Original Article

Mortality Predictors in Hospitalized Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

Sadhna Priya, Nausheen Saifullah, Saima Akhter, Asha Devi

ABSTRACT

Objectives: To determine predicting factors for in-hospital outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

Methodology: A prospective cross-sectional validation study was performed in Jinnah Postgraduate Medical Center Karachi, Pakistan from 2019 to 2020 at the Chest Medicine department, a largest public tertiary care center in Karachi. All the patients with other inflammatory diseases such as malignancy, Arthritis, Inflammatory bowel diseases, connective tissue disorders, bronchiectasis (radiologically proven or history of phlegm expectoration >30 ml/day) or history of Tuberculosis were excluded. Patients with a recent history of use of antibiotic treatment or systemic steroids (prednisolone equivalent to >20 mg/day) in the preceding two months on medical record were also excluded from the study. Ethical Approval was taken from Institutional Research committee. All the patients who were presented to ER with Acute exacerbation of COPD was included in the study, AECOPD was defines Anthonisen criteria. Data was entered into SPSS version 21 for statistical analysis of the data.

Results: Total 157 study participants were included into the study with predominance of male gender (n=106, 67.5%). The average age of study participants was 65.1 ± 11.41 years. Age was significantly higher among non-survivors than survivors (p=0.037). PH level at 4 hours was significantly lower in survivors (p=0.038). Heart rate (p=0.026) and respiratory rate (p=0.018) were significantly higher among non-survivors at 4 hours. Among NLR, PLR, PCO2, PO2 and HCO3, a higher sensitivity of 92.59% for NLR and lower specificity of 6.15% PCO2 was determined. None of these parameters had area under the curve significantly higher than 0.5. Multivariable logistic regression showed that age and PCO2 were independently predictors of mortality.

Conclusion: The present study found that increasing age and PCO2 were significant predictors of mortality in in patients with acute exacerbation of chronic obstructive pulmonary disease. NLR has high sensitivity and low specificity in determining the mortality

KEYWORDS: Chronic Obstructive Pulmonary Disease, In Hospital-Outcomes, Neutron Lymphocyte Ratio, Platelet Lymphocyte Ratio

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and its adverse outcomes are foremost health concern globally.[1] It is characterized by low-grade chronic systemic inflammation with raised cytokines and biomarkers including C-reactive protein (CRP), Interleukin 6(IL-6) and surfactant protein D (SPD).[2] Patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) have compromised quality of life and possess high risk mortality.[3] Numerous biomarkers of systemic inflammation have recently been assessed to predict mortality, however excessive costs and technical factors prevent their clinical use.[4] Recently, researchers have been working to explore biomarkers which could be more efficient and cost effective to predict mortality. Blood

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neutrophil-to-lymphocyte ratio (NLR) has been emerging valuable predictor of inflammatory conditions and is used for risk stratification of different adverse outcomes among patients with acute coronary syndrome, pancreatitis, sepsis and infectious conditions.[5] This index is a rapid, easy and cost-effective method which is a calculated index derived from a routine complete blood count test in clinical practice.[3] NLR has been reported to be higher in AECOPD patients than in stable patients and is associated with severity of COPD[6,7, 8] Recently few international studies have evaluated the role of Platelet Lymphocyte Ratio (PLR) in patients with COPD.[9,10] To the best of our knowledge no such study has been done before in our Pakistani population so far. Results of international studies cannot be generalized on our local population due to gene variations of different populations in patients with COPD.[11] Aim of this study is to determine the predictors for in-patient outcome of patients with AECOPD and accuracy of NLR and PLR in predicting in-hospital mortality in these patients. Results of our study will not only provide the local evidence but also pave the way for planning preemptive approach in such patients.

METHODOLOGY

A prospective cross-sectional study was performed in Jinnah Postgraduate and Medical Center Karachi, Pakistan from 2019 to 2020 at the Chest Medicine department, a largest public tertiary care center in Karachi, focuses on medical care, teaching, research and provides healthcare service. This study was approved by Institutional review board of JPMC with letter number (2-81/2020-GFNL/4290/ JPMC) and informed consent was obtained from all subjects or their closest family member accompanying each patient. All the relevant history including history of patient's smoking habit and biomass exposure was taken. Additionally, clinical information was entered on a structured performa by research team only and patient's confidentiality was maintained strictly. A Current smoker is considered as a person who has smoked in last four weeks of his admission, while Ex-smoker is considered as a person who has smoked more than 100 cigarettes in their lifetime but has not smoked in the last 28 days as per CDC guidelines. Biomass term was used to describe any fuel derived from crop residues, wood, crops and animal waste.

Previously conducted study showed that in-hospital mortality rate was 11.5% among AECOPD patients (REF). Using 95% confidence interval and 5% precision, a sample of total 157 patients is required. Sample size calculation was performed on online calculator Open-Epi. Non-Probability consecutive sampling was done. All consecutive patients, from both genders, and older than 16 years with clinical diagnosis of AECOPD, who came to Emergency Department or outpatient Department (OPD of Chest Medicine Department JPMC were included in the study. These patients were known cases of Chronic Obstructive Pulmonary Disease. Acute exacerbation was labeled when they met Anthonisen criteria; Increase in sputum production, increase in Dyspnea or presence of purulent sputum. All the patients with other inflammatory diseases such as malignancy, Arthritis, Inflammatory bowel diseases, connective tissue disorders, bronchiectasis (radiologically proven or history of phlegm expectoration >30 ml/day) or history of Tuberculosis were excluded. Patients with a recent history of use of antibiotic treatment or systemic steroids (prednisolone equivalent to >20 mg/day) in the preceding two months on medical record were also excluded from the study. Peripheral venous blood samples were obtained using ethylene ediaminetetraacetic acid (EDTA), containing blood collector within 24 h after the admission. As a marker of systemic inflammation, NLR was measured as absolute neutrophil count divided by absolute lymphocyte count. PLR was calculated as the platelet count divided by absolute lymphocyte count. Both of PLR and NLR were obtained from the same automated blood samples for the study. Using NLR cut-off of >4.19 [12] and PLR cut-off of >235 [13] based on previous literature, sensitivity and specificity for AECOPD were measured. Patients who were discharged alive were considered as survivors whereas cases of in-hospital mortality were non-survivors. Data was entered into SPSS version 21 for statistical analysis of the data. Frequencies and percentages were computed for categorical variables. Numerical variables were summarized as mean ± standard deviation or median with inter-quartile range (IQR) as appropriate. Assumption of normality was tested with Shapiro-wilk test.

Categorical study variables were compared between survivors and non-survivors using Chi-square or Fisher-exact whereas all of the non-normal numerical variables were compared through independent sample t-test or Mann-Whitney U test depending on the assumption of normality. Performance of biomarkers to predict mortality was assessed with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and by. ROC analysis. P-value ≤0.05 was considered as statistically significant.

RESULTS

Total 157 study participants were included into the study with predominance of male gender (n=106, 67.5%). The average age of study participants was 65.1 ± 11.41 years. Out of these 125 participants with smoking exposure, majority were ex-smokers (n=75, 60%) while remaining were current smokers (n=50, 40%). Out of 157 admitted patients, 27(17.2%) patients died during their hospital stay. Comparison of demographics and clinical variables is presented in Table 1. Mean age among survivor and non-survivor was 64.08 ± 10.73 and 70.04 ± 13.38 which significantly different (p=0.037). PH level at 4 hours of admission was significantly lower in survivors (p=0.038). Heart rate (p=0.026) and respiratory rate (p=0.018) were significantly higher among non-survivors at 4 hours. At 24 hours, median heart rate (p=0.009) and respiratory rate (p=0.004) were significantly higher in non-survivors than survivor group. Table 3 presents the diagnostic accuracy of NLR, PLR, PCO_2, PO_2 and HCO_3. Figure 1 depicts receiver operative characteristics curve to predict mortality. Area under the curve for NLR, PLR, PCO_2, PO_2 and HCO_3 was 0.617 (95% CI: 0.50 – 0.73, p=0.057), 0.55 (95% CI: 0.42 – 0.68, p=0.429), 0.40 (95% CI: 0.27 – 0.54, p=0.115), 0.55 (95% CI: 0.42 – 0.68, p=0.41) and 0.34 (95% CI: 0.25 – 0.51, p=0.048) respectively. On Univarite analysis, age and PCO2 were associated with mortality. Multivariable model was adjusted with other covariates with p<0.25 and it was found age and PCO2 were independently associated with mortality even after adjusting effects of other confounding variables (Table 4).

Table 1: Comparison of demographics among survivors and non-survivors (n= 157)

Variables	Survivor n=130	Non-survivors n=27	P value
Gender			
Male; n (%)	87 (66.9)	19 (70.4)	0.728
Female; n (%)	43 (33.1)	8 (29.6)	
History of diabetes; n (%)	15 (11.5)	2 (7.4)	0.739
History of HTN; n (%)	49 (37.7)	7 (25.9)	0.245
History of biomass; n (%)	46 (35.4)	10 (37)	0.870
History of smoking; n (%)	102 (79.1)	20 (74.1)	0.567

p value <0.05 considered significant

Table 2: Comparison of clinical features among survivors and non-survivors

Variables	Survivor n=130 Mean ±SD?? (Range) Median (IQR)	Non-survivors n=27 Mean ±SD (Range) Median (IQR)	P value
Baseline PH value	7.29 (7.23 - 7.34)	7.26 (7.19 - 7.34)	0.131
Baseline pCo2	68 (55.95 - 81.78)	57.40 (45.60 - 83)	0.418
Baseline pO2	60 (46 - 81.44)	68 (44 - 105)	0.378
Baseline HCO3	31.50 (26.90 - 36.25)	26.40 (23.60 - 34.70)	0.098
Baseline SO2	87 (71.15 - 91.05)	88 (76 - 93)	0.545
Baseline heart rate	98 (88 - 102)	98 (82 - 110)	0.982
Baseline respiratory rate	28 (24 - 32)	30 (24 - 36)	0.075
Neutrophils	8500 (7800 - 9000)	8800 (8300 - 9200)	0.068
Lymphocytes	1000 (600 - 1800)	800 (400 - 1400)	0.195
Platelets	238500 (176750 - 324500)	218000 (139000 - 324000)	0.699
Neutrophil lymphocyte ratio	7.85 (4.68 – 14.29)	11 (5.85 – 22.50)	0.057*
Platelet lymphocyte ratio	214 (128.13 – 448.48)	236.67 (135 – 545)	0.429

NIV: Non-invasive ventilation p value <0.05 considered significant

Table 3: Diagnostic accuracy of different patients' parameters

Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NLR (>4.19)	92.59	21.54	19.68	93.3
PLR (>235)	51.85	55.38	19.44	84.71
PCO2 (>44)	81.48	6.15	15.28	61.54
PO2 (<70)	51.85	33.85	14	77.19
HCO3	77.78	14.62	15.91	76

NLR= Neutrophil-to-lymphocyte ratio, PLR= Platelet-lymphocyte ratio, PCO2 = Partial pressure of carbon dioxide, PO2 = Partial pressure of oxygen, HCO3= Bicarbonate

Figure 1: Receiver operating characteristic curve for NLR, PLR, PCO2, PO2, HCO3 to predict mortality.

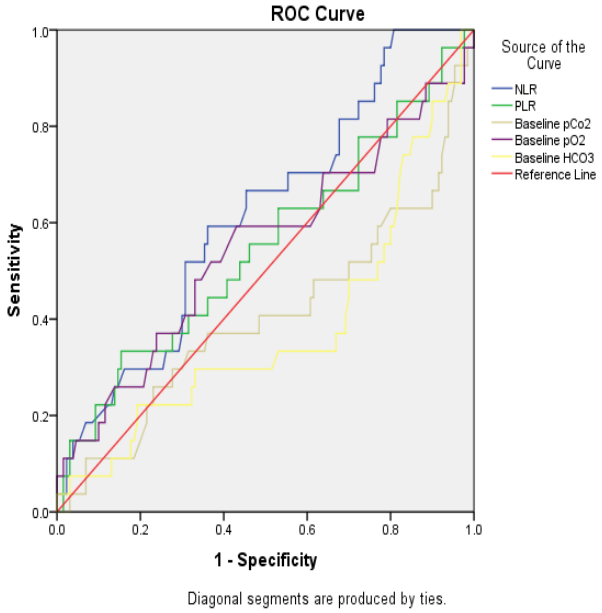

Table 4: Predictors of mortality on univariate and multivariable logistic regression

Variable	OR (95% CI)	P value	A OR (95% CI)	P value
Age	1.05 (1.01 - 1.09)	*0.015	1.06 (1.01 -1.09)	0.009
Gender				
Male	1.17 (0.48 - 2.9)	0.728	-	-
Female	Ref		-	-
Diabetic	0.61 (0.13 - 2.85)	0.533	-	-
Hypertension	0.58 (0.23 - 1.47)	0.249	0.52 (0.19 -1.43)	0.207
History of biomass	1.07 (0.46 - 2.5)	0.870	-	-
Current smoker	0.71 (0.28 - 1.8)	0.469	-	-
NIV application	1.63 (0.35 - 7.56)	0.533	-	-
PCO2				
≤44	3.47 (1.04 - 11.58)	*0.043	4.80 (1.25 -18.37)	*0.022
>44	Ref		-	-
PO2				
<70	0.55 (0.24 - 1.27)	0.163	0.46 (0.18 - 1.16)	0.099
≥70	Ref			
HCO3				
<24	1.67 (0.60 - 4.67)	0.329	-	-
≥24	Ref		-	-
NLR				
≤4.19	3.43 (0.76 -15.37)	0.107	3.83 (0.79 - 18.67)	0.096
>4.19	Ref		Ref	
PLR				
≥235	1.34 (0.58 - 3.07)	0.493	-	-
<235	Ref		-	-

P value <0.05 considerd significant

DISCUSSION

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is frequent cause of hospitalization of prolong duration and has associated with significant morbidity and mortality provoked by deteriorating clinical symptoms, declining lung function, and high readmission rates.[14] More precise likelihood of survival and readmission in hospitalized patients with AECOPD by Identifying the factors and sighting a simple and reliable biomarker that can accurately assess the mortality risk during hospitalization and is of great importance for the management of AECOPD patients and rational allocation of medical resources. The mortality in our study was 17.2% (n=27), while in-hospital mortality risk ranges from 4-30% during AECOPD in various studies.[15] Similar study conducted in south India, overall mortality rate was 34.92%, and higher number probably explains small sample size of their study and also was done on patients requiring ICU care.

There are number of variables that have been studied in patients with AECOPD to predict the in-hospital mortality. [16, 17] Age is one of the risk factor that is associated with increased in-hospital mortality, one such reason given that Increasing age or patients aged more than 75 years were significantly associated with mortality during hospitalization, as the patients' FEV1 declines at a more accelerated rate in older COPD patients than younger ones.[18] Our study showed increased mortality with age (70.04 ± 13.38) with P value of 0.037, similar to the one study where age was independently found to be statistically significant for in-hospital mortality in patients with AECOPD[19].

In our study Comorbidities were not significantly different among survivor and non- survivor groups, consistent with the reports by Mehta et al and Morasert et al and showed no correlation of smoker COPD patients compared to those of women and Biomass smoke-COPD, although results were not statistically significant.[15,18] The explanation was probably higher proportion of comorbidities with mortality, and reported increased chances of mortality with greater number of packs years.[15] Most of the patients in our study in non- survivor group were men and Tobacco smoker men than women and differences

in underlying inflammation between two risk groups. Similar to one study reported, the concentration of serum cytokines involved in pro-inflammatory and angiogenic mechanisms decreased in women with COPD-BS compared to those with COPD-TS explains the differences in inflammation and its outcome. [20]

Clinical findings include tachycardia increased respiratory rate and the severity of the acute exacerbation as per Anthonisen criteria, are all independently associated with in-hospital mortality [21, 22, 23]. Our study showed Heart rate (p=0.026) and respiratory rate (p=0.018) were significantly higher among non-survivors at 4 hours of admission. Also, at 24 hours, median heart rate (p=0.009) and respiratory rate (p=0.004) were significantly higher in the non-survivors as compared to the survivor group, corresponding to the one report that showed respiratory rate on admission was significantly associated with higher risk of death.[24]

Blood gas values have been proven to be predictive of in-hospital mortality at the time of admission, the relationship between in-hospital mortality in COPD and decompensated acidosis is well established.[15] Acidosis was associated with shorter interval to death signifying that these patients are acutely unwell.[25.] Contradicting to these reports PH level at 4 hours of admission was significant lower in survivors with significant p value =0.038 in our study. In stable COPD, hypercapnia is a strong independent predictor of mortality.[26,27] One study reported PCO2 as independent predictor of mortality in patients with AECOPD.[19] Gunen et al also showed increased mortality rate in COPD hospitalized patients with higher PCO2.[28] Similar to previous reports our study showed PCO2 was independently found to be statistically significant predictors of in- hospital mortality of AECOPD patients.

COPD is associated with both heightened airway and systemic inflammation and during states of exacerbation and rouse the increase of the NLR and PLR, which may be used as prognostic markers of inflammation for patients with AECOPD.[29] Raised NLR and PLR are part of cascade of heightened systemic inflammation and AECOPD is associated with increase systemic inflammation therefore rise in NLR and PLR can be used as prognostic markers among patients with AECOPD.[29] CRP is a classical inflammatory maker, and has been successfully to predict prognosis of patients with AECOPD.[30] Taylan et al reported that increased NLR is as useful as CRP in the evaluation of elevated inflammation in AECOPD. The NLR is useful for the early identification of potential acute exacerbations in patients with COPD who have normal levels of traditional markers.[31] Our study showed diagnostic accuracy of NLR at threshold of >4.19 showed higher sensitivity and NPV while lower specificity and PPV. For platelet-lymphocyte ratio (PLR) at threshold ≥235, showed the sensitivity of 51.85% and specificity of 55.38% and diagnostic accuracy by 19.44% PPV and 84.71% NPV, which is of lower predictive accuracy than with the NLR. Our results are supported by recent research from different areas of World but sensitivity of NLR in our population is higher when compared to others. Rahimirad etal has showed that neutrophil-lymphocyte ratio has 87% sensitivity and 40% specificity in prediction of in-hospital mortality in patients with acute exacerbation of COPD.[32] Moreover, Liu J, et al. has demonstrated that NLR has sensitivity of 71.4% and specificity of 74.2% in prediction of in-hospital mortality in patients with AECOPD.[12] Yao C, et al. has showed that NLR has sensitivity of 81.08% and specificity of 69.17% while PLR has sensitivity of 64.86% and specificity of 58.27% in prediction of in-hospital mortality in patients with AECOPD.[9] In addition, two studies supported that elevated NLR correlation with long-term mortality in patients with COPD.[33, 34] Although the NLR and PLR was found to be sensitive marker of inflammation and thus predicting mortality, but the results were not found to be statistically significant on both univariate and multivariable logistic regression.

CONCLUSION

The present study found that increasing age and PCO2 were significant predictors of mortality in in patients with acute exacerbation of chronic obstructive pulmonary disease. NLR has high sensitivity and low specificity in determining the mortality.

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Authors' Contribution	
Sadhna Priya	Study design, acquisition of data and manuscript writing. Revised and approved the articles.
Nausheen Saifullah	Study design, acquisition of data and manuscript writing. Revised and approved the articles.
Saima Akhter	Study design, data analysis and interpretation and write up of results. Revising manuscript critically for important intellectual content.
Asha Devi	Study design, acquisition of data, data analysis and interpretation, revised and approve the manuscript.
	All authors are equally accountable for accuracy, integrity of all aspects of the research work.

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