International Journal of Research and Review
Vol. 9; Issue: 10; October 2022
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Correlation Between Neutrophil to Lymphocyte Ratio Baseline with Spirometry Test in Severe Coronavirus Disease 2019 (COVID-19)

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DOI: https://doi.org/10.52403/ijrr.20221029

ABSTRACT

Background/aim: The sequelae of the post-COVID-19 syndrome can affect lung function. The neutrophil-lymphocyte ratio is one of the markers of increased inflammation in SARS-CoV-2 virus infection. Based on this, the researchers wanted to assess the relationship between baseline NLR levels and spirometry tests in severe COVID-19 survivors.
Methods: This research is an observational analytic study with a cross-sectional design conducted at Prof. Dr. IGNG Ngoerah Hospital Denpasar from January 2022 to July 2022. Univariate analysis displays the mean, standard deviation, and relative frequency for categorical data. Bivariate analysis was performed by chi-squared test. The multivariate analysis used was multiple logistic regression to assess the relationship between baseline NLR levels and covariates with the spirometry test.
Results: Subjects who participated in the study were 80. As many as 58 subjects (72.5%), the baseline NLR value was 3.58%, and the median NLR was 5.41% (1.19-514%). On spirometry examination, there were restrictions on 41 subjects (51.2%), mild Restriction in 38 subjects (47.5%), Obstruction in 8 subjects (10%), benign Obstruction in 5 subjects (6.3%). The multivariate correlation between baseline NLR and spirometry results (FVC, FEV1, FEV1/FVC, and FEF 25-75%) showed no relationship
Conclusion: There is no relationship between high baseline NLR and FVC, FEV1, FEV1/FVC, and FEF25-75% values.

Keywords: COVID-19, CRP, Lymphocyte, FVC, FEV1/FVC, FEF 25-75

INTRODUCTION

The neutrophil-lymphocyte ratio is one of the markers of systemic inflammation obtained by dividing the absolute neutrophil count and absolute lymphocyte count. The NLR ratio reflects the balance between the severity of inflammation and the body's immune status [1]. The study by Imran et al. in 2020 showed that NLR was positively correlated with the severity of COVID-19 ($p < 0.001$) and as an independent risk for severe COVID-19 pneumonia with an OR of 1.264 (95% CI 1.046-1.526, $p = 0.015$). Erdogan, Can and Gönüllü, (2021) showed that NLR was better than Lymphocyte to Monocyte ratio (LMR) in determining the prognosis of COVID-19 patients [2].

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 FEF25-75% 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.

A study by Goërtz *et al.*, (2020) in the Netherlands and Belgium showed a partial recovery of symptoms three months after symptom onset. In this study, the most frequently experienced symptoms, both at symptom onset and at the time of re-evaluation, were fatigue and dyspnea, accounting for more than 70 percent of all subjects [3]. Furthermore, in the study of Moreno-pérez *et al.*, (2021) at 12 weeks post-COIVD-19, 34 of 269 had restrictions on spirometry, and 5 of 269 had obstruction [4].

The facts above show that the NLR value has the potential as 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 NLR of COVID-19 patients at the beginning of treatment can be a reference for providing early medical rehabilitation management for patients who are 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 used is a cross-sectional study conducted at Prof. Dr. I.G.N.G. 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. I.G.N.G. 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/ musculo-skeletal 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) patients who 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 color 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 $p < 0.05$.

RESULT

This research was conducted in the period from December 2021 to May 2022. In that period, a total of 80 subjects were obtained. The mean age was found to be 51 ± 14.55 years. Based on age category, subjects aged less than 65 were 66 subjects (82.5%). Male sex obtained as many as 45 subjects (56.3). The median height was obtained at 165 ± 10.17cm, while the average weight was received at 70.70 ± 13.32kg. There were also 17 subjects (21.3%) with comorbid hypertension and 20 subjects (25%) with comorbid diabetes mellitus characteristic data in Table 1.

The median duration from confirmation to subject recruitment was 30 weeks (table 5.1). Based on the duration category since confirmed, the group with a period of more than 16 weeks was found to be 55 subjects (68.8%). The median length of stay was nine days, with a minimum value of 3 days and a maximum of 30 days. In the length of stay category, subjects who received

treatment for more than or equal to 14 days were 17 subjects (21.3%). A total of 58 subjects (72.5%) had NLR values at the beginning of the examination during treatment above 3.58 percent. The median overall NLR score was 5.41 percent, with the lowest score of 1.19 percent and the highest score of 514 percent.

Table 1. Characteristics Subject

Variable	**n=80**
Age, mean ± S.B.	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)
NLRb, median (min-max)	5.41 (1.19-514)
High NLR, n (%)	58 (72.5)
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)

NLR (Neutrophil-Lymphocyte ratio), FVC (Force Vital Capacity), FEV1 (Force Expiration Volume 1 second), FEF 25-75% (Force Expiration Flow 25-75%), data is normally distributed, b Data is not normally distributed.

Bivariable analysis using cross tabulation was performed on the independent variables NLR and AaDO2 values, on the dependent variable, namely FVC, FEV1, FEV1/FVC, and test results FEF25-75%. It can be seen in Table 2 subjects with high NLR values and also having FVC <80% on spirometry examination were 34 (58.6%) of 58 subjects. Some subjects show high NLR values with FVC values >80% 24 (41.4%). 7 (31.8%) subjects from 22 subjects had normal NLR values with FVC values <80%. And at normal NLR values with FVC values > 80%, 15 subjects (38.5%). The NLR value with the FVC value significantly obtained a prevalence ratio (PR) of 1.8 with a 95% confidence interval range from 0.963 to 3.525 (p = 0.032).

Table 2 Relationship between NLR and spirometry results

Variable		Spirometry Results		PR	95% CI		*p-value*
					Lower	*Upper*	
		FVC <80%	FVC >80%				
NLR	Height	34 (58.6%)	24 (41.4%)	1.8	0.963	3,525	0.032*
	Normal	7 (31.8%)	15 (68.2%)				
		FEV1 <75%	FEV1 >75%				
NLR	Height	18 (31.0%)	40 (69.0%)	1.4	0.577	3,229	0.464
	Normal	5 (22.7%)	17 (77.3%)				
		FEV1/FVC <75%	FEV1/FVC >75%				
NLR	Height	7 (12.1%)	51 (87.9%)	2.6	0.346	20,359	0.317
	Normal	1 (4.5%)	21 (95.5%)				
		FEF 25-75% < 65%	FEF 25-75% > 65%				
NLR	Height	19 (32.8%)	39 (67.2%)	1.2	0.553	2,609	0.636
	Normal	6 (27.3%)	16 (72.7%)				

NLR (Neutrophil-Lymphocyte ratio), FVC (Force Vital Capacity), FEV1 (Force Expiration Volume 1st second), FEF25-75% (Force Expiration Flow 25-75%); a: Analysis using chi-square; * Has a significant effect (p-value <0.05)

In the multivariate logistic regression analysis of variables associated with FEV1/FVC values in severe COVID-19 survivors (Table 3), no related variables were found after passing through the stages of multivariate analysis.

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

Variable	PR	CI95%		*p-value*
		Lower	*Upper*	
FVC	2.4	0.602	0.722	0.215
FEV1	0.7	0.160	3,074	0.639
FEV1/FVC	7.6	0.214	37,256	0.432
FEF25-75%	0.6	0.174	2.499	0.540

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

DISCUSSION

In this study, there were 80 survivors of severe COVID-19 who met the study inclusion criteria. 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%). In a study by Moreno-Perez et al., 141 patients with post-COVID-19 were found with a median of 58.2% (95% CI 51.0-65.2) of patients with severe pneumonia. The median age of the patients was also 56.0 (42.0-67.5) in the same study Moreno-Perez et al., (2021) [4].

Male sex was found more in this study, namely 45 subjects (56.3%). In a previous study conducted at Prof. Dr. I.G.N.G. Ngoerah Central General Hospital Denpasar, there were 63 males (70%) compared to 27 (30%) women in patients with severe COVID-19 [5]. In a study by Moreno-Perez et al. in Spain, there were more males than females [4]. More males than females could be associated with higher ACE2 receptor expression in males). in Asia than women [6].

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 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 [6]. 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 [7].

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 by Rees *et al.*, (2020) and Thai *et al.*, (2020) it was reported that the median length of treatment was nine days [8,9].

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 [10]. One study showed that smoking could increase ACE2 expression and the patient's susceptibility, making symptoms more severe [11].

The neutrophil-lymphocyte ratio (NLR) obtained a median of 5.41 (1.19-514) in this study. Where obtained a high NLR with a value of 3.85% is 72.5% (n = 58) and a normal NLR is 27.5% (n = 22). The results of the bivariable analysis are in table 2, NLR with restriction spirometry results. The NLR variable with FVC value has a p-value = 0.032, which indicates a relationship between NLR and FVC value. However, after the multivariate analysis test with logistic regression, the results obtained are FVC, FEV1, FEV1/FVC, and FEF25-75%.

A study by Liu et al. also said that a high NLR value indicated severe cases and poor prognosis [12]. In a study by Eslamijouybari

et al., (2020) in COVID-19 patients, a significantly high NLR value was obtained compared to control patients. It was said that 103 (19.55) patients died and the mean NLR in patients who died was significantly high (p = 0.000). The NLR reflects the balance between innate (i.e., neutrophil) and adaptive (i.e., lymphocytes) immune responses in the body. Elevated NLR values are susceptible to the development of COVID-19 infection [13]

This study conducted spirometry examinations in post-COVID-19 patients by assessing FVC, FEV1, FEV1/FVC, and FEF25-75%. 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 if the value of 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 by Moreno-pérez *et al.*, (2021) of 269 post-COVID-19 patients with restriction spirometry with FVC value less than 80% predicted 12.6% (n = 34) and in patients without a history of previous lung disease with 227 patients obtained 2.7% (n = 6) [4].

From the meta-analysis conducted by Castro al, the six studies analyzed were 0.15 (CI 0.09-0.22; p-value = 0.03) [14]. 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 [15].

The FEV1 value was obtained in this study with an average of 84.85 ± 17.64, and the FEV1/FVC value was obtained at 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) [4]. 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 [16]

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., from COVID-19 patients who are athletes, the FEF 25-75% 25% (n = 6) is low with a mean of 98% (78.5-108.5) (Klara et al., 2021). From the study by Cort *et al.*, (2020), patients with severe COVID-19 (n = 109) had an FEF of 25-75%, a median of 110±35 [17]. This is suspected to be due to mucus plugs in the small airways in COVID-19 patients [18].

Based on the bivariate test, the relationship between NLR values at the time of initial exposure to COVID-19 and restriction results (FVC <80%) was found to be a significant relationship. This found a significant relationship with PR 1.8 (95% CI: 0.963-3.525; p = 0.032). However, when doing a multivariate test, it was found that NLR was unrelated to Restriction. P.R.'s result was 2.4 (95% CI: 0.602-0.722; p = 0.215). This showed that high NLR did not affect the incidence of Restriction based on the FVC. value. (< 80%) statistically. This is possible because the interrelation between variables causes it. In this case, the inflammatory factor did not affect the multivariate analysis. Different from the study conducted by Anastasio et al. (2021),

in patients with high NLR during hospitalization, it was found that at the time of evaluation, a low FVC. value was found in 222 patients (p = 0.03) [19].

From a study conducted by Li X (2020), the occurrence of Restriction and disruption of the small airways after an autopsy showed inflammation in the lung interstitium, infiltration of alveolar inflammatory cells, fibrous hyperplasia, and destruction of the alveolar structure [20]. It is estimated that the pathological changes that cause lung compliance are suspected-to decrease, which causes restrictions on lung function [17]. Infiltration of inflammatory cells in the lung parenchyma caused by infection can trigger the process of fibrosis formation, as evidenced by chest CT scans in COVID-19 survivors, and even fibrosis can last up to 7 years [21,22]. As a result of the excessive active pro-inflammatory cytokines, they are continuously causing damage and repair of cellular tissue that is not balanced. Normally, 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) [23]. Pulmonary fibrosis in lung tissue is caused by tissue damage due to inflammation, destruction of tissue structures, fibroblast proliferation, and a significant accumulation of extracellular matrix. So that the pulmonary function examination can provide restriction results [24].

Based on the bivariate test, the relationship between the NLR value at the time of initial exposure to COVID-19 and the result of FEV1 <75% (Obstruction) found there was no significant relationship. At the time of multivariate analysis, there was no relationship between NLR and obstruction outcome. This shows that in this study, there was no significant difference between the patient's NLR and the results of obstruction spirometry after the patient recovered. There is a study conducted by Niyatiwatchanchai *et al* it was found that in the acute phase of COVID-19, patients with severe degrees had more lung inflammation than mild or moderate degrees, and increased inflammatory mediators and cytokines with the finding of increased NLR and spirometry examinations were also carried out in post-COVID-19 patients with spirometry results still within normal limits and no differences in spirometry results for differences in disease severity [25]. The neutrophil-lymphocyte ratio is a relationship between innate immunity (neutrophils) and adaptive immunity (lymphocytes) that can be used as a predictor of inflammation to determine the prognosis of inflammation, including COVID-19, where the higher the NLR, the worse the prognosis of the disease [26].

Based on the bivariate test, the relationship between the NLR value at the time of initial exposure to COVID-19 and the results of FEV1/FVC <75% (Obstruction) found no significant relationship. At the time of multivariate analysis, there was no relationship between NLR and obstruction outcome. This shows that in this study, there was no significant difference between the patient's NLR and the results of obstruction spirometry after the patient recovered. By the explanation above, it can be concluded that post-COVID-19 had a better NLR before because of a good prognosis.

Based on the bivariate test, the relationship between NLR values at the time of initial exposure to COVID-19 and FEF results of 25-75% (small airway obstruction) found no significant relationship. At the time of multivariate analysis, there was no relationship between NLR and the outcome of small airway obstruction. This shows that in this study, there was no significant difference between the patient's NLR and the results of small airway obstruction spirometry after the patient recovered. The

explanation for why this can happen is similar to the explanation above that NLR is a prognosis for inflammation, so the higher the NLR, the worse the prognosis. In post-COVID-19, the previous NLR was better because of the excellent prognosis.

Multivariate analysis also found a relationship between hypertension and FEF25-75%. Obtained PR 3.3 (95% CI 1.014-11.041; p = 0.047. That this shows that hypertension has a subject with a history of hypertension has the possibility of experiencing small airway obstruction 3.3 times compared to subjects without a history of hypertension, with a probability range ranging from 1.014 to 11.041 with a p-value of 0.047. In patients with COVID-19 with a history of hypertension, there is a disturbance in ACE2 and the Renin-Angiotensin System (RAS). The possible mechanism is due to the binding of SARS-CoV-2 to ACE2, which results in the degradation of angiotensin II, increasing blood pressure.

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. A drawback that should be considered is that 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

No relationship exists between high baseline NLR and FVC., FEV1, FEV1/FVC, and FEF25-75% values.

Acknowledgement: All patients, all authors, and I are grateful to two anonymous reviewers for their valuable comments on the earlier version of this paper.

Conflict of Interest: There are no conflicts of interest to declare by any of the authors of this study.

Source of Funding: This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

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How to cite this article: Ida Bagus Janantara Wirakusuma, I Ketut Agus Somia, Ni Luh Eka Arisanti, Ida Bagus Ngurah Rai, Ida Ayu Jasminarti Dwi Kusumawardani, Ni Wayan Chandrawati. Correlation between neutrophil to lymphocyte ratio baseline with spirometry test in severe coronavirus disease 2019 (COVID-19). *International Journal of Research and Review*. 2022; 9(10): 249-256. DOI: *https://doi.org/10.52403/ijrr.20221029*

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