Journal of Institute of Medicine Nepal
Institute of Medicine, Kathmandu, Nepal

OPEN ACCESS

Original Article

JIOM Nepal. 2023 Apr;45(1):5-10.

Factors determining Outcomes in Hospitalized Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Niraj Bam[1], Dharmendra Sapkota[2], Sandip Kuikel[3]

Author(s) affiliation

[1]*Department of Pulmonology and Critical Care, Maharajgunj Medical Campus, Tribhuvan University Teaching Hospital, Institute of Medicine, Maharajgunj, Kathmandu, Nepal*

[2]*Department of Internal Medicine, Maharajgunj Medical Campus, Tribhuvan University Teaching Hospital, Institute of Medicine, Maharajgunj, Kathmandu, Nepal*

[3]*Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University, Maharajgunj, Kathmandu, Nepal*

Corresponding author

Niraj Bam, MBBS, MD
nirajbam@hotmail.com

Submitted
Oct 21, 2021

Accepted
Feb 2, 2023

ABSTRACT

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is frequently accompanied by increased local and systemic inflammation brought on by airway infection, pollution, or other airway insults. This study aimed to find the factors determining outcomes in patients hospitalized with acute exacerbation of COPD.

Methods

An analytical study among diagnosed cases of AECOPD was conducted. Bivariate regression model followed by Multinomial logistic regression (MNLR) was used to contrast outcome variables. A p-value less than 0.05 was considered statistically significant in all analyses.

Results

A total of 126 patients with a mean age of 72.04±9.75 years were included in the study. Most of the patients were current smokers or past smokers, cor-pulmonale was present in 34.9% of patients. The most common co-morbidity was hypertension (41.2%). Most (55.6%) patients had early discharge, 31.7% (40) patients had late discharge and 12.7% (16) patients had mortality as the outcome. After bivariate analysis, among all variables of the study qualified to be included in the multivariate MNLR model, Neutrophil Lymphocyte ratio (NLR) was found to be a significant predictor of late discharge in comparison with early discharge while Age and NLR were found to be a significant predictor of Mortality in comparison with late discharge among patients with AECOPD.

Conclusion

Older age and higher NLR predicted mortality in comparison to longer hospital stay (>5days). Since NLR is a common variable in both the outcome (early vs late discharge and late discharge vs mortality), NLR can be used to predict the outcome (early discharge, late discharge, and mortality) of patients with AECOPD.

Keywords
AECOPD; chronic obstructive pulmonary disease; factors; outcomes; predictors

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) prevalence, morbidity, and mortality vary across countries and across different groups within countries. It is reported to be more than 210 million globally.[1] In Nepal there were 960,737 Nepalese suffering from COPD in 2016 and it was estimated that 16,302 people died from COPD in 2016.[2] Previous studies of selected patient populations have estimated in-hospital mortality from acute exacerbation of COPD (AECOPD) to range from 4% to 30% in Nepal.[3] Despite the high number of COPD-related hospitalizations, determinants of the outcome of patients hospitalized for this acute deterioration in the clinical course of COPD are little known.

Many studies have assessed different factors as predictors of mortality. Although clinical variables such as age, smoking history, dyspnea, exacerbation history, and body mass index (BMI) are somewhat useful to model these subtypes, assess disease severity, and predict disease progression, a large amount of unexplained variance remains.[4,5]

In this study, the authors tried to find out the factors that can predict the outcome in patients hospitalized due to AECOPD. The measures of outcome in this study were early discharge (duration of hospital stay ≤5 days), late discharge (duration of hospital stay >5 days), and in-hospital mortality. The current study differs from previous studies in that it compares outcomes; early discharge, late discharge, and mortality; with variables age and laboratory values at admission (blood pH, pCO_2, serum urea, creatinine, total bilirubin, and neutrophil to lymphocyte ratio (NLR)).

METHODS

A prospective observational study was conducted in the Department of Pulmonology and Critical Care of Tribhuvan University Teaching Hospital (TUTH). It aimed to find out the determinants of outcome in patients hospitalized with the diagnosis of AECOPD. It was conducted from December 2020 to June 2021 analyzing patients' data after receiving approval from the Institutional Review Committee of the Institute of Medicine. Known cases of COPD with the diagnosis of AECOPD admitted in different wards of TUTH were included in the study. Patients who got discharged against medical advice i.e, Leave against Medical Advice (LAMA) or Discharge on Patient Request (DOPR), who refused to give consent, and who had co-morbidities like cancer that are proven to alter the variables (like NLR); were excluded from the study.

Probability random sampling was used to select the patients diagnosed with AECOPD. Among the AECOPD cases admitted in the department, cases were randomly selected as per convenience of the author. Sample size was calculated using the Daniel formula. The static for the 95% confidence interval (95%) used in the study was 1.96 and allowable error was kept at 5%. With a previously reported prevalence of 8.5%,

Sample size = $[z^2 \times p(1-p)]/e^2$

z = 95% confidence interval (standard value of 1.96)

p = prevalence of COPD in Nepal[6] = 8.5%

e = 5% allowable error (standard value of 0.05)

Sample size $= 1.96^2 \times 0.085 \times 0.915 / 0.05^2$

$= 120$

The sample size of 132 was obtained after adding a 10% non-response rate.

Data was collected by interviewing each patient and reviewing the admission report to note the laboratory findings. All the patients in the study were followed to their discharge or in-hospital mortality. Data was collected in a self-made data collection form.

It was a non-interventional observational study. There were no risks or benefits to the patients involved in the study. Hospital Protocol was followed during management of the study population. The identity of each patient was kept confidential.

The dependent variable in the study was the outcome of the patient admitted with the diagnosis of AECOPD. The measure of outcome was classified into early discharge (discharge within 5 days of admission), late discharge (discharge after 6th day or more from admission), and in-hospital mortality. Data related to patient profile and laboratory findings on admission were noted at the time of admission. Patient profile data included patient age, sex, smoking status, comorbidities, blood pH, pCO_2, serum urea, creatinine, total bilirubin, and neutrophil-to-lymphocyte ratio (NLR).

All the data was collected in Microsoft Excel (Ver. 2016) and statistical analysis was performed using SPSS ver 26. The demographic data and patient profile were presented as frequency and percentage. Age and laboratory data (blood pH, pCO_2, serum urea, creatinine, total bilirubin, and NLR) were used to predict the outcome of patients admitted with AECOPD. To determine the significant factors influencing the outcome of the patient, which is ordinal in nature, an ordinal logistic regression model was tried. Because the assumption of the test of parallel lines in ordinal logistic regression was violated, multinomial logistic regression (MNLR) was used after verifying the adequacy of the model by different model adequacy tests. We contrasted early discharge vs late discharge and late discharge vs in-hospital

mortality. The missing contrast between early discharge and in-hospital mortality can be obtained in terms of the other two. Bivariate analysis was performed to assess the association of each of the independent variables and dependent variables. Explanatory variables, which were identified by bivariate analysis at p-value < 0.25, were selected (P value was taken 0.25 to include more number of variables to be fitted in MNLRM) and entered a multivariate regression model to identify predictors of outcome in patients with AECOPD. p-value < 0.05 was considered statistically significant in all analyses.

RESULTS

A total of 132 patients were selected for the study and 6 patients were excluded later because they were discharged on DOPR, so a total of 126 patients were included in the study. Patients' ages ranged from 47 to 94 with a mean age of 72.04±9.75 years. Most of the patients belonged to the age group 71 to 80 years and 55.6% (70) of the patient were female. Eighty-one percent of patients were current smokers or past smokers, and cor-pulmonale was present in 34.9% of patients. The most common co-morbidity in patients with AECOPD was hypertension, followed by diabetes mellitus. The hematological co-morbidities reported in the study were anemia, thrombocytopenia, leukemia, and polycythemia. Amongst the patients included in the study, 55.6% (70) of patients admitted with AECOPD had early discharge, 31.7% (40) patients had late discharge and 12.7% (16) patients had mortality as the outcome.

Bivariate regression test of the outcome of patients with AECOPD revealed that the variables age, blood pH, pCO_2, serum urea, creatinine, total bilirubin, and NLR at the time of admission had statistical significance. (Table 2) They were included in the multivariate MNLR model to calculate the regression coefficient, p-value, and odds ratio for each category.

Analysis to find out the factors that determine the outcome of patients admitted with AECOPD by the MNLR model was done by contrasting early discharge vs late discharge and late discharge vs mortality (table 3). The reference category in both models was late discharge. From the fitted MNLR, the variable NLR (OR=0.72, p-value<0.05) was seen to be significant to the model early discharge vs late discharge. On the other hand, age (OR=1.158, p-value<0.05) and NLR (OR=1.493, p-value<0.05) were seen to be significant to model late discharge vs mortality of patients with AECOPD. The odds ratio for NLR is seen to be 0.72 for the model early discharge vs late discharge, which reveals that the odds of early discharge relative to late discharge decrease by 0.72 per unit increase in NLR. Similarly,

Table 1. Distribution of study population as per patient characteristics, comorbidity and outcome

Characteristics	Number (%)
Age group (years)	
≤60	17 (13.5%)
61-70	38 (30.2%)
71-80	44 (34.9%)
81-90	25 (19.8%)
>90	2 (1.6%)
Sex	
Male	56 (44.4%)
Female	70 (55.6%)
Smoking	
Yes	102 (81%)
No	24 (19%)
Cor pulmonale	
Present	44 (34.9%)
Absent	82 (65.1%)
Co-morbidities	
Hypertension	52 (41.2%)
Diabetes	33 (26.1%)
Hematological	10 (7.9%)
Atrial fibrillation	7 (5.6%)
Hypothroidism	6 (4.7%)
Outcome	
Early discharge	70 (55.6%)
Late discharge	40 (31.7%)
Mortality	16 (12.7%)

Table 2. Bivariate analysis of the desired variables

Characteristics	Early discharge	Late discharge	Mortality	p value
Age (years)	71.8±9.5	69.7±8.81	78.69±10.58	0.005
pH	7.39±0.05	7.34±0.09	7.28±0.12	<0.001
pCO_2	43.81±15.34	55.02±22.25	60.1±26.14	0.001
Urea (mmol/L)	5.83±3.23	9.94±5.58	9.77±3.03	<0.001
Creatinine (umol/L)	76.84±33.27	119.48±64.16	115.94±43.86	<0.001
Total bilirubin (gm/l)	12.09±9.49	18.65±14.19	15.38±7.90	0.01
NLR	4.32±1.44	6.03±3.22	13.89±10.29	<0.001

Table 3. Final fitted model for explaining outcome in patients with AECOPD

Variables	Estimated coefficient	p-value	Odds ratio	95% CI for odds ratio		Estimated coefficient	p-value	Odds ratio	95% CI for odds ratio	
				Lower bound	Upper bound				Lower bound	Upper bound
Intercept	-31.44					37.27				
Age	0.02	0.44	1.02	0.96	1.08	0.14	<0.01	1.15	1.037	1.29
pH	4.83	0.27	125.5	0.02	722930	-7.06	0.29	<0.01	<0.01	491.33
pCO_2	-0.02	0.09	0.97	0.94	1	-0.004	0.90	0.99	0.93	1.06
Urea	-0.08	0.46	0.92	0.73	1.15	0.07	0.57	1.08	0.82	1.41
Creatinine	-0.02	0.08	0.98	0.95	1	-0.01	0.29	0.98	0.95	1.01
Total bilirubin	0.01	0.50	1.01	0.96	1.06	0.01	0.65	1.01	0.94	1.09
NLR	-0.32	0.01	0.72	0.56	0.92	0.40	<0.01	1.49	1.15	1.92

the odds ratio for age and NLR is 1.158 and 1.493 for the model late discharge vs mortality, which means the odds of mortality relative to late discharge increases by 1.158 and 1.493 per unit change in age and NLR respectively.

To determine the cutoff value at which NLR best-predicted mortality in patients with AECOPD, a receiver operating characteristic (ROC) curve was constructed which showed NLR had maximum sensitivity of 87.5% and specificity of 90.9% when the cutoff value of NLR was taken to be 8.1 and the area under the curve (AUC) was 0.909.

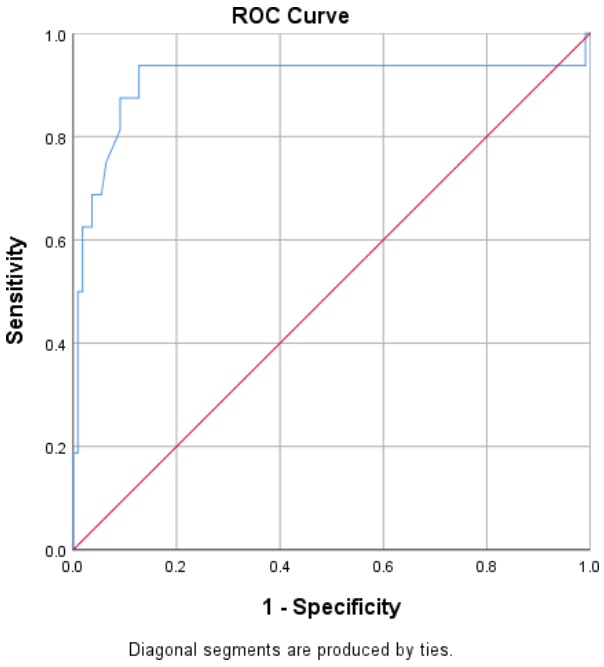

Figure 1. Receiver operating characteristics (ROC) curve for NLR predicting mortality in patients with AECOPD

The likelihood ratio test for the overall significance of all coefficients for the predictor as well as the significance of a single predictor in the model was performed which revealed the likelihood chi-square value to be 100.621 and final -2Log Likelihood value to be 139.5 with the p-value 0.04. This showed that at least one or likely most of the coefficients were not zero and indicated that all the predictors had a significant contribution to predicting the outcome. Here the chi-square test for the model was significant showing the acceptable fitting of the MNLR model. The classification accuracy rate was 79.4% which is greater than chance accuracy, thus the classification accuracy was satisfied. The overall goodness of fit of the estimated model was tested using deviance, and the non-significant deviance chi-square statistic with a p-value of 1 suggested that the estimated model fits well with the MNLR model. To measure the proportion of variation in the outcome that could be explained by the predictors in the model, pseudo-R-square was calculated. Here, Negelkerke R2 was found to be 0.646, which indicates that 65% variation in the outcome categories was explained by explanatory variables. Other pseudo-R-square values i.e., Cox and Snell, and McFadden had the value of 0.550 and 0.419 respectively.

DISCUSSION

The present study was conducted to explore the factors associated with the outcome of patients admitted with AECOPD. This study also contributes new data related to the mortality in COPD patients hospitalized with an acute exacerbation. Based on the results of estimates of the MNLR model, NLR has been found the most influential variable on the outcome of patients with AECOPD. NLR predicts mortality with a sensitivity of 87.5% and a specificity of 90.9% when the cutoff value of 8.[1]

was taken. The overall in-hospital mortality rate in patients with AECOPD was 12.7% whereas most patients had early discharge as the outcome.

The rate of in-hospital mortality for COPD patients hospitalized with acute exacerbation has been reported to be between 2.5% and 30%, depending on the methodology of data collection and the patient population.[7,8] The results of our study fall in this range and correspond with the in-hospital mortality rate of a study done among 1,016 adult patients with AECOPD which reported an in-hospital mortality rate of 11%.[9]

Knowledge about the prognosis of disease and factors that predict the poor outcome is important to help physicians to advise patients on the expected natural course of an illness. Several risk factors that predict death from AECOPD have been identified in prior studies. Many clinical and laboratory parameters are shown to have value in predicting the outcome of patients hospitalized with COPD.[10-13] Some of the studied parameters include clinical parameters like age, sex; comorbidities, laboratory values like arterial PCO_2 level, serum pH level, serum albumin level, serum urea, and creatinine, sodium, and potassium level arterial PCO_2 level, serum pH level, serum albumin level, serum urea level, serum creatinine level, serum sodium level, serum potassium level. A study done among 100 patient with AECOPD in a tertiary care center in Nepal found that FEV1/FVC impairment, decreased pH, increased pCO_2, current smoking status, and presence of biomass exposure are associated with prolonged hospitalization, ICU admission, and death.[14] Similarly a study done among 599 AECOPD patient in University hospital found that admission between Thursday and Saturday, heart failure, diabetes, stroke, high arterial PCO_2, and low serum albumin level were associated with a prolonged LOS.[15] Another prospective study among 437 AECOPD patient at the Hospital Clinic of Barcelona found that the presence of an mMRC ≥2 and acute respiratory acidosis at admission independently increased the risk of a prolonged hospital stay in patients with AECOPD.[16] However, the factors used in our study had no significance to predict the outcome in a patient admitted with AECOPD when entered into the MNLR model. NLR as a predictor of mortality is reported in previous studies too,[17-19] but to our knowledge, this study is the first one to report its usefulness to predict outcome as early discharge, late discharge, and mortality by using the MNLR model.

In COPD, there are basically functional and structural alterations primarily caused by long-term inhalation of harmful particles. Decrease in endogenous protective mechanism against oxidative stress via Nrf2, the altered immune response of the airway inflammatory cells, exaggerated cellular senescence of the lung structural cells, and cell death with expanded inflammation occur in patients with COPD.[20] Neutrophil to lymphocyte ratio is the ratio of absolute neutrophil count to absolute lymphocyte count. NLR is increased when there is an increase in the number of neutrophils and/or a decrease in the number of lymphocytes as a result the activated neutrophils could release inflammatory cytokines and proteolytic enzymes. Lymphocytes play an important role in the immune system, and lymphopenia is associated with a high risk of infection and mortality.[21] Thus, an increase in inflammatory response with a decrease in immune function may explain the poorer outcome in patients with AECOPD with high NLR. A retrospective study done among 303 AECOPD patient in University Hospital found that at a cut-off value of 6.15, the sensitivity and specificity of NLR in predicting in-hospital mortality were 81.08% and 69.17%, respectively, with an AUC of 0.803.18 Our study found a sensitivity and specificity higher than this study when the cutoff value for NLR was 8.1.

The strength of this study is the definition of the outcome as we classified the outcome into three groups and used the MNLR model to predict the factors that could determine the outcome. The limitations of this study are the small sample size and a small mortality group which possibly caused the study to be underpowered. Also, this was a single-center study and thus it cannot give a general idea of mortality in patients with AECOPD. We did not take into consideration the severity of COPD as per GOLD classification or the frequency of exacerbation. Many variables like co-morbidities, smoking status, presence of cor-pulmonale, mode of ventilation, and other laboratory parameters that may have influenced the outcome in the patients were not included in the study.

CONCLUSION

Neutrophil Lymphocyte ratio though a simple, cheap, and easy-to-use marker, can be used to predict the outcome (early discharge, late discharge, and mortality) of patients with AECOPD. It is also a promising marker in predicting mortality in patients with AECOPD with high sensitivity and specificity.

FINANCIAL SUPPORT

The author(s) did not receive any financial support for the research and/or publication of this article.

CONFLICT OF INTEREST

The author(s) declare that they do not have any conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Bousquet J, Kiley J, Bateman ED, et al. Prioritised research agenda for prevention and control of chronic respiratory diseases. Eur Respir J. 2010 Nov 1;36(5):995–1001.
2. Adhikari TB, Neupane D, Kallestrup P. Burden of COPD in Nepal. Int J Chron Obstruct Pulmon Dis. 2018 Feb 9;13:583–9.
3. Patil SP, Krishnan JA, Lechtzin N, et al. In-Hospital Mortality Following Acute Exacerbations of Chronic Obstructive Pulmonary Disease. Arch Intern Med. 2003 May 26;163(10):1180.
4. Celli BR, Cote CG, Marin JM, et al. The body- mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004 Mar 4;350(10):1005–12.
5. Puhan MA, Garcia-Aymerich J, Frey M, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet Lond Engl. 2009 Aug 29;374(9691):704– 11.
6. Adhikari TB, Acharya P, Högman M,et al. Prevalence of Chronic Obstructive Pulmonary Disease and its Associated Factors in Nepal: Findings from a Community-based Household Survey. Int J Chron Obstruct Pulmon Dis. 2020;15:2319-2331
7. Seneff MG, Wagner DP, Wagner RP, et al. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. Jama. 1995;274(23):1852–7.
8. Fuso L, Incalzi RA, Pistelli R, et al. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. Am J Med. 1995;98(3):272–7.
9. Connors Jr AF, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med. 1996;154(4):959–67.
10. de Torres JP, Cordoba-Lanus E, López-Aguilar C, et al. C-reactive protein levels and clinically important predictive outcomes in stable COPD patients. Eur Respir J. 2006 May;27(5):902–7.
11. Chakrabarti B, Angus RM, Agarwal S, et al. Hyperglycaemia as a predictor of outcome during non-invasive ventilation in decompensated COPD. Thorax. 2009 Oct;64(10):857–62.
12. Brat K, Plutinsky M, Hejduk K, et al. Respiratory parameters predict poor outcome in COPD patients, category GOLD 2017 B. Int J Chron Obstruct Pulmon Dis. 2018 Mar 26;13:1037–52.
13. Schünemann HJ, Dorn J, Grant BJ, et al. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest. 2000 Sep;118(3):656–64.
14. Sijapati M, Bhatta N, Khanal B, et al. Study of factors determining outcomes in the hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease (COPD). J Univers Coll Med Sci. 2014;2(2):28–34.
15. Wang Y, Stavem K, Dahl FA, et al. Factors associated with a prolonged length of stay after acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Int J Chron Obstruct Pulmon Dis. 2014 Jan 20;9:99–105.
16. Crisafulli E, Ielpo A, Barbeta E, et al. Clinical variables predicting the risk of a hospital stay for longer than 7 days in patients with severe acute exacerbations of chronic obstructive pulmonary disease: a prospective study. Respir Res. 2018;19(1):1–12.
17. Xiong W, Xu M, Zhao Y, et al. Can we predict the prognosis of COPD with a routine blood test? Int J Chron Obstruct Pulmon Dis. 2017;12:615.
18. Yao C, Liu X, Tang Z. Prognostic role of neutrophil–lymphocyte ratio and platelet– lymphocyte ratio for hospital mortality in patients with AECOPD. Int J Chron Obstruct Pulmon Dis. 2017;12:2285.
19. Duman D, Aksoy E, Agca MC, et al. The utility of inflammatory markers to predict readmissions and mortality in COPD cases with or without eosinophilia. Int J Chron Obstruct Pulmon Dis. 2015;10:2469.
20. Hikichi M, Mizumura K, Maruoka S, et al. Pathogenesis of chronic obstructive pulmonary disease (COPD) induced by cigarette smoke. J Thorac Dis. 2019 Oct;11(Suppl 17):S2129– 40.
21. Ye Z, Ai X, Liao Z, et al. The prognostic values of neutrophil to lymphocyte ratio for outcomes in chronic obstructive pulmonary disease. Medicine (Baltimore). 2019 Jul 12;98(28):e16371.