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Research Article

STUDY TO KNOW PREDICTORS OF MORTALITY IN PATIENTS OF ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract:

Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) result in increased morbidity, mortality and tremendous socioeconomic burden. Predicting in hospital mortality may aid prognostication, planning for the site of care, i.e., ward versus intensive care units, and better individualization of treatment.

Aim of Study: This study aims in predicting in hospital mortality in patients of AECOPD based on the parameters measured at the time of admission.

Methods: Known COPD patients in acute exacerbations admitted in a tertiary care hospital were interrogated for clinical history and examination. All relevant laboratory tests including arterial blood gas analysis, complete blood count, liver and renal function tests, and random blood sugar were done. Based on outcome, patients were grouped into survivors and no survivors. Parameters recorded were then subjected for univariate analysis to get their statistical significance. All significant variables on univariate analysis were then analysed further with multivariate analysis.

Results: Out of the total 140 patients included in the study, 24 (17%) died during their hospital stay. Of the various acute-phase parameters recorded at the time of the admission, only five qualified to be predictors of in hospital mortality based on univariate and multivariate analyses. These were partial pressure of carbon dioxide in arterial blood (PaCO_2) (odds ratio [OR], 95% confidence interval [CI] = 1.067, 0.993–1.146), pH (OR, 95% CI = 0.001, 0.001–0.584), serum glutamic pyruvate transaminase (SGPT) (OR, 95% CI = 1.032, 1.006–1.059), sodium (OR, 95% CI = 0.779, 0.689–0.881), and random blood sugar (OR, 95% CI = 1.018, 1.007–1.029). With these five factors combined, area under receiver operating characteristic (ROC) curve was 0.9684, sensitivity 79.18%, specificity 96.55%, positive predictive value 82.61%, negative predictive value 95.73%, and correctly classify acute exacerbation in 93.57%. Good survival can be expected if these parameters are within normal limits.

Conclusion: pH, PaCO_2 , SGPT, serum sodium, and random blood sugar at the time of admission are independent predictors of mortality in patients of AECOPD. These can be helpful in developing a prediction tool of in hospital mortality in such patients.

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INTRODUCTION:

Chronic Obstructive Pulmonary Disease (COPD) is a chronic disease involving the airways, lung parenchyma, and pulmonary vasculature and also has considerable systemic manifestations. The disease is progressive with possible gene–environment interaction and hence can be prevented by avoiding exposure to the noxious particles. The most common studied attributing risk factor is cigarette smoking in any form. Exacerbations and comorbidities play their role in contributing to overall severity. [1]

The disease is one of the most important causes of death worldwide. The Global Burden of Disease Study projected it to become the third leading cause of death globally by the year 2020, while a newer projection estimated it to be the fourth one by 2030.[2] An exacerbation is an acute event in patients of COPD with increased baseline respiratory symptoms requiring additional treatment other than the usual ongoing treatment.[1] These events have negative effects on the patient's quality of life, accelerate the decline in lung function, are associated with significant mortality, and pose a great socioeconomic burden.[3-5]

In hospitalized patients, the mortality is approximately 10% during the hospital stay. It may go up to 40% during the 1st year of discharge from the hospital in mechanically ventilated patients. The all-cause mortality during the 3 years of hospitalization is as high as 49%.[5,6] Therefore, prompt management of exacerbations, early detection, and prevention are crucial in the overall management of COPD patients.

In developing countries like Pakistan, the direct attributable medical cost seems less appealing figure wise, but there is tremendous impact of COPD on both workplace and home productivity. The disease may force two individuals to leave the workplace for each case, i.e., the affected individual and a healthy family member to take care of the disability of the former at home.

Identifying the patients depending on the factors predicting mortality is of utmost importance to reduce the poor outcome of exacerbation. There are many indices which can predict mortality in stable COPD patients such as BODE index and ADO index, but only few scoring systems are available for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) such as DECAF score (the dyspnea, eosinopenia, consolidation, acidaemia, and atrial fibrillation) and BAP-65 (blood urea nitrogen, altered mental status, pulse >109 beats/min, and age >65 years). [7, 8]

Hence, the present study is intended to identify the possible predictors or parameters at the time of admission which can help predict the mortality in AECOPD.

METHODS:

This prospective, observational study was conducted in Department of Respiratory Medicine, Jinnah Hospital Lahore. A total of 140 eligible patients were recruited.

All patients who had been admitted for an AECOPD during April 2010 to June 2011 were included. An exacerbation was defined by the presence of an increase in at least one of the following three symptoms: dyspnoea, cough, sputum amount and/or purulence severe enough to warrant hospital admission. All patients were documented cases of COPD previously confirmed with pulmonary function test (forced expiratory volume in one second/forced vital capacity <0.7 and irreversible airway obstruction) and were receiving a combination of various bronchodilators. During hospital admission, patients were treated with a standard protocol consisting of intravenous administration of corticosteroids (0.5 mg/kg), theophylline, nebulized salbutamol, and ipratropium bromide. Oxygen therapy was titrated according to the results of blood gas analyses and pulse oximetry.

Patients who presented with exacerbation of COPD without any documentary evidence of COPD before present event, known COPD mimics such as bronchial asthma, bronchiectasis, congestive heart failure, those with comorbidities such as known diabetes, renal disease, hepatic disease, neurological disease, coronary artery disease, patients with multiple organ failure, hemodynamic instability, and those patients who were not giving consent were excluded.

All eligible patients underwent detailed history, clinical examination, and relevant investigations such as complete blood count, renal and liver function tests, random blood sugar, haemoglobin A1c, X-ray chest poster anterior view, electrocardiogram, echocardiography, and arterial blood gas (ABG) analysis.

All patients were managed primarily according to Global Initiative for Chronic Obstructive Lung Disease guideline protocol with other required conservative management, for example, raised blood sugar was managed with insulin with target value of 180 mg/dl. Based on outcome after hospital stay, patients were divided into two groups:

Group 1 (Non survived or Expired) – This group includes those patients who died during hospital stay.

Group 2 (Survived) – This group includes all those patients who survived during hospital stay and discharged to home.

All demographic, clinical, and laboratory parameters were compared between these two groups.

Statistical methods

Discrete data were analyzed by cross-tables using descriptive method. Continuous data were analyzed by univariate analysis. Univariate and multivariate analysis to derive hazard ratio was done using Cox proportional hazard model. $P < 0.05$ was considered as statistically significant association.

RESULTS:

A total of 140 patients were enrolled, out of which 116 survived and 24 patients died during the hospital stay. Hence, the overall inhospital mortality rate for AECOPD was 17% [Figure 1]. Actual mortality may have been high if comorbidities such as ischemic heart disease and congestive heart failure were also included.

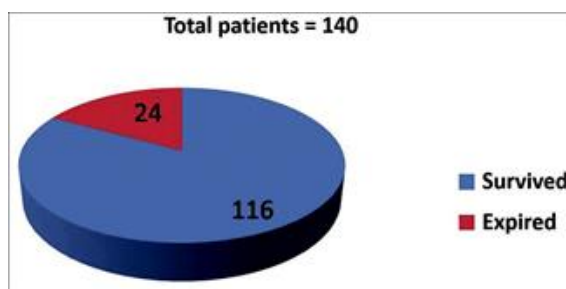


Figure 1: Survival rate in patients with chronic obstructive pulmonary disease admitted with acute exacerbation

The mean (\pm standard deviation) age of the patients who survived was significantly lower ($P = 0.046$) at 61.24 (± 8.228) years as against those who died during hospital stay 65.62 (± 5.830) years [Figure 2]. There were 30 females and 110 male participants in this study [Figure 3]. Males outnumbered females by almost four times [Figure3]. It may be partly because of the fact that smoking is more prevalent in males and women tend to present later in the course of the disease [Table 1].

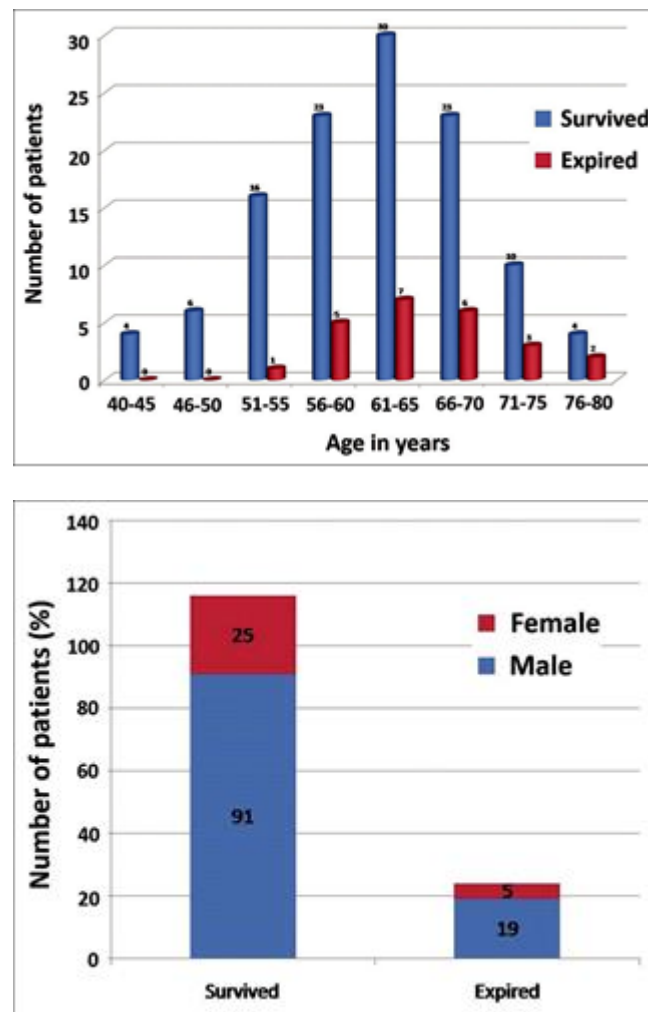
Ninety-two patients (65.7%) in the study were smokers, mostly male, indicating that smoking is an important risk factor for COPD. History of previous hospitalization due to an acute episode was more in the non-surviving group (75%) as compared to surviving (59%) depicting an elevated mortality rate (odds ratio 2) [Table 1].

Univariate analysis

Important laboratory parameters at the time of admission were analyzed by univariate analysis [Table 2].

In the ABG, the partial pressure of carbon dioxide in arterial blood (PaCO_2) was significantly high (72.08 mmHg vs. 53.23 mmHg, $P < 0.05$) and pH significantly low (7.303 vs. 7.397, $P < 0.05$) in the no surviving group while other factors such as PaO_2 and HCO_3^- were statistically insignificant. These findings suggest a poor survival if exacerbation is accompanied by a type 2 respiratory failure at the time of admission.

	<i>n</i>	Survived	Expired
Total patients (%)	140	116 (83)	24 (17)
Age (years), mean \pm SD		61.24 \pm 8.23	65.62 \pm 5.83
Sex			
Male	110	91	19
Female	30	25	5
Smoking habits			
Smoker	92	73	19
Non-smoker	48	43	5
Number of pack years (mean \pm SD)		18.21 \pm 8.44	23.83 \pm 4.22
Prior hospital admission, <i>n</i> (%)		68 (59)	18 (75)
Total duration of years (mean \pm SD)		13.51 \pm 5.52	16.62 \pm 5.9



In COPD patients, prerenal type of renal failure is common, and COPD patients often have high urea and creatinine level than the general population. There were no significant differences ($P > 0.05$) in renal parameters between the two groups in our sample.

Electrolyte imbalance is common in COPD patients and tends to get exaggerated in acute exacerbation due to fluid retention. In our study, no surviving group had more severe hyponatremia as compared to the survived group (sodium 124.63 vs. 135.95 mEq/dl, $P < 0.05$). Other electrolytes such as serum potassium and calcium were not significantly different in both the groups.

Although polycythaemia is known to occur in COPD patients due to chronic hypoxia, in developing countries like Pakistan, anaemia is more common due to poor nutrition. Patients in the survived group had a mean haemoglobin 12.96 g% whereas it was higher in patients of expired group with mean haemoglobin of 13.29 g%. The difference was not statistically significant ($P = 0.716$).

Infection is an important cause of exacerbation in COPD patients. The total leukocyte count tends to be higher in both the groups. The increase was more in no surviving group (15,300 cells/mm³ vs. 13,054 cells/mm³), but the difference was not significant statistically.

Raised blood sugar during acute phase may have a deleterious effect on the outcome. The blood sugar at the time of admission was significantly higher in the non-surviving group (231.63 vs. 164.62 mg%, $P = 0.035$).

Liver function test was found to be deranged significantly in non-surviving group with raised liver transaminases serum glutamic oxaloacetate transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT) and lower serum albumin level. Albumin level may reflect the ongoing poor nutritional status of the patient while both the transaminases and the albumin derangements may show the severity of acute phase and possibly impending multi-organ dysfunction.

Table 2: Univariate and multivariate analysis of the various acute-phase variables recorded at the time of admission

Variable	Univariate analysis		P	Multivariate analysis	
	Mean±SD			OR (95% CI)	OR (95% CI)
	Survived (n=116)	Nonsurvived (n=24)			
Age (years)	61.28±8.267	63.50±0.48	0.219	(0.979-1.097)	
PO ₂ (mmHg)	57.52±16.74	55.88±16.5	0.659	1.036)	
PCO ₂ (mmHg)	53.23±15.25	72.09±33.1	0.000	(0.968-1.021)	
pH	7.39±0.07	7.30±0.1	0.000	(1.021-1.067)	
HCO ₃ ⁻ (mmol/L)	32.16±8.9	34.7±12.7	0.238	1.043)	1.067 (0.993±1.146)
SO ₂ (%)	85.99±9.8	78.5±15.6	0.005	(0.000-0.001)	
Total protein (mg) (%)	5.93±0.63	6.4±0.89	0.005	0.000)	0.000 (0.000±0.584)
Albumin (mg) (%)	3.42±0.33	3.18±0.34	0.002	1.028 (0.98-1.075)	
SGOT (IU/L)	46.12±36.9	89.17±78.2	0.001	0.95 (0.92-0.985)	
SGPT (IU/L)	39.28±28.37	64.46±49.2	0.004	(1.314-4.699)	
Urea (mg) (%)	62.7±20.17	67.7±22.7	0.519	2.485)	
Creatinine (mg) (%)	1.46±0.63	1.42±0.44	0.782	(0.021-0.436)	
Sodium (mmol/L)	135.95±6.1	124.63±10.8	0.000	0.095)	
Potassium (mmol/L)	4.42±1.02	4.19±0.88	0.309	(1.006-1.025)	
Hemoglobin (g) (%)	12.97±2.6	13.29±2.52	0.716	1.015)	
Total leucocyte count (cells/cumm)	13054±3990	15300±9715	0.074	(1.005-1.028)	
Random blood sugar (mg) (%)	164.62±20.51	231.63±64	0.011	1.017)	1.032 (1.006±1.059)
Total bilirubin (mg) (%)	1.23±0.96	1.27±1.13	0.860	(0.992-1.016)	
Direct bilirubin (mg) (%)	0.62±0.68	0.50±0.27	0.439	1.004)	

$P < 0.05$ is considered statistically significant. SD: Standard deviation, CI: Confidence interval, OR: Odds ratio, SGOT: Serum glutamic oxaloacetate transaminase, SGPT: Serum glutamic pyruvate transaminase
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Multivariate analysis

All parameters which were significant on univariate analysis (PaCO₂, pH, albumin, SGOT, SGPT, sodium, and random blood sugar) were analysed by multivariate analysis [Table 2]. The model receiver

operating characteristic comprising of these five parameters was correctly classifying 93.57%, and area under curve above median level was 96.8%

[Figure 4]. The five factors when combined have a sensitivity of 79.18%, specificity 96.55%, positive predictive value 82.61%, and negative predictive value of 95.73%. This means that if these factors are normal at the time of admission, one can expect a good survival.

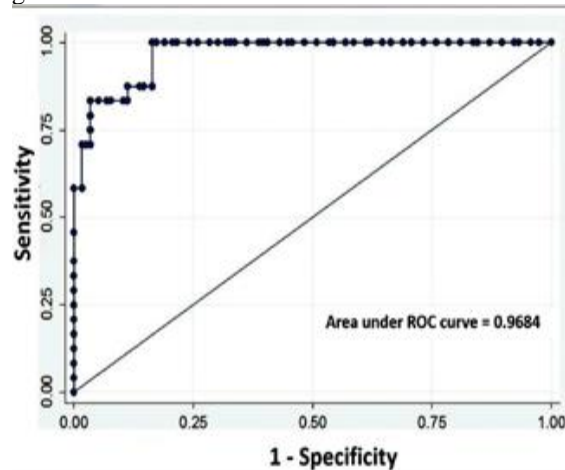


Figure 4: Model receiver operating characteristic curve comprising of the five parameters which were significant on multivariate analysis. It correctly classified the acute exacerbation in 93.57% with area under curve above median level 96.8%, sensitivity of 79.18%, specificity 96.55%, positive predictive value 82.61%, and negative predictive value 95.73%

DISCUSSION:

A total of 140 patients of COPD (diagnosed based on old spirometry reports) who presented in hospital with acute exacerbation were enrolled in this study; 24 patients (17%) expired during hospital stay and 116 patients were discharged at the end of hospital stay. In all in hospital cases of mortality, progressive respiratory failure was the primary cause of death. This observation was partially supported by study done by Connors *et al.* who reported an in-hospital mortality of 11% [6].

In the study done by Groenewegen *et al.*, mortality rate was 8% during hospital stay which increased to 16% by 3-month follow-up, 18% in 6-months follow-up, and 23% after 1 year.[9]

Age has been shown to be an important determinant of survival in COPD patients. This finding was also seen in the present study. Age has been associated with an accelerated decline in lung function. It is important to detect and treat the symptoms of COPD at an earlier stage to prevent this decline. This is in accordance with the observation made by Hansen *et al.*[10]

In this study, five factors were seen predicting mortality in patients. These factors were pH, PaCO₂, sodium, random blood sugar (RBS), and SGPT (also called alanine aminotransferase or alanine transaminase).

PaCO₂ is usually elevated in chronic COPD as well in AECOPD. Elevation of PaCO₂ is due to alveolar hypoventilation and ventilation perfusion mismatch. Raised PaCO₂ causes decrease in pH which is an indicator of acidosis. In chronic condition, elevated PaCO₂ is usually compensated by elevation of bicarbonates so that pH is maintained at normal or near normal range while in acute exacerbation, there is none or only partial compensation by the kidney. Respiratory acidosis was a predictor of mortality in this study. This is in accordance with the observation made by Gray-Donald *et al.*,[11] but contrary to that of Connors *et al.*[6]

In our study, albumin was lower in nonsurviving group. Although univariate analysis showed this difference to be significant, multivariate analysis did not confirm that. This observation was contrary to the study by Khilnani *et al.*[12] who concluded serum albumin in the first 24 h of admission to be independent predictor of mortality in patients of AECOPD. Albumin has a longer half-life of approximately 18 days, and because of this fact, it is unlikely to change with development of acute respiratory failure in patients with COPD. On the other hand, albumin is known to reflect the underlying nutritional status and to be affected by the severity of chronic illness. These factors are of obvious significance in deciding the outcome of stable COPD patients. In our study, liver enzymes such as SGOT and SGPT were elevated significantly in expired group as compared to survived group. This difference was significant in univariate analysis while only SGPT came out as mortality predictor in multivariate analysis. Liver enzymes as mortality predictors have not been mentioned in most studies in the literature.

Renal failure in AECOPD was not found as a mortality predictor. Mean urea level was higher in expired group while serum creatinine was relatively lower but not significant statistically. This is supported by many studies such as studies by Groenewegen *et al.*[9] and Seneff *et al.*[13]. This was contrary to the study of Bhatt *et al.*[14] who observed that serum creatinine at admission is an independent predictor of mortality. Electrolyte imbalance was significant in this study. Sodium was lower in expired group as compared to survival group, and this difference was significant statistically. Chronic COPD patients most often develop pulmonary arterial hypertension followed

by right heart enlargement and failure (cor pulmonale). This condition leads to fluid retention and causes hyponatremia. However, there are conflicting reports in the literature. [9,12-14]

Hyperglycaemia at the time of admission is one of the mortality predictors in AECOPD. Previous studies had not commented on random blood sugar at the time of admission as mortality factor. Diabetes is one of the important comorbidities in cases of COPD. Although patients who were known diabetics were excluded in this study, previous studies have showed that patients with diabetes are more prone to get secondary infection, an important etiological factor for acute exacerbations in stable COPD patients. Patients with diabetes also have high incidence of coronary artery disease which is also an important cause of mortality in patients of COPD. Mannino *et al.* [15] and Yeh *et al.* [16] in their studies show that there is an increased prevalence of diabetes among COPD patients and that diabetes is independently associated with reduced lung function.

There was no significant difference in haemoglobin and total leukocyte count level in both groups. Ittyachen *et al* found in their study that anaemia is a mortality predictor in AECOPD in rural settings [17].

This study has been capable of identifying some statistically competent acute-phase variables predicting the in-hospital mortality of patients presenting with AECOPD patients. Limitations to get the variables into a prediction tool include small sample size and exclusion of known diabetics. We strongly feel that a multicentric study with sufficient number of patients must be further undertaken to have a definite guideline for triage and appropriateness of acute care.

CONCLUSION:

PaCO₂, arterial pH, serum sodium level, random blood sugar, and SGPT levels measured at the time of admission are important predictors of mortality in AECOPD. All these five parameters combined together have a specificity of 96.5% and sensitivity of 80%. Hence, these can be used to predict and prognosticate in terms of inpatient mortality.

Conflicts of interest

There are no conflicts of interest.

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