762 positive cases with 281,762 recovered cases and 12,431 deaths [3]. Cases of COVID-19 as an emergency health condition with high transmission rates and cases of death in critical patients. Clinical monitoring and appropriate treatment strategies are essential to reduce case fatality. C-reactive protein (CRP) levels can be used in the initial diagnosis of pneumonia, and patients with severe pneumonia have high CRP levels. Research shows that in the early stages of COVID-19 there is a positive correlation between CRP and lung lesions and may reflect disease severity [4]. The same study showed that plasma CRP levels were positively correlated with the severity of COVID-19 [5].

In addition to CRP, the laboratory parameter used to assess the presence of inflammation is the Erythrocyte Sedimentation Rate (ESR). Erythrocyte

Sedimentation Rate (ESR) is one of the tests of the inflammatory response, although it is non-specific, but can be useful clinically. The ESR value is related to changes in plasma proteins and increases in various physiological disorders such as infection, inflammation, degeneration and malignancy [6]. The same study showed that there was an increase in ESR levels in COVID-19 sufferers in China. In addition, there is a relationship between ESR values with CRP and hemoglobin in patients with COVID-19 [7]. Erythrocyte Sedimentation Rate and CRP are the two most frequently measured laboratory tests in assessing the response of a systemic inflammatory process [6]. Thus, CRP and ESR may be very important as components of the diagnosis required in individuals with multiple comorbidities and intensive care units.

2. Methods

This research is an analytical observational study. This research conducted at the Education Hospital of Hasanuddin University as one of the hospitals that conducts examinations of COVID-19 patients in May until August 2021. Etchical recomedation by health research etchic committee faculty of Public Health University of Jember No. 55/KEPK/FKM-UNEJ/VI/2021.

The study population was COVID-19 sufferers who were treated at the Education Hospital of Hasanuddin University, Makassar. The samples in this study were patients with COVID-19 which were characterized by positive RT-PCR results and fulfill of inclussion criteria as positive RT-PCR COVID-19, Aged 21-70 years and signed of informed concent. The exclusion Criteria are lysis, icteric and lipemic samples, Pregnant and breastfeeding and suffering from malignancy.Materials and tools are rotators, plate, disposable stirring rod, ESR tube, auto ESR analyzer, CRP Latex reagent, Negative control reagent, Positive control reagent and Sodium citrate 3.2%

Erythrocyte Sedimentation Rate Check by Added blood sample into the ESR tube containing the anticoagulant Sodium citrate 3.2% Up to the limit on the tube and ESR check by Auto ESR Analyzer using the Westergreen method. Results are read in the first 30 minutes and the second 30 minutes. C-reactive protein Check by qualitative test. Placed 50 l of serum (Sample), Positive Control and negative control onto each of the dark circles on the plate. Then, added CRP latex reagent to each black circle containing the sample, positive and negative control and homogenized and run the rotator at a speed of 1000 rpm for 2 minutes. Observe the agglutination, Non Reactive : No agglutination and reactive: Agglutination is formed in the sample circle

3. Results

Characteristics of Research Subjects

The population in this study were patients who were confirmed positive based on the results of the RT-PCT examination at RSPTN UNHAS Makassar during June-August 2021. Only 32 subjects met the inclusion criteria. The characteristics of the subjects in this study were age, gender, results of laboratory tests consisting of CRP and ESR. Patient characteristics can be seen in Table 1.

Table 1. Basic characteristics of study subjects in patients with confirmed COVID-19

Subject Characteristic	Result
Age (years)	51,01 ± 16,38
Gender	
Male	14 (56,2 %)
Female	18 (43,8 %)
CRP (mg/dL)	48.00 (6.00-384.00)
ESR (mm/hour)	63.00 (8.00-150.00)

Based on Table 1, the average age of the subjects was 51.01 years which consisted of 14 (56.2%) female subjects and 18 (43.8%) male subjects. The results of the CRP showed that the median CRP value was 48.00 mg/dL with a minimum value of 6.00 mg/dL and a maximum value of 384 mg/dL. On ESR the median value was 63.00 mm/hour with a minimum value of 8.00 mm/hour and a maximum value of 150.00 mm/hour.

Relationship between CRP and ESR by gender

The results of the CRP and ESR were grouped by gender (Table 2). Based on the results in table 2 shows that there is a relationship between CRP and gender. The CRP value in male was obtained a higher median value of 96.00 with a maximum value of 384.00 compared to CRP levels in female. In female CRP levels obtained a median value of 24.00 with a maximum value of 96.00. There was no significant difference in the grouping of ESR values based on gender ($p>0.05$) while the ESR values based on sex were found to be significantly different ($p<0.05$). This shows that CRP levels are influenced by gender.

Relationship between CRP and ESR

The percentage distribution of normal and abnormal CRP and ESR results is shown in Table 3. ESR levels were grouped into 2 groups, normal and abnormal, according to criteria based on gender.

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Meanwhile, CRP levels are grouped into 2, namely, 6mg/dL (normal) and > 6 mg/dL (abnormal).

Based on the results of the Spearman Correlation test listed, in table 3 the correlation coefficient value (r) = 1,000 ($p<0.05$), a strong positive correlation which indicates there is a significant relationship between CRP levels and ESR in COVID-19 patients without comorbidities. This shows that the CRP and ESR values simultaneously affect each other. The increase in the ESR value will be accompanied by an increase in the CRP value.

Table 2. Overview of CRP and ESR examination results by gender in COVID-19 confirmed patients

Parameter	Gender		p value
	Male	Female	
ESR (mm/hour)	73.00 (8.00-150.00)	31.00 (13.00-108.00)	0,067
CRP (mg/dL)	96.00 (6.00-384.00)	24.00 (6.00-96.00)	**0,040***

**significant, P value : Nonparametric correlation test*

Table 3. The relationship between the results of the CRP and ESR examinations in patients with confirmed COVID-19

Parameter		CRP		Coefisien corelasion (r)	p value
		Normal	**Abnormal**		
ESR	**Normal**	1 (12,5%)	1 (4.2)%)	1.000	**0,030***
	Abnormal	7 (87,5%)	23 (95.8%)		

**significant, P value : nonparametric spearman correlation*

4. Discussions

This study involved subjects with confirmed COVID-19 without comorbidities who were treated at the Hasanuddin Mahassar University Hospital. This study is an analytic observational study with a total of 32 subjects who met the inclusion criteria and signed the informed consent. COVID-19 causes serious public health problems worldwide due to the high level of vulnerability to risk of death. Although treatments and prevention for COVID-19 are still in the process of being developed, various laboratory studies have been reported. This study was conducted by examining the levels of CRP and ESR values in patients who were confirmed to be COVID-19 through RT-PCR and had no comorbidities.

In this study, the number of female subjects was more than that of male subjects, unlike other studies conducted in Indonesian population. Different results conducted in Jakarta on 30 samples obtained male subjects as many as 17 people (56.7%) and female subjects as many as 13 people (43.3%) [8]. Another study conducted in Manado found that male subjects higher than women with 23 (57.5%) male and 17 (42.5%) female. The increase in cases in men indicates that women are less susceptible to viral infections. macrophage and neutrophil activity accompanied by a higher response and antibody production in women. In humans, cytokine production following ex vivo stimulation of monocytes with lipopolysaccharide (LPS) is greater in cells from males than females, with evidence that hormone-based contraceptive use in females further reduces the production of cytokines, including IFNγ and TNFa [9]. In addition, the expression of Angiotensin Converting Enzyme 2 (ACE2) was found to be higher in male than female kidneys. This may explain why men have a higher susceptibility to COVID-19 infection than women [10]. But in this study it was found that the number of subjects in women was more than men. A concomitant study reported by [11] with 82 female subjects (64.57%) and 45 male subjects (35.43%).

Based on age, the mean age was 51 years. A study with a mean age similar to this study was reported by Zhu et al. (2020) which shows a mean age of 50.9 years. In addition, the mean age in this study was slightly lower than the study conducted in Manado with the mean age of the subjects 54.4 years [10]. Adults

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were more susceptible to infection than children. This is due to the higher transmission rate. The longer duration of the viral shedding process in adults is the cause of the higher risk of exposure. In addition, the high number of cases in adults is due to various comorbidities at that age accompanied by high mobility and interaction in the work environment. Other suggested reasons include children having a more active innate immune response, healthier respiratory tracts because they have not been exposed to as much cigarette smoke and air pollution as adults, and fewer underlying disorders. A more vigorous immune response in adults may also explain a detrimental immune response that is associated with acute respiratory distress syndrome [12].

Other studies show that the mortality rate is more vulnerable at the age of > 60 years. This is probably due to a weaker immune system compared to those under 60 years of age. Ageing is associated with modified function of both innate and adaptive immunity. The changes occurring in ageing immune system are responsible for increased severity and deadliness of COVID-19 in the elderly. The phenomena describing changes in the aging immune system are immunosenescence and inflammageing, which develop in time depending on challenges to the individual immune system (immunobiography). Thus, the immunosenescence and inflammaging may aggravate, but also may be aggravated by SARS-CoV-2 infection [13]. In addition, other findings suggest that the mortality rate in male appears to be higher than in female. This trend is likely due to the generally immune response in male resulting in a less robust immune response and greater susceptibility to various infectious agents. Some study show that in the plasma of male patients has higher levels of several cytokines like IL-8, compared to female patients. The higher plasma levels of IL-8 are significantly correlated with the decrease in lymphocytes, and lymphopenia (especially the decrease in T cells) is predictive of COVID-19 disease progression [14]. In contrast, female have stronger innate and adaptive immune responses and are relatively resistant to viral infections. Furthermore, previous studies revealed that ACE2 as a receptor for SARS-CoV2 is highly expressed in normal male lung tissue, whereas in female receptors, ACE2 expression can be downregulated by 17β-estradiol [15].

C-Reactive Protein and ESR are the most common tests performed to assess the inflammatory response. In this study, the median value for CRP and ESR levels was higher than the normal limit. This shows that in COVID-19 patients there is an increase in CRP and ESR levels. This study found that 24 subjects with COVID-19 experienced increase in CRP levels. The median value of CRP levels obtained in this study was 48.00. A study with the same median value was conducted by Wang (2020) which showed that in COVID-19 patients with disease progression from non-severe to severe it was 43.8 (12.3–101.9). This indicates that there is an increase in CRP levels as an early marker in predicting the severity of COVID-19 patients and helps health workers to identify treatments at an early stage. The same study conducted by Chen et al. (2020) showed that there was an increase in ESR and CRP in COVID-19 patients. The increase in these parameters as markers of inflammation reached 85% for ESR and 86% for CRP levels. Based on the report of Mus et al. (2021) that CRP in the group of patients with severe conditions increased than patients in the group of mild conditions.

Research studies have also looked at CRP and ESR levels as well as various other inflammatory markers. Most cases of COVID-19 show elevated CRP and ESR levels but procalcitonin levels are usually normal. Elevated procalcitonin levels may indicate bacterial coinfection. On hospitalization, many cases of pneumonia have normal serum procalcitonin but, in cases requiring intensive care unit management, elevated procalcitonin levels. In addition, elevated D-dimer levels and more severe lymphopenia have been shown to be associated with mortality [17]. Another study conducted by Zhu et al. (2020) by comparing various laboratory parameters in COVID-19 patients with severe and non-severe symptoms. In this study, it was found that there was no difference between ESR levels in patients with mild symptoms and patients with severe symptoms. Different things were found in CRP levels, which were found to be significant differences. C- Reactive Protein as an acute phase reactive protein, and parallels the severity of inflammation. A previous study and a recent study revealed its role in predicting the severity of patients with SARS and SARS-CoV-2.

This study showed a strong correlation between CRP and ESR examinations. The correlation between CRP and ESR shows a positive and strong correlation. The same study conducted by Zhang et al. (2020) showed that CRP had a significant positive effect on the ESR. An increase in CRP also resulted in a significant increase in ESR. SARS-CoV-2 infection triggers an inflammatory storm in patients with COVID-19. To enable the human body to have non-specific resistance to defeat the virus, CRP plays a positive role in the inflammatory response. In addition, studies have shown that continuous measurement of the inflammatory marker CRP can be used as a predictor of prognostic factors. A plausible explanation is that infection with the novel coronavirus causes a significant increase in CRP, which leads to an increase

in ESR. In addition, according to Mus et al. (2021) that increased CRP levels indicate an inflammatory process during infection with COVID-19.

C-Reactive Protein (CRP) as a protein produced by the liver that is determined in response to inflammation. Generally, CRP levels are much higher in bacterial infections than in viral infections. Severe cases show significantly higher CRP levels than non-severe patients. This suggests that CRP can be a marker of severity in COVID-19 patients [18]. Erythrocyte Sedimentation Rate as a non-specific test. Elevated levels of ESR can be found in various acute inflammatory processes, acute and chronic infections, tissue damage (necrosis), rheumatoid, collagen disease, malignancies and physiological stress conditions (pregnancy). The ESR is not for some hematologists unreliable because it is not a specific test. In addition, ESR levels can be influenced by physiological factors that can lead to inaccurate findings [19]. ESR levels are also influenced by various factors, such as anemia, pregnancy, hemoglobinopathies, hemoconcentration, and use of anti-inflammatory drugs [6].

Based on this finding, although less specific than CRP, ESR could serve as an alternative method to measure the level of inflammation in COVID-19 particularly in peripheral health centers

The limitation in this study was the number of subjects is less because most of the confirmed COVID-19 patients suffer from comorbid diseases so they must be excluded. In addition, most of the patients were not willing to be research subjects, thus reducing the amount of data obtained. Several significant values in this study such as the relationship between CRP values and gender and the relationship between ESR and CRP required a large sample size and multicenter study to confirm these results.

5. Conclusion

The conclusion was the average age of the subjects was 51 years consisting of 14 (56.2%) female subjects and 18 (43.8%) male subjects. The median value of CRP was 48.00 mg/dL and the median value of ESR was 63.00 mm/hour. There is a significant difference between the CRP values in male and female subjects and there is a significant relationship between CRP and ESR values with a strong positive relationship.

Ethical Approval

Etchical recomedation by health research etchic committee faculty of Public Health University of Jember No. 55/KEPK/FKM-UNEJ/VI/2021.

Conflicts of Interest

There is no conflict interest in this research

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Author Contributions

Conceptualization, RM and RA; methodology, RM, RA and I; software, RM; validation, RM, RA, I, TA; formal analysis, RM; investigation, RM; resources, RM; data curation, RM; writing—original draft preparation, RM; writing—review and editing, RM; funding acquisition, RM.

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Reference

1. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;18:1–13.

2. Susilo A, Rumende CM, Pitoyo CW, Santoso WD, Yulianti M, Sinto R, et al. Coronavirus Disease 2019 : Tinjauan Literatur Terkini Coronavirus Disease 2019 : Review of Current Literatures. J Penyakit Dalam Indones. 2020;7(1):45–67.

3. Satgas. Satuan tugas penanganan COVID-19. 2020.

4. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect [Internet]. 2020;50(4):332–4. Available from: https://doi.org/10.1016/j.medmal.2020.03.007

5. Chen W, Zheng KI, Liu S, Yan Z, Xu C, Qiao Z. Plasma CRP level is positively associated with the severity of COVID-19. Ann Clin Microbiol Antimicrob [Internet]. 2020;19:1–7. Available from: https://doi.org/10.1186/s12941-020-00362-2

6. Bayu Fajar Wibowo, Manjas M, Sahputra RE,

Erkadius. Hubungan pemeriksaan LED dan CRP pada penegakkan diagnosis Spondilitis Tb di RSUP dr. M. Djamil Padang tahun 2014-2016. Maj Kedokt andalas. 2018;41(2):69–77.

7. Zhang W, Yuan Y, Zhang S, Jin C, Wu L, Mei H, et al. Erythrocyte Sedimentation Rate in COVID-19 Infections. Guizhou University School of Medicine, China; 2020.

8. Permana A, Yari CE, Aditya AK. Gambaran D-Dimer Dan Limfosit Pada Pasien Terkonfirmasi Covid-19 Di. 2021;7(1):62–71.

9. Jacobsen H, Klein SL. Sex Differences in Immunity to Viral Infections. Front Immunol. 2021;12(August):26–9.

10. Berhandus C, Ongkowijaya JA, Pandelaki K. Hubungan Kadar Vitamin D dan Kadar C-Reactive Protein dengan Klinis Pasien Coronavirus Disease 2019. 2021;9(28):370–8.

11. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis. 2020;95:332–9.

12. Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? J Microbiol Immunol Infect. 2020;53(3):371–2.

13. Witkowski JM, Fulop T, Bryl E. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information. Mech Ageing Dev. 2022;(January).

14. Takahashi T, Wong P, Ellingson MK, Lucas C, Klein J, Israelow B, et al. Sex differences in immune responses to SARS-CoV-2 that underlie disease outcomes. MedRxiv. 2020;

15. Ysrafil Y, Astuti I, Mus R, Gama NI, Rahmaisyah D, Nur'Amalia R. A summary of coronavirus disease 2019: What we should know? Pharm Sci. 2020;26(Suppl 1):S24–35.

16. Mus R, Thaslifa T, Abbas M, Sunaidi Y. Studi Literatur: Tinjauan Pemeriksaan Laboratorium pada Pasien COVID-19. J Kesehat Vokasional. 2021;5(4):242.

17. Ozdemir O. Coronavirus Disease 2019 (COVID-19): Diagnosis and Management (narrative review). Erciyes Med J. 2020;42(3):242–7.

18. Wang G, Wu C, Zhang Q, Wu F, Yu B, Lv J, et al. C-Reactive Protein Level May Predict the Risk of COVID- 19 Aggravation. Open Forum Infect Dis. 2020;7(5):1–5.

19. Selva P. Skripsi hubungan kadar c-reaktif protein (crp) dan laju endap darah (led) pada pasien. Universitas SUmatera Utara, Medan; 2016.