Correlation between C-Reactive Protein (CRP) and lymphocyte levels in the acute phase with spirometry test in severe Coronavirus Disease 2019 (COVID-19) survivors after twelve weeks

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Abstract---The examination of pulmonary functions after COVID-19 exposure is still limited, thus making it difficult for clinicians to determine the patient's evaluation steps after confirmed COVID-19. This study aims to identify the relationship between inflammatory parameters, consisting of CRP and lymphocyte levels during the acute phase with FVC, FEV1/FVC, and FEF25-75 values in severe COVID-19 survivors after twelve weeks. This study of observational analytics uses a cross-sectional study design conducted on COVID-19 survivors. Data analysis used the S.P.S.S. program. The bivariate analysis showed that there was a significant relationship between CRP levels and FVC values (p=0,028; PR=2,82) and there was no significant relationship between CRP and FEV1/FVC values (p=1,905; PR=2,53) and FEF 25-75 (p=0,436;PR=1,45), there was no lymphocyte association with FEV1/FVC (p=0.670;PR=1.33), FVC (p=0,323;PR=1,56), and FEF 25-75 (p=0,207; PR=1,83). The results of the multivariate test found that CRP levels (p=0,036; PR=2,95), age >65 years (p=0,028;PR=4.16), history of DM (p=0,004;PR=10,47) are correlate with FVC ≤ 80%. History of DM is a predictor that correlate to FEV1/FVC ≤75% (p=0,004;PR=10,47). CRP levels are a parameter significantly related to FVC values, while lymphocytes are not related to spirometry tests on severe COVID-19 survivors after twelve weeks.

Keywords---COVID-19, CRP, Lymphocyte, FVC, FEV1/FVC, FEF25-75

Introduction

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This disease first appeared in December 2019 in Wuhan, China. Data to the WHO (World Health Organization), at the beginning of August 2022, the world reached 578 million confirmed cases with death rates6.4 million. While in Indonesia, there are 6.21 million confirmed cases of COVID-19, with 157,000 deaths. COVID-19 has clinical symptoms ranging from asymptomatic, mild, moderate, severe, and critical. Patients generally experience recovery in the second to sixth week (WHO., 2022)

Post-COVID-19 syndrome is a symptom that patients still experience after being declared cured of COVID-19 infection. The symptoms experienced by patients are good, with mild to severe symptoms. Symptoms can be felt by patients after three months and even persist. Symptoms can include shortness of breath, fatigue, chest pain, joint pain, palpitations, ageusia, anosmia, cognitive symptoms (memory and attention deficits), and psychological distress (feeling lonely, anxiety, depression, and sleep disturbances). As much76% of survivors had persistent symptoms, and 50% had abnormalities on plain radiographs after three months post-hospitalization (Huang et al., 2021).

Shortness of breath is a symptom afterCOVID-19which patients often complain about after recovering fromCOVID-19. A large study conducted in Wuhan, China,

found that patients with COVID-19, after three months were declared cured, had impaired diffusion capacity, especially in patients with severe symptoms. This happens because the lungs infected with COVID-19 have fibrosis during the healing process (Bazdyrev et al., 2021).

Viral invasion, thrombosis, hyperreactivity of the immune system, and hormonal dysregulation are the causes of the acute manifestations of COVID-19, but it is not clear what the post-COVID-19 syndrome is. Dennis et al. (2021) showed that there is an ongoing inflammatory process in patients who are recovering.

Inflammatory markers in COVID-19 patients, such as elevated CRP and lymphopenia, occur in patients with an acute phase of infection. High inflammation in the acute phase can cause damage to lung tissue in the form of fibrosis, which can cause symptoms after COVID-19 infection in the form of shortness of breath. Studies on the increase in CRP and lymphopenia in the acute phase to the symptoms experienced by COVID-19 survivors are still limited (Bazdyrev et al., 2021; Patria and Sabirin, 2021; Zhao et al., 2021)

Spirometry is one of the tests to assess lung function. The results can determine the presence of pulmonary function disorders in obstruction, restrictive or mixed. Spirometry results are said to be normal if the forced vital capacity (FVC) value is > 80% predictive value, forced expiratory volume/ forced vital capacity (FEF1/FVC) > 75%, and FEF 25-75% > 65%. The results of Spirometry are said to be obstructed if the FEV1/FVC 75% predictive value, restriction if the FVC 80%, and mixed type disorder if the FEV1/FVC predictive value 75% and FVC 80% predictive value, FEF 25-75% less or equal to 65 indicates the presence of small airway obstruction (Klain et al., 2022)

The results of the Spirometry itself are highly correlated with the severity of COVID-19. Guler conducted an observational study on 106 COVID-19 survivors after four months with severe/acute symptoms and mild/moderate symptoms while hospitalized in Switzerland by examining lung function and found that there was a very significant lung function abnormality, namely a decrease in total lung capacity (TLC) % predictive (86% vs. 102%), forced vital capacity (FVC) % predicted (86.6% vs. 95.6%), and forced expiratory volume in the first 1 second (FEV1) predicted (89.4% vs. 94%). Furthermore, COVID-19 patients with moderate or critical symptoms had a higher FEV1/FVC ratio than patients with mild or moderate symptoms (94.7% vs. 84.2%) (Guler et al., 2021)

The literature regarding post-COVID-19 pulmonary function examinations is still limited, making it difficult for clinicians to determine steps in evaluating patients after COVID-19 is confirmed. This is the basis for the authors to determine the function of pulmonary ventilation to perform a spirometry examination by knowing the value, FEV1/FVC, FEF25-75in COVID-19 survivors after twelve weeks had been hospitalized at Sanglah Hospital with severe degrees. The author wants to know whether there is a disturbance in the FVC value, FEV1/FVC, FEF25-75 on survivors every COVID-19 after twelve weeks and then look for its relationship with CRP and lymphocyte levels in the acute phase.

Method

This research is analytic observational, with the design used being a cross-sectional study conducted at Sanglah Hospital Denpasar. The research will start from December 2021 to May 2022. Research ethics permit from Udayana University with number 2879/UN14.2.2VII.14/LT/2021. Inclusion criteria: (1) Patients with severe post-COVID-19 who are hospitalized at Sanglah 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 lung disease (asthma, chronic obstructive pulmonary disease, lung malignancy), abnormalities/ musculoskeletal deformities, and renal failure, (3) Patients with secondary infection, before the time of hospitalization due to COVID-19, (4) Patients with absolute and relative contraindications to Spirometry. Absolute contraindications include Increased intracranial pressure, space-occupying lesion (SOL.) on the brain, retinal detachment, and others. Meanwhile, the relative contraindications include hemoptysis of unknown cause, pneumothorax, unstable angina pectoris, scrotal hernia, inguinal hernia, umbilical hernia, Hernia Nucleus Pulposus (HNP.) depending on the severity, and others (Coates et al., 2013), (5) Patients with pregnancy and (6) Patients who refused to participate in the study and (7) 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 an anamnesis of identity (name, age, gender, educational history, employment status) and medical history will be taken. The subject also underwent a physical examination of the lungs starting from inspection, palpation, percussion, and auscultation sequentially, spirometry examination to see the value of FVC, FEV1/FVC, FEF25-75, and taking 3 milliliters of blood from veins for examination of CRP and X lymphocytes. During the acute phase, based on medical records. The results of the data analysis were processed using the help of the SPSS program. Data analysis in this study consisted of descriptive statistical analysis, bivariable analysis, and multivariable analysis with a significance value of $p < 0.05$.

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. This result is similar to a previous study at Sanglah Hospital, which obtained a mean age of 54.41 ± 14.17 (Pambudi et al., 2022).

Table 1
Characteristics Subject

Characteristics	n=80 (%)
Age, mean ± S.D.	51.4±14.55
≥65year	14 (17.5%)
< 65year	66 (82.5%)
Gender	
Male	45 (56.3%)
Female, n	35 (43.8%)
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)	77.70 (3.2-2561,00)
Height	32 (40%)
Normal	48 (60%)
Absolute lymphocytes, mean ± SD	1128.78 (516.99)
low	35 (43.8%)
Normal	45 (56.3%)
Median FEV1/FVC value (min-max)	88.78 (62.87)
≤ □75	10 (12.5%)
>75, n(%)	70 (87.5%)
Mean FEV1 value ± SD	84.37 (17.13)
Median FVC value (min-max)	78.5 (32-133.68)
≤80	43 (53.8%)
>80	37 (46.3%)
FEF 25-75 median value (min-max)	84 (39-178)
≤65	26 (32,5%)
>65	54 (67.5%)

CRP .: C-Reactive Protein; FEV1:Forced expiratory volume in one second, FVC.: Forced vital capacity, FEF: Forced Expiratory Flow

This study found that most patients with severe COVID-19 infection were aged less than 65 years, namely 82.5%, compared to those aged more than 65 years, namely 17.5%. This result is similar to the study by Lv et al. (2020), which

showed that more severe COVID-19 survivors were aged <65 years. Older age has been reported as a significant predictor of mortality and is considered a major factor in disease severity. Elderly patients (≥ 65 years) usually have a weaker immune response. Therefore, elderly patients are more susceptible to acute respiratory distress syndrome and death. This is also inconsistent with a meta-analysis in China which found that patients older than 65 were a risk factor for disease progression in patients with COVID-19 (OR = 6.06, 95% CI (3.98, 9.22), P <0.00001)(Zheng et al., 2020). This difference may be because the study was conducted cross-sectionally among survivors or in patients who had recovered from COVID-19, making it possible that patients aged less than 65 years were more likely to be COVID-19 survivors.

Based on gender characteristics, it was found that in this study, more males than females experienced severe COVID-19 infection. This is to several previous studies. A meta-analysis of 3.111.714 reported global cases has shown that male patients are almost three times more likely to require intensive care unit care and have a higher chance of death than women (Peckham et al., 2020). According to the latest data from the Chinese Centers for Disease Control and Prevention (C.D.C.), the ratio of male infection to female infection is 2.7:1, and men are more likely to have severe attacks than women (Ding et al., 2020). Another study by Jin et al. in China also found that male cases tended to be more severe than women (p = 0.035), and in the public data set, the number of men who died from COVID-19 was 2.4 times that of women (70.3 vs. 29.7%, p= 0.016 (Jin et al., 2020). This occurs due to the expression of ACE2 receptors (receptor recognition of SARS-Cov-2 in the respiratory tract is higher in males, and 17β-estradiol is also found to decrease ACE2 receptor expression, especially in women (Brake et al., 2020; Zhu et al., 2020)

In this study, the mean body mass index of 17.5% of patients was found to be obese. Previous research in Saudi Arabia revealed that obese patients exhibit severe COVID-19 risk factors and influence disease presentation. But in this study, the BMI limit was 40 kg/m2 compared to those with normal weight (Alqahtani et al., 2022). Research in New York also found that BMI> 40 kg/m2 were more likely to be hospitalized and exhibit more severe symptoms (Petrilli et al., 2020). Research in France also found that a high frequency of obesity (BMI>30) required intensive care for SARS-CoV-2. Disease severity increases with BMI, where obesity is a risk factor for SARS-CoV-2 severity, which requires increased attention to preventive measures in susceptible individuals (Simonnet et al., 2020). In general, obesity reduces lung compliance and increases airway resistance due to fat accumulation around the ribs and abdomen, which can lead to ventilation and perfusion imbalances. As evidenced by a decrease in FEV1 and FVC in mild and moderate obesity. In obese patients, proinflammatory and anti-inflammatory factors are also imbalanced. In obese patients, there is a decrease in adiponectin (anti-inflammatory) and an increase in leptin (pro-inflammatory). The proinflammatory cytokines that are activated in adipose tissue are TNF alpha, IL-6, MCP-1, and IL-1ß (Ahmed et al., 2020)

Based on smoking history, it was found that 27.5% of patients had a previous history of smoking while the other 72.5% had no history of smoking. Based on the previous meta-analysis, it was found that patients with a history of smoking were

found to be positively associated with severe disease (OR = 1.40, 95% CI: 1.06-1.85). Smoking suppresses antiviral mechanisms and alters several patterns of cytokines that play a role in innate mucosal immunity (Da Silva, Moreira, and Martins, 2020); virus replication and the severity of COVID-19 will increase to some extent as a result. One study showed that smoking could also increase ACE2 expression, increasing the patient's susceptibility to more severe symptoms (Brake et al., 2020).

A meta-analysis in China showed that the proportion of underlying diseases such as hypertension, diabetes, cardiovascular disease, and respiratory disease was statistically significantly higher in critical/mortal patients compared to non-critical patients (diabetes: OR=3.68, 95% CI (2 .68, 5.03), P < 0.00001; hypertension: OR=2.72, 95% CI (1.60.4.64), P=0.0002; cardiovascular disease: OR=5.19, 95% CI(3.25, 8.29), P < 0.00001; respiratory disease: OR=5.15, 95% CI (2.51, 10.57), P < 0.00001) (Zheng et al., 2020). Other studies in Pakistan also show that the severity of the disease increases with the increase in co-morbidities. The groups most susceptible to severe grade results are patients with diabetes and hypertension (Shoaib et al., 2021).

Based on previous medical history, it was found that in patients with severe COVID-19, 20% had a history of hypertension, and 23.8% had a history of diabetes mellitus. In diabetes, there is an increase in glycolysis which helps increase the replication of the SARS Cov-2 virus. In DM, there is also dysregulation of the immune system, such as a decrease in the sub-type of T lymphocytes, namely CD3, CD4, and CD8, through the process of apoptosis. So in DM, patients more often found lymphopenia. In DM patients, there is also a decrease in phagocytosis by neutrophils, chemotaxis, and intracellular destruction, as well as a decrease in the performance of NK. cells (Saikat Sen, 2021). In patients with hypertension, there is an imbalance of cytokines, such as an increase in IL 7, IL 6, granulocyte-macrophage colony-stimulating factor, and TNF. This occurs because of binding to the receptor angiotensin-converting enzyme-2 with SARS Cov-2. ACE-2 is an enzyme that catalyzes angiotensin II into Angiotensin 1-7, which is a peptide that resists proinflammatory, pro-oxidation, and vasoconstrictive effects (Rothan and Byrareddy, 2020)

The data obtained in this study showed that in the previous history of COVID-19, the patient's CRP value was high in 40% of patients. Recent studies have shown that CRP positively correlates with different infection severity levels. Early expansion of plasma CRP levels has increased the likelihood of plasma leakage. Therefore, CRP levels can early predict severe COVID-19-associated pneumonia (Yitbarek et al., 2021). In this regard, despite blood markers that appear to be associated with severity and mortality, CRP levels were markedly elevated in patients with severe SARS-CoV-2 infection (Ali, 2020). Another study in Iran also found that receiver operating characteristic (ROC) curve analysis found that CRP could be used as an independent factor in predicting the severity of COVID-19 (Sadeghi-Haddad-Zavareh et al., 2021). A previous study in Gianyar also stated that CRP levels >8.9 mg/L significantly affected the severity of COVID-19 patients with a p-value of 0.000 (p<0.005). The higher the initial CRP level of a COVID-19 patient, the higher the severity (Ulandari and Widyaningsih, 2021).

Absolute lymphocyte values in severe COVID-19 patients were low in 43.8% of cases. Since the first descriptive study in China regarding COVID-19 infection, lymphocyte count has become an interesting marker. This has been associated with severe COVID-19, and COVID-19 mortality is reported to have significantly lower lymphocyte counts than survivors (Ruan et al., 2020). Meta-analysis showed that patients with a poor prognosis had lower lymphocyte counts (mean difference 361.06 □ µL [-439.18,-282.95], p<0.001) compared with those with a good prognosis(Huang and Pranata, 2020). Lymphocyte counts that remain lower after the first week after the onset of symptoms are highly predictive of death in adults with COVID-19 in the hospital. These predictors can help clinicians identify patients with poor prognoses and may help guide clinical decision-making at an early stage (Zhang et al., 2021).

In the spirometry calculation in this study, most of the patients with a history of severe COVID-19 were more than 16 weeks, and it was found that the FEF1/FVC value was greater than 75 in 87.5% of respondents, and only 12.5% had a value below 75. This is similar to a meta-analysis conducted to assess lung function in COVID-19 survivors, where normal lung function values were found in COVID-19 patients, indicating no significant change in lung function in COVID-19 survivors from 14 days after being declared healed(Patria and Sabirin, 2021). However, different results were found in a follow-up study one year after recovery from COVID-19, which showed functional lung impairment was widespread in COVID-19 survivors one year after discharge from the hospital, and persistent lung function impairment was found in about 40 patients. % of survivors. FEV1/FVC with a mean of 80.90% ±8.46 and FEV1/FVC<70 only one person (4%) (Yan et al., 2021).

This study found that 53.8% of patients had an FVC value of less than 80%, and the most FEF25-75 mean value was more than 65, at 67.5%. A previous study found abnormally high rates of pulmonary ventilation function in COVID-19 patients before hospital discharge, with restrictive ventilation dysfunction and minor airway dysfunction accounting for 50% of all patients (Li et al., 2020). A retrospective analysis in China also found that the pulmonary function of patients with COVID-19-induced pneumonia predominantly manifests as impaired restrictive ventilation and small airway obstruction, which increased in critically ill patients (Lv et al., 2020). Another cohort analysis also found the proportion and severity of minor airway dysfunction, suggesting that COVID-19 is more likely to be associated with diffuse pulmonary epithelial damage and small airway obstruction (Mo et al., 2020).

Relationship of CRP Levels to Values of FVC, FEV1/FVC, and FEF25-75

The results of the bivariate test showed that in this study, there was no relationship between the patient's CRP and the presence of obstruction based on the FEV1/FVC after the patient recovered, as shown in Table 2. This is supported by previous studies, which showed no significant difference in the size of the FEF1/FVC among the survivors. COVID-19 with different disease severity indicates that patients with mild, moderate, and severe degrees have normal FEV1/FVC values or no obstructive disorders found in COVID-19 survivors (Yan et al., 2021).

Table 2
Bivariable analysis of the relationship between CRP levels in the Acute Phase with the value of FVC, FEV1/FVC value, FEF 25-75 value for survivors of severe COVID-19

Variable	Value			PR	95% Confidence Interval		p-values
					Lower	Upper	
		FVC					
		Restriction	Normal				
CRP level	High	22 (68.8%)	10 (31.3%)	2.82	1.105	7,242	0.028
	Normal	21 (43.8%)	27 (56.3%)				
		FEV1/FVC					
		obstruction	Normal				
CRP level	High	6 (18.8%)	26 (81.3%)	2.53	0.655	9.84	1.905
	Normal	4 (8.30%)	44 (91.7%)				
		FEF 25-75					
		obstruction	Normal				
CRP level	High	12 (37.5%)	20 (62.5%)	1.45	0.564	3,762	0.436
	Normal	14 (29.2%)	34 (70.8%)				

CRP .: C-Reactive Protein; FEV1:Forced expiratory volume in one second, FVC: Forced vital capacity, FEF: Forced Expiratory Flow; analysis using chi-square; * Has a significant effect (p-value < 0.05)

The bivariate test of initial CRP levels with FVC patients found significant results with OR 2.82 (95% CI: 1.10-7.24; p = 0.028), indicating that high CRP affects the incidence of restriction based on FVC values (≤80 %). This is also supported by multivariate analysis, which showed that subjects with high CRP levels (>90 mg/L) had a 2.95 times chance of experiencing restriction (FVC 80%) when compared to subjects with normal CRP levels 90 mg/L. with a probability range in the population ranging from 1.07 to 8.15 with a p-value of 0.036.

Several previous studies support the findings of this study. A meta-analysis stated that common complications up to 6 months after recovery from COVID-19 are: impaired carbon monoxide diffusion capacity (27% prevalence, 95% confidence interval (CI) 15-45%), leading to a decrease in CVP, creating a restrictive situation in the lungs. This condition is increasingly found in patients with severe COVID-19 conditions, where the CRP value will be higher in severe patients. Infiltration of inflammatory cells in the lung parenchyma caused by infection can trigger the process of fibrosis formation, as evidenced by CT scans of the chest in COVID-19 survivors, and even fibrosis can last up to 7 years (Ahmed et al., 2020; Ulandari and Widyaningsih, 2021).

As a result, excessive proinflammatory cytokines are continuously active, causing imbalanced tissue damage and repair. Usually, the damaged alveolar cells are replaced by bronchial stem cells, and the fibrous tissue formed is degraded after the new alveoli are formed. When a cytokine storm or ARDS occurs, there is damage to the alveolar basement membrane, which causes fibroblasts to continue to be produced. Factors that play a role are epidermal growth factor (EGF),

transforming growth factor-alpha (TGF-α), and angiogenesis by vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) (Ojo et al., 2020). Pulmonary fibrosis in lung tissue is caused by tissue damage due to inflammation, destruction of tissue structures, fibroblast proliferation, and the accumulation of large amounts of the extracellular matrix so that the pulmonary function examination can provide restriction results (Lv et al., 2020).

The Relationship of Lymphocyte Levels to the Value of FVC, FEV1/FVC, and FEF25-75

The results of bivariable analysis on lymphocyte levels during the acute phase on the independent variables FVC, FEV1/FVC, FEF 25-75, using chi-square tests. In this study, there was no statistically significant relationship between lymphocyte levels during the acute phase and values FVC, FEV1/FVC, and FEF 25-75in survivors of severe COVID-19. The calculation results can be seen in Table 3.

Table 3.
Bivariable analysis relationship between lymphocyte levels in the acute phase and the value of FVC, FEV1/FVC value, and value25-75 for survivors of severe COVID-19

Variable	Value			PR	95% Confidence Interval		p-value
					Lower	Upper	
		FVC					
		Restriction	Normal				
Lymphocyte level	Low	21 (60.0%)	14 (40.0%)	1.56	0.642	3,833	0.323
	Normal	22 (48.9%)	23 (51.1%)				
		FEV1/FVC					
		Obstruction	Normal				
Lymphocyte level	Low	5 (14.3%)	30 (85.7%)	1.33	0.354	5.026	0.670
	Normal	5 (11.1%)	40 (88.9%)				
		FEF 25-75					
		Obstruction	Normal				
Lymphocyte level	Low	14 (40.0%)	21 (60.0%)	1.83	0.712	4,719	0.207
	Normal	12 (26.7%)	33 (73.3%)				

CRP : C-Reactive Protein; FEV1:Forced expiratory volume in one second, FVC: Forced vital capacity, FEF: Forced Expiratory Flow; an Analysis using chi-square; * Has a significant effect (p-value < 0.05)

Based on the value of lymphocyte levels, the bivariate test did not find a relationship between low lymphocyte levels and the incidence of obstruction based on the FEV1/FVC value. Low lymphocyte levels at the beginning of patients exposed to severe COVID-19 attacks also did not have a significant relationship with FVC and FEF 25-75 values after the patient recovered. These results are similar to previous studies showing that lymphopenia is associated with palpitations and increased troponin I in COVID-19 survivors. Lymphopenia, as a prognostic factor affecting the prognosis of COVID-19, is associated with a cytokine storm, one of the most important causes of multi-organ injury primarily affecting the heart. This study suggests that the degree of lymphopenia in the

acute stage could also be a prognostic factor influencing the rehabilitation of COVID-19(Liang et al., 2020).

Like all pathogens, SARS-CoV-2 uses several mechanisms to inactivate and evade the host immune response. SARS-CoV-2 also dysregulates the host interferon response. The poor T cell response may result from the lack of interferon production driven by SARS-CoV-2, as interferon enhances T cell survival and effector function. Interferons are cytokines secreted by host cells in response to viral infection. Interferons bind to cell surface receptors and act as transcription factors, regulating the expression of hundreds of genes whose protein products target viruses at various levels. SARS-CoV-2 expresses at least ten proteins that enable it to resist induction or evade the antiviral activity of interferon, enabling the virus to survive better by rendering the host's innate immune response inefficient (Le Bert et al., 2020; Rothan and Byrareddy, 2020)

Apart from these innate immune disorders, SARS-CoV-2 can initiate host immune signaling pathways. If the virus is not successfully contained, this results in the production of proinflammatory cytokines such as interleukin-6 and the recruitment of neutrophils and myeloid cells. This causes hyperinflammation and, in some cases, cytokine storm syndrome. Severe COVID-19 can also result in functional fatigue and decreased numbers of T lymphocytes (particularly CD4+ T cells, CD8+ T cells) and natural killer cells (Ribero et al., 2020).

The human body's leukocyte types are 65-70% polymorphonuclear, 25-35% lymphocytes, 1-3% eosinophils, and 1% basophils. Meanwhile, the percentage of lymphocytes itself is divided into helper T lymphocytes (65%), cytotoxic T lymphocytes (35%), and B lymphocytes as immunoglobulin producers (20%). Helper T lymphocytes, with the most significant percentage, are only responsible for producing cytokines that activate macrophages and other inflammatory cells that do not directly affect the destruction of infected cells. In contrast, a small percentage of cytotoxic T cells directly impact the destruction of infected cells (Abul, Abbas., Andrew, Lichtman., 2020). Because the percentage of lymphocytes that can play a role in damage to alveolar cells and interstitial tissue is minimal, coupled with the presence of ACE2 receptors on the surface of lymphocytes that lymphocytes become targets for lysis in COVID-19 infection, lymphopenia in severe COVID-19 patients cannot be used as a benchmark for damage to the lung parenchyma. In addition, lymphocytes have a limited half-life compared to CRP Under normal circumstances, the half life of B lymphocytes is 41 days, T helper cells are 63 days, and cytotoxic T cells are 93 days, while CRP levels in the blood begin 4-10 hours after inflammation and peak at 48 hours with a half life of 19 hours. But persist as long as possible, as long as there is inflammation and infection (Kaur et al., 2008; Zhao et al., 2021).

Multivariate Relationship to the Value of FVC, FEV1/FVC, and FEF25-75

The next step is to determine the relationship between CRP, absolute lymphocytes during the acute phase, and confounding variables with values of FVC, FEV1/FVC, FEF 25-75us ing multivariate logistic regression analysis. The results are obtained in Table 4.

Table 4

Multivariate Analysis of Logistic Regression of Variables Associated with the Value of FVC ≤80%, FEF1/FVC value ≤75%, and FEF 25-75% value ≤65% in Severe COVID-19 Survivors more than twelve weeks

Variable	p-value	Prevalence Ratio	95% Confidence Interval	
			Lower	Upper
FVC value ≤80%				
Absolute Lymphocyte Level 1000 mg/L	0.36	1.59	0.587	4,332
CRP level	0.036*	2.95	1.074	8.154
Age > 65 years	0.028*	6.46	1,248	33,453
DM history	0.004*	4.16	1,167	14,878
HT history	0.425	1,718	0.405	7,298
FEV1/FVC value ≤75%				
Absolute Lymphocyte Level 1000 mg/L	0.66	1.6	0.229	10,018
CRP level	0.33	2.3	0.418	13,435
DM history	0.004*	10.47	2,123	51,722
HT history	0.093	4.13	0.790	21.595
FEF value 25-75% ≤65%				
Absolute Lymphocyte Level 1000 mg/L	0.30	1.73	0.601	4,982
CRP level	0.63	1.3	0.438	3,923
65 years old	0.30	1,960	0.545	7,055
DM history	0.596	2,742	0.853	8,813
HT history	0.056	3.45	0.971	12,283

CRP : C-Reactive Protein; FEV1:Forced expiratory volume in one second, FVC.: Forced vital capacity, FEF: Forced Expiratory Flow; * Has a significant effect (p-value < 0.05)

Based on multivariate analysis, subjects with a history of DM had the possibility of experiencing obstruction (FEV1/FVC <75%.) as much as 10.4 times when compared to subjects without a history of DM, with a probability range in the population ranging from 2.12 to 51.72. with a p-value of 0.004. Subjects with a history of DM also had a 4.16 times possibility of experiencing restriction compared to subjects without a history of DM (probability range 1.167 - 14,878; p-value 0.028). Hyperglycemia showed a role in worsening COVID-19 prognosis (Caballero et al., 2020). The poor prognosis is thought to be due to multi-organ complications caused by hyperglycemia in COVID-19 patients, which can last until the patient recovers from COVID-19 (Liu et al., 2020).

In the multivariate test, it was found that patients aged > 65 had a 6.46 times possibility of experiencing restriction compared to patients aged 18≤ 65 (probability range 1.248 - 33.453; p-value 0.026). COVID-19 generally presents as an acute respiratory syndrome but is mild in most patients. Previous research has proven that age >65 years is a significant cause of death and fulminant disease in COVID-19 survivors (Laher et al., 2021). Impaired diffusion capacity,

restrictive ventilation defects, and decreased exercise capacity that persists post-discharge and has been associated with disease severity are more common in patients >65 years of age (Mo et al., 2020). With age, the respiratory system has anatomical, physiological, and immunological changes. The estimated decrease in FEV1 is 25-30 ml/year starting at age 35-40 and can double to 60 ml/year after age 70.

Multivariate analysis showed no association between CRP and lymphocyte levels in the acute phase with small airway obstruction or FEF values 25-75% ≤65% in severe COVID-19 survivors. This is to previous research that COVID-19 survivors experience more restriction conditions and not obstruction conditions (Lv et al., 2020; Mo et al., 2020; Méndez et al., 2021)

The advantage of this study is that this study is the first study to look for the relationship between spirometry results (FVC, FEV1/FVC, and FEF25-75) of COVID-19 survivors with inflammatory biomarkers in the acute phase in Bali so that this research can be used as a basis for further research. This study can also be developed to assess spirometry results in post-COVID-19 patients after one year.

This study has several limitations that should be considered. First, the research design is cross-sectional, allowing us to see a relationship but not infer causality. Second, the lack of baseline pulmonary function data before disease onset makes it challenging to compare these with post-illness outcomes. These three studies only performed a spirometry examination once, namely when the patient was more than 12 weeks old as a COVID-19 survivor, so they could not find out how the changes in lung function were in COVID-19 survivors. Fourth, this study did not objectively assess physical activity in post-COVID-19 patients but only through history taking.

Conclusion

Based on the results of the study, it can be concluded:
1. There is a significant relationship between levels in the acute phase with FVC values , and there is no significant relationship between CRP in the acute phase to the value of FEF1/FVC and FEF25-75 in survivors of severe COVID-19 after twelve weeks.
2. There is no relationship between lymphocyte levels in the acute phase with the value of FVC, FEV1/FVC, FEF25-75 in survivors of severe COVID-19 after twelve weeks.

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