Iranian Journal of Microbiology

Volume 17 Number 6 (December 2025) 1042-1048
DOI: http://doi.org/10.18502/ijm.v17i6.20375

ORIGINAL ARTICLE

Association of inflammatory scoring tools with spirometry indices in COVID-19 patients: a single center cohort study

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Received: September 2024**, Accepted:** September 2025

ABSTRACT

Background and Objectives: Patients with COVID-19 have spirometry parameters linked to various biological markers, including CRP, NLR, MPV, RDW, and APACHE II score. The objective of this study was to investigate the association of inflammatory scoring tools with spirometry indices in a three-month follow-up of COVID-19 patients.

Materials and Methods: Spirometry records of 369 COVID-19 cases with complications were analyzed at baseline and three months after discharge. Generalized linear models and logistic regression analysis were performed to compare the variables using SPSS version 25 software.

Results: The baseline NLR was 3.20 (95% CI: 2.96, 3.43); PCT was 0.26 (95% CI: 0.25, 0.27); and MPV was 7.23 (95% CI: 7.10, 7.35). We found that the effects of NLR, CRP, and APACHE II score on the respiratory indices FEV1 and FEV1/FVC three months after discharge had an inverse relationship. Patients with asthma had significantly lower FEV1 and FEV1/FVC values, and the level of FVC did not have any significant difference between people with asthma and COPD patients.

Conclusion: CRP, NLR, and APACHE II score are among the main factors that are directly related to respiratory indices and they are considered to be appropriate indicators of prognosis for these conditions in COVID-19 patients.

Keywords: COVID-19; Biomarkers; Respiratory function tests; Prognosis; Biological factors; Inflammation mediators

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a coronavirus that appeared in China in late 2019 and quickly spread across the globe, has posed a serious threat to global health,

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claiming the lives of millions of people worldwide (1). Coronavirus disease of 2019 (COVID-19), named for SARS-CoV-2 infection, primarily affects the lungs, but it can also harm other organs (2). Organ damage can lead to long-term health risks. Predicting the morbidity and mortality rates of COVID-19 patients has increasingly posed a challenge for healthcare systems globally since the onset of the pandemic. Research reveals the potential usefulness of certain analytical markers, proteins, and blood parameters (3). The alterations in the aforementioned factors offer diagnostic insights regarding the existence of a COVID-19 infection within the body. They also provide vital information for predicting complications and developing treatment plans for managing COVID-19 infection (4).

The ratio of lymphocytes to neutrophils (NLR) is a biological factor that changes in various conditions such as tumors, pancreatic cancer, chronic obstructive pulmonary disease (COPD), and cardiovascular diseases. Higher NLR values at intensive care unit (ICU) admission are linked to worse clinical symptoms in COVID-19 involved individuals (5). Additionally, the mean platelet volume (MPV) is a measurable complete blood count (CBC) parameter in which recent studies represent a connection between the severity of COVID-19 and the presence of larger and younger platelets, making this observation a powerful indicator for evaluating platelet activity (6). Furthermore, high levels of C-reactive protein (CRP) can be found in patients with severe pneumonia. Therefore, CRP is not only a key parameter for diagnosing and assessing severe lung infections, but also a valuable prognostic marker. High CRP levels indicate a higher risk of disease worsening and a longer hospital stay (7). Lactate dehydrogenase (LDH) is another important biomarker, as initial data from COVID-19 patients have shown a significant difference in LDH levels between those with severe disease and those without severe symptoms. These results suggest that high LDH levels are associated with a higher chance of severe disease and COVID-19 mortality (8). Additionally, elevated procalcitonin (PCT) levels have been shown to correlate positively with COVID-19 severity (9). Moreover, the acute physiology and chronic health evaluation (APACHE) II score is a valid and practical scoring system used to evaluate and differentiate patients with a high risk of severe medical conditions. It allows the classification of acute patients based on their physiological parameters, enabling the selection of optimal treatment strategies. This not only gives patients hope for effective future treatment but also highlights the importance of starting the recovery process as soon as possible (10).

The impact of SARS-CoV-2 on global health necessitates further investigation of inflammatory markers and lung function. Comprehending these indicators is essential for enhancing patient outcomes and directing effective treatment strategies. In this study, we demonstrate that different biological markers, such as CRP, NLR, MPV, red cell distribution width (RDW), and APACHE II score, are associated with spirometry parameters in a follow-up for three months in patients with COVID-19. We hope that by finding a significant association, we will be able to apply the appropriate treatment strategies in the areas of prognosis and diagnosis to cope more effectively with COVID-19.

MATERIALS AND METHODS

Patients and study design. In this prospective cohort study, we included 369 COVID-19 patients admitted to Firoozgar Hospital, Tehran, Iran. These patients were confirmed cases, verified by positive RT-PCR tests and supported by positive CT scan results. During hospitalization and the subsequent three-month follow-up, a thorough assessment, including spirometry and blood tests, was performed. In addition, vital demographic and clinical data such as age, clinical symptoms, baseline laboratory indicators, clinical measurements, and underlying medical conditions were carefully recorded. Importantly, we deliberately excluded individuals with blood malignancies from the study group, ensuring the homogeneity and relevance of our patient sample. A checklist was filled out for each participant at the baseline and follow-up step. The checklist data included all demographic, clinical and paraclinical data of each participant, which was used for further analysis. We obtained data from each patient's records at the hospital repository and used it for the analysis.

Measurements. Data were collected from the hospital repository at the patients' baseline admission and at their three-month follow-up after discharge. In this study, patients who met the inclusion criteria first had

their baseline spirometry indexes and disease complications recorded, and were then contacted after three months for their follow-up. Their complications and spirometry indexes were assessed again and used for further analysis. The primary objective of this research is to examine the correlation between spirometry scores and a range of inflammatory markers, which include NLR, PCT, MPV, CRP, LDH, ferritin, in addition to the APACHE II score. We used Spearman's correlation to evaluate associations between inflammatory markers and pulmonary function tests. Additionally, we used generalized linear models to evaluate the combined effect of inflammatory markers and the APACHE II score on respiratory indices (FEV1/FVC, FVC, and FEV1) three months after patient discharge.

The forced vital capacity (FVC) is a crucial test of lung function. It measures how much air the patient can breathe out forcefully after taking a deep breath. The FEV1 (Forced expiratory volume) is the amount of air that comes out in the first second of the FVC test. The FEV1/FVC ratio shows what percentage of the FVC is achieved in one second. The actual ratio, not the predicted one, is used to interpret the results (11-13). Interpretation of spirometry parameters was done according to guidelines (14), and the correlation coefficient of their scores with inflammatory markers was calculated.

Statistical analysis. We performed statistical analysis on the collected data using generalized linear models to enable comparative evaluations. Moreover, we used logistic regression analysis to measure the impact of the dataset on the final outcome. We used SPSS version 25 software for data analysis, ensuring rigorous and systematic analysis of the obtained information. P-values < 0.05 were considered as statistically significant.

Ethics Statement. The study protocol was approved by the ethics committee of the Iran University of Medical Sciences, located in Tehran, Iran, under the code: IR.IUMS.FMD.REC.1400.278.

RESULTS

Patients demographics. A comprehensive investigation analyzed data from 369 hospitalized patients diagnosed with COVID-19. Of them, 238 cases after three-month follow-up met the inclusion criteria and had sufficient data for analysis. The study cohort (n=238) had an average age of 56.11 years (95% CI: 54.35, 57.87), with 55% of patients being male (n=130). The average body mass index (BMI) was 26.33 kg/m² (95% CI: 25.81, 26.85). Among the patients, 76% (n=180) were nonsmokers, while 24% (n=58) were identified as smokers. Notably, 26% of participants had comorbidities, with hypertension and ischemic heart disease/congestive heart failure (IHD/CHF) each accounting for 14% (n=33), and chronic obstructive pulmonary disease (COPD) at 12% (n=28). Baseline mean values for key inflammatory markers were as follows: NLR (neutrophil-to-lymphocyte ratio), 3.20 (95% CI: 2.96, 3.43); PCT (procalcitonin), 0.26 (95% CI: 0.25, 0.27); and MPV (mean platelet volume), 7.23 (95% CI: 7.10, 7.35). Refer to (Table 1) for a comprehensive summary of baseline values for other relevant laboratory indicators and clinical measurements in the patient cohort.

Spirometry parameters analysis. Table 2 shows the relationship between baseline inflammatory factors, the APACHE II score, and respiratory indices (FEV1/FVC, FVC, and FEV1) three months post-hospital discharge. Moreover, it shows that the FEV1 index has a negative linear relationship with the baseline levels of NLR, CRP, and the APACHE II score. This means that lower FEV1 values, indicating more severe obstructive disease, are related to higher levels of NLR, CRP, and the APACHE II score three months later. Also, there was a significant negative linear relationship between the baseline CRP levels and the FVC index three months after discharge ($P = 0.044$). This implies that higher baseline CRP levels, indicating more severe restrictive disease, are related to lower FVC values at the same time. On the other hand, PCT and MPV had a positive correlation, meaning that higher levels of these factors were related to higher FVC values. Moreover, patients with higher baseline levels of NLR, CRP, and the APACHE II score had a negative linear relationship with the FEV1/FVC index. This suggests that lower FEV1/FVC values, indicating more severe obstructive disease, are related to higher levels of NLR, CRP, and the APACHE II score three months later (Table 2).

We used a generalized linear model to examine how NLR, CRP, APACHE II score, and a history of respiratory diseases affected FEV1, FVC, and FEV1/FVC

Table 1. Fundamental characteristics of individuals infected with COVID-19.

Characteristics	Values
Demographic	
Age (Year); Mean ± SD (95%Cl)	56.11 ± 17.21 (54.35, 57.87)
Sex; n (%)	
Male	130 (55)
Female	108 (45)
Positive report for smoking; n (%) BMI	58 (24)
(kg/m^2); Mean ± SD (95%Cl)	26.33 ± 5.11 (28.81, 26.85)
Positive report for comorbidities; n (%)	
Diabetic	61 (26)
Hypertension (HTN)	33 (14)
Ischemic heart disease (IHD/CHF)	33 (14)
Chronic obstructive pulmonary disease (COPD)	28 (12)
Asthma	26 (11)
Chronic kidney disease (CKD)	21 (9)
Congestive heart failure (CHF)	19 (8)
Cerebrovascular accident (CVA)	19 (8)
Interstitial lung disease (ILD)	11 (5)
Laboratory indexes; Mean ± SD (95%Cl)	
NLR	3.20 ± 2.30 (2.96, 3.43)
PCT	0.26 ± 0.08 (0.25, 0.27)
MPV	7.23 ± 1.23 (7.10, 7.35)
CRP	82.08 ± 42.96 (77.68, 86.47)
Ferritin (Per 100)	4.53 ± 3.30 (4.19, 4.87)
LDH (Per 100)	5.27 ± 2.75 (4.99, 5.55)

BMI: body mass index; NLR: neutrophil to lymphocyte ratio; PCT: Procalcitonin; MPV: mean platelet volume; CRP: C-reactive protein; LDH: lactate dehydrogenase

Table 2. The relationship between fundamental blood inflammatory factors and APACHE II scores in relation to FEV1, FVC, and the FEV1/FVC ratio among patients with COVID-19*

Factor	FEV1 (N=238)		FVC (N=238)		FEV1/FVC (N=238)	
	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value
NLR	-0.134	0.039**	-0.098	0.131	-0.169	0.009***
PCT	0.004	0.957	0.213	0.001***	0.027	0.679
MPV	-0.049	0.448	0.209	0.001***	-0.054	0.403
CRP	-0.131	0.043**	-0.131	0.044**	-0.132	0.042**
Ferritin	0.098	0.132	0.002	0.970	0.094	0.150
LDH	0.028	0.663	-0.013	0.838	0.042	0.517
APACHE II	-0.129	0.047**	-0.127	0.050	-0.159	0.014**

*Spearman was used for analyzing bivariate correlation; ** Correlation is significant at the 0.05 level; *** Correlation is significant at the 0.001 level

NLR: neutrophil to lymphocyte ratio; PCT: Procalcitonin; MPV: mean platelet volume; CRP: C-reactive protein; LDH: lactate dehydrogenase; APACHE II: Acute Physiology and Chronic Health Evaluation II

levels three months after leaving the hospital. The model considered the main effects of these variables (Table 3). Only a history of asthma had a significant impact on FEV1 levels. Patients with an asthma history had an average FEV1 level 29 units lower than those without such a history.

FVC levels had significant relationships with several factors; patients with a history of ILD had an average FVC level 14.97 units lower than those without such a history (P<0.001). Patients with a history of asthma had an average FVC level 5 units higher than those without such a history (P=0.03). Also, for every unit increase in CRP, the average FVC level three months after discharge decreased by 0.05 units (P=0.021). In contrast, for every unit increase in Procalcitonin (PCT) or Mean Platelet Volume (MPV), the average FVC level three months after discharge increased by 16.98 units (P=0.039) and 1.75 units (P=0.002), respectively.

There was no significant relationship between FEV1/FVC levels and asthma three months after discharge in patients with a history of asthma. Therefore, the average FEV1/FVC level at this time in patients with an asthma history was only 0.21 units lower than in patients without such a history (Table 3).

DISCUSSION

While most COVID-19 patients recover and resume their normal health after treatment, some may experience symptoms that last for weeks or months. People with mild illness who do not need hospitalization can also have persistent or late symptoms (15). Furthermore, more than 75% of COVID-19 patients reported at least one long-term effect six months after the onset of the disease (16). COVID-19 is mainly characterized by pneumonia, but its most serious and fatal outcomes are related to cardiovascular complications. The nervous system is also severely impacted by COVID-19. A study showed that about 40% of COVID-19 patients had neurological symptoms due to the infection (17).

A study found that the combination of the APACHE II score, NLR, and expired tidal volume was more effective in predicting the failure of Non-Invasive Ventilation (NIV) than the APACHE II score, NLR, or expired tidal volume alone (18). Moreover, ferritin and LDH levels increased significantly in the moderate and severe stages of the disease (19). The APACHE II score has also been shown to be independently associated with inpatient mortality

Table 3. Effecting factors on FEV1, FVC and FEV1/FVC in COVID-19 patients

Factor	FEV1; N=238		FVC; N=238		FEV1/FVC; N=238	
	B ± SE (95%Cl)	P-value	B ± SE (95%Cl)	P-value	B ± SE (95%Cl)	P-value
NLR	-0.59 ± 0.64 (-1.86, 0.66)	0.355			-0.007 ± 0.005 (-0.01, 0.004)	0.218
CRP	-0.02 ± 0.05 (-0.12, 0.07)	0.632	-0.05 ± 0.02 (-0.09, -0.008)	0.021	0.00009 ± 0.00004 (-0.001, 0.001)	0.830
APACHE II	0.028 ± 0.20 (-0.37, 0.43)	0.894			-0.001 ± 0.001 (-0.004, 0.002)	0.596
PCT			16.98 ± 8.20 (0.89, 33.06)	0.039		
MPV			1.75 ± 0.57 (0.63, 2.87)	0.002		
COPD	-1.29 ± 1.63 (-4.50, 1.91)	0.430	1.44 ± 2.18 (-2.83, 5.71)	0.509	-0.01 ± 0.01 (-0.03, 0.01)	0.445
Asthma	-29.13 ± 1.85 (-32.78, -25.49)	<0.001	5.46 ± 2.51 (0.53, 10.38)	0.030	-0.217 ± 0.01 (-0.24, -0.18)	<0.001
ILD	1.10 ± 2.10 (-3.02, 5.24)	0.600	-14.97 ± 2.79 (-20.44, -9.50)	<0.001	0.02 ± 0.01 (-0.01, 0.05)	0.261

* Generalized linear models were used for comparison.

in COVID-19 patients (20). The APACHE II score had a high predictive ability for hospital mortality in COVID-19 patients, with a sensitivity of 96.15% and a specificity of 86.27% (20).

We examined the association between baseline inflammatory markers and the APACHE II score and post-discharge respiratory measures, namely FEV1/FVC, FVC, and FEV1, three months after discharge. We found a negative relationship between the levels of NLR, CRP, and the APACHE II score and the FEV1 measure, meaning that lower FEV1 values were related to higher levels of NLR, CRP, or APACHE II score. On the other hand, the baseline CRP level showed a negative linear relationship with the FVC measure, while a positive relationship was seen for PCT and MPV. Higher CRP, NLR, and APACHE II scores were associated with lower FVC values, indicating that systemic inflammation may contribute to reduced pulmonary capacity. Moreover, the baseline levels of NLR, CRP, and the APACHE II score had a negative relationship with the FEV1/FVC measure. A higher FEV1/FVC measure was related to lower levels of NLR, CRP, and the APACHE II score. Additionally, we explored the combined effects of NLR, CRP, the APACHE II score, and a history of respiratory disease on FEV1, FVC, and FEV1/FVC values three months after discharge. We found that only asthma significantly affected FEV1 and FEV1/FVC values. The FVC value was significant for all factors in the model except for COPD, which had no significant effect. These results agree with other previous studies. A study showed a moderate connection between the ICU stay length and the APACHE II scores, especially for FVC, FEV1, and changes in peripheral oxygen saturation (SpO2) values in COVID-19 patients (21). Another study showed that the main abnormality observed was a reduction in DLCO (diffusing capacity of the lungs for carbon monoxide), followed by lower FEV1 and FVC(22). Sun et al.'s study (2021) showed significant positive relationships between NLR and white blood cell counts, NLR and CRP levels, and NLR and PCT levels, as shown by the statistical analysis (23). Concerning MPV, a recent study has indicated its potential in offering valuable insights for the diagnosis and prognosis of sepsis and COVID-19. Additionally, MPV has been proposed as an inflammatory marker for serious conditions such as pneumonia and coronary heart diseases (24). Another study showed a correlation between standard platelet measures (PLT, MPV, PCT, PDW) and CRP and different symptoms of depression (25). As Yuksel et al. found in their study, high levels of MPV, NLR, and MPV-NLR can be used as simple markers for predicting mortality and mental decline in COVID-19 (26). Our study results support the association between inflammatory markers, the APACHE II score, and post-discharge respiratory measures as reported by another research. This suggests that these markers could be useful in predicting the severity and outcomes of COVID-19 in hospitalized patients.

This study has some limitations, mainly its prospective design. Also, the number of patients with COVID-19-related complications was relatively small. Future studies ought to focus on incorporating a broader and more varied patient demographic to enable a more reliable and accurate statistical analysis. It is important to recognize that this study did not consider various other inflammatory, hematological, and clinical variables. Therefore, there is an urgent need for more studies that examine the effect of these additional factors on the occurrence of complications from COVID-19. Such comprehensive studies are crucial for improving our knowledge of the disease and its management.

In conclusion, this thorough study has offered useful insights into the connection between laboratory markers and clinical outcomes. The main goal of this study was to investigate the relationship among factors affecting COVID-19-related complications. The results showed several significant associations between different biomarkers and health outcomes. When evaluating the long-term impact on respiratory function, our study showed a negative relationship between NLR, CRP, APACHE II score, and post-discharge FEV1 and FEV1/FVC values, especially in asthmatic patients. This indicates the lasting effect of inflammatory factors and the APACHE II score on respiratory health in these individuals. However, the level of FVC did not have a significant impact on patients with COPD. Our study provides essential data for clinicians and researchers, revealing the complex relationship between various laboratory markers and clinical outcomes in COVID-19 patients. These findings have the potential to improve risk assessment, patient management, and treatment strategies in the ongoing fight against this pandemic.

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