Original Article

DOI: 10.7860/JCDR/2018/35775.11832

Clinical Tools and Biochemical Markers to Assess Short-Term Mortality in Acute Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

Internal Medicine Section

GOVIND NARAYAN SRIVASTAVA[1], MANOJ MEENA[2], ANKIT PATEL[3], ASHOK SINGH CHARAN[4], MUKESH GOYAL[5], PIYUSH ARORA[6], RAMNIWAS MEENA[7]

ABSTRACT

Introduction: Acute exacerbation of COPD is one of the leading causes of death worldwide.

Aim: This study was aimed to study the role of clinical tools and biochemical markers which have significant impact on short-term mortality in COPD patients presenting with acute exacerbation.

Material and Methods: A total of 50 patients were studied. Patients of age >40 years having COPD exacerbation and presenting with two of the three cardinal features of exacerbation: increase in amount of cough, increase in purulence of cough, increase in baseline dyspnoea which were severe enough to necessitate a hospital admission, were evaluated after admission. A thorough history taking and clinical examination was performed. Along with this, all necessary laboratory parameters were studied. Study population was followed for 30 days. Data were analysed using Chi-square test and multivariate regression analysis using SPSS version 16.0.

Results: Out of 50 patients, 30% (15/50) did not survive despite treatment. Parameters such as, history of mechanical ventilation in past one year, low GCS (Glasgow Coma Scale), raised JVP (Juglar Venous Pressure), low pH and raised IL-6 levels were significantly associated with mortality in multivariate analysis (p-value <0.05).

Conclusion: Severity of disease as well as severity of present exacerbation was related with short-term mortality. Interleukin-6 is an independent predictor of mortality. Parameters like past history of mechanical ventilation and raised JVP point towards the need of overall better management of COPD patients not only during exacerbations.

Keywords: 30- day mortality, C- Reactive Protein, Interleukin- 6

INTRODUCTION

COPD is a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation, that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. It is currently fourth leading cause of death in the world [1] but is projected to be third leading cause by 2020 [2]. Estimates suggest there are 30 million COPD patients in India at present. India contributes a significant and growing percentage of COPD mortality which is estimated to be amongst the highest in the world; i.e., more than 64.7 estimated age standardized death rate per 100,000 amongst both sexes [3].

In long-term follow-up, mortality is likely to be more influenced by the general characteristics of the patient's COPD than the severity of the acute exacerbation of COPD that lead to hospital admission. Mortality occurring in less than 90 days after presentation to a hospital (short-term mortality), with an acute exacerbation of COPD, usually includes in-hospital mortality, and factors related to the severity of the exacerbation are likely to play more important role in the short-term rather than in the mid or long-term follow-up [4]. A robust clinical prediction tool could help reduce morbidity and mortality. No comprehensive data is available in this subject in context of Indian population. Moreover, many studies in west have focused on 90 days mortality [5,6]. Therefore, studies that assess prognostic indices in shorter duration of exacerbation are warranted in this subset of population.

The primary objective of this study was to identify easy to use clinical tools that can help as predictor of short-term mortality after acute exacerbation of COPD. The secondary objectives were, to know the relation of biochemical markers such as Interleukin-6 and C-reactive protein with short term mortality.

MATERIALS AND METHODS

This prospective observational study was conducted in Sir Sunderlal Hospital, Banaras Hindu University, from June 2016 to April 2017 after approval of the university ethical committee in May 2016.

Patients were recruited prospectively from Chest ward, Department of TB and Respiratory diseases, Emergency department and Acute care unit, Department of General Medicine. Inclusion criteria were age more than 40 years and COPD patient presenting with an increase in at least two of the following three symptoms [7]: dyspnoea, cough and sputum purulence severe enough to warrant hospital admission. Exclusion Criteria included patients that presented with exacerbation of other chronic respiratory diseases like Bronchial asthma, Interstitial lung disease and bronchiectasis, co-morbidity expected to limit survival to less than 12 months (malignancy) and refusal to give consent by patient or their kin.

Total of 57 patients were screened to undergo the study. However, two patients withdrew consent for the study. One patient was diagnosed with squamous cell carcinoma and two patients were diagnosed as Asthma COPD overlap, hence were excluded. Two patients were lost to follow-up. Finally data of 50 patients was analysed in this study.

A thorough history was taken and patients were evaluated for various clinical parameters at the time of presentation. During hospital admission, all the patients were treated with standard protocol including oxygen support, oral or intravenous antibiotics and oral

or intravenous steroid as recommended by treating physician. Non-invasive Ventilation and Invasive ventilation was done whenever mandated and possible. Patients were followed for 30 days through daily rounds if admitted and through telephone if discharged. They were later classified into two groups Survived or Non-survived depending on 30 day mortality.

STATISTICAL ANALYSIS

Univariate analysis of each variable was performed using Chi-square method for categorical data and coefficient of correlation for continuous data. Variables that were significantly associated ($p<0.05$) were subjected to multivariate regression analysis. The data was analysed accordingly using SPSS version 16.0.

RESULTS

Out of 50 study subjects, 30% (15/50) did not survive. Mean age of entire cohort was 65.52±11.00 years. 36% patients were >70 years of age. A descriptive data at presentation of entire cohort is given in [Table/Fig-1]. Mean Cumulative smoking years for non-survivor group were 41.87±12.677 years with minimum being 10 years and maximum 58 years. In overall cohort one patient did not report any form of smoke exposure and 5 patients having biomass exposure.

Among the participants, 16% did not report any previous use of bronchodilators. Most of the patients belonged to COPD Group D (66%), followed by Group C (28%) while none belonged to Group A. Secondary infection was present in 85.7% (30/35) cases in survivor group and in 80% (12/15) cases in non- survivor group, with fever and increased purulence of sputum as predominant initial symptoms. Laboratory parameters are shown in [Table/Fig-2].

Mean total duration of illness in non-survivor group was 8.00±5.606 years with 24 years being maximum duration and 3 years being minimum duration. [Table/Fig-3] shows results of univariate analysis of all the variables considered in this study with p-value <0.05 considered significant.

Parameters such as number of pack years, history of mechanical ventilation in past one year, low GCS, respiratory rate, use of accessory muscle, pedal oedema, raised JVP and cyanosis were found significant in history and examination. Among lab parameters raised serum creatinine, serum potassium, pCO_2, serum bicarbonate and serum CRP level, serum IL-6 level along with low pH, oxygen saturation, body mass index and FEV1% predicted were significant. Multivariate logistic regression was done for all these significant variables. [Table/Fig-4] shows results of regression analysis.

Patient Characteristic	Survived (n=35)	Died (n=15)	Total Cohort (n=50)
Age* (years)	65.34±11.064	65.93±11.222	65.52±11.000
Sex (M/F %)	(54.28/45.71)	(53.3/46.7)	(54/46)
Total duration of illness* (years)	6.14±4.460	8.00±5.606	6.70±4.850
Pack year* (years)	25.21±8.675	41.87±12.677	30.31±12.602
History of MV**	5.7%	86.7%	30%
Glasgow Coma Scale*	14.91±0.507	13.73±0.884	14.56±0.837
Systolic Blood Pressure* (mm Hg)	128.63±13.423	122.53±15.519	126.80±14.205
Diastolic Blood Pressure* (mm Hg)	77.71±7.763	75.07±9.647	76.92±8.361
Respiratory Rate* (breaths/ minute)	29.74±3.381	35.00±2.420	31.32±3.941
Use of accessory muscle**	45.7%	100%	62%
Clubbing**	8.6%	20%	12%
Jugular Venous Pressure**	20%	86.7%	40%
Pedal oedema**	31.4%	93.3%	50%
Cyanosis**	5.7%	66.7%	24%

[Table/Fig-1]: Descriptive data of study population at admission.
*= Mean± SD, **= (Present/ N) %, MV=Mechanical ventilation

Lab Investigation*	Survived (n=35)	Died (n=15)	Total Cohort (n=50)
Haemoglobin (mg/dl)	11.33±2.16	12.97±3.75	12.54±2.85
Total Leukocyte Count (cells/cubic mm)	12440±5124.5	12940±4386.0	12540±4876.5
Creatinine (mg/dl)	1.05±0.44	1.44±0.71	1.16±0.56
Urea (mg/dl)	56.03±37.48	77.53±39.84	62.48±39.08
Sodium (mEq/L)	134.03±7.06	129.27±10.70	132.60±8.50
Potassium (mEq/L)	4.26±0.89	5.18±0.99	4.54±1.01
RBC (mg/dl)	101.2±38.9	110.3±45.8	104.0±40.8
pH	7.35±0.08	7.19±0.08	7.30±0.11
SpO_2 %	93.05±7.58	82.58±11.61	89.91±10.09
pO_2 (mm Hg)	133.15±51.22	113.88±49.91	127.37±51.11
pCO_2 (mm Hg)	59.25±19.77	84.99±12.99	66.97±21.48
HCO_3 (mEq/L)	30.13±6.08	35.56±5.65	31.76±6.41
Anion Gap (mEq/L)	8.56±4.11	10.42±5.02	9.12±4.43
FEV1% predicted	62.40±11.57	27.00±5.60	53.93±18.47
Body Mass Index (Kg/m^2)	25.58±2.60	22.78±2.00	24.74±2.74
C-Reactive Protein (mg/dl)	0.689±0.264	1.686±0.470	0.988±0.570
Interleukin-6 (pg/ml)	247.91±108.94	431.53±97.25	294.68±88.62

[Table/Fig-2]: Laboratory parameters at admission.
*= Mean±SD

Parameters	OR	95% CI	p-value
Age	0.17	0.11-0.43	0.864
Total Duration of illness	1.24	0.87-1.57	0.218
Pack year	5.35	2.65-18.86	<0.001
History of MV	1.35	0.57-4.87	<0.001
GCS	5.97	3.40-11.78	<0.001
Systolic Blood Pressure	1.40	1.10-3.23	0.167
Diastolic Blood Pressure	1.02	0.22-7.83	0.310
Respiratory Rate	5.44	1.89-22.14	<0.001
Use of accessory muscle	1.34	1.12-3.54	<0.001
Clubbing	2.46	1.55-4.49	0.432
Pedal oedema	3.70	2.14-5.92	0.003
JVP	3.97	1.83-6.28	<0.001
Cyanosis	1.78	0.88-3.42	0.021
Haemoglobin	4.72	1.97-11.36	0.523
TLC	0.35	0.12-2.53	0.724
Platelet	4.05	3.77-38.20	0.125
Creatinine	2.33	1.17-9.56	0.024
Urea	1.82	1.38-7.62	0.074
Sodium	1.86	1.25-5.37	0.069
Potassium	3.23	1.98-21.77	0.002
RBS	0.71	0.29-1.99	0.479
pH	6.37	4.67-36.76	<0.001
SpO_2 %	3.79	1.56-7.49	<0.001
pO_2	1.22	1.20-15.78	0.225
pCO_2	4.61	3.12-16.73	<0.001
HCO_3	2.95	1.07-5.75	0.005
Anion Gap	1.36	1.01-13.43	0.177
FEV1 % predicted	9.73	2.46-78.45	<0.001
BMI	3.71	2.81-5.70	0.001
CRP	9.55	6.78-43.67	<0.001
IL-6	2.23	1.76-3.52	<0.001

[Table/Fig-3]: Univariate analysis for significant association.

Parameters	OR	95% CI	p-value
Pack year	3.87	0.78-15.35	0.435
History of MV	6.78	3.54-29.66	0.007
GCS	1.59	1.24-3.50	0.002
Respiratory rate	1.94	1.47-4.26	0.769
Use of accessory muscle	9.46	2.89-48.34	0.09
Raised JVP	2.32	2.18-3.90	<0.001
Pedal oedema	0.68	0.24-7.89	0.09
Cyanosis	6.44	2.38-36.46	0.528
Creatinine	0.37	0.13-2.53	0.193
Potassium	5.73	4.18-17.37	0.264
pH	1.20	0.83-1.98	<0.001
SpO_2	1.67	1.26-2.88	0.732
PCO_2	4.49	3.88-6.42	0.623
Bicarbonate	0.77	0.42-1.56	0.272
FEV1 % predicted	10.23	2.64-68.35	0.069
BMI	2.49	1.34-9.43	0.168
CRP	1.89	1.12-4.49	0.337
IL-6	0.59	0.23-3.38	0.006

[Table/Fig-4]: Multivariate analysis.

History of mechanical ventilation in past one year, low GCS, raised JVP, low pH and raised IL-6 levels were significant in multivariate analysis (p-value <0.05).

DISCUSSION

In our study, age was not a predictive factor for short-term mortality. This stands in contrast with findings of a 2003 study [8]. They however studied 1 year mortality rate following exacerbation. Some retrospective studies [9,10] have also shown age as a predictive factor for mortality. However, later few studies [11,12] had findings similar to the present study. Mean age in this study was 65.52±11.00 years and similar age has been reported by another Indian study [13]. Cumulative smoking history (pack year) has been established as predictor of mortality in stable COPD by previous studies. It was found to be significant in acute exacerbation in our study on univariate analysis and supported by recent study in India [14], they looked at mortality following exacerbation, for 18 months. However on multivariate analysis, we did not find it to be affecting mortality in acute exacerbation.

History of mechanical ventilation in past one year was present in 86% of patients in non-survivor group whereas only 5.7% of patients in survivor group were put on assisted ventilation. This represents progressive severity of disease. This was also found to be an independent predictor of mortality in our study. Another study for in-hospital mortality supports this finding [15]. Worsening of clinical signs that represent respiratory distress (increased respiratory rate, use of accessory muscle, cyanosis) and cor-pulmonale (pedal oedema, raised jugular venous pressure) were found to be significant on univariate analysis. Raised JVP was found to be independent predictor of mortality. This is supported by a 2008 study [16], however they looked at patients presenting only to Emergency Department and those requiring immediate ventilation were excluded. Low GCS was an independent predictor of mortality. Similar findings were reported by other studies [16,17]. These results do suggest that worsening symptoms if overlooked, results in increased short term mortality and hence point towards need for more approachable treatment centers and patient awareness methods, so that early escalation of care if and when required can be easily administered.

Serum creatinine and potassium were not independent predictors of mortality. However, creatinine, sodium, potassium and total leucocyte count are a part of APACHE II score which has shown promise in predicting mortality in COPD patients admitted in ICU [11,15]. In acute exacerbation patient often presents with altered blood gases as a result of poor ventilation. In this study, changes in ABG (pH, arterial oxygen saturation pCO_2, bicarbonate ion) were significantly associated with mortality. On multivariate analysis we found pH was the only independent predictor of short-term mortality. Acidaemia has been shown to be related with short-term mortality by other studies [9,17,18].

FEV1 has long been used in COPD as the principal variable determining the presence of disease, its severity and response to different modalities of treatment. In Intermittent Positive Pressure Breathing (IPPB) trial, FEV1 was most accurate predictor of mortality in COPD patients who were followed for 3 years [19]. In our study FEV1 was not an independent predictor of mortality, while FEV1 was not available for 4 individuals in non-survived group. Use of inhaled bronchodilators in form of LABA/LAMA or LABA/ICS combination was not significant in predicting mortality. What we found alarming was approximately 16% of the patients had never used inhalers partly due to never seeking appropriate medical attention due to socio-economic constraints or due to sheer absence of health literacy among general populace.

C-reactive protein is a marker of inflammation and correlated with degree of pulmonary inflammation in COPD. A study in 2007 [20] showed that CRP is a strong long-term predictor of COPD outcome. In our study, CRP was significantly raised in univariate analysis in non-survivor group, representing overall inflammatory process. Another study in same year did not find CRP to be a predictor of mortality over 6 month's period [21]. However, CRP levels were raised in exacerbation. Interleukin-6 plays a central role in host defence due to its wide range of immune and haemotopoietic activities and ability to induce the acute phase response. In this study, Interleukin-6 levels were raised in non-survivor group and were significant on multivariate analysis. Similar results were obtained by recent studies [22,23]. Both the studies concluded that Interleukin-6 is a better prognostic marker.

LIMITATION

Some of the limitations of this study are, it was a single centre study with small cohort size. We did not look at associated co-morbidities and their effect on short term mortality. A few studies [24,25] have found co-morbidities as significant predictor of 30 day mortality. Similarly use of oral glucocorticoid was not a parameter in our study but has been found significant in predicting one year mortality after exacerbation in a 2003 study [8]. Our study had higher in-hospital mortality than other studies [15], which reported 24.5 % in-hospital mortality probably due to high burden of disease and very few resources to manage respiratory emergencies. Also, we did not exclude the patients that were comatose or required immediate Non-Invasive or Invasive ventilatory support.

CONCLUSION

We were able to identify factors that predicted short-term mortality in acute exacerbation of COPD. Severity of disease as well as severity of present exacerbation was related with short-term mortality. This study provides clinical parameters that can be easily used in emergency ward to decide early escalation of care and informing patients and next of kin about probable short-term risk. Interleukin-6 in itself is an independent predictor of mortality. We would also like to point out that parameters like past history of mechanical ventilation and raised JVP point towards the need of overall better management of COPD patients, not only during exacerbations. There is a need for health education as well as better infrastructure, so that this disease and its exacerbation could be managed effectively.

REFERENCES

[1] Lazano R, Naghvi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for global burden of disease study 2010. Lancet. 2012;380(9859):2095-128.

[2] Mathers CD, Loncar D. Projection of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2007;3(11):e442

[3] Salvi S, Agarwal A. India needs a national COPD prevention and control programme. J Assoc Physician India. 2012;60 supple:5-7.

[4] Almagro P, Soriano JB, Cabrera FJ, Boixeda R, Alonso-Ortiz MB, Barreiro B, et al. Short- and Medium-term Prognosis in Patients Hospitalized for COPD Exacerbation. Chest. 2014;145(5):972-80.

[5] Mortensen EM, Copeland LA, Pugh MJ, Restrepo MI, deMolina RM, Nakashima B, et al. Impact of statins and ACE inhibitors on mortality after COPD exacerbations. Respir Res. 2009;10:45.

[6] Connolly MJ, Lowe D, Anstey K, Hosker HS, Pearson MG, Roberts CM. British Thoracic Society and the Royal College of Physicians Clinical Effectiveness Evaluation Unit (CEEu). Admissions to hospital with exacerbations of chronic obstructive pulmonary disease: effect of age related factors and service organization. *Thorax.* 2006;61:843–48.

[7] Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet. 2007;370(9589):786-96.

[8] Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality related factors after hospitalization for acute exacerbation of COPD. Chest. 2003;124:459–67.

[9] Warren PM, Flenley DC, Millar JS, Avery A. Respiratory failure revisited: acute exacerbations of chronic bronchitis between 1961–68 and 1970–76. Lancet. 1980;1:467–70.

[10] Fuso L, Antonelli Incalzi R, Pistelli R, Muzzolon R, Valente S, Pagliari G, et al. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. Am J Med. 1995;98:272–77.

[11] Nevins ML, Epstein SK. Predictors of outcome for patients with COPD requiring invasive mechanical ventilation. Chest. 2001;119:1840–49.

[12] Breen D, Churches T, Hawker F, Torzillo PJ. Acute respiratory failure secondary to chronic obstructive pulmonary disease treated in the intensive care unit: a long term follow up study. *Thorax.* 2002;57:29-33.

[13] Chandra D, Kalplatha K, Guntupalli, Gulleria R. Hypotension is a predictor of mortality in acute exacerbation of COPD. Indian J Chest Dis Allied Sci. 2007;49:13-18.

[14] Kamdar DJ, Patel DK. A prospective study of predictors of mortality in acute exacerbation of COPD: an Indian perspective Int J Adv Med. 2017;4(2):362-66.

[15] Ai Ping C, Lee KH, Lim TK. In-hospital and 5-year mortality of patients treated in the ICU for acute exacerbation of COPD: a retrospective study. Chest. 2005;128:518–24.

[16] Roche N, Zureik M, Soussan D, Neukirch F, Perrotin D. Urgence BPCO (COPD Emergency) Scientific Committee. Predictors of outcomes in COPD exacerbation cases presenting to the emergency department. Eur Respir J. 2008;32:953–61.

[17] Onadeko BO, Khadadah M, Abdella N, Mukhtar M, Mourou M, Qurtom M, et al. Prognostic factors in the management of exacerbation of chronic obstructive pulmonary disease in Kuwait. Med Princ Pract. 2005;14:35–40.

[18] Roberts CM, Lowe D, Bucknall CE, Ryland I, Kelly Y, earson MG. Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. Thorax. 2002;57:137–41.

[19] Anthonisen NR, Wright EC, Hodgkins JE. Prognosis in chronic obstructive pulmonary disease. Am Rev Respir Dis. 1986;133:14–20.

[20] Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;175:250–55.

[21] Stolz D, Christ-Crain M, Morgenthaler NG, Leuppi J, Miedinger D, Bingisser R, et al. Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. Chest. 2007;131:1058–67.

[22] Shafiek H, Abd-elwahab N, Baddour M, Degady A, El-hoffy M, et al. (2016) Outcome predictors of severe acute exacerbation of chronic obstructive pulmonary disease: role of inflammatory biomarkers. Int J Respir Pulm Med 3:047.

[23] Helmy TA, Baess AI, Monsif DAA, Elnasharty AAA. Role of CRP and IL-6 in predicting the prognosis of ICU admitted patients with acute exacerbation of COPD. Egypt J Chest Dis Tuberc. 2014;63(4):829-35.

[24] Faustini A, Marino C, D'Ippoliti D, Forastiere F, Belleudi V, Perucci CA. The impact on risk-factor analysis of different mortality outcomes in COPD patients. Eur Respir J. 2008;32:629-36.

[25] Santibanez M, Garrastazu R, Ruiz-Nuñez M, Helguera JM, Arenal S, Bonnardeux C, et al. Predictors of Hospitalised exacerbations and mortality in COPD. PLoS One. 2016;11(6):e0158727.

PARTICULARS OF CONTRIBUTORS:

1. Professor, Department of Respiratory Medicine, Institute Of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
2. Assistant Professor, Department of Respiratory Medicine, Jawahar Lal Nehru Medical College, Ajmer, Rajasthan, India.
3. Junior Resident, Department of Respiratory Medicine, Institute Of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
4. Junior Resident, Department of Respiratory Medicine, Jawahar Lal Nehru Medical College, Ajmer, Rajasthan, India.
5. Assistant Professor, Department of Respiratory Medicine, Jawahar Lal Nehru Medical College, Ajmer, Rajasthan, India.
6. Assistant Professor, Department of Respiratory Medicine, Jawahar Lal Nehru Medical College, Ajmer, Rajasthan, India.
7. Assistant Professor, Department of General Surgery, Institute Of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr Manoj Meena,
1/H/383, Sector 1, Indira Gandhi Nagar, Jagatpura, Ajmer, Rajasthan, India.
E-mail: manojchest@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jan 29, 2018**
Date of Peer Review: **Mar 27, 2017**
Date of Acceptance: **Apr 14, 2018**
Date of Publishing: **Jul 01, 2018**