Chest Heart Journal
Vol. 46, No. 2, July 2022

ORIGINAL ARTICLE

Eosinopenia and Neutrophil to Lymphocyte Count Ratio as a Predictor of Outcomes in Patients Admitted with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Md. Shafiqul Alam Patowary[1], Mushfiq Newaz Ahmed[1], Mohammad Fazle Rabbi[2], Mohammad Shahjahan Siddike Shakil[3] ,Md. Khairul Anam[4], Bipul Kanti Biswas[5]

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Abstract:

Background: *Acute exacerbation of chronic obstructive pulmonary disease (COPD) is a frequent cause of hospital admission and is associated with high resource utilization. Several biochemical markers have been studied as outcome predictors in patients admitted with acute exacerbation of COPD, but their measurement often requires significant resources. Neutrophil to lymphocyte count ratio and eosinophil count is easily obtained from a complete blood picture. Whether eosinopenia and neutrophil to lymphocyte count ratio (NLR), as a potential marker, can predict outcomes in patients admitted with acute exacerbation of COPD is yet to be verified.*

Materials and methods: *This cross-sectional observational study was conducted in the Department of Respiratory Medicine at the National Institute of Diseases of the Chest and Hospital from April 2021 to May 2022. A total of 116 diagnosed cases of COPD, admitted to the hospital with acute exacerbation, were enrolled in this study. NLR was calculated, and eosinopenia was observed from a complete blood count at admission. All data were collected in a performed questionnaire. NLR and eosinopenia (individually and in combination) were evaluated to predict non-invasive and invasive ventilation requirements. Statistical analysis of the findings was carried out using the Statistical Package for Social Sciences version 23. In addition, the Receiver Operating Characteristics (ROC) curves were constructed to identify an optimal cut-off value of NLR for predicting hospital outcomes.*

Result: *In this study, NLR e"9.6 was significantly associated with predicting the need for non-invasive ventilation (AUC of 0.824, sensitivity of 83.9%, specificity of 70.6%) and NLR e"12.95 with predicting the need for invasive ventilation (AUC of 0.864, the sensitivity of 92.3%, specificity of 75.7%,). The sensitivity and specificity of eosinopenia for predicting non-invasive ventilation were 54.8% and 94.1%; for invasive ventilation, 69.2% and 87.4%, respectively. For the combined eosinopenia and NLR, the sensitivity and specificity for predicting non-invasive ventilation were 54.8% and 98.8%; for invasive ventilation, 69.2% and 94.2%, respectively.*

Conclusion: *NLR and eosinopenia from peripheral blood can be used to predict hospital outcomes in patients admitted with AECOPD. However, combined eosinopenia and NLR rather than individual are good predictors of the need for mechanical ventilation.*

Keywords: *Neutrophil to lymphocyte count ratio, eosinopenia, acute exacerbation of COPD(AECOPD)*

[Chest Heart J. 2022; 46(2) : 64-72]

DOI: http://dx.doi.org/10.33316/chab.j.v46i2.2019655

1. Medical Officer, National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka.
2. Medical Officer, OSD, DGHS.
3. Registrar, National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka.
4. Director (Acting) and Associate Professor of Respiratory Medicine, NIDCH, Mohakhali, Dhaka.
5. Associate Professor of Respiratory Medicine, NIDCH, Mohakhali, Dhaka.

Correspondence to: Dr Md. Shafiqul Alam Patowary, Medical Officer, National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh. Cell: 01967992304, e-mail: shafiqulalam83@gmail.com

Submission on: 4 June, 2022 **Accepted for Publication:** 23 June, 2022

Available at http.//www.chabjournal.org

Introduction:

COPD is a complex and heterogeneous disease. It is a disabling condition characterized by poorly reversible airflow limitation and inflammation[1]. It is a leading cause of morbidity and mortality worldwide that induces an economic and social burden that is both substantial and increasing[2]. The worldwide prevalence of COPD is 10.1% in people 40 or older. It is the third leading cause of death worldwide, caused 3.23 million deaths in 2019. With the increasing prevalence of smoking in developing countries and ageing populations in high-income countries, the prevalence of COPD is expected to rise over the next 40 years. By 2060 there may be over 5.4 million deaths annually from COPD and related conditions[3]. For the diagnosis of COPD, spirometry is necessary. A post-bronchodilator FEV1/FVC ratio <0.70 confirms persistent airway limitation. In Bangladesh, the prevalence of COPD was estimated at around 12.5% and outdoor air pollution, smoking habit, and indoor air pollution from biomass fuel burning are known factors contributing to the high prevalence of COPD in Bangladesh[4]. Exacerbation of COPD is responsible for a significant impact on patients. Exacerbations are associated with a negative effect on health status, increasing hospitalisation rate, readmission, and disease progression[5].

On average, COPD patients generally experience 0.5 to 3.5 times the acute exacerbations of COPD per year. Acute exacerbation of COPD is the leading cause of death in COPD patients, with death rates of 6.7% in the hospital[6]. Accurately assessing the severity of an acute exacerbation of COPD and predicting the outcome of hospitalization is crucial for clinical care and the efficient use of scarce medical resources. It is difficult to predict the clinical behaviour of these individuals during an exacerbation. Kawamatawong, Apiwattanaporn and Siricharoonwong conducted a study showing that procalcitonin and CRP are not statically significant in predicting mechanical ventilation and mortality in AECOPD.[7] In a study, Gomez- Rosero et al. estimate the clinical utility of C Reactive Protein (CRP), Mean Platelet Volume (MPV), eosinophil count, and neutrophil/lymphocyte ratio (NLR) as in-hospital prognostic factors in patients with acute exacerbation of COPD.[8] After multivariate analysis adjusted for confounding variables, the NLR ratio was the only marker significantly associated with the risk of dying or being admitted to the ICU. IL-6 and TNF-á also studied as a predictor of hospital outcomes in AECOPD, but their use in routine clinical practice has limitations. In one study, copeptin and neutrophil CD64 (nCD64) were found to be significant predictors of short- and long-term prognosis among patients with acute exacerbations of COPD[9]. But these are not feasible in our community. A prediction scale (DECAF) is developed for patients hospitalized with acute exacerbation of COPD, which is practically difficult to apply in rural areas. So, we need a simple, readily available, and cost-effective parameter to predict the clinical outcomes of patients with acute exacerbation of COPD. The inflammatory status of COPD exacerbation involves various factors, such as immune cells, including neutrophils and lymphocytes, whose activity permanently damages the pulmonary tissue. Since inflammation is an integral part of COPD, circulating biomarkers that show inflammation status, such as the Neutrophil to Lymphocyte count ratio (NLR), can be considered a potential predictor of outcomes in patients admitted with an acute exacerbation of COPD.

Moreover, total leukocyte and neutrophil count have historically been used as a marker of infection. An association has also been found between infection and lymphocyte count. An increased peripheral blood NLR is an independent marker of mortality in patients with bacteremia that is related to acute exacerbation of COPD[10].

Eosinopenia is already proposed as a marker of infection, differentiating infectious from non-infectious causes of elevated CRP and identifying sepsis or bacteremia. In a study, Partouche et al. showed that persistent eosinopenia with the diagnosis of bacterial infection predicted hospital mortality in older patients[11]. Eosinopenia is also proposed as a predictor of short- and long-term prognosis in some diseases, including acute exacerbation of COPD. However, Emami Ardestani and Alavi-Naeini observed no statistically significant link between eosinophil count and in-hospital outcomes in acute COPD exacerbation cases[12]. In another research, in acute exacerbation of COPD, outcomes were similar between the eosinophilic and non-eosinophilic groups when they were followed up for six months after hospitalization.

Both these parameters' role in the acute exacerbation of COPD remains ambiguous and controversial. So, it needs further evaluation. Therefore, it is imperative to conduct this research to determine whether eosinopenia has a significant role in predicting hospital outcomes in patients

admitted with acute exacerbation of COPD. Additionally, to determine the cut-off value of NLR for our socioeconomic background to properly distribute our limited treatment facility resources to the patients with acute exacerbations of COPD.

Methods:

This cross-sectional observational study was conducted in the Department of Respiratory Medicine of the National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, from April 2021 to May 2022. The study protocol was approved by the Institutional Review Board (IRB) of NIDCH. Patients admitted to NIDCH with acute exacerbation of COPD were enrolled in this study. The exclusion criteria were any other known chronic lung disease, any haematological disorder-active or in the past medical history, active malignancy, and worsening of respiratory symptoms associated with other acute causes. We also excluded patients with clinically and radiologically confirmed pneumonia. Finally, 116 cases were selected according to inclusion and exclusion criteria. Eligible participants were being explained about the study, and written informed consent obtained from all participants. Enrolled subjects were given a predesigned questionnaire in locally understandable language. Clinical examinations were done, and BMI was calculated. ABG, CBC, and other relevant biochemical tests were done. Eosinophil count and NLR were calculated from the CBC report. All the data were recorded systematically in a preformed data collection sheet. Statistical analyses were conducted using the Statistical Package for Social Science version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA. Data were presented in frequency, percentage, mean, and standard deviation as applicable. The chi-square test was used to assess categorical data. Sensitivity, specificity, positive predictive value, and negative predictive value of eosinopenia (An absolute eosinophil count $\leq 0.04\times10^3/\mu l$) and NLR(The ratio of absolute neutrophil and lymphocyte count) were calculated for validity as a predictor of hospital outcomes in patients admitted with acute exacerbation of COPD. The Receiver Operating Characteristic (ROC) curve with area under the ROC curve was performed to measure the accuracy of NLR to predict the hospital outcomes and to identify its cut-off values for further analysis. All statistical tests were performed at 5% levels of significance. A p-value of <0.05 was considered statistically significant.

Results:

Table-I

Demographic characteristics of the study populations (n=116)

Demographic characteristics	Frequency (Number of patients)	Percentage
Age (years)		
41-50	6	5.2
51-60	46	39.7
61-70	47	40.5
71-80	15	12.9
>80	2	1.7
Mean±SD	63.1	±8.0
Range (min-max)	48.0	-86.0
Sex		
Male	109	93.97
Female	7	6.03
Residence		
Rural	68	58.6
Urban	48	41.4

Table-II

Distribution of the study population according to Smoking status and biomass exposure(n=116)

Smoking status and biomass exposure	Frequency (Number of patients)	Percentage
Smoker	113	97.4
Current smoker	9	7.8
Ex-smoker	104	89.65
Never smoker	3	2.55
Biomass exposure		
Yes	3	2.6
No	113	97.4

Table-III

Clinical presentation of the study population (n=116)

Clinical presentation	Frequency (Number of patients)	Percentage
Increased breathlessness	112	96.6
Increased cough	97	83.6
Increased sputum production	87	75.0
Fever	21	18.1
Fatigue	78	67.2

Table-IV

Baseline laboratory profile (complete blood count, biochemical test, and arterial blood gas analysis) of the study population (n=116)

	Mean±SD
CBC	
Hb (g/dl)	12.4±1.5
ESR (mm/1st hr)	36.1±18.9
T/C of WBC (K/µl)	11.7±3.4
T/C of Platelet (K/µl)	302.0±92.9
Neutrophils (K/µl)	9.9±3.3
Lymphocyte (K/µl)	1.30±0.83
NLR	9.8±5.7
Eosinophil (K/µl)	0.20±0.25
Biochemical test	
RBS (mmol/L)	6.6±2.4
Serum creatinine (mg/dL)	1.15±0.41
Serum bilirubin (mg/dL)	0.67±0.28
Serum SGPT (IU/L)	40.9±9.5
ABG	
P^H	7.4±0.1
PCO_2 (mmHg)	54.4±19.5
PO_2 (mmHg)	69.4±23.4
HCO_3 (mmHg)	32.1±9.5

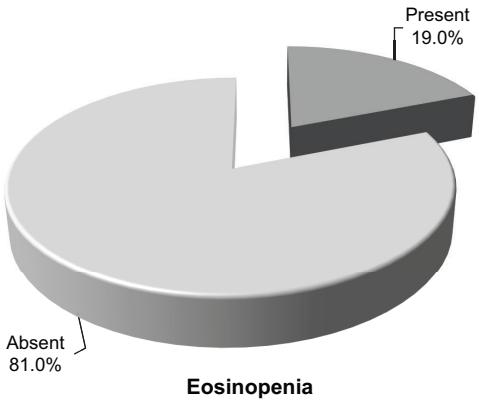

Fig.-1: *Pie chart diagram showing cases with eosinopenia of the study populations (n=116)*

Table-V

Hospital outcomes of the study populations (n=116)

Outcomes	Number of patients	Percentage
Need for Non-invasive ventilation		
Yes	31	26.7
No	85	73.3
Need for Invasive ventilation		
Yes	13	11.2
No	103	88.8

Table-VI

Association of eosinopenia with hospital outcomes of the patients admitted with acute exacerbation of COPD (n=116)

Eosinopenia	Non-Invasive Ventilation				df	Chi value	P value
	Yes (n=31)		No (n=85)				
	N	%	N	%			
Present	17	54.8	5	5.9	1	35.42	0.001s
Absent	14	45.2	80	94.1			
	Invasive Ventilation						
	Yes (n=13)		No (n=103)				
	N	%	N	%			
Present	9	69.2	13	12.6	1	24.07	0.001s
Absent	4	30.8	90	87.4			

s= significant

P value reached from chi-square test

Table-VII

Sensitivity, specificity, accuracy, positive and negative predictive values of the eosinopenia for prediction of hospital outcomes in the patients admitted with acute exacerbation of COPD

Validity test	Non-Invasive Ventilation	Invasive Ventilation
Sensitivity	54.8	69.2
Specificity	94.1	87.4
Accuracy	83.6	85.3
Positive predictive value	77.3	40.9
Negative predictive value	85.1	95.6

Table-VIII

Receiver-operator characteristic (ROC) curve of NLR for prediction of non-invasive ventilation in the patients admitted with acute exacerbation of COPD.

	Cut of value	Sensitivity	Specificity	Std. Error	Area under the ROC curve	95% Confidence interval (CI)		P value
						Lower bound	Upper bound	
NLR	≥9.6	83.9	70.6	0.043	0.824	0.740	0.909	0.001

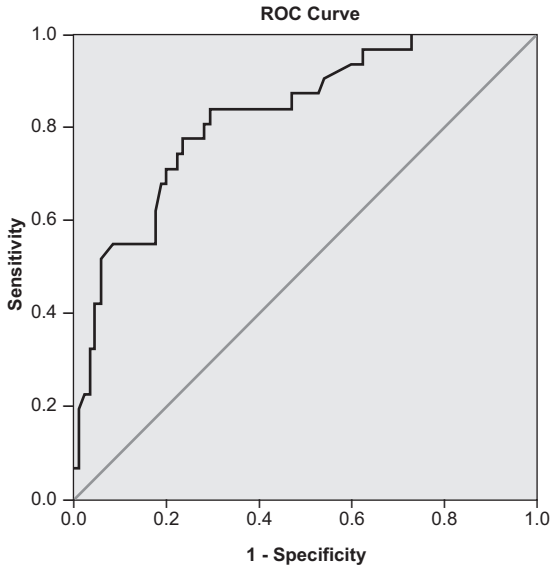

Fig 2: *Receiver-Operating Characteristics curve of NLR for predicting non-invasive ventilation in the patients admitted with acute exacerbation of COPD*

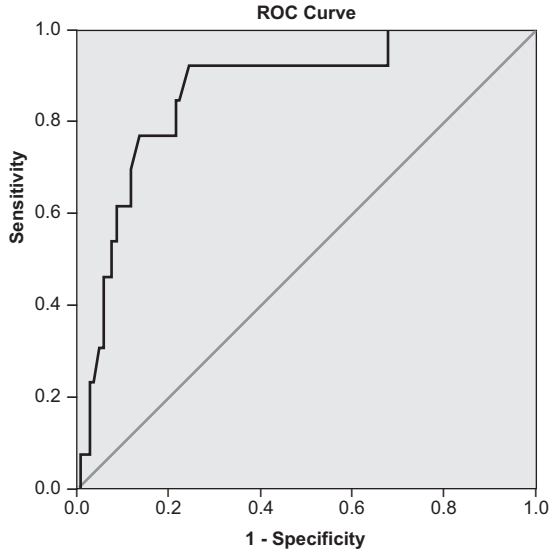

Fig. 3: *Receiver-operating characteristics curve of NLR for predicting invasive ventilation in the patients admitted with acute exacerbation of COPD.*

Table-IX

Receiver-operator characteristic curves of NLR for predicting invasive ventilation in the patients admitted with acute exacerbation of COPD.

	Cut of value	Sensitivity	Specificity	Std. Error	Area under the ROC curve	95% Confidence interval (CI)		P value
						Lower bound	Upper bound	
NLR	≥12.95	92.3	75.7	0.052	0.864	0.763	0.966	0.001

Table-X

Association between NLR with hospital outcomes of the patients admitted with acute exacerbation of COPD (n=116)

NLR	Non-Invasive Ventilation				df	Chi value	P value
	Yes (n=31)		No (n=85)				
	N	%	N	%			
≥9.6	26	83.9	25	29.4	1	27.35	0.001[s]
<9.6	5	16.1	60	70.6			
	Invasive Ventilation						
	Yes (n=13)		No (n=103)				
	N	%	N	%			
≥12.95	12	92.3	25	24.3	1	24.60	0.001[s]
<12.95	1	7.7	78	75.7			

s= significant

P value reached from chi squire test

Table-XI

Sensitivity, specificity, accuracy, positive and negative predictive values of NLR for prediction of hospital outcomes in the patients admitted with acute exacerbation of COPD

Validity test	Non-Invasive Ventilation	Invasive Ventilation
Sensitivity	83.9	92.3
Specificity	70.6	75.7
Accuracy	74.1	77.6
Positive predictive value	51.0	32.4
Negative predictive value	92.3	98.7

Table-XII

Association between combined eosinopenia and NLR with hospital outcomes (n=116)

Eosinopenia and NLR ≥9.6	Non-Invasive Ventilation				df	Chi value	P value
	Yes (n=31)		No (n=85)				
	N	%	N	%			
Present	17	54.8	1	1.2	1	49.90	0.001[s]
Absent	14	45.2	84	98.8			
Eosinopenia and	Invasive Ventilation						
NLR ≥12.95	Yes (n=13)		No (n=103)				
	N	%	N	%			
Present	9	69.2	6	5.8	1	41.22	0.001[s]
Absent	4	30.8	97	94.2			

s= significant

P value reached from chi squire test

Table-XIII

Sensitivity, specificity, accuracy, positive and negative predictive values of the combined eosinopenia and NLR predicting hospital outcomes in the patients admitted with AECOPD.

Validity test	Non-invasive Ventilation	Invasive Ventilation	Death
Sensitivity	54.8	69.2	51.0
Specificity	98.8	94.2	91.5
Accuracy	87.1	91.4	87.9
Positive predictive value	94.4	60.0	35.7
Negative predictive value	85.7	96.0	95.1

Discussion:

This cross-sectional study was conducted to assess the usefulness of the eosinopenia and neutrophil to lymphocyte count ratio as a predictor of outcomes in patients admitted with acute exacerbation of Chronic Obstructive Pulmonary Disease.

The present study observed that the majority (40.5%) of the cases are 61 to 70. The mean age was 63.1±8.0 years. Biradar, Teli, and N[13] also described a similar finding, where the mean age of the study population was 62.06 ±10.783 years. Among the 116 cases, 109 (93.97%) were male, and 7 (6.03%) were female. Similar findings were observed by Lee et al. where males were 91.4%, and females were 8.6% in their study population.[14] In the current study, 97.5% were a smoker. Among them, 9 (7.8%) were current smokers, and 104 (89.65%) were ex-smokers. In this study, three subjects (2.6%) were found to have been exposed to biomass.

Regarding the baseline laboratory profile, this study showed that the mean neutrophil count, lymphocyte count, and NLR were 9.9±3.3(K/µl), 1.30±0.83(K/µl), and 9.8±5.7, respectively. In addition, the mean eosinophil count was 0.20±0.25(K/µl).

In the present study, among the 116 cases, peripheral blood eosinopenia was present in 22 (19%) cases. On the other hand, in a study in Poland, Karauda et al. observed eosinopenia in 36% of the study population, and Biradar, Teli and N. in India observed 46% eosinopenia in their study group. Geographical location, ethnic variation, and phenotypic variation may cause such differences.

According to the current study, non-invasive ventilation was required by 26.7% (31 cases) of the total participants (n=116). However, the demand for non-invasive ventilation was 23% in a prior study[15]. Which is comparable to this one. In the present study necessity for invasive ventilation was 11.2% (13 cases). In a study in China, Teng, Ye and Xue observed that invasive ventilation was needed by 5% of the study population[16].

In the present study, 17 from the eosinopenic group (n=22) and 14 from the non-eosinopenic group (n=94) required non-invasive ventilation, where the difference was statistically significant ($p< 0.05$ from the chi-square test). The sensitivity, specificity, accuracy, PPV, and NPV of eosinopenia for the prediction of non-invasive ventilation were 54.8%, 94.1%, 83.6%, 77.3%, and 85.1%, respectively. Furthermore, regarding mechanical ventilation, Iranian population data also demonstrated statistical significance, where eosinopenia was discovered to be 69.57% sensitive, 63.64% specific, 36.36% PPV, and 87.5% NPV predicting the need for non-invasive ventilation.

In the current study, 9 out of 22 cases from the eosinopenic group needed invasive ventilation, whereas 4 from the non-eosinopenic group (94 cases) required invasive ventilation. Again, a statistically significant difference ($p< 0.05$ from the chi-square test) was observed between them. This study found eosinopenia to be 69.2% sensitive, 87.4% specific, 85.3% accurate, 40.9 % PPV, and 95.6 % NPV to predict the need for invasive ventilation.

In the present study, Receiver Operating Characteristics (ROC) with the area under the ROC curve analysis were performed to measure the accuracy of NLR for predicting the need for non-invasive and invasive ventilation and to identify its cut-off values for further research.

Based on the ROC curves, for non-invasive ventilation, NLR had an area under curve 0.824 (95% CI 0.740-0.909; p<0.05). NLR was used to develop Receiver Operating Characteristics (ROC), which provided a cut-off value of 9.6 with 83.9% sensitivity, 70.6% specificity, 74.1% accuracy, 51.0% PPV, and 92.3% NPV for predicting non-invasive ventilation. In the prediction of non-invasive ventilation requirements, elevated NLR was identified when the value was ≥9.6, and the difference was statistically significant (p<0.05). In a study done by Rajasurya and Gudivada (2019), the authors showed that NLR at the time of admission in patients with acute exacerbation of COPD was a reliable biomarker to predict the use of mechanical ventilation, which is consistent with the findings of the current study[17].

For invasive ventilation, Receiver Operating Characteristic (ROC) was constructed using NLR, which gave a cut-off value of 12.95, with 92.3% sensitivity, 75.7% specificity, 77.6% accuracy, 32.4% PPV, and 98.7% NPV for predicting invasive ventilation. NLR had an area under the ROC curve of 0.864 (95 % CI 0.763-0.966; p<0.05). In predicting invasive ventilation requirements, elevated NLR was identified when the value was ≥12.95 and the difference was also statistically significant (p<0.05). Teng, Ye and Xue (2018) in their study observed that the AUC of the NLR for predicting invasive ventilation was 0.732 (95 % CI 0.656-0.807; p<0.05). The sensitivity and specificity were 54.3% and 84.8 %, respectively, when 10.345 was used as the critical NLR value. In a study in China, the author observed that increased NLR was significantly associated with a higher risk of worse outcomes in the patients admitted with acute exacerbation of COPD. Furthermore, ROC analysis revealed that with a cut-off value of 10.23, NLR could predict in hospitals worse outcomes of severe acute exacerbation of COPD (sensitivity 62.1%, specificity 92.0%, AUC 0.833)[18].

In the present study, combined eosinopenia and NLR ≥9.6 were present in 18 (representing 15.5%) out of the 116 cases; among them, 17 cases needed non-invasive ventilation. Whereas 14 from the non-eosinopenic and NLR < 9.6 group required non-invasive ventilation. A statistically significant difference (P< 0.05 from the chi-square test) was also observed between them. The sensitivity, specificity, accuracy, PPV, and NPV of combined eosinopenia and NLR ≥9.6 for predicting non-invasive ventilation were 54.8%, 98.8%, 87.1%, 94.4%, and 85.7%, respectively.

In this study, 15 cases (12.9 %of the study group) had combined eosinopenia with NLR ≥12.95, and 9 of those 15 needed invasive ventilations. Whereas 4 (representing 3.96%) from the non-eosinopenic and NLR <12.95 group required invasive ventilation. The difference was statistically significant (p <0.05 from the chi-square test). Eosinopenia and NLRe" 12.95 had sensitivity, specificity, accuracy, PPV, and NPV of 69.2%, 94.2%, 91.4%, 60.0%, and 96.0%, respectively, for the prediction of invasive ventilation.

Any published research data was not found regarding combined eosinopenia and NLR (at a specific cut-off value) with sensitivity, specificity, PPV, and NPV to predict mechanical ventilation (invasive or non-invasive). So current studies in this aspect could not be compared with others.

Conclusion:

In acute exacerbation of COPD, combined eosinopenia and NLR rather than individual are good predictors of mechanical ventilation (invasive and non-invasive ventilation) requirement.

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