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The association of baseline C-reactive protein and D-dimer levels with six-minute walk test in severe COVID-19 survivors

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***Abstract*---**The post-COVID-19 syndrome can affect the patients' activities. The hyperinflammatory response resulting in permanent organ system damage or prolonged inflammation is thought to cause persistent symptoms. Inflammatory and coagulation markers C-reactive protein (CRP) and d-dimer may increase in acute phase of SARS-CoV-2 infection and associated with unexpected outcome. Therefore, the researcher wanted to assess the association of baseline CRP and d-dimer levels with the six-minute walk test (6MWT) in severe COVID-19 survivors. This is a cross-sectional, observational analytic study. A total 80 participants were included in this study. The proportion of subjects with poor results of 6MWT was 71.3%. Bivariate analysis of high baseline level of CRP and d-dimer, and age 65 years old on the 6MWT showed significant results, with prevalence ratio (PR) consecutively 1.8 (95% CI1.408-2.284;p= <0.001),1.4 (95% CI1.165-1.796;p=0.018) , and 1.5 (95% CI 1.287-1.831; p= 0.008). Based on multivariate analysis, only high baseline level of CRP was significant (PR = 1.8, 95% CI 1.051-3.136; p = 0.032). The proportion of severe COVID-19 survivors with poor 6MWT was high. There is a significant association between high baseline levels of CRP with a poor 6MWT in severe COVID-19 survivors.

***Keywords*---**CRP, d-dimer, 6MWT, severe COVID-19 survivors.

Introduction

Coronavirus disease 2019 (COVID-19) does not only induce clinical issues during the acute infection phase. The course of the disease may differ in each case, and some people with COVID-19 may experience persistent symptoms or conditions referred to as a post-COVID-19 syndrome. It is unclear how the post-COVID-19 syndrome occurs, but the hyperinflammatory response that results in continuous organ system damage and prolonged inflammation is thought to play a role in the pathogenesis (Goërtz et al., 2020; Lopez-Leon et al., 2021; Stavem et al., 2021; Burhan, 2022). The persistent condition suffered by survivors, in addition to interfering with the patient's daily living, can also affect their productivity, especially those previously active (Anastasio et al., 2021; Nalbandian et al., 2021; Wu et al., 2021).

Most studies assessed the role of biomarkers in COVID-19, mainly their function during the acute phase. C-reactive protein (CRP) is a marker sensitive to inflammation, infection, and tissue damage. High levels of CRP in COVID-19 have been linked to unexpected outcomes, such as worsening acute respiratory distress syndrome and death. Higher CRP means have been obtained in patients

with persistent COVID-19 symptoms (Luo et al., 2020; Smilowitz et al., 2021; Pambudi, 2022).

D-dimer is a product of the degeneration of fibrin crosslinking by plasmin activity in the fibrinolytic system, often used as one of the diagnostic supports for thrombosis-related disease. In COVID-19, it has been proven that coagulation function is impaired, characterized by the increase in serum d-dimer levels. Some studies have found that high levels of d-dimer may persist over a long period (Marchandot et al., 2020; Sayed et al., 2020; Asakura and Ogawa, 2021; Nalugo et al., 2021; Zhan et al., 2021).

Studies of various biomarkers in COVID-19, such as CRP and d-dimer, are limited in the relationship with long-term functional capacity changes. The main goal of this study was to determine the proportion of poor six-minute walk test (6MWT) results in severe COVID-19 survivors. Second, this study aims to determine the association of baseline CRP and d-dimer levels with a 6MWT in severe COVID-19 survivors.

Method

This is an analytical observational study with a cross-sectional design. The study was conducted from January to May 2022 in Prof. Dr. IGNG Ngoerah General Hospital. The inclusion criteria were severe COVID-19 survivors confirmed based on positive SARS-CoV-2 reverse transcription polymerase chain reaction (rt-PCR) results previously received treatment in the Prof. Dr. IGNG Ngoerah General Hospital, aged 18 years old and at least 12 weeks have passed since being confirmed with COVID-19. Exclusion criteria in this study are patients with incomplete medical record data, the presence of secondary infections until the time of being treated for COVID-19, and patients with comorbid diseases before being confirmed with COVID-19 (including heart failure, chronic lung disease, musculoskeletal deformities, chronic renal failure, and malignancy), pregnancy, patients with contraindications for conducting a 6MWT by American Thoracic Society (ATS) guidelines, patients who underwent medical rehabilitation therapy after COVID-19 infection, the presence of vestibular disorders, and those who refused to participate.

Data was collected in outpatient service by consecutive sampling. Subjects who met the requirements after applying the exclusion criteria met a 6MWT on a 15-meter track with test procedures according to ATS guidelines. At the same time, baseline CRP and d-dimer levels during hospitalization were taken from medical records. The results of the 6MWT were then categorized based on "poor" (<483 meters for males and <442 meters for females) and "normal" (≥483 meters for males and ≥442 meters for females). Baseline CRP and d-dimer levels were each categorized into "high" and "normal," which were grouped by the category of 6MWT. Subjects unable to complete the test will be considered as drop out.

The Shapiro-Wilk test was used for the normality test. Univariate analysis displayed the mean, standard deviation, relative frequency, and percentage for categorical data. The chi-square test performed bivariate analysis—Cox regression to assess the relationship between baseline CRP and d-dimer levels and

covariates with the 6MWT. The entire data was analyzed with IBM® SPSS® Statistics 25.0 software.

Results and Discussion

A total of 80 COVID-19 survivors were included in this research. None of the subjects dropped out of this study. The characteristics of the research subjects are found in Table 1. The mean age ± SB is 51.4 ± 14.55 years, with relatively more gender being male (56.3%). These results are not much different from the study by Huang et al., (2021), which examined the consequences six months after COVID-19 infection in Wuhan, China. The study found a median age of 57 (48-65) with a male percentage of 52 percent in patients previously treated with oxygen supplementation. Sixty-five years or older is a risk factor for severe COVID-19 and death. Older people tend to have immune defects. This condition may explain why more severe COVID-19 survivors are found at fewer than 65 years (Chen et al., 2021)

Table 1.
Demographic and clinical characteristics

Variable	n = 80
Age, year	51.4±14.55
65 years old	14 (17.5%)
Male	45 (56.3%)
BMI, kg/m2	25.9 ± 4.21
Obesity	14 (17.5%)
Smoker	22 (27.5%)
Hypertension	16 (20%)
Diabetes mellitus	19 (23.8%)
Duration from confirmed, week	30 (12-32)
Duration from confirmed 12-16 weeks	25 (31.3%)
Los[a], day	9 (3-30)
Los 14 days	17 (21.3%)
CRP[a], mg/L	60.45 (2.1-330.7)
High baseline CRP	28 (35%)
D-dimer[a], µg/mL	1.0 (0.13-22.24)
High baseline d-dimer	17 (21.3%)
6MWT, meters	400.5 ± 79.96
Poor 6MWT	57 (71.3%)

a non-normal data distribution, shown as median (min-max); BMI: Body Mass Index; LOS: Length of stay; CRP: C-reactive protein; 6MWT: six-minute walk test

The average body mass index (BMI) was 25.9 ± 4.21 kg/m2, indicating that the average subject was overweight. Obesity was obtained as much as 17.5 percent. Similar results were obtained in the study by Vimercati et al., (2021) in Bari, Italy. Although it was conducted on a specific population (health workers), the study found a mean BMI of 24.8 ± 4.2 in subjects with post-COVID-19 syndrome. This study found that in addition to respiratory problems when first infected, a BMI greater than or equal to 25 kg/m2 increased the risk of post-COVID-19 syndrome (OR = 1.6, 95% CI 1.05-2.56; p-value = 0.029). Another study that assessed

obesity as a risk factor was conducted by Aminian et al., (2021) found that moderate and severe obesity (BMI 35 kg/m2) was associated with a greater risk of post-acute COVID-19 sequelae. Compared with patients with normal BMI, the risk of needing hospitalization was 28 and 30 percent higher in moderate and severe obesity, respectively. In general, it is known that obesity is a condition that can trigger inflammation, thrombotic disease, and immune system disorders and is associated with cardiovascular, pulmonary, and metabolic diseases. Obesity is a significant risk factor for developing severe degrees of COVID-19 and death from COVID-19.

Based on smoking history, it was found that 27.5 percent were active smokers and the remaining 72.5 percent had no smoking history. A recent study reported that the expression of the ACE2 gene was more prevalent in subjects who smoked than non-smokers. This may impact smokers' susceptibility to infection with SARS-CoV-2 (Brake et al., 2020). Twenty percent of subjects in this study had comorbid hypertension. A meta-analysis study by Yang et al., (2020) shows that hypertension is the most common comorbid in patients with confirmed COVID-19, which is 17 ± 7 percent, 95% CI 14-22 percent. The association of SARS-CoV-2 with ACE2 suggests the involvement of hypertension in the pathogenesis of COVID-19. Angiotensin Converting Enzyme-2 is a critical element of the renin-angiotensin-aldosterone system (RAAS), an essential hormonal pathway involved in the pathogenesis of hypertension (Kamyshnyi et al., 2020).

Comorbid diabetes mellitus was obtained by 23.8 percent (n = 19). The study by Huang et al., (2021) that examined the consequences of COVID-19 patients six months after discharge from the hospital found that the proportion of subjects with diabetes mellitus was 11 percent of the total subjects requiring oxygen supplementation during treatment. This difference is probably related to the two studies' different sample sizes and study populations. Diabetes mellitus is a condition that can affect the immune system due to impaired chemotaxis of neutrophil cells and phagocytic function, which tends to cause diabetics to be susceptible to infection (Singh et al., 2020).

The group with a confirmed duration of more than 16 weeks was found to be more, which was 68.8 percent, with a median of 30 (12-32) weeks. The median length of stay was 9 (3-30) days and the subjects who received treatment for more than or equal to 14 days were 21.3 percent (n = 17). This characteristic of the length of stay is similar to the study by Goshayeshi et al., (2021) in Iran, which received a median length of stay of 9 (6-14) days. Data that can be biased can occur for the length of stay, considering that the length of stay at various COVID-19 treatment sites follows the local service protocol. Subjects with CRP levels at the time of treatment are above 90 mg/L, as much as 35 percent, with a median CRP level of 60.45 (2.1-330.7) mg/L. This result is similar to the study by Niyatiwatchanchai et al., (2022), which found a median CRP of 67.8 (28, 8-122.6) mg/L. The study by Sirayder et al., (2022) found that the average CRP value for severe COVID-19 was 42.3 ± 46.5 mg/L. Previous research in Prof. Dr. IGNG Ngoerah General Hospital in Denpasar by Pambudi et al., (2022) showed the average CRP level in severe COVID-19 was 123.7 ± 108.9. This value is slightly different from this study but it may related to the different sample distribution between the two studies.

Subjects with a d-dimer level of more than or equal to 2.6 g/ml obtained 21.3 percent with a median d-dimer level of 1.0 (0.13-22.24) g/ml. Different results were obtained in the study by Eksombatchai et al., (2021) with a median of d-dimer 0.287, interquartile range 0.189-0.447 g/ml (units converted from ng/ml) for total subjects (n= 87), and 0.545, the range interquartile 0.427-2.510 g/ml, in the group with severe pneumonia (n = 7). These differences may be related to the different research sample criteria of the two studies. Another study by Sirayder et al., (2022) found a mean value of d-dimer of 0.829 ± 1.027 µg/ml (units converted from µg/L).

This study measures the distance traveled in the 6MWT in meters and determines the cut value according to the study by Nusdwinuringtyas, (2018) to categorize subjects into groups with poor 6MWT results and normal 6MWT results groups. To date, no studies have assessed the proportion of poor and normal 6MWT results in COVID-19 survivors. This study showed that the proportion of patients with poor 6MWT results was 71.3 percent.

Based on the bivariate analysis results in Table 2 there was a significant association of high baseline CRP levels and poor results on the 6MWT (PR = 1.8, 95% CI 1.408-2.284; p = <0.001). A study with a different design but showing results in line with this study was conducted by Sirayder et al., (2022). The study examined the long-term characteristics of lung function, functional capacity, and quality of life in subjects with a history of severe COVID-19. Specifically, it assessed the correlation of CRP with the 6MWT and found that CRP levels were negatively correlated with the distance of the 6MWT (r = -0.460, p = 0.01).

Several studies evaluated functional capacity in COVID-19 survivors hospitalized in the acute phase. The study by Bretas et al., (2022) in Brazil assessed 6MWT in hospitalized patients on day 45 and day 180. This study found a significant improvement at the two measurement times. Separately, this study noted an increase in CRP levels and other inflammatory markers from normal values between the group receiving treatment in the standard room and the group receiving intensive care. However, it did not assess its relationship with the functional status studied.

Another study by Ferioli et al., (2022) in Bologna, Italy, evaluated clinical improvement at two examination times (two and six months after acute COVID-19 infection) using parameters of clinical symptoms, pulmonary function test, 6MWT, and blood gas analysis. Similar to previous studies, this study also only identified a significant improvement in the average six-minute walking test mileage and the percent predicted prospectively assessed. Data on CRP at the time of hospital admission were presented in this study, but based on the mean value, no significant increase in levels was found (6 ± 6, p = 0.092), so no comparison could be made.

A prospective study by Moreno-pérez et al., (2021)examining the incidence and risk factors for the COVID-19 post-acute syndrome, including baseline CRP and d-dimer, found that CRP was not an independent risk factor for the development of post-acute COVID-19 syndrome. This difference is most likely related to the

subject's characteristics, the cut-off value of the parameters studied, and the different criteria for evaluating the study's final results.

The results of this study support the theory inflammatory process in the early stages of the disease plays a role in the formation of sequelae in COVID-19 survivors. C-reactive protein is not a specific marker of COVID-19, but an increase from the normal threshold is related to the degree of inflammation. Decreased functional capacity in COVID-19 survivors may be a multiorgan cumulative impact of the inflammatory process in COVID-19.

Table 2.
Result analysis bivariate all variables with 6MWT

Variable	6MWT		PR	95% CI	p-value
	Poor	Normal			
CRP					
> 90 mg/L	28 (100%)	0 (0.0%)	1.8	1.408-2.284	<0.001*
90 mg/L	29 (55.8%)	23 (28.7%)			
D-dimer					
2.6 g/ml	16 (94.1%)	1 (5.9%)	1.4	1.165-1.796	0.018*
< 2.6 g/ml	41 (65.1%)	22 (34.9%)			
Age					
65 years old	14 (100%)	0 (0.0%)	1.5	1.287-1.831	0.008*
< 65 years old	43 (65.2%)	23 (34.8%)			
Sex					
Male	31 (68.9%)	14 (31.1%)	0.9	0.703-1.223	0.628
female	26 (74.3%)	9 (25.7%)			
Obesity					
Obese	11 (78.6%)	3 (21.4%)	1.1	0.822-1,547	0.746
Non-obese	46 (69.7%)	20 (30.3%)			
Smoking status					
Smoker	14 (63.6%)	8 (36.4%)	0.9	0.605-1.219	0.411
Non-smoker	43 (74.1%)	15 (25.9%)			
Hypertension					
Yes	14 (87.5%)	2 (12.5%)	1.3	1.012-1.676	0.133**
No	43 (67.2%)	21 (32.8%)			
Diabetes mellitus					
Yes	17 (89.5%)	2 (10.5%)	1.4	1.165-1.796	0.079**
No	40 (65.6%)	21 (34.4%)			
Duration from confirmed					
12-16 weeks	16 (64.0%)	9 (36%)	0.9	0.616-1.197	0.425
> 16 weeks	41 (74.5%)	14 (25.5%)			
Length of stay					
14 days	15 (78.9%)	4 (5.9%)	1.1	0.860-1,528	0.563
< 14 days	42 (65.1%)	19 (34.9%)			

*statistically significant; **meet the criteria for multivariate analysis (p < 0.25)

Based on the results of multivariate Cox regression analysis on variables with a significant prevalence ratio value and meeting the criteria, including CRP levels, d-dimer levels, age, comorbid history of hypertension, and diabetes mellitus, the results of the six-minute walk test, significant results were obtained only at CRP levels (PR 1.8, 95% CI 1.051-3.136; p = 0.032) (Table 3). These results suggest that high CRP levels are independently associated with poor 6MWT results.

Table 3.
Result of Multivariate analysis using Cox regression

Variable	PR	95% CI	p-value
High baseline CRP level	1.816	1.051-3.136	0.032*
High baseline d-dimer level	1,120	0.596-2.108	0.724
Age 65 years old	1.574	0.826-2.999	0.168
Hypertension	0.951	0.492-1.841	0.882
Diabetes mellitus	1,290	0.705-2.358	0.409

*statistically significant

C-reactive protein is an acute phase inflammatory protein secreted mainly by the liver. C-reactive protein is widely used as a marker of the involvement of the inflammatory process in a pathological condition. Smilowitz et al., (2021) have demonstrated a strong relationship between CRP levels and venous thromboembolism, acute kidney injury, critical illness, and mortality in COVID-19. The long-term impact of inflammation on COVID-19 has been demonstrated by a study by SeyedAlinaghi et al., (2021), who found a prolonged recovery period for COVID-19 survivors at high baseline CRP levels. In-line studies indicate that inflammation at the onset of COVID-19 infection is not limited to the acute phase of the infection.

The levels of d-dimer which in the previous bivariate analysis showed significant (PR = 1.4, 95% CI 1.165-1.796; p = 0.018), the Cox regression analysis showed no significant results (PR 1.120 95% CI 0.596-2.108; p = 0.724). This result may be caused by the interrelation between variables or a confounding effect. The role of inflammation in developing COVID-19 sequelae may predominate, and elevated d-dimer levels from the normal threshold may be part of the inflammatory process. It is also possible that other conditions accompanying the onset of inflammation at the onset of COVID-19 infection, such as comorbid diseases, have contributed to the increase in baseline d-dimer.

The six-minute walk test did not explain the mechanism of the limitation of physical exercise. Test results can be influenced by various factors, including those not related to cardiorespiratory status. In addition to chronic conditions such as chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and chronic heart failure, the results of the 6MWT are influenced by age, anthropometry, peripheral arterial disease, musculoskeletal problems, nutritional status, and cognitive function (Heresi and Dweik, 2011).

A study conducted on a population with chronic heart disease found that age and anthropometry are independent predictors of the 6MWT results, so they need to be considered in interpreting the test results. Age over 75 years and BMI over 25 kg/m2 tend to get mileage less than 300 meters, so it needs to be considered when categorizing patients based on prognostic cutout values (Pepera, Ingle and Sandercock, 2015) Regular physical exercise can affect the results of the 6MWT. Research by Zampogna et al., (2021) showed that a series of exercise programs in pulmonary rehabilitation in COVID-19 survivors proved effective in improving recovery. In addition to offering an increase in motor performance and lower extremity function, patients undergoing pulmonary rehabilitation also showed an increase in exercise tolerance as measured using a 6MWT.

In this study, most factors that influence the results of the 6MWT have been controlled, both by analysis and research design. The study design controlled the presence of chronic heart failure, chronic lung disease, and musculoskeletal disease. Age, which in the covariate analysis showed significance after multivariate analysis with comorbid hypertension and diabetes mellitus, showed insignificant results as a confounding factor. The effect of physical exercise on test results was partially controlled through the study design by excluding subjects who were currently or had undergone a medical rehabilitation program after treatment during the acute phase of infection. Research subjects may perform regular physical activity outside the medical rehabilitation program of a health facility. In this condition, the researcher did not control both the analysis and the research design because the magnitude of the activity was difficult to measure and greatly limited the recruitment of research samples if applied to the exclusion criteria.

There are several weaknesses in this study that can be considered as a basis for better further research. First, this study only used a field test to determine the outcome, so the presence of organic abnormalities could not be specifically explained. Second, this study did not assess the effect of early onset of symptoms, which is related to the limitations of secondary data. Third, this study did not distinguish the potential role of SARS-CoV-2 virus variants that may provide different clinical features or "phenotypes" due to the unavailability of data. Finally, the investigators were unable to fully control physical exercise outside the hospital medical rehabilitation program.

Conclusion

The proportion of severe COVID-19 survivors with poor 6MWT was high. There is a significant association between high baseline levels of CRP with a poor 6MWT in severe COVID-19 survivors. The study results can be used as primary data regarding the characteristics of survivors of severe COVID-19 for more than 12 weeks and are expected to include other degrees of COVID-19 to broaden the generalizability of the results. In-depth investigation and management to prevent physical activity limitations of post-COVID-19 patients need to conduct, some of which can be in the form of mandatory evaluations of patients who have received hospital treatment, as well as integrated activities with public health-based programs.

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