



(RESEARCH ARTICLE)



## Correlation between CRP levels and RALE Score in COVID-19 patients with hypertension

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### Abstract

Coronavirus Disease 2019 (COVID-19) is a disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. Hypertension is one of the comorbidities of COVID-19 which has a 1.442 times greater risk of worsening the body's condition than patients without hypertension. Radiographic Assessment of Lung Edema (RALE) score is a radiologic numerical scoring system in determining the severity of lung lesions based on the degree of consolidation and density of opacification on chest X-rays. Examination of CRP levels in COVID-19 patients is the initial examination of hospital admission to assess the inflammation that occurs. Therefore, the researcher aims to analyze the correlation of the CRP level examination in representing the severity of COVID-19 disease experienced by patients using the RALE score. The research method used was cross sectional analytic observational method. The subjects in the study were patients diagnosed with COVID-19 with comorbid hypertension at Dr. Moewardi Hospital, Surakarta in March 2021 - March 2022. The data obtained were then analyzed using Mann-Whitney U test and Spearman's rho bivariate correlation analysis. The results analyzed from 115 patient samples obtained the mean RALE score was 13.75. As for CRP levels, this study obtained an average of 8.0473 mg/dl. In this study, there was a significant correlation with a weak correlation level and one way correlation direction between RALE score and CRP levels ( $p = 0,02$ ;  $r = 0.287$ ). In conclusion, There is a significant relationship between the RALE score of thoracic photographs and CRP levels of COVID-19 patients with hypertension

**Keywords:** COVID-19; C - reactive protein (CRP); RALE score; Hypertension

### 1. Introduction

Coronavirus Disease 2019 (COVID-19) is a disease caused by a virus in the Coronaviridae family, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This disease is contagious among animals and humans. On January 30, 2020, the World Health Organization (WHO) determined COVID-19 as a Public Health Emergency of International Concern (PHEIC), and on March 11, 2020 the disease was determined as a pandemic in the world [1]. As of October 20, 2021, WHO reported that the total positive cases of COVID-19 were 241,413,380 with 4,912,122 deaths in the world. Meanwhile, in Indonesia, there were 4,237,201 positive cases of COVID-19 with 143,077 deaths [2]. As of October 20, 2021, WHO reported a total of 241,413,380 positive cases of COVID-19 with 4,912,122 deaths in the world. Meanwhile, in Indonesia, there were 4,237,201 positive cases of COVID-19 with 143,077 deaths [2].

Symptoms of COVID-19 can be divided into mild symptoms, moderate symptoms or severe symptoms. This can be influenced by various risk factors, one of which is comorbidities such as hypertension, diabetes mellitus, and asthma. Hypertension is a condition of the body when the increase in blood pressure is high enough in the arteries. Normal blood

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pressure is 90/60 mmHg- 120/80 mmHg. A comorbid history of hypertension can increase the risk of mortality in COVID-19 patients [3].

There was an increase in C-Reactive Protein (CRP) and Interleukin-6 (IL-6) levels in COVID-19 patients. Increased CRP levels are associated with increased production of excessive inflammatory cytokines in COVID-19 patients. Inflammatory cytokines play a role in the defense and immune system against COVID-19 infection. In COVID-19 patients, there is an increase in inflammatory cytokines so that it can become a cytokine storm. Cytokine storms and tissue damage processes in COVID-19 patients can induce the production of CRP. Increased CRP levels can be one of the early indications of COVID-19 disease [4].

In a study by Luo examined the medical records of COVID-19 patients and found that CRP levels can be used as a screening and determinant of the severity of COVID-19 infection [5]. In a study also showed the same results, namely as many as 92.85% of samples of COVID-19 patients had increased CRP levels. In COVID-19 patients with elevated CRP levels, it indicates that there is inflammatory stress and can lead to the appearance of severe clinical manifestations and even death in patients [6].

Thoracic radiology photos in COVID-19 patients have a very important role. The thoracic radiographic examination has 2 score systems, namely the Brixia score and the RALE score, which is done by dividing the lungs into 2 regions, the left lung and the right lung. Each lung is given a score from 0 to 4 with a maximum score of 8. With this score system, it can categorize whether the symptoms of shortness of breath are included in the mild or severe level [7]. This study aims to analyze the effectiveness of examining CRP levels in representing the severity of COVID-19 disease (radiological profile) experienced by patients using the RALE score.

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## 2. Material and methods

This study is an analytic observational study with a cross-sectional approach. The study was conducted at Dr. Moewardi Hospital Surakarta using medical record data and thoracic x-rays. The research subjects were patients with COVID-19 comorbid hypertension who were treated in the COVID-19 isolation treatment room and radiology installation at Dr. Moewardi Surakarta Hospital. The inclusion criteria of the study subjects included patients diagnosed with COVID-19, patients who performed thoracic radiography and CRP examinations, and patients aged  $\geq 18$  years with comorbid hypertension. Exclusion criteria in this study include patients with incomplete medical record data, patients with a history of pulmonary TB treatment, and patients aged  $> 18$  years with comorbid DM. The study sample amounted to 98 samples with sampling using simple random sampling technique.

The independent variable of this study is the CRP level of COVID-19 patients. CRP is one of the acute inflammatory proteins in COVID-19 patients. The dependent variable of this study is the RALE score. RALE score is a scoring performed on thoracic radiographs in an ordinal manner. Thoracic radiography is a supporting examination with the help of electromagnetic wave radiation which aims to provide an overview of the inside of the thorax. In this study, the population used was COVID-19 patients with comorbid hypertension at Dr. Moewardi Hospital and in the period between March 2021 - March 2022.

The data analysis technique in this study used the Mann-Whitney U test, which is a correlation test for ratio and ordinal data. This test was performed to determine the difference between the average RALE scores of patients with normal and high CRP levels. Data will be tested for normality with the Kolmogorov-Smirnov test because the sample size is greater than or equal to 50. The results of the normality test show that the data are normally distributed so the Pearson test will be used.

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## 3. Results

### 3.1. Sample Characteristics

A total of 115 patients with a diagnosis of COVID-19 with comorbid hypertension at Dr. Moewardi Hospital, Surakarta in March 2021 - March 2022, who met the inclusion and exclusion criteria were involved in this study.

An overview of the basic characteristics of research subjects of COVID-19 patients with comorbid hypertension based on age and gender can be seen in table 1 below.

**Table 1** Sample Characteristics

| Variable         |               | N (%)        |
|------------------|---------------|--------------|
| <b>Age</b>       |               |              |
|                  | <20           | 1 (0.87%)    |
|                  | 21-40         | 8 (6.96%)    |
|                  | 41-60         | 51 (44.34%)  |
|                  | 61-80         | 52 (45.23%)  |
|                  | >80           | 3 (2.6%)     |
| <b>Gender</b>    |               |              |
|                  | Male          | 68 (59.1%)   |
|                  | Female        | 47 (40.9%)   |
| <b>CRP Level</b> |               |              |
|                  | Normal        | 11 (9.57%)   |
|                  | High          | 104 (90.43%) |
| <b>Drug</b>      |               |              |
|                  | Ramipiril     | 28 (24.34%)  |
|                  | Lisinopril    | 1 (0.87%)    |
|                  | Candesartan   | 73 (63.48%)  |
|                  | Valsartan     | 1 (0.87%)    |
|                  | Bisoprolol    | 36 (31.3%)   |
|                  | Propanolol    | 4 (3.48%)    |
|                  | Amlodipine    | 76 (66.1%)   |
|                  | Nifedipine    | 5 (4.3%)     |
|                  | Nicardipine   | 10 (8.7%)    |
|                  | Furosemide    | 61 (53%)     |
|                  | Spironolacton | 15 (13%)     |
|                  | Clonidine     | 20 (17.4%)   |

Table 2 shows the characteristics of RALE score. The determination of the RALE score in this study is a scale calculated from the X-ray on the date the patient was hospitalized. The results of the thoracic X-ray examination taken in this study have been assessed using the RALE score method and obtained an average of 13.75. RALE score data obtained after assessment, namely with a minimum score of 4 and a maximum of 48 and with a median of 8 from 115 total samples of COVID-19 patients admitted to Moewardi Hospital during the period March 2021 to March 2022.

**Table 2** Description of COVID-19 RALE Score at Moewardi Hospital

| Variable   | n   | Mean $\pm$ Standard Deviation | Median (Min - Max) |
|------------|-----|-------------------------------|--------------------|
| RALE score | 115 | 13.75 $\pm$ 12.373            | 8 (4 - 48)         |

Table 3 shows the characteristics of CRP Level Examination Results. The results of the laboratory examination of CRP levels taken in this study showed an increase in CRP levels in 107 (90.7%) COVID-19 patients with minimum data of

CRP levels of 0.01 mg/dL and the highest of 35.84 mg/dL in COVID-19 patients treated at Moewardi Hospital during the period March 2021 to March 2022.

**Table 3** Description of CRP Level Examination Results of COVID-19 Patients at Moewardi Hospital

| Variable            | n   | Mean ± Standard Deviation | Median (Min - Max)     |
|---------------------|-----|---------------------------|------------------------|
| CRP                 | 115 | 8.0473 ± 7.48151          | 5.58<br>(0.01 - 35.84) |
| Normal (<0,9 mg/dL) | 11  |                           |                        |
| High (≥ 0,9 mg/dL)  | 104 |                           |                        |

### 3.2. Data analysis

Data from the results of the study were tested for normality with the Kolmogorov-Smirnov test because the number of samples used was  $\geq 50$ , namely 115 samples. The results of the normality test for the CRP and RALE score variables using the Kolmogorov test showed that the data were not normally distributed because the significance value of  $p = 0.02$ . Data distribution is considered normal if the  $p$  value is  $> 0.05$ , and not normally distributed if the  $p$  value is  $< 0.05$ . The variables of gender, comorbidities, and medication were not tested for normality because they were nominal categorical variables.

Furthermore, the results of the non-parametric Mann-Whitney U test were carried out and the results are described in table 4, there is a difference in the significance value of the degree of RALE score higher in COVID-19 patients with high CRP levels ( $\geq 0.9$  mg/dL) than COVID-19 patients with normal CRP levels ( $< 0.9$  mg/dL). The results of the non-parametric Mann-Whitney U test for the variables of CRP levels and RALE score show that the hypothesis is accepted because the Asymp. Sig  $< 0.05$ . The hypothesis is accepted if the Asymp.Sig value is  $< 0.05$  and the hypothesis is rejected if the Asymp Sig value is  $> 0.05$ . So there is a difference in the average RALE score of COVID-19 patients with comorbid hypertension with normal CRP and high CRP.

**Table 4** Non-parametric Mann-Whitney U test of COVID-19 Patients with Average RALE Score at Moewardi Hospital

|            | CRP Classification | N   | Mean Rank | Sum of Ranks |
|------------|--------------------|-----|-----------|--------------|
| RALE score | Normal             | 11  | 31.50     | 346.50       |
|            | Tinggi             | 104 | 60.80     | 6323.50      |
|            | Total              | 115 |           |              |

|                        | RALE score |
|------------------------|------------|
| Mann-Whitney U         | 280.500    |
| Wilcoxon W             | 346.500    |
| Z                      | -2.800     |
| Asymp. Sig. (2-tailed) | 0.005      |

To determine the correlation between CRP levels and RALE score of COVID-19 patients, a bivariate test was conducted using Spearman's rho correlation test because the research data was not normally distributed. In the Spearman's rho bivariate correlation test, the relationship between variables is declared unidirectionally correlated if the Spearman's rho ( $r$ ) value is positive and there is a significant correlation if the significance value ( $p$ )  $< 0.05$ .

The results of the Spearman's rho bivariate correlation test in the study showed a significance value ( $p$ ) of less than 0.05, and a Spearman's rho ( $r$ ) value of 0.287, so there is a significant correlation between CRP levels and RALE score in the picture of COVID-19 patients with a weak correlation level. The direction of the correlation between CRP levels and RALE score in this study was found to be unidirectional, which means that the higher the CRP levels, the higher the patient will also be because the positive Spearman's rho value was obtained.

**Table 5** Research Sample Correlation Test Using Spearman's rho Test

|            |   | <b>CRP</b> |
|------------|---|------------|
| RALE score | r | 0,287      |
|            | p | 0,002      |
|            | N | 115        |

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#### 4. Discussion

This study is an observational study with a cross sectional approach. The purpose of this study was to determine whether there is a relationship between CRP levels and severity of RALE Score in COVID-19 patients with hypertension in COVID-19 patients at Moewardi Hospital, Surakarta.

The results showed that the average CRP level of 115 COVID-19 patients treated at Moewardi Hospital was 8.0473 mg/dL, where the normal level of CRP itself was >0.9 mg/dL. where the RALE acceptance score is positively correlated with several hemograms such as CRP and inflammatory parameters in patients with COVID-19 [8].

Increased CRP levels are related to the overproduction of inflammatory cytokines in COVID-19 patients. Cytokines fight microbes but when the immune system becomes hyperactive, it can damage lung tissue. Thus, CRP production is induced by inflammatory cytokines and causes an increase in CRP levels.

The mean RALE score of 115 COVID-19 patients treated at Moewardi Hospital was 13.75, with a minimum RALE score of 4 and a maximum RALE score of 4.

The average RALE score in this study is lower than the research conducted by Aggarwal et al. [9], where the average RALE score in that study was 26.63. This is in line with research from Marques et al.[8], that the RALE admission score is positively correlated with several hemograms and inflammatory parameters in patients with COVID-19 with evidence that the RALE score correlates with the inflammatory status of patients with COVID-19, which can predict the worsening of COVID-19 during hospitalization.

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#### 5. Conclusion

Based on the results of this study, it was found that there was a significant correlation with a weak correlation level and one way correlation direction between CRP levels and RALE score

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#### Compliance with ethical standards

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##### *Disclosure of conflict of interest*

This study has no conflicts of interest.

##### *Statement of ethical approval*

The Research Ethics Committee at Dr. Moewardi Hospital Surakarta issued the ethical clearance approval letter, No. 893/VI/HREC/2022.

##### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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## References

- [1] Kementerian Kesehatan. KESIAPAN KEMENKES DALAM MENGHADAPI OUTBREAK NOVEL CORONAVIRUS (2019-nCoV)[Internet]. 2020 Jan. Available from: <https://www.papdi.or.id/pdfs/817/dr%20Siti%20Nadia%20%20Kemendes%20RI.pdf>
- [2] World Health Organization. Hypertension [Internet]. Who.int. World Health Organization: WHO; 2021. Available from: <https://www.who.int/news-room/fact-sheets/detail/hypertension>
- [3] Drew C, Adisasmita AC. Gejala dan komorbid yang memengaruhi mortalitas pasien positif COVID-19 di Jakarta Timur, Maret-September 2020. *Tarumanagara Medical Journal*. 2021 Apr 30;3(1):42–51.
- [4] Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. *Journal of Medical Virology*. 2020 Jun 9;2(1).
- [5] Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, et al. Prognostic value of C-reactive protein in patients with COVID-19. *Clinical Infectious Diseases*. 2020 May 23;71(16):2174–9
- [6] Bedah S, Chairlan, Sari IN. Respons C-Reactive Protein (CRP) dan Laju Endap Darah (LED) Sebagai Petanda Inflamasi Pada Pasien Covid-19. *Jurnal Ilmiah Analisis Kesehatan*. 2021 Sep;7(2):157–64.
- [7] Warren MA, Zhao Z, Koyama T, Bastarache JA, Shaver CM, Semler MW, et al. Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. *Thorax*. 2018 Jun 14;73(9):840–6.
- [8] Marques P, Fernandez-Presa L, Carretero A, Gómez-Cabrera M-C, Viña J, Signes-Costa J, et al. The radiographic assessment of lung edema score of lung edema severity correlates with inflammatory parameters in patients with coronavirus disease 2019—Potential new admission biomarkers to predict coronavirus disease 2019 worsening. *Frontiers in Medicine*. 2022 Aug 11;9.
- [9] Aggarwal Y, Malhotra A, Arora D, Kumar A, Bhandari V. Correlation of chest radiographic findings and coagulation abnormality with disease severity in COVID-19 positive patients. *Acta Medica International*. 2021;8(2):155