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Correlation between alveolar-arterial oxygen tension difference gradient baseline with spirometry test in severe coronavirus disease 2019 (COVID-19)

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***Abstract*---**Alveolar-arterial Oxygen Tension Differences are one of the oxygenations that can increase SARS-CoV-2 virus infection. Based on this, the researchers wanted to assess the relationship between the baseline AaDO2 gradient and spirometry tests in severe COVID-19 survivors. This research is an observational analytic study with a cross-sectional design. The analysis was carried out in bivariate and multivariate tests assisted by using SPSS 26. The subjects who participated in the study were 80 people. Subjects with AaDO2 values > 39.4 mmHg 70% (n=56), median AaDO2 gradient was 60.45 (2.75 - 548.2 mmHg). The relationship between baseline AaDO2 analysis and spirometry results showed that it was associated with FVC and FEF25-75% results, respectively (PR) 18.6 (95% CI 3.978-87.401 p = <0.001) and (PR) 7.7 (95% CI 1.606-3.724 p = 0.011) and no significant with FEV1 and FEV1/FVC values. This study concludes a relationship between a high baseline AaDO2 gradient with FVC and FEF values of 25-75% in severe adult COVID-19 survivors. There was no relationship between a high baseline AaDO2 gradient and FEV1 and FEV1/FVC values.

***Keywords*---**AaDO2, Spirometry Test, Severe COVID-19 Survivors.

Introduction

Decreased diffusion function is one of the functional disorders that occur in COVID-19, especially COVID-19 pneumonia, due to infiltration of the alveoli by inflammatory cells. The higher the diffusion disturbance that occurs, the more severe lung damage and an increased risk of post-Covid-19 lung function decline (Wiersinga et al., 2020). AaDO2 is one of the mechanisms to determine the cause of hypoxia. Diffusion disorders that occur in COVID-19 patients due to inflammatory cell infiltration will be indicated by an increase in AaDO2 values due to high differences in O2 pressure in the alveoli and arteries, an increase in AaDO2 > 25 mmHg even in asymptomatic COVID-19 patients (Munker *et al.*, 2021).

Spirometry is an examination to assess lung function. The results can determine whether the lung is obstructed or reactive in the large airways by calculating the values of FEV1, FVC, and FEV1/FVC; while the FEF 25-75% to assess the presence of disturbances in the small airways. In COVID-19 patients, spirometry is used to assess lung function in post-COVID-19 patients. The spirometry results are highly correlated with the severity of COVID-19. In Indonesia, spirometry data for post-COVID-19 patients is still limited.

The facts above show that the AaDO2 gradient can potentially be a risk marker for COVID-19 patients to experience impaired lung function in the form of post-COVID-19 infection. It is hoped that knowing the AaDO2 of COVID-19 patients at the beginning of treatment can be a reference for early medical rehabilitation management for patients at high risk of experiencing impaired function, both obstructive and restrictive so that it can provide a better prognosis of morbidity and quality of life.

Method

This research is analytic observational, with the design being a cross-sectional study conducted by Prof. Dr IGNG. Ngoerah Hospital Denpasar. The research will start from December 2021 to May 2022. Research ethics permit from Udayana University with number 2763/UN14.2.2VII.14/LT/2021. Inclusion criteria: (1) Patients with severe post-COVID-19 who are hospitalized at Prof. Dr IGNG. Ngoerah Hospital, (2) Age above 18 years, and (3) It has passed 12 weeks since confirmed COVID-19. Exclusion criteria: (1) 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, (2) Patients with infection at the time of hospitalization due to COVID-19, (3) Patients who have incomplete medical record data. (4) Patients with pregnancy, (6) Patients with contraindication of spirometry and (7) refused to participate in the study.

Patients who met the criteria for the study sample recorded information on identity, demographic characteristics, medical history and objective examination of the patient's medical record. Instruments for spirometry examination, such as a calibrated spirometry (spirolab III colour serial number: A 23-053. 14614), mouthpiece, nose cover, scale, pulse oximeter (fingertip pulse oximeter, model: LK88) and meter. The data analysis in this study consisted of descriptive statistical analysis, bivariable analysis, and multivariable analysis with a significance value of $p < 0.05$.

Results and Discussion

In this study, there were 80 survivors of severe COVID-19 who met the study inclusion criteria, characteristics data in Table 1. In this study, it was found that most subjects with severe post-COVID-19 were aged less than 65 years, 66 subjects (82.5%) compared to those aged more than or equal to 65 years, namely 14 subjects (17.5%). A meta-analysis study by Castro et al. showed that the average age of post-COVID-19 patients was 46.7 ± 13.7 and 69.1 ± 7.8 (Torres-Castro, 2021). The research that has been carried out is compared with other

research, where the age under 65 years is more than the age above or equal to 65 years.

Male sex was found more in this study, namely 45 subjects (56.3%). In a previous study conducted at Prof. Dr. IGNG. Ngoerah Central General Hospital Denpasar, there were 63 males (70%) compared to 27 (30%) women in patients with severe COVID-19 (Pambudi et al., 2022). Research conducted by Castro et al. in Chile, the meta-analysis research conducted found that there were more males than females (Castro et al., 2021). More males than females can be attributed to higher ACE2 receptor expression in Asian males than females (Albitar et al., 2020). In multivariable logistic regression analysis, it was found that the male gender was 1.7 times more at risk) was a significant predictor of severe COVID-19 infection (Fisher and Ryan, 2021)

Table 1
Characteristics of research subjects

Variable	n=80
Age, mean ± SB	51.4±14.55
65 years, n (%)	14 (17.5%)
Male, n (%)	45 (56.3%)
Smoking, n (%)	22 (27.5%)
Hypertension, n (%)	16 (20%)
Diabetes mellitus, n (%)	19 (23.8%)
Duration since confirmed, median (min-max)	30 (12-32)
Duration since confirmed 12-16 weeks, n (%)	25 (31.3%)
Length of stay, median (min-max)	9 (3-30)
Length of stay 14 days, n (%)	17 (21.3%)
AaDO2b gradient, median (min-max)	60.45 (2.75-548.20)
High AaDO2 gradient, n (%)	56 (70%)
FVCa, mean ± SB	79.39 ± 17.31
FEV1a, mean ± SB	84.85 ± 17.64
FEV1/FVCa, mean ± SB	87.22±9.35
FEF 25-75%b, median (min-max)	88.10 (39-178)
FEF 25-75% < 65% predicted, n (%)	25 (31.3%)
FEF 25-75% > 65% prediction, n (%)	55 (68.8%)
Restriction, n (%)	41 (51.2%)
Mild Restriction, n (%)	38 (47.5%)
Moderate Restriction, n (%)	2 (2.5%)
Weight Restriction, n (%)	1 (1.3%)
Obstruction, n (%)	8 (10%)
Mild obstruction, n (%)	5 (6.3%)
Moderate obstruction, n (%)	3 (3.8%)
Severe obstruction, n (%)	0 (0.0%)

AaDO2 (Alveolar-Artery Oxygen Tension Different), FVC (Force Vital Capacity), FEV1 (Force Expiration Volume 1st second), FEF 25-75% (Force Expiration Flow 25-75%), a: data is normally distributed, b: Data is not normally distributed.

Previous medical conditions or history, such as hypertension and diabetes mellitus, affect the worsening of the clinical course of COVID-19 patients. An innate immune disorder can cause this condition. In conditions with diabetes

mellitus, there is an increase in coagulation activity, and it has been shown that the treatment of diabetes and hypertension increases the risk of developing or worsening COVID-19 (Albitar *et al.*, 2020). In what has been done, hypertension is 20% (n=16), and subjects with comorbid DM are 23.8% (n=19). A study in Mexico determined that among 32,583 patients (12,304 cases and 20,279 controls), having at least one comorbidity was a risk factor for developing COVID-19 and increasing the severity of COVID-19 (Gallo Marin *et al.*, 2021)

In this study, more subjects had a duration from confirmation to the recruitment of subjects of more than 16 weeks, 68.8% (n = 55), with a median of 30 (12-32) weeks. While the length of stay, subjects who received treatment for at least 14 days were 21.3% (n=17) with a median (3-30) of treatment. In a study conducted by Rees et al, it was reported that the median length of treatment was nine days (Rees *et al.*, 2020)

Based on smoking history, it was found that 27.5% of the subjects had a 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 (PR = 1.40; 95% CI: 1.06-1.85). Smoking suppresses antiviral mechanisms and changes the pattern of cytokines that play a role in innate immunity (Da Silva, Moreira and Martins, 2020). One study showed that smoking could increase ACE2 expression and increase the patient's susceptibility, so symptoms become more severe (Brake *et al.*, 2020).

Alveolar-artery tension is a different way of measuring changes between the alveoli and the arteries. In this study, 80 subjects, 70% (n = 56) had an AaDO2 gradient of more than 39.4 mmHg and 30% (n = 24) had an AaDO2 gradient of less than or equal to 39.4 mmHg, with a median obtained of 60.45 (2.75-548.20). A study conducted by Viska et al found an AaDO2 gradient at baseline with a median of 33.0 (19.2-49.8) (p-value = 0.004) and AaDO2 with a median of 33.4 (16.8-90) non-ICU care. 49,5) (p-value = 0.01). In a study conducted by Viska et al., the AaDO2 gradient improved upon discharge from the hospital, so it was concluded that AaDO2 was more sensitive to monitoring post-COVID-19 acute phase lung damage (Visca *et al.*, 2021). In COVID-19 patients, especially patients with severe and critical degrees, Ventilation and perfusion problems occur, resulting in shunting. The examination uses blood gas analysis to determine the presence of hypoxemia in COVID-19 patients accurately.

This study conducted spirometry examinations in post-COVID-19 patients by assessing FVC, FEV1, FEV1/FVC, and FEF 25-75%. From these examinations, it can be concluded that there is Restriction, obstruction, or obstruction in the small airways. In this case, the mean FVC is 79.39 ± 17.31. For FVC values less than or equal to 80% predictions obtained 51.2% (n = 41) and more than 80% predictions 48.8% (n = 39). Subjects are also said to be restricted FVC is less or equal to 80%, so it is said to be subject to a Restriction of 51.2% (n = 41). Restrictions are divided into mild, moderate, and severe. Subjects with light restriction 47.5% (n = 38), moderate restriction 2.5% (n = 2), and severe restriction 1.3% (n = 1). In the study of Moreno-Perez et al, of 269 post-COVID-19 patients, with Restriction spirometry with an FVC value of less than 80%, the

prediction was 12.6% (n = 34). In patients without a history of previous lung disease, with 227 patients, it was 2.7% (n = 6) (Moreno-pérez *et al.*, 2021).

From the meta-analysis conducted by Castro al, from the 6 studies, 0.15 (CI 0.09-0.22; p-value = 0.03) (Torres-Castro, 2021). Such occurrences occur in the occurrence of mucus plugs in the small airways in severe COVID-19 patients so that it can explain impaired ventilation function. In addition, there is also injury to the lungs and weakness in the neuromuscular, so there is a decrease in lung function (Huang *et al.*, 2020).

The FEV1 value obtained in this study with an average of 84.85 ± 17.64, and the FEV1/FVC value obtained an average of 87.22 ± 9.35. From the results of these two values, it is concluded that obstruction and normal results exist. There were 10% (n = 8) obstruction, 6.3% mild obstruction (n = 5), moderate obstruction 3.8 (n = 3), and no subjects with severe obstruction were found. From the results of spirometry performed by Moreno-Perez et al., obstruction was found to be 1.9% (n = 5), and in patients, without pulmonary disease disorders it was found to be 1.4% (n = 3) (Moreno-pérez *et al.*, 2021).Similar to the meta-analysis of Castro et al., the prevalence of obstruction was 0.07% (CI 0.04-0.11; p-value = 0.31). Patients with obstruction may have a history of smoking or airway hyperresponsiveness (Huang *et al.*, 2020).

In this study, the FEF value was 25-75%, with an average of 88.10 (39-178). A 25-75% FEF result on spirometry is indicated to assess whether there is an obstruction in the small airways. From this study FEF 25-75% which is less than or equal to 65% 31.3% (n = 25) and more than 65% 68.8% (n = 55). From a study conducted by Klara et al, on COVID-19 patients who are athletes, the FEF 25-75% 25% (n = 6) is low with a mean of 98% (78.5-108.5) (Bothe, 2021). From the study by Corte-Telles et al., patients with severe COVID-19 (n = 109) had an FEF of 25-75%, a median of 110±35 (Corte-telles et al, 2021). This is suspected to be due to mucus plugs in the small airways in COVID-19 patients (Huang *et al.*, 2020).

In this study, the bivariate AaDO2 analysis test with spirometry results was obtained in Table 2, and the results of the multivariate analysis were obtained in Table 3. From the bivariate test of the relationship between the AaDO2 gradient at the time of initial exposure to severe COVID-19 and the results of spirometry, namely Restriction, a significant relationship was obtained with PR 14.8 (95% CI: 3.895-56.065; p=<0.01) indicates that a high AaDO2 gradient has an effect on the incidence of Restriction based on the FVC value (< 80%). This is also supported by a study conducted by Labarca et al., where a high AaDO2 gradient was obtained after a follow-up examination four months after COVID-19 (Labarca *et al.*, 2021). In a study by Santus et al., a restriction pattern was found in post-COVID-19 patients with a high AaDO2 gradient (Santus *et al.*, 2021)

At the time of the multivariate test, it was still found that there was a relationship between the AaDO2 gradient and the occurrence of Restriction 14.7 times compared to the normal AaDO2 gradient with a probability range ranging from 3.936 to 69.085 with a p-value = <0.001. So it is evident that there is a relationship between the AaDO2 gradient in severe COVID-19 patients and

Restriction in post-COVID-19 patients. The occurrence of restrictions in subjects with post-COVID-19 may occur due to fibrosis in the lungs after COVID-19. According to research conducted by Myall et al., there are 39% of subjects with fibrosis, and there is a restriction in these subjects (Myall *et al.*, 2021) With the condition of high AaDO2 gradient in severe patients, the occurrence of fibrosis in the lung parenchyma is increasing.

The occurrence of restrictions in post-COVID-19 there are several mechanisms. One of them is dead cells, primarily type II alveolar epithelial cells which function as epithelial barrier stabilization so that proinflammatory cytokines increase, which in turn causes fibroblasts which lead to fibrosis (Desai *et al.*, 2022).

Table 2
Relationship between AaDO2 and spirometry results

Variable		Spirometry Results		PR	95% CI		p-value
					Lower	Upper	
		FVC <80%	FVC >80%				
AaDO2	Height	38 (67.9%)	18 (32.1%)	5.4	1,855	15,886	<0.001*
	Normal	3 (12.5%)	21 (87.5%)				
		FEV1 <75%	FEV1 >75%				
AaDO2	Height	23 (41.1%)	33 (58.9%)	0.6	0.474	0.733	0.051
	Normal	0 (0%)	24 (100%)				
		FEV1/FVC <75%	FEV1/FVC >75%				
AaDO2	Height	8 (14.3%)	48 (85.7%)	0.9	0.770	0.954	0.051
	Normal	0 (0%)	24 (100%)				
		FEF 25-75% <65%	FEF 25-75% > 65%				
AaDO2	Height	23 (41.1%)	33 (58.9%)	4.9	1,261	19,270	0.004*
	Normal	2 (8.3%)	22 (91.7%)				

AaDO2 (Alveolar-Artery Oxygen Tension Different), FVC (Force Vital Capacity), FEV1 (Force Expiration Volume 1st second), FEF 25-75% (Force Expiration Flow 25-75%)

aAnalysis using chi-square

*Has a significant effect (p-value <0.05)

Table 3
Multivariate Analysis of Logistic Regression FVC, FEV1, FEV1/FVC and FEF 25-75% with AaDO2 in Severe COVID-19 Survivors

Variable	PR	CI95%		p-value
		Lower	Upper	

Variable	PR	CI95%		p-value
		Lower	Upper	
FVC	18.6	3.978	87,401	<0.001*
FEV1	1118335645	<0.001	-	0.998
FEV1/FVC	146338031,2	<0.001	-	0.998
FEF25-75%	7.7	1,606	37,214	0.011*

* Has a significant effect (p-value < 0.05)

In this study, the results of multivariate FVC with covariates found that there was a relationship between FVC with body weight >70kg with PR 0.2 (CI 95%: 0.076-0.761; p=0.015), indicating a significant relationship between FVC with body weight greater than or equal to 70kg. This is supported by the research of Wang et al. in China. It was found that in overweight subjects, there was a significant relationship to a decrease in the FVC value (p = 0.02). This happens because, first, there is an increase in the diaphragm in overweight individuals, so this change causes a decrease in lung function and extra work when breathing. Moreover secondly, there is an accumulation of fat on the chest wall, so there is an obstacle to direct chest movement or impaired muscle function in the intercostal space. Third, in obesity, an increase in the release of inflammatory markers (eg leptin) into the lungs, resulting in disturbances in airway diameter (Wang *et al.*, 2021)

The bivariate test of the relationship between the AaDO2 gradient at the initial exposure to severe COVID-19 and spirometry results, namely FEV1 <75% (obstruction), showed no significant relationship. This shows that in this study, there was no relationship between AaDO2 patients and the presence of obstruction after the patient recovered. The same thing was found in the Labarca et al. study, that there was no obstruction in severe post-COVID-19 patients with high AaDO2 gradients at the time of initial admission to the hospital because, in COVID-19, there is rarely damage to the larger respiratory tract, so that it does not occur significant airway obstruction (Labarca *et al.*, 2021).

Based on the bivariate test of the relationship between the AaDO2 gradient at the initial exposure to severe COVID-19 and spirometry results, namely FEV1/FVC <75% (obstruction), there was no significant relationship. This shows that in this study, there was no relationship between AaDO2 patients and the presence of obstruction after the patient recovered. The same thing was found in the Labarca et al. study, that there was no obstruction in severe post-COVID-19 patients with high AaDO2 gradients at the time of initial admission to the hospital because, in COVID-19, there is rarely damage to the larger respiratory tract, so that it does not occur significant airway obstruction (Labarca *et al.*, 2021).

Based on the bivariate test of the relationship between the AaDO2 gradient at the time of initial exposure to severe COVID-19 with an FEF value of 25-75% (< 65%), there was a significant relationship with PR 7.7 (95% CI: 1.640-35.845; p = 0.004) showed that a high AaDO2 gradient affects the incidence of small airway obstruction based on FEF values of 25-75% (< 65%). No studies have found a high AaDO2 value with an FEF of 25-75%. In a study conducted by Labarca et al., with a high AaDO2 value and a mean FEF of 25-75% in severe COVID-19, 114.3±40.6 without an explanation of the relationship. The relationship between

AaDO2 and FEF of 25-75% can occur because a high AaDO2 gradient increases morbidity in COVID-19 patients, and during spirometry examination, a mucus plug occurs in the small airways, resulting in a low FEF value of 25-75% (Huang *et al.*, 2020; Labarca *et al.*, 2021)A multivariate test was also carried out, and it was also found that there was a relationship between the AaDO2 gradient of severe COVID-19 patients with a low FEF of 25-75% as much as 7.7 times compared to the average AaDO2 gradient, with a probability range in the population ranging from 1.601 to 37,214 with a p-value = 0.011, so that there is a proven relationship between the AaDO2 gradient in severe COVID-19 patients with an FEF of 25-75% less or equal to 65% in post-COVID-19 patients (Labarca *et al.*, 2021).

The injury to the lungs, tiny airways, and the possibility of interference with ACE2 are located in the peripheral airways, which is expressed by type II alveolar epithelium produced by surfactant so that when the injury occurs, it causes leakage in the microvasculature. Moreover, in areas with poor perfusion or no perfusion due to an infiltration in the lung parenchyma, the lung becomes stiff due to hypocapnia pneumoconstriction. It causes a decrease in surfactant production (Swenson and Swenson, 2021).

This research is the first research conducted so that it can be used as a reference for other research. This study can also be developed to assess spirometry results in post-COVID-19 patients after one year—weaknesses in this study that must be considered. The lack of baseline pulmonary function data before disease onset makes it difficult to compare outcomes after an illness. In this study, they only performed a spirometry examination once at 12 weeks or more as a COVID-19 survivor, so they could not determine the course of changes in lung function after COVID-19. Moreover, this study did not objectively assess physical activity in post-COVID-19 patients.

Conclusion

There is a relationship between a high baseline AaDO2 gradient with FVC and FEF values of 25-75% in severe adult COVID-19 survivors. There was no relationship between a high baseline AaDO2 gradient and FEV1 and FEV1/FVC values.

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