Original Research

The Neutrophil Lymphocyte Ratio as a Predictor of Acute Exacerbations Among Patients with COPD in Uganda

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Running Head: **Neutrophil Lymphocyte Ratio in COPD Patients in Uganda**

Keywords: COPD; exacerbations; acute exacerbations of COPD; biomarkers; neutrophil lymphocyte ratio;

Abbreviations:
COPD- Chronic Obstructive pulmonary Disease
NLR- Neutrophil Lymphocyte Ratio
LMIC- Low- and Middle-Income Country
SSA-Sub Saharan Africa
mMRC- Modified Research Council

Published online January 18, 2024 https://doi.org/10.15326.jcopdf.2023.0443

ROC- Receiver Operator Curve
FEV- Forced Expiratory Volume

Funding Support: The study was funded by GlaxoSmithKline (GSK Africa NCD open Lab), grant number 8868. GSK did not participate in the design, implementation, analysis or results of the study. Research reported in this publication was supported by the Forgarty International Centre of the National Institute of Health (award number D43 TW011401).

Date of Acceptance: December 23, 2023 | ***Publication Online Date:*** January 18, 2024

Citation: Alupo P, Katagira W, Mukunya D, et al. The neutrophil lymphocyte ratio as a predictor of acute exacerbations among patients with COPD in Uganda. *Chronic Obstr Pulm Dis*. 2024; Published online January 18, 2024. https://doi.org/10.15326.jcopdf.2023.0443

This article has an online supplement.

Abstract

Background: The Neutrophil to Lymphocyte ratio (NLR) is an inexpensive biomarker that potentially predicts Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD). We evaluated the association of baseline NLR and respiratory hospitalisation risk within one year among COPD patients in Uganda, Low- and Middle-Income Country.

Methods: 312 COPD patients were followed up for 1 year. Clinical characteristics and exacerbation rate were collected. Poisson regression with robust variance estimators were used to measure the association between NLR and hospital admissions due to COPD exacerbations. Receiver-operator characteristic (ROC) curves and the area under the curve were used to assess the ability of NLR to predict AECOPD.

Results: The median (Q 1, Q 3) age was 64.00 years (53.00, 71.00). Females comprised 50.96% (n=159) of the cohort, and 71.2% (n=222) of participants had moderate or severe COPD. 9.9% (n=31) of participants experienced a COPD exacerbation during the period of follow up. At baseline, the median (Q 1, Q 3) NLR ratio among participants who experienced an exacerbation was 1.46 (0.92, 2.33) compared to 1.03 (0.72,1.42) among those who did not experience one during the follow-up period (p=0.002). Using Youden and Liu's methods, the optimal NLR cut-off for predicting COPD exacerbation was 1.17. This cut-off resulted in a ROC curve area of 0.64 (95% CI: 0.56, 0.73).

Conclusion: The NLR could be used as a risk predictor for hospital admissions due to COPD exacerbations in low- and middle-income countries. A cut-off of 1.17 was an independent predictor of hospitalization due to acute exacerbations COPD within one year.

Published online January 18, 2024 https://doi.org/10.15326.jcopdf.2023.0443

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death globally, and the burden is disproportionately concentrated in low- and middle-income country (LMIC) settings (1)(2). COPD is a heterogeneous lung condition characterised by chronic respiratory symptoms due to abnormalities in the airways and/or alveoli that cause persistent and often progressive airflow obstruction (3). The most widely known risk factor for the development of COPD is tobacco smoke exposure, and most of the resulting knowledge about COPD is derived from cohorts in high-income country (HIC) populations, where tobacco-associated disease is prevalent. COPD in LMICs is often a result of distinct exposures including biomass exposure and infectious diseases i.e., HIV, tuberculosis)(4)(5)(6).These varied risk factors have a different pathway of effect on the lung compared to tobacco smoke and thus likely result in different immunological profiles (7).

COPD is characterized by recurrent exacerbations, which are typically a result of increased inflammation due to respiratory infections or environmental factors (8). Acute exacerbations of COPD (AECOPD) are a common cause of hospitalization and are associated with substantial mortality and socio-economic burden (9)(10). Dalal *et al* found in a U.S. patient population database that frequent exacerbators are estimated to incur up to 3 times more healthcare costs compared to infrequent exacerbators, with substantial financial burden that is out of reach for patients in resource-limited settings(11). Furthermore, patients who experience frequent COPD exacerbations develop accelerated lung function decline and are at increased risk of future exacerbations, cerebrovascular events, myocardial infarction, and mortality(12)(13)(14)(15). Preventing exacerbations thus greatly alleviates the burden of COPD and the impact on the quality of life of patients suffering from COPD, especially in LMICs where the burden is most profound.

Published online January 18, 2024 https://doi.org/10.15326.jcopdf.2023.0443

Biomarkers to predict COPD exacerbations and mortality have been of increasing interest to identify individuals at risk. The neutrophil to lymphocyte ratio (NLR) is a biomarker that has been recognized as an indicator of inflammation. It has been associated with increased disease severity, hospitalization, malnutrition, and mortality in various chronic diseases such as cardiovascular disease, chronic kidney disease and in critically ill patients (16)(17). Among those with COPD, there has been increasing literature demonstrating that NLR is a valid marker of disease severity and predictor of exacerbations and disease outcomes (18)(19)(20).To further support this, a systematic review of studies in HICs in Asia found that high NLR was associated with significantly higher risk of COPD exacerbations, and therefore may be an independent predictor for COPD exacerbations(21). Additionally, the potential for racial variation of this marker has been studied, with Azab *et al* demonstrating the existence of racial difference in the NLR in a population in the United States of America, recommending the need to have different cut offs for different races(22). There is a need to validate biomarkers to predict COPD exacerbations in LMICs, where the risk factors, and inflammatory profiles among those with COPD are distinct. We aimed to evaluate the potential role of NLR in predicting COPD exacerbations at one year in an outpatient clinic population in Uganda, and to identify the appropriate NLR cut off that predicts exacerbations in this population

Methods

Study setting and Participants

We screened adults aged ≥ 30 years of age with clinical features or a prior diagnosis of COPD, who presented to three tertiary referral hospitals in Kampala (Mulago National

Referral Hospital, Kiruddu Referral Hospital Chest Clinic, and the Makerere University Lung Institute). These are all referral health facilities and thus attracted both rural and urban participants from all over the country, who were referred from peripheral facilities for more advanced management. We excluded participants who had active pulmonary tuberculosis and other important co-morbid diseases likely to affect participation or outcomes, such as lung cancer and asthma, as deemed by the investigational team. Participants who were currently having a COPD exacerbation at the point of first contact with the clinical team were not enrolled at that point but requested to return when symptoms improved, and the exacerbation resolved. Participants were enrolled from July 2019 through March 2021. We obtained baseline NLR from the complete blood counts measurement for all participants and followed them longitudinally every three months for one year assessing clinical outcomes, including exacerbation and hospitalization outcomes. Participants provided written informed consent. The study was approved by the Mulago Hospital research and Ethics committee (MHREC 1451) and the Uganda National Council for Science and Technology (HS 2483).

Variables and Measures

Spirometry was conducted by trained spirometry technicians, using the Vitalograph pneumotrac spirometer (Bukingham, UK) to measure pulmonary function. We obtained three acceptable measurements in accordance with American Thoracic Society (ATS)/European Respiratory Society (ETS) guidelines(23). COPD diagnosis was defined as post-bronchodilator forced expiratory volume in 1 second (FEV_1)/force vital capacity (FVC) ratio below 0.7 with symptoms including dyspnea, chronic cough, sputum production, wheezing/chest tightness, and/or recurrent chest infections in the context of a history of risk factors (24). Demographic characteristics including educational attainment, history of tuberculosis treatment, biomass exposure, and tobacco use were collected using standardized

questionnaires as self-reported by participants and confirmed by medical records. Exacerbation history was self-reported by participants. COPD severity was defined by Global Obstructive Lung Disease (GOLD) criteria based on lung function using the Global Lung Index (GLI) Mixed Ethnic Reference Equations (25). Body mass index (BMI) was calculated as the ratio of body weight to height (kg/m2). The degree of dyspnea was assessed using the modified Medical Research Council (mMRC) dyspnea scale(26).The mMRC dyspnea score ranges from 0 to 4 and increases with the severity of dyspnea. All laboratory tests, including differential counts of leukocytes, such as neutrophils and lymphocytes were performed at the Makerere University core laboratory, which is certified by the College of American Pathologists (CAP). The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count.

Outcomes

A COPD exacerbation was defined as an acute deterioration in the patient's respiratory symptoms (i.e., dyspnea, sputum amount or purulence, or cough/wheeze) that warranted additional treatment above the standard treatment, and this often translated into a visit to a health facility. The participants were provided with patient diaries to record symptom worsening and medications received while they were away from the facility. Patients were followed serially with scheduled clinic visits every three months for clinical evaluation. Their exacerbation history over the past three months was also collected during this visit.

D) Biostatistical Analysis

Data was analysed using Stata version 17.0 (Stata Corp LLC, College Station, Texas, United States of America). We assessed continuous variables using means with standard deviations or medians with interquartile ranges and categorical variables using frequencies and

percentages. Independent means were compared using Student's t-tests whereas medians (non-parametric continuous distributions) were compared using the Mann-Whitney U Test. We constructed receiver-operator characteristic (ROC) curves using the 'roctab' command in Stata to show the predictive ability of NLR. Optimal cut-off values for predicting hospitalization were determined for NLR using the maximal Youden Index and Liu's index. Youden's index objectively calculates the optimal cut-off. It takes into account the sensitivity and specificity and is used to estimate the diagnostic effectiveness of various cut off points; (17) whereas Liu's index calculates the optimal cutoff point while maximizing the product of sensitivity and specificity (18). To estimate risk ratios between levels of NLR and hospitalization, we used generalized linear regression models from the Poisson family with log links and robust variance estimators. In multivariable analysis, NLR, smoking status, age and sex were selected a priori. Other variables were considered for multivariable analysis based on literature or if they had a p-value ≤ 0.200 at univariable analysis. The final model comprised of variables selected a priori; those with p-values of ≤ 0.05; and identified confounders. In addition to the above multivariable analysis, we performed a supplementary analysis (time to event) using cox proportional hazards model.

Results

457 participants were screened, and among these individuals 312 completed the study measurements and were thus included in this analysis. Among the 312, 209 completed the 1 year follow up period; 79 were lost to follow up and 24 died. **(Fig.1)**. The mean age was 62.77 years (SD 13.61), the mean BMI was 22.23 kg/m^2 (SD 6.07), 50.96% (n=159) were women, 6.73% (n=21) were current smokers, 32.05% (n=100) were former smokers, and 67.63% (n=211) reported a history of being exposed to biomass smoke. Additionally, at study

enrolment 17.63% (n=55) of the participants reported having a history of exacerbations in the past one year **(Table 1).** In comparison, among those who were lost to follow up, the median age was 67 (52,76), 44 (55.7%) were male, and 7 (8.56%).

The mean FEV_1 and FVC percent predicted were 65.30 (SD 25.84) and 91.35 (SD 27.37), respectively. 29.49% (n=92) of participants had severe disease by GOLD stage, and 69.87% (n=218) had mild or moderate disease. 19.23% (n=60) participants were on baseline short acting beta agonist inhalers and 8.65% (n=27) on inhaled corticosteroids. 7.69% (n=24) were on combination inhalers.

During the follow up period of one year, 9.94% (n=31) participants experienced at least one COPD exacerbation. Using Youden and Liu's methods, the optimal NLR cut-off for predicting COPD exacerbation was 1.17. This cut-off resulted in a ROC curve area of 0.64 (95% CI: 0.56, 0.73). The sensitivity, specificity, positive predictive value, and negative predictive value of ROC curve was 61.2%, 67.7%, 16.2%, and 94.5% respectively **(Figure 2).**

After adjusting for participant age, sex, FEV_1, exacerbation history (at baseline), and dyspnea at baseline, participants with an NLR values ≥ 1.17 were 2.3 times as likely to experience a COPD exacerbation during the year of follow-up as those with an NLR ratio <1.17 (aRR 2.31, 95% CI:0.999, 5.346; p=0.050) **(Table 2)**.

On evaluating the association between the NLR and clinical parameters including the oxygen saturation (SpO_2), mMRC dyspnea score, BMI, and FEV_1 we found no statistically

significant association. We found results obtained using GLM to be like those obtained using cox proportional hazards model (Supplement Table 1, Supplement Figure 1 & 2).

Discussion

Our findings suggest that in this African population of patients with COPD with diverse risk factors for COPD, NLR can predict COPD exacerbations with a sensitivity of 61.2%, specificity of 67.7%, and an AUC of 0.64. We observed that participants who had an NLR ≥ 1.17 were 2.3 times as likely to get an AECOPD resulting in hospitalization within one year compared to those with an NLR ratio of under 1.17. We found no other studies in sub-Saharan Africa have evaluated the NLR in combination with other risk factors. Therefore, our findings suggest NLR could serve as a biomarker for COPD exacerbation in an African population.

Our findings are consistent with several studies that have reported NLR being a predictor of exacerbations in COPD in HIC settings (27)(20)(28). However, to the best of our knowledge, no such study has been conducted in a population with COPD in sub-Saharan Africa where etiologies of COPD can differ, and the burden of disease is disproportionately higher than HICs. Previous studies in LMIC settings have found that elevated NLR was associated with higher odds of COPD exacerbation (28–30). For example, Sharma and colleagues found that NLR was an adequate predictor for exacerbations in patients with COPD in India with a higher cut-off of 3.4 and AUC of 0.806(28). However, their population had a lower prevalence of self-reported biomass exposure at 23.3-26.7% compared to our population. The predictive effect of NLR could be explained by the fact that COPD is a chronic inflammatory disease of the airways and lungs that leads to persistent airway limitation and systemic inflammation (31).This systemic inflammation plays a significant role in the pathology of

COPD (32)(33). While the exact mechanism of the pathology may not be well understood, neutrophils play a prominent role, as demonstrated by the prominence of neutrophilic inflammation in COPD. Progressively, activated neutrophils release oxygen radicals and proteolytic enzymes such as matrix metalloproteinases and elastase, which ultimately lead to emphysema (34)(35).The neutrophil-mediated response also contributes towards the severity of airway obstruction(36). Neutrophilia is well recognized as a marker of infection, whereas lymphocytopenia is a predictor for bacteremia (37). Thus, the combination of neutrophils and lymphocytes as a single composite indicator (the NLR) is potentially more powerful as an indicator of the clinical status of patients with COPD than a single parameter alone. However, little is known about the performance of this biomarker in settings where tobacco exposure is not the primary risk factor for COPD.

The sensitivity, specificity, and AUC of the NLR in predicting exacerbations in this population was comparable with the findings by Lee and colleagues, which had a comparable sensitivity specificity and AUC of 60.0%, 60.9% and 0.63 respectively. It was however lower than the sensitivity, specificity, and AUC of 75.3%, 70.7% and 0.80 demonstrated by Sharma *et al*. Notably, our optimal NLR cut of 1.17 was low, compared to other studies (28,38,39). This could be explained by the fact that their populations had tobacco smoke as the predominant exposure, compared to this population which has biomass as the predominant exposure. However, the low AUC of 0.64 and positive predictive value of 16.2%, despite the high negative predictive value of 94.5%, may suggest that the NLR may be more useful as a supportive test to the clinical evaluation in patients with COPD, rather than a stand-alone test to predict COPD exacerbations.

Published online January 18, 2024 https://doi.org/10.15326.jcopdf.2023.0443

When combined with other established risk factors for COPD exacerbation, NLR may have a role in LMIC settings, which experience a disproportionately high burden of global disease-related morbidity and mortality. Given the accessibility and low cost of this biomarker's use, there is thus potential for the NLR test to be integrated in routine clinical care of these patients and can be used to support the management of the patient, over and above the clinical evaluations. Given that a significant portion of COPD-related costs is driven by exacerbations, the ability of the NLR to offer additional clinical context to predict exacerbations gives NLR the potential to reduce healthcare costs associated with severe COPD exacerbations and hospitalisations by proactively managing the patient aggressively before exacerbation onset or warrants hospitalization (40,41).This is especially significant in LMIC settings where resources are finite.

Strengths and Limitations

To the best of our knowledge, this is the first study evaluating the NLR as a predictor of COPD exacerbations in sub-Saharan Africa. This robust baseline patient assessment and prospective data collection over one year follow-up is a strength of our study. Because the catchment area of this study includes a national referral hospital and tertiary care center, we have included extensive and diverse populations increasing generalizability of findings. Participants were followed serially for 12 months increasing validity of findings. Limitations include the relatively small sample size, potential bias with the patient population given they were enrolled from national referral facilities which usually receive patients with more advanced disease, and NLR measured at one point in time at study enrollment. Further work will need to be done to externally validate this measure in other LMIC populations with COPD.

Conclusion

The NLR was associated with future risk of COPD exacerbations among patients with COPD in this LMIC setting, who largely had COPD from non-tobacco smoke exposure. We estimated a NLR threshold of 1.17 at baseline as the predictor of exacerbations in this cohort. The NLR could therefore potentially be integrated into routine clinical care to support the management of patients with COPD in this setting. This could potentially translate into more effective management of COPD, better clinical outcomes with early intervention, and overall reduction of healthcare costs attributed to COPD exacerbations.

Acknowledgements:

Research reported in this publication was supported by the Forgarty International Centre of the National Institute of Health (award number D43 TW011401).

Mr Rogers Sekibira for offering data management support

Authorship Contribution statement:

All authors significantly contributed to the intellectual content of the manuscript and met the ICMJE guidelines for authorship.

Declaration of Interest statement

The authors have no conflict of interest to declare

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Published online January 18, 2024 https://doi.org/10.15326.jcopdf.2023.0443

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Table 1: characteristics of patients with of COPD who were enrolled into the study and followed up for a period of one year (N=312), divided by Neutrophil: Lymphocyte ratio (NLR).

Variable	**(NLR <1.17) (n=182)**	**(NLR> 1.17) (n=130)**	**Total (312)**
Age in years.			
Median (q_1, q_3))	65.00 (53.00- 72.00)	63.00 (52.00 - 71.00)	64.00 (53.00-71.00)
Age categorized. n (%)			
<60 years	70 (38.46)	54 (41.54)	124 (39.74)
≥ 60 years	112 (61.54)	76 (58.46)	188 (60.26)
Sex n (%)			
Male	85 (46.70)	68 (52.31)	153 (49.04)
Female	97 (53.30)	62 (47.69)	159 (50.96)
Education n (%)			
None	43 (23.63)	23 (17.69)	66 (21.15)
Incomplete primary	68 (37.36)	42 (32.31)	110 (35.26)
Complete primary	23 (12.64)	21 (16.15)	44 (14.10)
Incomplete secondary	20 (10.99)	24 (18.46)	44 (14.10)
Complete secondary	4 (2.20)	4 (3.08)	8 (2.56)
Tertiary	24 (13.19)	16 (12.31)	40 (12.82)
Tobacco Use n (%)			
Current Smoker	13 (7.14)	8 (6.15)	21 (6.73)
Former smoker	54 (29.67)	46 (35.38)	100 (32.05)
Never	115 (63.19)	76 (58.46)	191 (61.22)
History of biomass smoke exposure n (%)			
Yes	124 (68.13)	87 (66.92)	211 (67.63)
Previous TB Treatment n (%)			

Yes	32 (17.58)	33 (25.38)	65 (20.83)
BMI kg/m^3			
Underweight <18.5	51 (28.02)	45 (34.62)	96 (30.77)
Normal (18.5-24.9)	78 (42.86)	56 (43.08)	134 (42.95)
Overweight (25.0-29.9)	31 (17.03)	19 (14.62)	50 (16.03)
Obese ≥30	22 (12.09)	10 (7.69)	32 (10.26)
COPD stage at baseline by FEV_1 n (%)			
Mild FEV_1 ≥80%	54 (29.83)	34 (26.36)	88 (28.39)
Moderate FEV_1 50-79%	80 (44.20)	50 (38.76)	130 (41.94)
Severe FEV_1 30-49%	34 (18.78)	33 (25.58)	67 (21.61)
Very severe FEV_1 <30%	13 (7.18)	12 (9.30)	25 (8.06)

Published online January 18, 2024 https://doi.org/10.15326.jcopdf.2023.0443

Table 2: Multivariate analyses of associations with risk of COPD exacerbation

Variable	CRR1 [95% CI]	P-value	aRR2 [95% CI]	P-value
Neutrophil lymphocyte ratio				
<1.17	1 (reference)		1	
>=1.17	[1.22, 5.53]	0.013	2.31 [1.00, 5,35]	0.050
HIV status				
Negative	1 (reference)			
Positive	1.08 [0.44, 2.69]	0.862		
BMI				
Underweight	1 (reference)			
Normal (18.5-24.9)	0.78 [0.37, 1.64]	0.513		
Overweight (25.0-29.9)	0.30 [0.07, 1.30]	0.109		
Obese ≥	1.17 [0.44, 3.08]	0.756		
Age in years				
<60	1 (reference)		1	
>=60	0.83 [0.43, 1.62]	0.589	0.76 [0.34, 1.73]	0.518
Smoking status				
Ever smoked	1 (reference)			
Never smoked	1.16 [0.58, 2.32]	0.678	0.50 [0.21-1.19]	0.118
History of Hypertension				
No	1 (reference)			
Yes	1.58 [0.77, 3.26]	0.212		
Previous TB treatment				
Yes	1 (reference)			
No	1.11 [0.48, 2.60]	0.805		

Published online January 18, 2024 https://doi.org/10.15326.jcopdf.2023.0443

Sex				
Male	1 (reference)		1	
Female	1.83 [0.91, 3.67]	0.090	1.97 [0.73, 5.35]	0.179
Post-Bronchodilator FEV_1				
Mild >=80%	1 (reference)		1	
Moderate 50-79 %	0.60 [0.21, 1.74]	0.357	0.39 [0.10, 1.48]	0.167
Severe 30-49%	2.81[1.21, 6.53]	0.016	1.95 [0.68, 5.54]	0.212
Very severe <30%	1.59 [0.44, 5.73]	0.475	1.78[0.48,6.56]	0.389
mMRC Dyspnea Score				
1	1 (reference)		1	
2 to 4	2.30 [1.08,4.88]	0.031	2.36 [1.14, 4.90]	0.021
History of Exacerbations in the past one year				
No	1 (reference)		1	
Yes	3.13 [1.64, 5.97]	0.001	2.56 [1.21, 5.44]	0.014

[1] ***CRR*** *means crude risk ratio*

[2] ***aRR*** *means adjusted risk ratio*

Figure 1. Study Flow Diagram

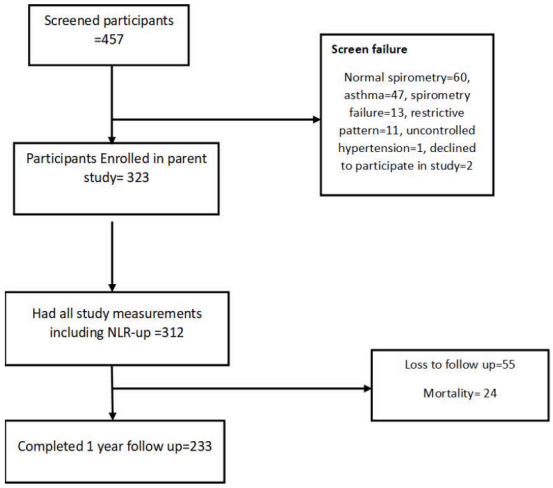
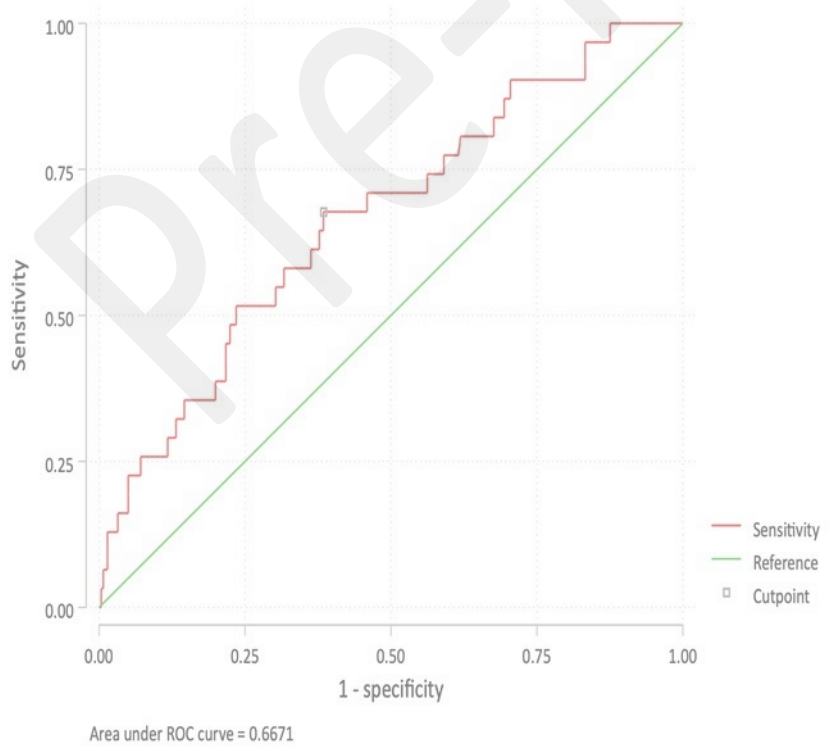


Figure 2: Using Youden and Liu's methods, the optimal NLR cut-off for predicting COPD exacerbation was 1.17. This cut-off resulted in a ROC area of 0.64 (95% CI: 0.56, 0.73).



Online Supplement

Supplement Table 1.

Multivariate analyses of associations with risk of COPD exacerbation using cox-proportional hazards model

Variable	cHR[1] [95% CI]	P-value	aHR[2] [95% CI]	P-value
Neutrophil lymphocyte ratio				
<1.17	1		1	
≥1.17	2.96 [1.39, 6.33]	0.005	2.56 [1.02, 6.41]	0.044
HIV status				
Negative	1			
Positive	0.01 [0.39, 2.64]	0.976		
BMI				
Underweight	1			
Normal	0.85 [0.38, 1.89]	0.688		
Overweight	0.32 [0.07, 1.43]	0.135		
Obese	1.32 [0.46, 3.80]	0.608		
Age in years				
<60	1		1	
≥60	0.77 [0.38, 1.55]	0.459	0.65 [0.25, 1.74]	0.394
Smoking status				
Ever smoked	1		1	
Never smoked	1.30 [0.61, 2.77]	0.491	0.54[0.19, 1.56]	0.255
History of Hypertension				
No	1			
Yes	1.71 [0.79, 3.72]	0.174		
Previous TB treatment				

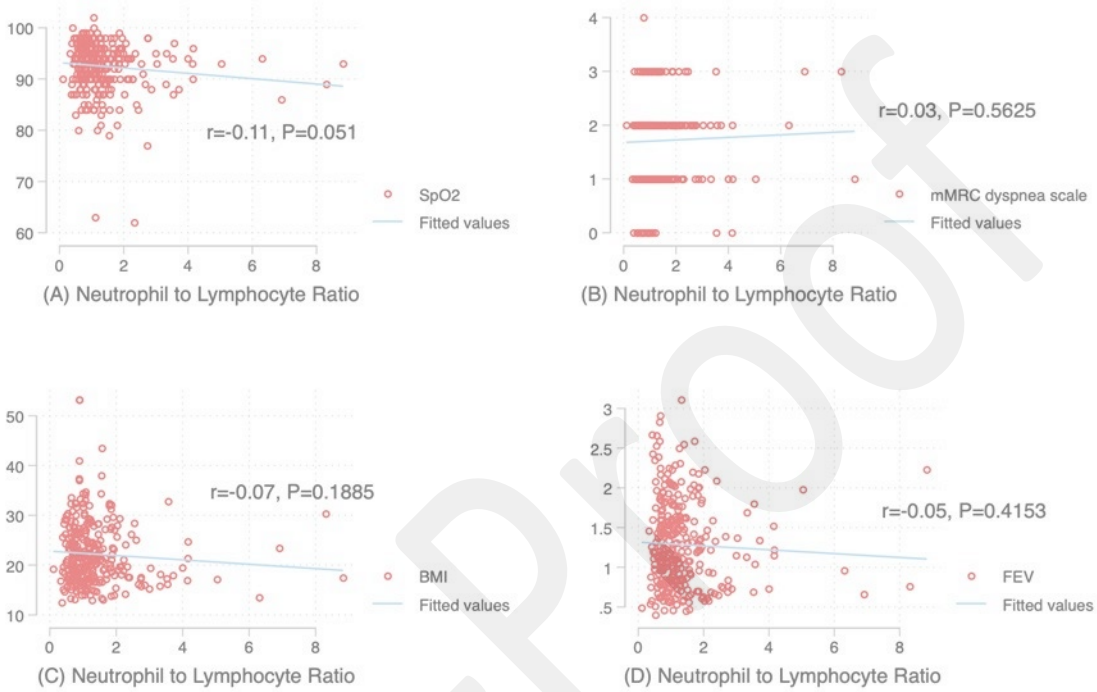
Yes	1			
No	1.10 [0.45, 2.67]	0.842		
Sex				
Male	1		1	
Female	1.81 [0.87, 3.78]	0.114	1.89 [0.64, 5.61]	0.252
POSTBD-FEV				
Mild >=80	1		1	
Moderate 50-79	0.67[0.22, 2.09]	0.494	0.43 [0.10, 1.81]	0.248
Severe 30-49	3.53[1.37, 9.10]	0.009	2.66 [0.80, 8.88]	0.111
Very severe <30	1.88 [0.47, 7.53]	0.371	2.48[0.48, 12.71]	0.277
mMRC Dyspnea				
1	1		1	
2 to 4	2.50 [1.09,5.71]	0.030	2.90 [1.11, 7.56]	0.030
Exacerbations at baseline				
No	1		1	
Yes	2.73 [1.56, 6.63]	0.002	1.89 [0.64, 5.61]	0.032

cHR[1]=Crude hazard ratio

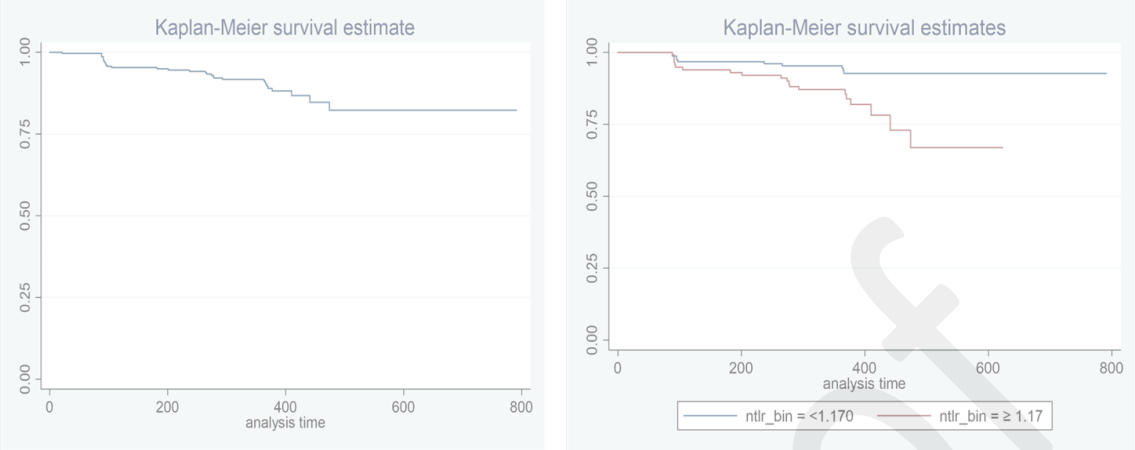
aHR[2]=adjusted hazard ratio

Published online January 18, 2024 https://doi.org/10.15326.jcopdf.2023.0443

Supplement Figure 1: correlation between neutrophil to Lymphocyte ratio (NLR) and clinical parameters at baseline. (A) NLR and SpO2, (B) NLR and mMRC, (C) NLR and BMI, (D) NLR and FEV_1. NLR at baseline was slightly correlated with SpO2.



Supplement Figure 2: Kaplan Meire survival graphs before and after stratification by neutrophil lymphocyte ratio.



Supplementary figures 2a and 2b showing Kaplan Meire survival graphs before and after stratification by neutrophil lymphocyte ratio.

Ntlr=Neutrophil Lymphocyte ratio.