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Original Research

The Neutrophil-to-Lymphocyte Ratio as a Predictor of Acute Exacerbations Among Patients With COPD in Uganda

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Abstract

Background: The neutrophil-to-lymphocyte ratio (NLR) is an inexpensive biomarker that potentially predicts acute exacerbations of chronic obstructive pulmonary disease (AECOPDs). We evaluated the association of baseline NLR and respiratory hospitalization risk within one year among chronic obstructive pulmonary disease (COPD) patients in Uganda, a low- and middle-income country.

Methods: A total of 312 COPD patients were followed for one year. Clinical characteristics and exacerbation rates were collected. Poisson regression with robust variance estimators was 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 AECOPDs.

Results: The median (Q 1, Q 3) age was 64 years (53, 71). Females comprised 50.96% (n=159) of the cohort, and 71.2% (n=222) of participants had moderate or severe COPD. A total of 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 cutoff for predicting COPD exacerbation was 1.17. This cutoff resulted in a ROC curve area of 0.64 (95% confidence interval: 0.56, 0.73).

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

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Abbreviations:

AECOPDs=acute exacerbations of chronic obstructive pulmonary disease; **aRR**=adjusted risk ratio; **AUC**=area under the ROC curve; **BMI**=body mass index; **CI**=confidence interval; **COPD**=chronic obstructive pulmonary disease; **CRR**=crude risk ratio; **FEV$_1$**=forced expiratory volume in 1 second; **FVC**=forced vital capacity; **GOLD**=Global initiative for chronic Obstructive Lung Disease; **HIC**=high income country; **LMIC**=low- and middle-income country; **mMRC**=modified Medical Research Council; **NLR**=neutrophil-to-lymphocyte ratio; **ROC**=receiver operator curve; **TB**=tuberculosis

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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 countries (LMICs).[1,2] COPD is a heterogeneous lung condition characterized 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 and tuberculosis.[4-6] 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 (AECOPDs) are a common cause of hospitalization and are associated with substantial mortality and socioeconomic 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 health care costs compared to infrequent exacerbators, with a 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.[12-15] Preventing exacerbations 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.

Biomarkers to predict COPD exacerbations and mortality have been of increasing interest in identifying 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 and 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 a predictor of exacerbations and disease outcomes.[18-20] To further support this, a systematic review of studies in HICs in Asia found that a high NLR was associated with a significantly higher risk of COPD exacerbations, and therefore, may be an independent predictor for COPD exacerbations.[20] Additionally, the potential for racial variation of this marker has been studied, with Azab et al demonstrating the existence of racial differences in the NLR in a population in the United States, recommending the need to have different cut-offs for different races.[21] 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 the NLR in predicting COPD exacerbations for one year in an outpatient clinic population in Uganda and to identify the appropriate NLR cutoff 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 3 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 comorbid 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 a baseline NLR from the complete blood count measurement for all participants and followed them longitudinally every 3 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, United Kingdom) to measure pulmonary function. We obtained 3 acceptable measurements in accordance with American Thoracic Society/European Respiratory Society guidelines.[22] COPD diagnosis was defined as postbronchodilator forced expiratory volume in 1 second (FEV_1) to forced 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.[23] 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 the Global initiative for chronic Obstructive Lung Disease (GOLD)[23] criteria based on lung function using the Global Lung Index Mixed Ethnic Reference Equations.[24] Body mass index (BMI) was calculated as the ratio of body weight to height (kg/m^2). The degree of dyspnea was assessed using the modified Medical Research Council (mMRC) dyspnea scale.[25] 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. 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 3 months for clinical evaluation. Their exacerbation history over the past 3 months was also collected during this visit.

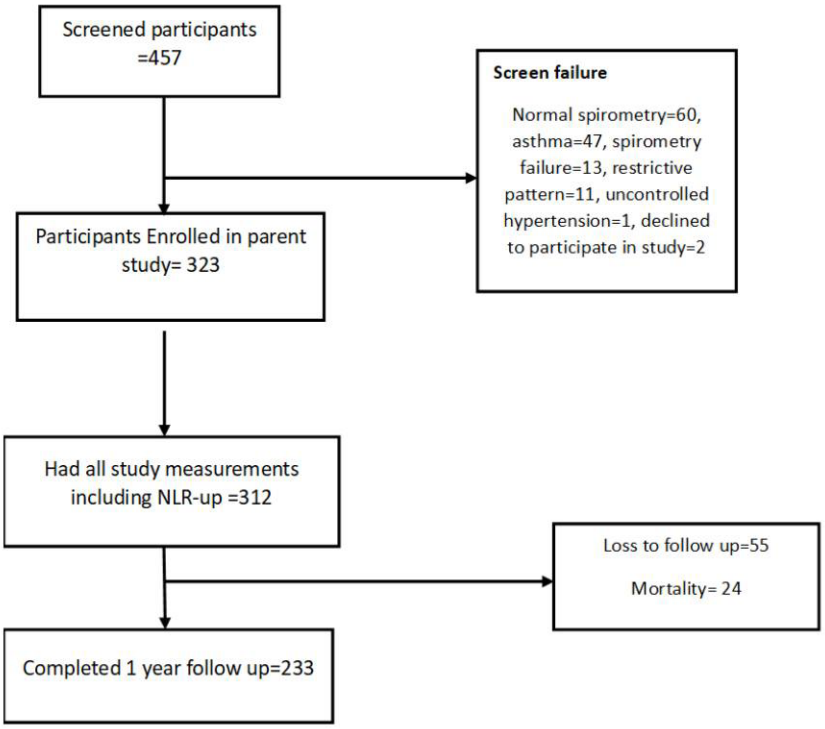
Biostatistical Analysis

Data was analyzed using Stata version 17.0 (Stata Corp LLC, College Station, Texas). 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 (nonparametric 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 the NLR. Optimal cutoff values for predicting hospitalization were determined for the NLR using the maximal Youden Index and Liu's index. Youden's index objectively calculates the optimal cutoff. It takes into account the sensitivity and specificity and is used to estimate the diagnostic effectiveness of various cutoff 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 was 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

A total of 457 participants were screened, and among these individuals, 312 completed the study measurements and were included in this analysis. Among the 312, a total of 209 completed the 1-year follow-up period; 79 were lost to follow-up and 24 died (Figure 1). The mean age was 62.77 years (standard deviation [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 enrollment, 17.63% (n=55) of the participants reported having a history of exacerbations in the past 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. The mean FEV_1 and FVC percentages predicted were 65.30 (SD 25.84) and 91.35 (SD 27.37), respectively. A total of 29.49% (n=92) of participants had severe disease as defined by GOLD,[24] and 69.87% (n=218) had mild or moderate disease. Among the participants, 19.23% (n=60) were on baseline short-acting beta2-agonist inhalers and 8.65% (n=27) on inhaled corticosteroids. A total of 7.69% (n=24) were on combination inhalers. During the follow-up period of one year, 9.94% (n=31) of participants experienced at least one COPD exacerbation. Using Youden and Liu's methods, the optimal NLR cutoff for predicting a COPD exacerbation was 1.17. This cutoff resulted in a ROC curve area of 0.64 (95% confidence interval (CI): 0.56, 0.73). The sensitivity, specificity, positive predictive value, and negative predictive value of the ROC

Figure 1. Study Flow Diagram



NLR=neutrophil-to-lymphocyte ratio

curve were 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 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 (adjusted risk ratio [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 the generalized linear model to be like those obtained using the Cox proportional hazards model (Supplement Table 1, Supplement Figures 1 and 2 in the online supplement).

Discussion

Our findings suggest that in this African population of patients with COPD with diverse risk factors for COPD, the NLR can predict COPD exacerbations with a sensitivity of 61.2%, specificity of 67.7%, and an area under the ROC curve (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 that 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 the NLR as a predictor of exacerbations in COPD in HICs.[20,26,27] 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 in HICs. Previous studies in LMICs have found that an elevated NLR was associated with higher odds of COPD exacerbation.[19,27,28] For example, Sharma and colleagues[27] found that the NLR was an adequate predictor for exacerbations in patients with COPD in India with a higher cutoff of 3.4 and an AUC of 0.806. 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 the 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.[29] This systemic inflammation plays a significant role in the pathology of COPD.[30,31] 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.[32,33] The neutrophil-mediated response also contributes to the severity of airway obstruction.[34] Neutrophilia is well recognized as a marker of infection, whereas, lymphocytopenia is a predictor for bacteremia.[35] Thus, the combination of neutrophils and lymphocytes as

Table 1. Characteristics of Patients With COPD Who Were Enrolled Into the Study and Followed for a Period of One Year[a] Segmented by Neutrophil-to-Lymphocyte Ratio

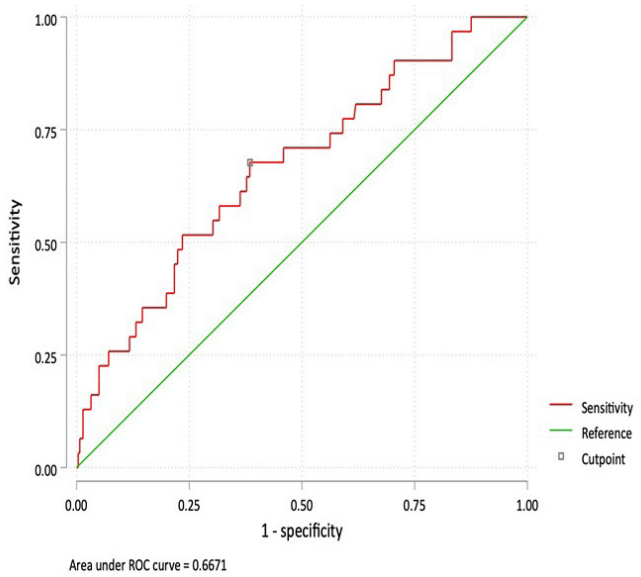
Variable	(NLR <1.17) (n=182)	(NLR> 1.17) (n=130)	Total (312)
Age in Years			
Median (q1, q3)	65.00 (53.00–72.00)	63.00 (52.00–71.00)	64.00 (53.00–71.00)
Age Categorized, n (%)			
<60 Years	70 (38.46)	54 (41.54)	124 (39.74)
≥60 Years	112 (61.54)	76 (58.46)	188 (60.26)
Sex, n (%)			
Male	85 (46.70)	68 (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)

[a]N=312

COPD=chronic obstructive pulmonary disease; NLR=neutrophil to lymphocyte ratio; TB=tuberculosis; BMI=body mass index; FEV_1=forced expiratory volume in 1 second

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 were comparable with the findings by Lee and colleagues,[36] 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.[27] Notably, our optimal NLR cutoff of 1.17 was low, compared to other studies.[27,36,37] 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 of patients with COPD, rather than a stand-alone test to predict COPD exacerbations. When combined with other established risk factors for COPD exacerbation, the NLR may have a role in LMICs 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 potential for the NLR test to be integrated into 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

Figure 2. Receiver Operator Curve Characteristics of the Neutrophil-to- Lymphocyte Ratio Predicting Exacerbations Among COPD Patients In Uganda



Using Youden and Liu's methods, the optimal neutrophil-to-lymphocyte ratio cutoff for predicting a COPD exacerbation was 1.17. This cutoff resulted in a ROC area of 0.64 (95% CI: 0.56, 0.73).

ROC=receiver operator curve; COPD=chronic obstructive pulmonary disease; CI=confidence interval

clinical context to predict exacerbations gives the NLR the potential to reduce health care costs associated with severe COPD exacerbations and hospitalizations by proactively managing the patient aggressively before exacerbation onset or hospitalization.[38,39] This is especially significant in LMICs 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 1-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 the generalizability of findings. Participants were followed serially for 12 months increasing the validity of the findings. Limitations include: (1) the relatively small sample size, (2) potential bias with the patient population given they were enrolled from national referral facilities which usually receive patients with more advanced disease, and (3) the 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.

Conclusions

The NLR was associated with future risk of COPD exacerbations among patients with COPD in this LMIC, where individuals largely have COPD from nontobacco smoke exposure. We estimated an 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 an overall reduction of health care costs attributed to COPD exacerbations.

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Author contributions: PA, BK, and RJ conceived and designed the study. DM, PO, and JN helped with statistical methods. DM and PO completed the data analysis and interpretation. PA and WK were involved in data acquisition and clinical data interpretation. PA drafted the first manuscript. TS, BK, and JH critically reviewed the first draft .TS, BK, RJ, JH,WK, A.K, JN, PO, NMR, and VK critically reviewed the subsequent versions. All authors approved the final version of the manuscript.

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Declaration of Interest

The authors have no conflicts of interest to declare.

Table 2. Multivariate Analyses of Associations With Risk of COPD Exacerbation

Variable	CRR [95% CI]	*P*-value	aRR [95% CI]	*P*-value
Neutrophil-to- 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		
Sex				
Male	1 (reference)		1	
Female	1.83 [0.91, 3.67]	0.090	1.97 [0.73, 5.35]	0.179
Postbronchodilator 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 Year				
No	1 (reference)		1	
Yes	3.13 [1.64, 5.97]	0.001	2.56 [1.21, 5.44]	0.014

COPD=chronic obstructive pulmonary disease; CRR=crude risk ratio; aRR=adjusted risk ratio; CI=confidence interval; BMI=body mass index; TB=tuberculosis; FEV_1=forced expiratory volume in 1 second; mMRC= modified Medical Research Council

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