The association of baseline C-reactive protein, D-dimer, and lymphocytes levels with health-related quality of life in severe COVID-19 survivors

Ida Ayu Ika Wari Utami

Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Bali, Indonesia, 80114
Email: ika_wari@yahoo.com

I Ketut Agus Somia

Tropic Infection Division of Internal Medicine Department, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Bali, Indonesia, 80114
Email: agus.somia@unud.ac.id
Orchid id: https://orcid.org/0000-0003-4168-9572

Ni Luh Putu Eka Arisanti

Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Bali, Indonesia, 80114
*Corresponding author email: eka.arisanti@unud.ac.id
Orchid id: https://orcid.org/0000-0003-4067-5611

Ida Bagus Ngurah Rai

Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Bali, Indonesia, 80114
Email: idabagus_ngurahrai@unud.ac.id
Orchid id: https://orcid.org/0000-0003-2670-1051

Ida Ayu Jasminarti Dwi Kusumawardani

Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Bali, Indonesia, 80114
Email: jasminarti@unud.ac.id
Orchid id: https://orcid.org/0000-0002-2716-5222

Ni Wayan Candrawati
Department of Pulmonology and Respiration Medicine, Faculty of Medicine,
Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Bali, Indonesia,
80114
Email: candrawati@unud.ac.id
Orchid id: https://orcid.org/0000-0002-6634-0994

I Gusti Ngurah Bagus Artana
Department of Pulmonology and Respiration Medicine, Faculty of Medicine,
Udayana University, Udayana University Hospital, Bali, Indonesia, 80114
Email: ignb_artana@unud.ac.id
Orchid id: https://orcid.org/0000-0003-1520-0163

Abstract---This study examined the association between baseline inflammatory markers and HrQoL (assessment using the SF-36 instrument) in severe COVID-19 survivors with cross-sectional observational analysis. The total subject is 80 people. Poor HrQoL findings based on the Physical Component Summary (PCS) were seen in 22 individuals (27.5%), and poor HrQoL findings based on the Mental Component Summary (MCS) were seen in 22 individuals (27.5%). The results showed that eight subjects (47.1%) with high D-dimer levels had poor PCS and MCS scores, with the same PR 2.1 (CI 95% 1.069-4.196;p=0.042). High levels of D-dimer and a duration of 12-16 weeks of confirmation were independently associated with PCS values with PR values of 5.5 (95% CI 1.190 – 25.144;p=0.029) and 4.5 (95% CI 1.402 – 14.647; p= 0.012). Meanwhile, a history of not taking routine medication for the treatment of comorbid diseases was a predictor that was independently associated with the MCS value, PR 0.3 (95% CI 0.115 – 0.956; p=0.041). This conclusion is CRP; absolute lymphocyte levels were not associated with HrQoL of severe COVID-19 survivors. Meanwhile, there is an association between D-dimer levels, duration of confirmation, and routine drug use for the treatment of comorbid diseases on the HrQoL of severe COVID-19 survivors.

Keywords---absolute lymphocytes, CRP, D-dimer, HrQoL, severe COVID-19 survivors.

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) was first reported in December 2019 in Wuhan City, Hubei Province, China. This virus became known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The incidence and control of COVID-19 varies by region and country. According to the Task Force for Handling COVID-19 (2021) in Indonesia, there were 2.26 million cases of COVID-19 and there were 1.92 million recovered cases recorded as of early July 2021. For the Bali area as of early July there were 44.2 thousand cases of COVID -19 and 41.6 thousand recovered cases, with a recovery index of 94.06%. For the city of Denpasar, there were 16.1 thousand positive cases of COVID-19 and 15.01

thousand recovered cases.(WHO Indonesia, 2021).

Study focusing on association between health literacy and health-related quality of life (HrQoL) shows that symptomatic COVID-19 patients have lower post-COVID HrQoL than those without symptoms.(Lindert, Jakubauskiene and Bilsen, 2021; Poudel *et al.*, 2021) Other studies have shown that COVID-19 survivors have a higher incidence of psychological distress in the early stages of recovery.(Asare-Nuamah *et al.*, 2021; Jones, Mitra and Bhuiyan, 2021) Another study found that persistent symptoms lasted more than 12 weeks from symptom onset. Symptoms include cough, fatigue, dyspnea, joint pain, chest pain, and psychological problems, such as post-traumatic stress disorder (PTSD), anxiety, depression, impaired concentration and sleep disorders. All of these symptoms certainly affect the quality of life of COVID-19 survivors.(Gill M *et al.*, 2018; Garrigues *et al.*, 2020; Torales *et al.*, 2020). The purpose of this study was to determine the association between baseline inflammation parameters and health-related quality of life (HrQoL) in severe COVID-19 survivors

Method

This research is analytic observational, with the design used being a cross-sectional study conducted at Prof.Dr.IGNG. Ngoerah General Hospital Denpasar, Bali. The research will start from December 2021 to May 2022. Research ethics permit from Udayana University with number 2657/UN14.2.2VII.14/LT/2021. Inclusion criteria: (1) Patients with severe post-COVID-19 who are hospitalized at Prof.Dr.IGNG Ngoerah General Hospital, (2) Age above 18 years, and (3) It has passed 12 weeks since confirmed COVID-19. Exclusion criteria: (1) Patients who have incomplete medical record data, (2) Patients who have conditions or a history of comorbid diseases including heart failure, chronic kidney disease stage V, (3) chronic hearth failure, (4) hepatic cirrhosis, (5) immunocompromised disease (cancer an HIV) (6) chronic cerebrovascular (completed stroke, old stroke), (7) Patients who refused to participate in the study and (8) Patients who have incomplete medical record data. Patients who meet the criteria for the study sample will be recorded with their medical record numbers, and identity. Data analysis in this study consisted of descriptive statistical analysis, bivariate analysis, and multivariate analysis. The entire data analysis process above uses the help of IBM software Statistical Product and Service Solutions (SPSS) 26.0 software.

Result and Discussion

In this study, there were 80 survivors of severe COVID-19 who met the study inclusion criteria. The characteristics of the research subjects are shown in Table 1. The mean age was 51.4 ± 14.55. These findings are comparable to an Indian study's mean age of 55.9 ± 12.37 (Albitar *et al.*, 2020; Clark *et al.*, 2020; Pambudi *et al.*, 2022). More severe COVID-19 survivors are 65. Age is an important determinant of death and illness severity. Patients over 65 have a weakened immune system. Elderly patients are more prone to ADS and mortality. T and B lymphocyte function is impaired in elderly people. Increased type 2 cytokine production may reduce virus control, prolong pro-inflammatory response, and poor result.(Soni *et al.*, 2021; Pambudi *et al.*, 2022).

This study included 45 males, or 56.3%. This is consistent with prior studies at Prof.Dr.IGNG Ngoerah General Hospital, Denpasar, which revealed more men (63, 70%) than females (27, 30%) among severe COVID-19 victims. Men were more likely to acquire severe COVID-19 (RR 1.18; 95% CI 1.10–1.27). Males are more likely to undergo severe COVID-19 attacks than females, according to the Chinese CDC.(Pijls *et al.*, 2021; Pambudi *et al.*, 2022) Male gender is independently related with COVID-19 severity, according to U.S. statistics. More males with severe COVID-19 may have greater ACE2 receptor expression than females, since SARS-CoV-2 binds to ACE2 receptors on host pneumocytes while 17-estradiol in women may lower ACE2 receptor expression (Gallo Marin *et al.*, 2021).

Table 1
Characteristics Subject

Characteristics	n=80 (%)
Age, mean ± SD	51,4±14.55
≥65year	14 (17.5)
< 65year	66 (82.5)
Gender	
Male	45 (56.3)
Female	35 (43.8)
Education	
Primary-High School	34 (42.5)
University	46 (57.5)
Marriage Status	
Marriage	72 (90)
Not marriage	8 (10)
BMI, mean ± SD	25,9 ± 4,21
Obesity	14 (17.5)
Not obese	66 (82.5)
Smoke	
Smoking	22 (27.5)
No smoking	58 (72.5)
Hypertension	
Hypertension	16 (20)
No hypertension	64 (80)
Diabetes mellitus	
Diabetes mellitus	19 (23.8)
No diabetes mellitus	61 (76.3)
Duration since confirmed, median (min-max)	30 (12-32)
12-16week	25 (31.3)
> 16week	55 (68.8)
Length of stay, median (min-max)	9 (3-30)
≥14 day	17 (21.3)
< 14day	63 (78.8)
CRP; median (min-max)	60.45 (2.1-330.7)
High	28 (35)
Normal	53 (65)
Absolute lymphocytes, mean ± SD	1200 (530)
Low	33 (41.3%)

Normal	47 (58.7%)
D-dimer; median (min-max)	1.0 (0.13-22.24)
High	17 (21.3)
Normal	63 (78.7)
PCS; mean ± SD	65.1±20.2
Poor	22 (27.5)
Good	58 (72.5)
MCS; median (min-max)	66.6 (12.6-100)
Poor	22 (27.5)
Good	58 (72.5)

DM (Diabetes mellitus), PCS (Physical Component Summary), MCS (Mental Component Summary), CRP (C-Reactive Protein)

In this study, 35% of the participants (n=28) had baseline CRP levels > 90 mg/L with a median of 61.8 (3.2 – 330.7), while in India, patients with severe COVID-19 had a mean CRP of 34.6 mg/L. (Soni, et al., 2021). Another study linked CRP levels to infection severity. Early plasma CRP elevation increases plasma leakage risk. CRP levels may indicate severe COVID-19 pneumonia (Yitbarek *et al.*, 2021). Another study in Iran also obtained results from the receiver operating characteristic (ROC) curve analysis, namely that CRP can be used as an independent factor in predicting the severity of COVID-19.(Sadeghi-Haddad-Zavareh M *et al.*, 2021). Coagulation abnormalities in COVID-19 patients reveal that thrombosis indicators have poor prognosis even in younger individuals. Elevated D-dimer levels are related with a bad outcome in COVID-19. In this study, 21.3% (n=17) of participants had baseline D-dimer levels > 2.6 g/ml, with a median of 1.0 (0.13 – 22.24).(Gallo Marin *et al.*, 2021) Studies reveal that severe COVID-19 increases fibrin polymerization and thrombosis risk. Greater D-dimer (> 2.59 g/ml) is related with a 17-fold increased risk of PE, while absence of anticoagulants is associated with a 4-fold increased risk (Bompard F *et al.*, 2020).

In this study, 41.3% of subjects had baseline absolute lymphocyte counts below 1.0×10^3 cells/mm^3, with a mean of $1.2 \times 10^3 \pm 0.53$. Gallo Marin, et al. (2021) found statistically significant decreases in the numbers of lymphocytes, CD4+ and CD8+ T cells, B cells, and NK cells in patients with severe COVID-19 illness compared with moderate or mild instances. A subgroup of T cells exhibited the greatest decline. Decreased CD4+ and CD8+ T cell numbers and functional diversity correspond with worse outcomes. In this study, 27.5% (n=22) had poor HrQoL based on the PCS, with an average of 65.1 ± 20.27. Qu et al. (2020) in China found a mean PCS of 72.65 ± 25.52 among severe COVID-19 survivors. Physical function, mobility, and work- and daily-related activities were most affected by declining health. Inactivity while isolation may have reduced COVID-19 survivors' physical ability and function.(Singh *et al.*, 2021). Association between levels of CRP, D-dimer, absolute lymphocytes and covariates with PCS in Table 2 and Table 3. Results of multivariate logistic regression analysis on PCS Table 4.

Table 2
Association between levels of CRP, D-dimer, and absolute lymphocytes with PCS

Variable		PCS (%)		PR	95% CI	p-value[a]
		Poor	Good			
CRP	High	9 (32.1%)	19 (67.9%)	1.3	0.629 – 2.628	0.495
	Normal	13 (25.0%)	39 (75.0%)			
D-dimer	High	8 (47.1%)	9 (52.9%)	2.1	1.069 – 4.196	0.042*
	Normal	14 (22.2%)	49 (77.8%)			
Absolute Lymphocytes	Low	11 (33.3%)	22 (66.7%)	1.4	0.702 – 2.889	0.328
	Normal	11 (23.4%)	36 (76.6%)			

PCS (Physical Component Summary), CRP (C-Reactive Protein); a Analysis using chi-square; * Significant (p value < 0,05); P value ≤ 0,25, multivariate test will be carried out

Table 3
Association between covariates and PCS (Physical Component Summary)

Variable	PCS		PR	95% IC	p-value
	Poor	Good			
Age (years)					
≥ 65 yo	8 (57.1%)	6 (42.9%)	2.7	1.407 – 5.158	0.006*
< 65 yo	14 (21.2%)	52 (78.8%)			
Sex					
Male	12 (26.7%)	33 (73.3%)	0.9	0.457 – 1.905	0.850
Female	10 (28.6%)	25 (71.4%)			
Marriage					
Yes	22 (30.6%)	50 (69.4%)	0.7	0.596 – 0.809	0.099*
No	0 (0%)	8 (100%)			
Education					
Primary to senior high school	16 (47.1%)	18 (52.9%)	3.6	1.578 – 8.249	0.001*
University	6 (13%)	40 (87%)			
Occupation					
No	14 (42.4%	19 (57.6%)	2.5	1.182 – 5.255	0.012*
Yes	8 (17%)	39 (83%)			
Obesity					
Yes	2 (14.3%)	12 (85.7%)	0.5	0.124 – 1.790	0.223*
No	20 (30.3%)	46 (69.7%)			
Smoker					
No	9 (40.9%)	13 (59.1%)	1.8	0.912 – 3.653	0.098*
Yes	13 (22.4%)	45 (77.6%)			
Hypertension					
Yes	6 (37.5%)	10 (62.5%)	1.5	0.700 – 3.213	0.317
No	16 (25%)	48 (75%)			
Diabetes Melitus					
Yes	4 (21.1%)	15 (78.9%)	0.7	0.275 – 1.851	0.471
No	18 (29.5%)	43 (70.5%)			

Variable	PCS		PR	95% IC	p-value
	Poor	Good			
On Medication					
Yes	11 (23.9%)	35 (76.1%)	0.7	0.364 – 1.501	0.403
No	11 (32.4%)	23(67.6%)			
Duration from confirmed					
12-16 week	13 (52%)	12 (48%)	3.2	1.568 – 6.440	0.001*
> 16 week	9 (16.4%)	46 (83.6%)			
LOS					
≥ 14 day	2 (11.8%)	15 (88.2%)	0.4	0.096 – 1.431	0.102*
< 14 day	20 (31.7%)	43 (68.3%)			

PCS (Physical Component Summary); LOS (Length of stay); a Analysis using chi-square; * Significant

Table 4
Results of multivariate logistic regression analysis on PCS

Variable	PR	95% CI	p-value
D-dimer	5.5	1.190 – 25.144	0.029*
Age	2.3	0.490 – 10.680	0.293
Marital status	2.5	0.445 – 14.062	0.298
Level of education	2.6	0.959 – 29.524	0.063
Occupation	2.0	0.468 – 8.959	0.341
Obesity	0.6	0.098 – 3.259	0.564
Smoking History	1.8	0.471 – 7.123	0.382
Duration from confirmed 12 – 16 weeks	4.5	1.402 – 14.647	0.012*
Length of stay 14 days	0.2	0.028 – 1.509	0.120

PCS (Physical Component Summary); * Significant

Poor MCS ratings were 27.5% (n=22) with a median of 66.6 (12.6 – 100). MeiXuan L., et al. (2021) found a significant difference in HrQoL between COVID-19 survivors and the general population (p 0.05). PCS 50, 53.6%, and MCS 50, 84.4%. This decline in mental component of COVID-19 survivors is consistent with the results other study in China, which states the existence of psychological disorders, such as insomnia and irritability, in COVID-19 survivors caused by long periods of isolation and fear of the long-term effects of the COVID-19 disease. This reveals that more than physical function affects life quality.(Meixuan *et al.*, 2021). Association between levels of CRP, D-dimer, absolute lymphocytes, and covariates with MCS Table 5 and Table 6. Results of multivariate logistic regression analysis MCS in Table 7.

Table 5
Association between levels of CRP, D-dimer, and absolute lymphocytes with MCS

Variable		MCS (%)		PR	95% IC	p-value[a]
		Poor	Good			
CRP	High	11 (39,3%)	17 (60,7%)	1,9	0,924 – 3,733	0,083
	Normal	11 (21,2%)	41 (78,8%)			

Variable		MCS (%)		PR	95% IC	p-value[a]
		Poor	Good			
D-dimer	High	8 (47,1%)	9 (52,9%)	2,1	1,069 – 4,196	0,042*
	Normal	14 (22,2%)	49 (77,8%)			
Absolute Lymphocytes	Low	12 (36,4%)	21 (63,6%)	1,8	0,839 – 3,481	0,137
	Normal	10 (21,3%)	37 (78,7%)			

MCS (Mental Component Summary), CRP (C-Reactive Protein); a Analysis using chi-square; * Significant (p value < 0,05); P value ≤ 0,25, multivariate test will be carried out

Table 6
Association between covariates and MCS

Variable	MCS		PR	95% CI	p-value
	Poor	Good			
Age (years)					
≥ 65 tahun	6 (42.9%)	8 (57.1%)	1.8	0.843 – 3.706	0.157*
< 65 tahun	16 (24.2%)	50 (75.8%)			
Sex					
Male	13 (28.9%)	32 (71.1%)	1.1	0.544 – 2.322	0.752
Female	9 (25.7%)	26 (74.3%)			
Marriage					
Yes	19 (26.4%)	53 (73.6%)	0.7	0.266 – 1.864	0.504
No	3 (37.5%)	5 (62.5%)			
Education					
Primary to senior high School	13 (38.2%)	21 (61.8%)	1.9	0.946 – 4.036	0.064*
University	9 (19.6%)	37 (80.4%)			
Occupation					
No	13 (39.4%)	20 (60.6%)	2.1	0.997 – 4.243	0.046*
Yes	9 (19.1%)	38 (80.9%)			
Obesity					
Yes	2 (14.3%)	12 (85.7%)	0.5	0.124 – 1.790	0.223*
No	20 (30.3%)	46 (69.7%)			
Smoker					
No	8 (36.4%)	14 (63.6%)	1.5	0.736 – 3.085	0.274
Yes	14 (24.1%)	44 (75.9%)			
Hypertension					
Yes	7 (43.8%)	9 (56.3%)	1.9	0.917 – 3.799	0.104*
No	15 (23.4%)	49 (76.6%)			
Diabetes Melitus					
Yes	7 (36.8%)	12 (63.2%)	1.5	0.719 – 3.123	0.296
No	15 (24.6%)	46 (75.4%)			
On Medication					
Yes	9 19.6%)	37 (80.4%)	0.5	0.248 – 1.057	0.064*
No	13 (38.2%)	21 (61.8%)			
Duration from confirmed					
12-16 week	9 (36%)	16 (64%)	1.5	0.752 – 3.086	0.251*

Variable	MCS		PR	95% CI	p-value
	Poor	Good			
> 16 week	13 (23.6%)	42 (76.4%)			
LOS					
≥ 14 day	6 (35.3%)	11 (64.7%)	1.4	0.643 – 3.002	0.417
< 14 day	16 (25.4%)	47 (74.6%)			

MCS (Mental Component Summary); LOS (Length of stay); a Analysis using chi-square; * Significant

Table 7
Results of multivariate logistic regression analysis MCS

Variable	PR	95% CI	p-value
CRP	2,2	0,769 – 6,352	0,141
D-dimer	2,0	0,589 – 6,741	0,267
Absolute Lymphocyte	2,2	0,760 – 6,387	0,146
Age	1,3	0,310 – 5,874	0,689
Level of education	2,1	0,643 – 6,808	0,220
Occupation	1,7	0,503 – 5,976	0,383
Obesity	0,6	0,105 – 3,577	0,587
History of Hypertension	3,2	0,945 – 10,789	0,062
History of not taking regular medication	0,3	0,115 – 0,956	0,041*
Duration from Confirmed	2,2	0,683 – 7,164	0,185

MCS (Mental Component Summary); * Significant

Wilkins et al. (2018)(Wilkins *et al.*, 2018) reported that C-Reactive Protein may detect systemic inflammation (CRP). CRP is used to predict inflammatory illnesses and measure acute to chronic inflammation. COVID-19 patients' CRP levels are also prognostic. In this investigation, baseline CRP levels did not correlate with HrQoL, PCS or MCS. Townsend, et al. (2020)(Townsend *et al.*, 2020) investigated 128 participants of both sexes and found no connection between CRP, neutrophils, lymphocytes, neutrophil-to-lymphocyte ratio, and lactate dehydrogenase and tiredness impacting QoL of COVID-19 survivors. Mandal, et al. (2021) showed that COVID-19 survivors' CRP levels fell from 76 mg/L to normal (1 mg/L) in the third month after confirmation. CRP levels in the blood grow 4-10 hours after inflammation and peak in 48 hours, with a half life of 19 hours, however CRP may linger in the blood as long as there is an inflammatory and infectious process.(Kaur *et al.*, 2008) This means COVID-19 survivors' chronic inflammatory process has improved. So that COVID-19 survivors' third-month HrQoL decline isn't due to chronic inflammation.

Severe COVID-19 survivors with high baseline D-dimer levels (>2.6 g/ml) had a 2.1 times increased probability of PCS and MCS values dropping after 12 weeks. Systemically activated coagulation pathways by cytokine storm mediators cause the prothrombotic state in COVID-19, causing microthrombotic deposition, capillary blockage, and tissue and organ damage. Damaged tissue causes additional inflammation and coagulopathy.(Leentjens J *et al.*, 2021). Depressed mood circumstances (depression) that alter MCS values are also related with high D-dimer levels.(Ellis *et al.,* 2020) BDI-II helps detect depression. In this study, the

baseline absolute lymphocyte level did not correlate with HrQoL in PCS or MCS. Townsend et al. (2020)(Fogarty *et al.*, 2020) found no association between neutrophils, lymphocytes, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and CRP and tiredness symptoms that influenced QoL in COVID-19 survivors. Lymphopenia in COVID-19 patients may be utilized as a measure of illness severity during the acute phase since severe SARS-CoV-2 infection causes hyperinflammation and cytokine storm syndrome, which can reduce T cells.(Chauhan, Wiffen and Brown, 2020).

This means lymphocytes play a minor part in killing infected cells, hence lymphopenia in COVID-19 victims cannot be used as a benchmark for lasting tissue damage that might affect the survivor's quality of life. Mandal et al. (2021) found that lymphocyte count rose from 0.95.103/L to 1.94.103/L. Helper T lymphocytes have a 63-day half life, cytotoxic T cells 93 days, and B lymphocytes 41 days.(Kaur *et al.*, 2008) This means COVID-19 survivors' chronic inflammatory process has improved. So that COVID-19 survivors' third-month HrQoL decline isn't caused by persistent inflammation. High D-dimer levels (> 2.6 g/ml) and a verified duration of 12 to 16 weeks predicted poor PCS scores in study individuals. COVID-19 survivors with high baseline D-dimer levels for 12-16 weeks were 5.5 and 4.5 times more likely to have low PCS scores. Post-COVID syndrome is a thrombosis sequelae. Post-COVID thrombosis sequelae may affect the respiratory, digestive, circulatory, neurological, and musculoskeletal systems. These problems will reduce survivors' physical activity and quality of life. After 12-16 weeks, COVID-19 survivors still have problems in carrying out their activities due to declining function of organ, including the respiratory system, which decreases their quality of life.(Ding *et al.*, 2020; Yong, 2021)

In a multivariable study of the Mental Component Summary (MCS) evaluation, regular medication consumption for comorbid treatment of COVID-19 survivors was the sole predictor of a low MCS score. Not taking concomitant medication regularly protects severe COVID-19 survivors. Taking medicine every day has a psychological impact that makes patients believe they have a severe ailment that needs daily treatment. This is consistent with a study in Singapore, which indicated that people with severe DM who took more than 1 kind of medicine (OAD or insulin alone) had greater mental issues.(Ding *et al.*, 2020; Yong, 2021). The weakness in this study is the information bias during questionnaire data collection. So to minimize the occurrence of this bias, the researcher has tested the validity and reliability of the questionnaire used and the researcher tried to create a conducive environment when filling out the questionnaire, and in filling out the questionnaire it was read directly by the researcher himself with the same duration of filling, namely 15 – 20 minutes. Second, this study did not assess the subjects' baseline HrQoL, so it could not compare the subjects' HrQoL before infection and after becoming a COVID-19 survivor, to see if there had been a worsening of HrQoL before the subject was infected with COVID-19.

Conclusion

There was no correlation between baseline CRP and absolute lymphocyte levels on HrQoL of severe COVID-19 survivors. Instead, there is an association between D-dimer levels, duration of confirmation, and routine drug use for the treatment of

comorbid diseases on the HrQoL of severe COVID-19 survivors.

Acknowledgments

References

Albitar, O., Ballouze, R., Ooi, J.P. and Sheikh Ghadzi, S.M. (2020) 'Risk factors for mortality among COVID-19 patients', Diabetes Research and Clinical Practice, 166, p. 108293. Available at: https://doi.org/10.1016/j.diabres.2020.108293.

Asare-Nuamah, P., Dick-Sagoe, C., Sakah, B.N., Muzee, H., Asamoah, J.O. and Kessie, K.O. (2021) 'Determinants of COVID-19 Response Strategies in Selected African Countries', Journal of Applied Social Science, 16(1), pp. 281–304. Available at: https://doi.org/10.1177/19367244211055799.

Bompard F, Monnier H, Saab I and et al (2020) 'Pulmonary embolism in patients with Covid-19 pneumonia', European Respiratory Journal [Preprint].

Brake, S.J., Barnsley, K., Lu, W., McAlinden, K.D., Eapen, M.S. and Sohal, S.S. (2020) 'Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19)', Journal of clinical medicine, 9(3). Available at: https://doi.org/10.3390/JCM9030841.

Brugliera L and et al (2020) 'Rehabilitation of COVID-19 patients', Journal of Rehabilitation Medicine, 52(4), pp. 2–4.

Chauhan, A.J., Wiffen, L.J. and Brown, T.P. (2020) 'COVID-19: A collision of complement, coagulation and inflammatory pathways', Journal of Thrombosis and Haemostasis, 18(9), pp. 2110–2117. Available at: https://doi.org/10.1111/jth.14981.

Clark, A., Jit, M., Warren-Gash, C., Guthrie, B., and Ong, K.L. (2020) 'Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study', The Lancet Global Health, 8(8), pp. e1003–e1017.

Del Valle, D.M., Kim-Schulze, S., Huang, H.-H., B and Gnjatic, S. (2020) 'An inflammatory cytokine signature predicts COVID-19 severity and survival', Nature Medicine, 26(10), pp. 1636–1643. Available at: https://doi.org/10.1038/s41591-020-1051-9.

Ding, T., Zhang, J., Wang, T., Cui, P., Chen, Z., Jiang, J and equally, C. (2020) 'A Multi-hospital Study in Wuhan, China: Protective Effects of Non-menopause and Female Hormones on SARS-CoV-2 infection', medRxiv, p. 2020.03.26.20043943. Available at: https://doi.org/10.1101/2020.03.26.20043943.

Ellis, R.J., Letendre, S.L., Atkinson, J.H., Clifford, D., Collier, A.C., Gelman, B.B., Marra, C., McCutchan, J.A., and Heaton, R.K. (2020) 'Higher levels of plasma inflammation biomarkers are associated with depressed mood and quality of life in aging, virally suppressed men, but not women, with HIV.', Brain, behavior, & immunity - health, 7, p. 100121. Available at: https://doi.org/10.1016/j.bbih.2020.100121.

Fogarty, H., Townsend, L., Ni Cheallaigh, C., Bergin, C., and Byrne, M. (2020) 'COVID19 coagulopathy in Caucasian patients', British journal of haematology, 189(6), pp. 1044–1049.

Gallo Marin, B., Aghagoli, G., Lavine, K., Yang, L., Siff, E.J., and Michelow, I.C. (2021) 'Predictors of COVID-19 severity: A literature review', Reviews in Medical Virology, 31(1), pp. 1–10. Available at: https://doi.org/10.1002/rmv.2146.

Gao M, Piernas C, Astbury NM and et al (2021) 'Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study', Lancet Diabetes Endocrinol, 9, pp. 350–9.

Garrigues, E., Janvier, P., Kherabi, Y., Le Bot, A., Hamon, A., Gouze, and Nguyen, Y. (2020) 'Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19.', The Journal of infection, pp. e4–e6. Available at: https://doi.org/10.1016/j.jinf.2020.08.029.

Gill M, Maheshwari V, Narang A and et al (2018) 'Impact on Cognitive Improvement Following Burr Hole Evacuation of Chronic Subdural Hematoma: A Prospective Observational Study', J Neurosci Rural Pract, 9(4), pp. 457–60.

Haris, R., Makmur, R., Andayani, T. and Kristina, S. (2019) 'Penilaian Properti Psikometrik Instrumen Kualitas Hidup (HRQol) pada Populasi Umum: Tinjauan Sistematik', JURNAL MANAJEMEN DAN PELAYANAN FARMASI (Journal of Management and Pharmacy Practice), 9. Available at: https://doi.org/10.22146/jmpf.41911.

Jana, S.K., K, N.B., Chattopadhyay, R., Chakravarty, B. and Chaudhury, K. (2010) 'Upper control limit of reactive oxygen species in follicular fluid beyond which viable embryo formation is not favorable.', Reproductive toxicology (Elmsford, N.Y.), 29(4), pp. 447–451. Available at: https://doi.org/10.1016/j.reprotox.2010.04.002.

Jones, E.A.K., Mitra, A.K. and Bhuiyan, A.R. (2021) 'Impact of COVID-19 on Mental Health in Adolescents: A Systematic Review.', International journal of environmental research and public health, 18(5). Available at: https://doi.org/10.3390/ijerph18052470.

Kaur, A., Di Mascio, M., Barabasz, A., Rosenzweig, M., McClure, H.M., Perelson, A.S., Ribeiro, R.M. and Johnson, R.P. (2008) 'Dynamics of T- and B-lymphocyte turnover in a natural host of simian immunodeficiency virus.', Journal of virology, 82(3), pp. 1084–1093. Available at: https://doi.org/10.1128/JVI.02197-07.

Leentjens J, Haaps TF, Wessels PF and et al (2021) 'COVID-19-associated coagulopathy and antithrombotic agents—lessons after 1 year', The Lancet Haematology [Preprint].

Lehmann, A., Prosch, H., Zehetmayer, S., Gysan, M.R., Bernitzky, D., Vonbank, K., Idzko, M. and Gompelmann, D. (2021) 'Impact of persistent D-dimer elevation following recovery from COVID-19.', PloS one, 16(10), p. e0258351. Available at: https://doi.org/10.1371/journal.pone.0258351.

Lindert, J., Jakubauskiene, M. and Bilsen, J. (2021) 'The COVID-19 disaster and mental health-assessing, responding and recovering.', European journal of public health, 31(Supplement_4), pp. iv31–iv35. Available at: https://doi.org/10.1093/eurpub/ckab153.

Liu, Jing, Li, S., Liu, Jia, Liang, B., and Zheng, X. (2020) 'Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients.', EBioMedicine, 55, p. 102763. Available at: https://doi.org/10.1016/j.ebiom.2020.102763.

Marosszeky, N. and Sansoni, J. (2005) 'Instrument review-SF-36® health survey (version 1.0) for use in Australia'.

Meixuan, L., Huang, L., Zheng, D., Zhang, L., and Zhang, Z. (2021) Health-related quality of life of COVID-19 survivors at 6 months after hospital discharge: a cohort study. Available at: https://doi.org/10.21203/rs.3.rs-176489/v1.

Mendy, A., Apewokin, S., Wells, A.A. and Morrow, A.L. (2020) 'Factors Associated with Hospitalization and Disease Severity in a Racially and Ethnically Diverse Population of COVID-19 Patients', medRxiv, pp. 1–24. Available at: https://doi.org/10.1101/2020.06.25.20137323.

Pambudi, I.G.P.B., Suryana, I.K., Rai, I.B.N., Kusumawardani, I.A.J.D., Candrawati, N.W., Sajinadiyasa, I.G.K. and Arisanti, N.L.P.E. (2022) 'High Neutrophil to Lymphocyte Ratio, C-Reactive Protein, Procalcitonin and D-dimer as Risk Factors for Severe COVID-19.', Medico-Legal Update, 22(1).

Pijls, B.G., Jolani, S., Atherley, A., Derckx, R.T., Dijkstra, J.I.R., Franssen, G.H.L., Hendriks, S., Richters, A., Venemans-Jellema, A. and Zalpuri, S. (2021) 'Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies', BMJ open, 11(1), p. e044640.

Poudel, A.N., Zhu, S., Cooper, N., Roderick, P., Alwan, N., Tarrant, C., Ziauddeen, N. and Yao, G.L. (2021) 'Impact of Covid-19 on health-related quality of life of patients: A structured review', PLOS ONE, 16(10), p. e0259164.

Sadeghi-Haddad-Zavareh M, Bayani M, Shokri M and et al (2021) 'C-Reactive Protein as a Prognostic Indicator in COVID-19 Patients', Interdisciplinary Perspective on Infectious Disease, 7(8), pp. 61–9.

Simonnet, A., Chetboun, M., Poissy, J., Raverdy, V., Noulette, J., Duhamel, A., Labreuche, J., Mathieu, D., Pattou, F. and Jourdain, M. (2020) 'High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation', Obesity, 28(7), pp. 1195–1199.

Singh, Y., Singh, A., Rudravaram, S., Soni, K.D., Aggarwal, R., Patel, N., Wig, N. and Trikha, A. (2021) 'Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio as Markers for Predicting the Severity in COVID-19 Patients: A Prospective Observational Study.', Indian journal of critical care medicine : 25(8), pp. 847–852. Available at: https://doi.org/10.5005/jp-journals-10071-23906.

Soni, S.L., Kajal, K., Yaddanapudi, L.N., Malhotra, P., Puri, G.D., Bhalla, A., Singh, M.P., Sehgal, I.S., Koushal, V., and Guru, R.R. (2021) 'Demographic & clinical profile of patients with COVID-19 at a tertiary care hospital in north India', Indian Journal of Medical Research, 153, pp. 115–125. Available at: https://doi.org/10.4103/ijmr.IJMR_2311_20.

Talman, S., Boonman-de Winter, L.J.M., De Mol, M., Hoefman, E., Van Etten, R.W. and De Backer, I.C. (2021) 'Pulmonary function and health-related quality of life after COVID-19 pneumonia', Respiratory medicine, 176, p. 106272.

Torales, J., O'Higgins, M., Castaldelli-Maia, J.M. and Ventriglio, A. (2020) 'The outbreak of COVID-19 coronavirus and its impact on global mental health.', The International journal of social psychiatry, 66(4), pp. 317–320. Available at: https://doi.org/10.1177/0020764020915212.

Townsend, L., Dyer, A.H., Jones, K., Dunne, J., Mooney, A., Gaffney, F., O'Connor, L., Leavy, D., O'Brien, K. and Dowds, J. (2020) 'Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection', PloS one, 15(11), p. e0240784.

Vehar, S., Boushra, M., Ntiamoah, P. and Biehl, M. (2021) 'Post-acute sequelae of SARS-CoV-2 infection: Caring for the "long-haulers".', Cleveland Clinic journal of medicine, 88(5), pp. 267–272. Available at: https://doi.org/10.3949/ccjm.88a.21010.

Wade, D.T. (2020) 'Rehabilitation after COVID-19: an evidence-based approach', Clinical medicine, 20(4), p. 359.

Wang, C., Yu, C., Jing, H., Wu, X., Novakovic, V.A., Xie, R. and Shi, J. (2022) 'Long COVID: The Nature of Thrombotic Sequelae Determines the Necessity of Early Anticoagulation', Frontiers in Cellular and Infection Microbiology, 12.

WHO Indonesia (2021) Coronavirus disease (COVID-19).

Wilkins, J., Ghosh, P., Vivar, J., Chakraborty, B. and Ghosh, S. (2018) 'Exploring the associations between systemic inflammation, obesity and healthy days: a health related quality of life (HRQOL) analysis of NHANES 2005–2008', BMC obesity, 5(1), pp. 1–12.

Yitbarek, G.Y., Ayehu, G.W., Asnakew, S., Ayele, F.Y., Gare, M.B., Mulu, A.T., Dagnaw, F.T. and Melesie, B.D. (2021) 'The role of C-reactive protein in predicting the severity of COVID-19 disease: A systematic review', SAGE Open Medicine, 9, p. 205031212110507. Available at: https://doi.org/10.1177/20503121211050755.

Yong, S.J. (2021) 'Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments', Infectious diseases, 53(10), pp. 737–754.

Zhao, Y., Shang, Y., Song, W., Li, Q., Xie, H., Xu, Q., Jia, J., Li, L., Mao, H. and Zhou, X. (2020) 'Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery', EClinicalMedicine, 25, p. 100463.

Zimmermann, P., Pittet, L.F. and Curtis, N. (2022) 'Long covid in children and adolescents', BMJ, 376, p. o143. Available at: https://doi.org/10.1136/bmj.o143.