Original Article

Association of neutrophil-to-lymphocyte ratio and CRP with spirometry in COPD patients in North India

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Abstract

Background: Patients with chronic obstructive pulmonary disease (COPD) who have high serum levels of C-reactive protein (CRP), a marker of low-grade systemic inflammation, exhibit reduced lung functions and a worse prognosis. The neutrophil-to-lymphocyte ratio (N/L ratio, NLR), obtained from a complete blood count, is an inexpensive and easily accessible inflammation marker. The NLR has proven useful in assessing the risk for patients with various cardiovascular conditions, different types of solid tumours, sepsis, and infectious diseases. Research indicates that COPD patients have significantly higher NLR values compared to healthy controls of the same age and sex, with these values increasing even more during acute COPD exacerbations compared to stable periods. Hence, identifying non-invasive and cost-effective tools to assess the severity of COPD in the PHC/CHC level would be beneficial as an early intervention. **Aim:** To study the relationship between N/L ratio and CRP levels and spirometry in COPD patients. Settings and Study Design: Observational cross-sectional study. **Methods and Material:** A total of 100 patients of an age > 40 years with a confirmed diagnosis of COPD according to GOLD (Global Initiative COPD patients) criteria were selected. With an informed consent, blood sample collection for N/L ratio and CRP along with spirometry was performed in all the patients. Statistical Analysis Used: SPSS software with Student t-test, Chi-square t-test, ANOVA, and Spearman correlation with 95% CI is used. $P<0.05$ is considered significant. **Results:** NLR was observed to be higher in the moderate grade of COPD patients. All the patients were observed with an abnormal (>5 mg/L) CRP level. FEV1, FVC%, FEV1/FVC%, N/L ratio, and CRP were significantly ($P < 0.0001$*) associated with severity COPD according to GOLD criteria. **Conclusions:** This study concludes that the FEV1, FVC, and FEV1/FVC ratio were lower in severe COPD patients, and it also reveals that individuals with severe COPD have elevated levels of serum CRP and N/L ratio, which correlates with the severity of COPD. Elevated N/L ratio and CRP level may be used as non invasive predictors and cost-effective tools for COPD patients at the Primary health centre level for screening of the severity of COPD patients.

Keywords: CHC, community health centre, COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FEV, forced expiratory volume; FVC, forced vital capacity; global initiative COPD patients, GOLD; N/L ratio, neutrophil-to-lymphocyte ratio; PHC, primary health centre

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of disability and death worldwide. In 2019, COPD was ranked as the sixth leading cause of death.[1] According to the 2017 Global Burden of Disease (GBD) survey, COPD accounted for 50% of all chronic respiratory disease cases and 69% of years lived with impairment. Over 90% of deaths related to COPD occur in low- and middle-income countries (LMICs).[2] COPD not only imposes a significant economic burden but also results in disability, a lower quality of life, reduced productivity, increased hospital admissions, and premature death.[3] Adeloye *et al.* estimated that the global prevalence of COPD is 11.37%. Rehman *et al.*'s 2019 analysis of the economic burden

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of COPD in Europe found that the annual cost of productivity loss per patient was the highest in Germany (€5735) and the lowest in Greece (€998)[39].

Patients experiencing dyspnea, chronic cough, and/or sputum production, with a history of exposure to COPD risk factors, should be assessed for COPD. Diagnosis in this context requires spirometry; a post-bronchodilator FEV1/FVC ratio below 0.70 indicates persistent airflow limitation and thus COPD. The spirometry criterion for airflow limitation is a post-bronchodilator fixed ratio of less than 0.70 for FEV1/FVC. This criterion is straightforward, independent of reference values, and has been used in numerous clinical trials that form the basis of most treatment guidelines. For non-specialist clinicians, diagnostic simplicity and consistency are crucial. Testing the reversibility of airflow limitation (e.g. measuring FEV1 before and after bronchodilator or corticosteroids) is no longer recommended. Research shows increased airway inflammation during COPD exacerbations, with patients often categorized as mild, moderate, or severe.[4-6]

Spirometry is the most reliable and objective method for assessing airflow limitation. Despite its high sensitivity, peak expiratory flow measurement alone is insufficient as the sole diagnostic test[7] due to its limited specificity. Accurate spirometric measurements can be obtained in any healthcare setting, and all providers caring for COPD patients should have access to spirometry.[7]

The neutrophil-to-lymphocyte ratio (N/L ratio, NLR) can serve as a new inflammatory marker to assess inflammation, particularly after COPD and coronary artery disease (CAD), according to recent studies.[6,8] NLR is also a cost-effective and practical marker for determining the severity of malignancies in patients with a previous oncological diagnosis. Additionally, NLR has been shown to be an independent predictor in certain clinical conditions, such as appendicitis and bacteraemia.[9,10]

COPD patients with elevated serum levels of C-reactive protein (CRP), an indicator of low-grade systemic inflammation, have worse lung functions and prognosis.[11] White blood cell (WBC) count and sub-types are well-known indicators of systemic inflammation. The NLR, derived from a full blood count with differential, is an inexpensive and easily accessible marker of inflammation. NLR has been used in the risk stratification of patients with various cardiovascular disorders, several types of solid tumours, sepsis, and infections.[12] Gunay *et al.* found that NLR values were notably higher in COPD patients compared to healthy control subjects of the same sex, and these values increased even more during acute COPD exacerbations compared to stable periods.

Aim

To study the association of N/L ratio and CRP with spirometry in COPD patients.

1. Objectives: To calculate the NLR in COPD patients.
2. To estimate the serum CRP in COPD patients.
3. To perform the spirometry in COPD patients.
4. To find association of N/L ratio and CRP with spirometry in severity of COPD patients.

Study design

Observational cross-sectional study.

Period of study

The study was carried out over a period of 18 months, from 2021 to 2022.

Sample size calculation

By taking a sample representative of the 95% confidence interval and applying the W. Daniel formula, the sample size requirement came out to be 100.

After obtaining ethical approval from the institutional Ethics committee (Reg No.:ECR/262/Inst/UP/2013/RR-19) and patient consent, 100 patients with COPD attending the Respiratory Medicine outpatient department and wards of KGMU Lucknow between the months of March 2021 and September 2022 were selected based upon inclusion and exclusion criteria. All the patients who were selected for the study underwent a complete clinical evaluation. Each subject was assessed for haematological testing of CRP, N/L ratio, and spirometry with filled consent forms.

Inclusion criteria

- All patients with a confirmed diagnosis of COPD were diagnosed with pulmonary function tests according to GOLD (Global Initiative COPD patients).
- Age of subjects > 40 years.

Exclusion criteria

- Age < 40 years
- Patients with and diagnosed as bronchial asthma, bronchiectasis, or bullous lung disorders.
- Patients with active pulmonary tuberculosis.
- Patients with hepatic disease, renal disease, and myocardial infarction
- Patients with pneumonia
- Patients in acute exacerbation with COPD

Statistical analysis

Data were entered in Microsoft Excel and analysed using statistical software SPSS version 26 (SPSS Inc., Chicago, IL, USA). The continuous variables were evaluated by mean (standard deviation) or range value when required. The dichotomous and continuous variables were presented in number/frequency and mean ± SD and were analysed using Chi-square and Student *t*-test. A *P* value of < 0.05 or 0.001 was regarded as significant.

Statistical tools

The statistical analysis was done using SPSS (Statistical Package for Social Science) Version 26.0 Statistical Analysis Software. The values were represented in number (%) and mean ± SD.

Results

The majority of the patients were in the age group of 51–60 [56 (56.00%)], followed by 41–50 [35 (35.00%)] and 61–70 [9 (9.00%)]. Male preponderance was observed [76 (76.00%)] over female [24 (24.00%)].

Based on severity GOLD 2020, most of the patients were observed with a moderate stage [73 (73.00%)], followed by severe [24 (24.00%)] and mild stages [3 (3.00%)] of COPD patients.

The mean forced expiratory volume in 1 s (FEV1) was the highest [86.67 ± 2.05] in mild COPD patients, followed by moderate [64.38 ± 7.24] and severe patients [41.83 ± 7.48]. Statistically, a high significant difference was observed in FEV1 value among COPD patients [$P < 0.0001$*] [Table 1].

The mean forced vital capacity (FVC) was the highest in patients with mild patients [91.53 ± 14.41], followed by moderate [62.33 ± 10.73] and severe COPD patients [61.21 ± 2.05]. Statistically, a high significant difference was observed in FCV value among COPD patients [$P < 0.0001$*] [Table 2].

The mean FEV1/FVC ratio was the highest in mild patients [0.69 ± 0.14], followed by moderate [0.67 ± 0.09] and severe COPD patients [0.62 ± 0.04]. Statistically, a significant difference was observed in FEV1/FCV ratio among COPD patients [$P = 0.0326$*] [Table 3; Figure 1].

NLR was observed to be higher in moderate patients [92 (92.00%)], followed by severe [7 (7.00%)] and mild COPD patients [1 (1.00%)].

The mean NLR was the highest in severe COPD patients [5.46 ± 0.63], followed by moderate [4.28 ± 0.65] and mild COPD patients [3.03 ± 0.12]. Statistically, a high significant difference was observed in N/L ratio among COPD patients [$P < 0.0001$*] [Table 4; Figure 2].

The mean CRP level was the highest in severe COPD patients [9.91 ± 0.79], followed by moderate [7.70 ± 0.76] and mild COPD patients [5.77 ± 0.21]. Statistically, a high significant difference was observed in CRP level among COPD patients [$P < 0.0001$*] [Table 5; Figure 3].

FEV1, FVC%, FEV1/FVC%, N/L ratio, and CRP were significantly [$P < 0.0001$*] associated with severity GOLD 2021 with 95% confidence interval [-0.7734 (-0.8436 to -0.6772)], [-0.5387 (-0.6680 to -0.3778)], [-0.6213 (-0.7865 to -0.2175)], [0.644 (0.5080 to 0.7486)], and [0.7523 (0.6489 to 0.8285)], respectively [Table 6; Figure 4].

Table 1: Relationship between FEV1 and severity of COPD

	Severity gold 2022						*P*
	Mild [*n*=3]		Moderate [*n*=73]		Severe [*n*=24]		
	Mean	SD	Mean	SD	Mean	SD	
FEV1	86.67	2.05	64.38	7.24	41.83	7.48	*F*=109.5, *P*<0.0001*

Table 2: Relationship between FVC and severity of COPD

	Severity gold 2022						*P*
	Mild [*n*=3]		Moderate [*n*=73]		Severe [*n*=24]		
	Mean	SD	Mean	SD	Mean	SD	
FVC %	91.53	14.41	62.33	10.73	61.21	2.05	*F*=46.29 *P*<0.0001*

Table 3: FEV1/FVC with severity of COPD

	Severity gold 2022						*P*
	Mild [*n*=3]		Moderate [*n*=73]		Severe [*n*=24]		
	Mean	SD	Mean	SD	Mean	SD	
FEV1/ FVC %	0.69	0.14	0.67	0.09	0.62	0.04	*F*=3.547 *P*=0.0326*

Table 4: Relationship between N/L Ratio and severity of COPD

	Severity gold 2022						*P*
	Mild [*n*=3]		Moderate [*n*=73]		Severe [*n*=24]		
	Mean	SD	Mean	SD	Mean	SD	
N/L ratio	3.03	0.12	4.28	0.65	5.46	0.63	*F*=39.30 *P*<0.0001*

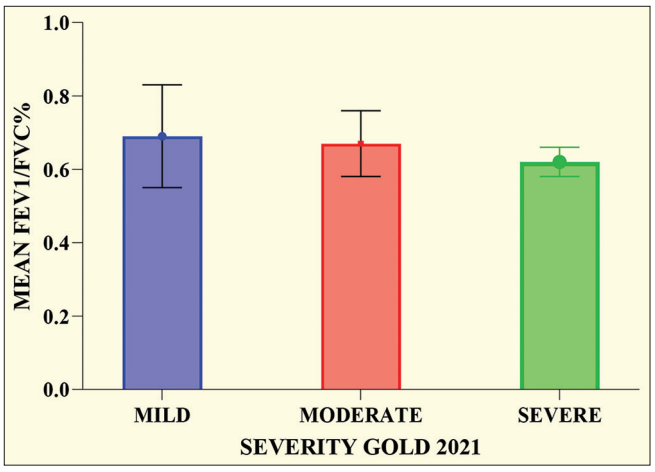

Figure 1: Graphical representation of forced expiratory volume in 1 s/ forced vital capacity ratio with severity of COPD

Discussion

In the current study, a total of 100 diagnosed COPD cases were enrolled, with patients being older than 40 years. The

Table 5: Relationship between CRP and severity of COPD

	Severity gold 2022						*P*
	Mild [*n*=3]		Moderate [*n*=73]		Severe [*n*=24]		
	Mean	SD	Mean	SD	Mean	SD	
CRP	5.77	0.21	7.70	0.76	9.91	0.79	*X*=91.81 *P*<0.0001*

Table 6: Correlation of severity GOLD 2021 with FEV1, FVC%, FEV1/FVC%, N/L ratio, and CRP

Severity gold 2021 vs.	Spearman *r*	95% confidence interval	*P*
FEV1	-0.7734	-0.8436 to -0.6772	<0.0001*
FVC%	-0.5387	-0.6680 to -0.3778	<0.0001*
FEV1/FVC%	-0.6213	-0.7865 to -0.2175	<0.0001*
N/L RATIO	0.644	0.5080 to 0.7486	<0.0001*
CRP	0.7523	0.6489 to 0.8285	<0.0001*

majority (56.00%) of the patients were aged between 51 and 60 years. There was a higher prevalence of males (76.00%) compared to females (24.00%). Patel JG *et al.*, 2015[13] conducted their study with patients aged between 51 and 60 years, observing a higher proportion of males than females. Similarly, Jain N *et al.*, 2011[14] found male dominance over females. Lee, H *et al.*, 2016[15] reported a mean age of 70.9 ± 7.8 years, with 91.4% of the patients being men. Yao, C *et al.*, 2012[16] showed that the total number of patients included more males than females, with a mean age of 61 years. In our study, this is attributed to more males attending OPD compared to females in Indian society and because males have been using tobacco in the form of smoking from the age of 25–30 years due to chronic tobacco use.

Notably, the mean FEV1 [86.67 ± 2.05], FVC [91.53 ± 14.41], and FEV1/FVC ratio [0.69 ± 0.14] were the highest in mild COPD patients, followed by moderate and severe patients. Patel JG *et al.*, 2015[13] found that FEV1 was lower in COPD patients compared to controls. Similarly, Rodriguez-Roisin R, *et al.*, 2009[17] reported that FEV1, FVC, and the FEV1/FVC ratio decreased with the severity of the disease.

NLR and CRP levels were significantly higher in moderate and severe COPD patients. Contrary to our study, Garcia-Rio F *et al.*, 2010[18] found that CRP levels were the same in mild and moderate COPD but slightly decreased in severe COPD. FEV1, FVC%, FEV1/FVC%, N/L ratio, and CRP were significantly [$P < 0.0001$*] associated with severity according to GOLD 2021, with 95% confidence intervals of [-0.7734 (-0.8436 to -0.6772)], [-0.5387 (-0.6680 to -0.3778)], [-0.6213 (-0.7865 to -0.2175)], [0.644 (0.5080 to 0.7486)], and [0.7523 (0.6489 to 0.8285)], respectively.

Tobacco addiction, a primary cause of disability and premature death, is driven by nicotine. Nicotine attaches to nicotinic cholinergic receptors, thus increasing neurotransmitter release and facilitating nicotine's complex effects in tobacco users. The release of dopamine, glutamate, and gamma-aminobutyric acid is essential for the development of nicotine dependence, whereas corticotropin-releasing factor seems to play a role in nicotine withdrawal. Nicotine addiction is highly heritable. Genetic studies show that genes involved in learning and neuroplasticity, as well as subtypes of nicotinic receptors, are associated with

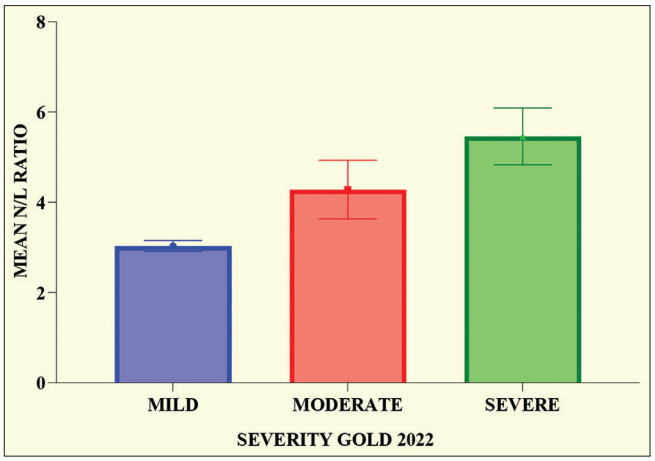

Figure 2: Graphical representation of association of NLR with severity of disease

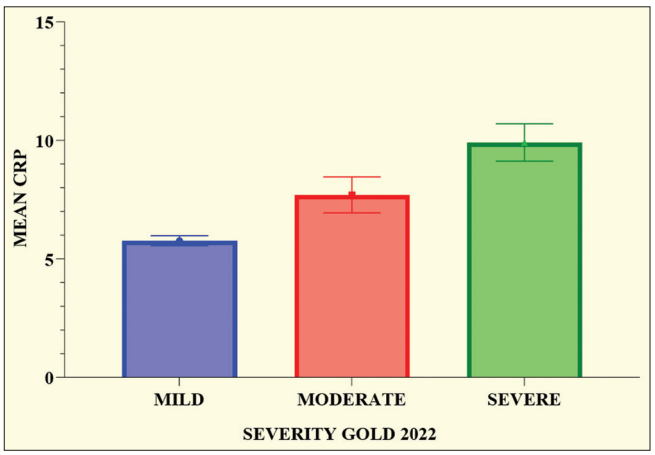

Figure 3: Graphical representation of association of COPD with CRP

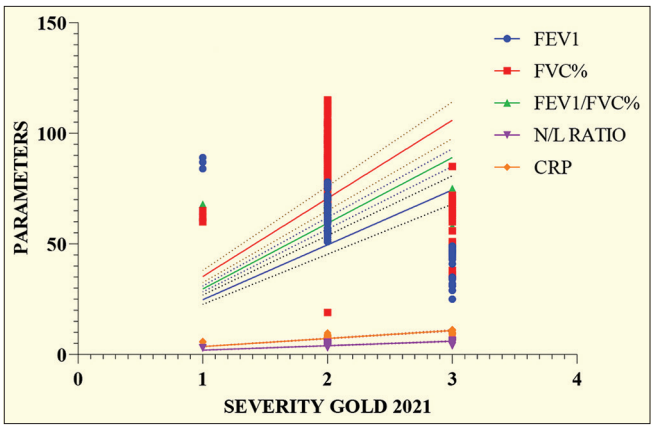

Figure 4: Representation of correlation of severity GOLD 2021 with FEV1, FVC%, FEV1/FVC%, N/L ratio, and CRP

the dependence. Nicotine is primarily metabolised by CYP2A6, and variability in nicotine metabolism influences susceptibility to tobacco dependency, treatment response, and lung cancer risk. Individuals with mental illness and substance misuse issues are disproportionately affected by tobacco addiction, making up a large proportion of current smokers.[19]

Spirometry is the most commonly used non-invasive test of pulmonary function, providing a comprehensive evaluation of lung function and an objective method for monitoring disease progression or improvement and therapy response over time. For diagnosing and classifying COPD, the post-bronchodilator forced expiratory volume in 1 second (FEV1) has been the gold standard. Since the groundbreaking longitudinal research by Fletcher and Peto,[20] COPD has been identified as a progressive disease characterised by an accelerated rate of FEV1 decline over time. In our study, patients with mild COPD had the highest FEV1, followed by those with moderate and severe COPD.

According to GOLD, COPD is diagnosed when the FEV1/FVC ratio is below 70%. Similarly, the ATS-ERS and NICE use FEV1/FVC < 70% post-bronchodilator as a diagnostic criterion for COPD, regardless of age. However, it is widely acknowledged that the FEV1/FVC ratio declines with age, and applying a uniform ratio across all ages might result in misclassifications, leading to underdiagnosis in younger individuals and overdiagnosis in older individuals.[21] Topalovic, M., *et al.*, 2015[22] found that in newly diagnosed COPD patients, FVC was significantly lower compared to those with unequivocally moderate COPD and control participants. This indicates that in this subgroup with discordant results, a low FVC might cause the FEV1/FVC ratio to exceed the lower limit. The ATS/ERS criteria also identify airway obstruction when a normal FEV1/FVC ratio (above the LLN) is paired with a low FVC within a normal total lung capacity. According to our study, FVC declined with increasing severity of COPD, and the FEV1/FVC% ratio was higher in mild COPD patients compared to those with moderate and severe COPD.

In chronic inflammatory diseases, leukocyte count and its sub-groups are recognised as inflammatory indicators.[23] Gan WQ *et al.*, 2004, identified NLR as an inflammation biomarker for clinical outcomes in COPD patients, driven by systemic inflammation and increased airway permeability. Moreover, the ratio of absolute neutrophil count to lymphocyte count (N/L ratio) was proposed as a potential, cost-effective inflammatory marker with prognostic and predictive value in systemic inflammatory diseases like cardiovascular diseases, kidney diseases, inflammatory bowel diseases, and familial Mediterranean fever.[24] To date, no research has been published on the N/L ratio and its association with COPD severity. In this study, we showed that severe COPD patients have a significantly higher N/L ratio than those with moderate and mild COPD. Higher neutrophils and lower lymphocytes indicated with elevated NLR. Activated neutrophils can release inflammatory cytokines and proteolytic enzymes (such as matrix metalloproteinase, calprotectin, and elastase), contributing to emphysema[25] and a reduction in FEV1.[26] This supports our previous finding that patients with severe COPD showed lower values of FEV1. Lymphocytes are essential for the immune system, and lymphopenia is associated with a high risk of infection[27] and mortality.[28] Thus, increased inflammatory response (neutrophils) and decreased immune function (lymphocytes) may explain the link between a high NLR and poor clinical outcomes in COPD patients.

The capability of NLR to forecast mortality in COPD patients remains controversial. Some previous studies[29] indicated that NLR could predict mortality in COPD patients, whereas one study[30] found that NLR was not a predictor of mortality with glucocorticoid use. Nevertheless, Duman *et al.*, 2015 demonstrated that NLR might independently predict mortality after accounting for steroid use.[40] Hence, data from previous studies indicated that NLR was a predictor of mortality in COPD patients.

Other researchers, including Lee *et al.*,[15] Halper-Stromberg *et al.*,[14] and Sakuri *et al.*,[31] showed that NLR levels were higher in COPD patients than in the control group and were positively correlated with disease severity. This could be due to a specific response associated with the chronicity of the disease in its most severe stage. Generally, non-specific cellular responses dominate COPD-related processes. However, in severe and chronic COPD, these pathways may become more specialised.

Recently, numerous researchers have shown interest in NLR as an inflammatory marker. Multiple studies have shown that NLR is a predictive marker for various inflammatory conditions, including cardiovascular diseases, kidney disease, and familial Mediterranean fever.[24] Concerning our research, four published papers investigate the significance of NLR in COPD patients. Günay E *et al.*, 2014[8] conducted a retrospective study with 178 stable COPD patients, 91 COPD patients in the acute exacerbation period, and 50 control cases. In the above study, NLR values in both COPD groups were significantly elevated than those of the control groups. Moreover, NLR was significantly higher in COPD patients during exacerbations compared to stable individuals. Additionally, their study identified a positive correlation between NLR and CRP levels. In prospective research following 386 individuals with mild and severe COPD for 10 years, NLR was found to be an independent predictor of increased all-cause mortality.[32] In a retrospective study of 140 stable COPD patients and 50 controls, it was suggested that NLR could be a simple, effective, and practical biomarker for the early diagnosis of metabolic syndrome.[33] Another retrospective study involving 100 COPD patients in the acute exacerbation phase and 50 healthy controls demonstrated that NLR could be used to detect high inflammation, similar to CRP, leukocyte count, and ESR.[34]

The predictive utility of CRP in individuals with ischaemic heart disease has been well established.[35] However, its relevance in monitoring stable COPD remains undetermined, particularly concerning the association between elevated CRP levels and

increased mortality rates.[35] This issue has sparked debate. Lomholt *et al.* in 2014,[36] through a meta-analysis, concluded that elevated CRP levels did not predict higher mortality in COPD patients. This conclusion was challenged by Leuzzi G *et al.* in 2017,[37] who asserted in their own meta-analysis that there exists a statistically significant relationship between elevated CRP levels and increased mortality [hazard ratio (HR) =1.53, 95% confidence interval (CI) =1.32–1.77]. Additionally, our findings indicated that patients with severe COPD exhibited higher CRP levels compared to those with mild and moderate COPD. It has been observed that elevated systemic CRP levels are linked with greater disease severity, deterioration in health, increased hospitalisations, and higher mortality rates in COPD.[38]

Conclusion

This study found that individuals with severe COPD typically have lower FEV1, FVC, and FEV1/FVC ratio values. It also suggests that severe COPD patients show higher levels of serum CRP and N/L ratio, which correlate with the disease's severity. These elevated N/L ratio and CRP levels could potentially serve as predictive indicators, although larger sample sizes and patient follow-ups are necessary for validation. This non-invasive and cost-effective approach could be implemented at primary healthcare (PHC) or community healthcare (CHC) levels to screen COPD severity.

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Conflicts of interest

There are no conflicts of interest.

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