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Original Research Article

Role of Plasma Proadrenomedullin (Proadm), Biomarkers, and Clinical Variables in Predicting the Morbidity and Mortality in Patients with Exacerbated COPD

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Abstract:

Background: The morbidity and mortality of Chronic Obstructive Pulmonary Disease (COPD) is always unpredictable and challenging the treating physician. To understand the relation COPD of exacerbated type, inflammatory biomarkers such as White Blood cell count (WBC count), C reactive protein, plasma Proadrenomedullin (ProADM), and procalcitonin (PCT) a prospective study was conducted.

Aim of the Study: To study the relation between biomarkers, and demographic and clinical signs in terms of morbidity and mortality in COPD patients.

Materials: 96 patients with COPD were analyzed with causes for hospitalization for both pneumonic- Group A- 43 (44.79%) and non-pneumonic- Group B- 53 (55.20%) COPD exacerbations with clinical signs required admission. The past history (vital status) was elicited with the help of structured interviews with family members.

Results: During the period of study for 18 months 07/96 (07.29%) died during the first 12 months of follow up. Another 10/ 89 (10.41%) pod the remaining patients died within 06 months of follow up. The mortality rate for the entire period of study was 17.70% (17/96 patients). The one year survival rate was 93% (n-96) and survival rate at the end of 18 months was 88.76% (n-89).

Conclusions: It is of interest to note that ProADM as a biomarker seem to be associated with vital status in COPD patients. ProADM in addition to other biomarkers like PCT and CRP improved the predictability in assessing the morbidity and mortality in COPD patients with or without pneumonia.

Keywords: Biomarkers, mortality, morbidity, COPD, Pneumonia and predictive value.

Introduction

The management of COPD patients in terms of increasing the survival rate, cost effective treatment protocols is possible with early identification of high risk patients. To predict the mortality currently, blood biomarkers either singly or in combination with demographic data, clinical signs, and /or laboratory variables have been tried by many authors. [1,2]

Among all the biomarkers available plasma proadrenomedullin (ProADM) stands alone as a promising biomarker. [3,4] Proadrenomedullin (ProADM) is a fragment located in the middle of the precursor molecule peptide adrenomedullin. This molecule is a surrogate for, the cardiovascular, metabolic, and immune regulatory systems. [5,6] Both the peptide adrenomedullin and the precursor are secreted stoichiometrically, when the adrenomedullin prohormone is processed into the mature hormone. [7] Among these two ProADM was found more stable, less biologically active, and hence more reproducible. [6] Earlier three papers were published which showed that ProADM accurately predicts independently all causes of mortality in COPD patients; either exacerbated or non-exacerbated situations. [5] Combined with BMI, airflow obstruction, dyspnea, Exercise capacity index (BODE), and ProADM enhanced the prognostic power of COPD patients instead of being used alone. [8]

Another study also supported the above studies that the ProADM additionally, has a good repeatability of the results without any change in the median levels in patients; immediately during the post-recovery period from severe exacerbation of COPD. [9] ProHOSP [8,9] which was a Swiss study that compared recommendation of antibiotics in COPD patients; using it only when procalcitonin (PCT), a systemic bacterial infection biomarker

was found elevated, and compared with evidence-based guidelines without PCT data. [10,11] In this context the present study was conducted to analyze the assessment of the association of ProADM, several other blood biomarkers, and demographic and clinical variables, alone or combined, among the COPD patients.

Type of Study: Prospective analytical study

Period of Study: Jan 2021 to Dec 2023

Institute of Study: Viswabharathi Medical College, Penchikalapadu, Kurnool, Andhra Pradesh.

Methods: 96 patients with the diagnosis of COPD and attending the OPD of Respiratory Medicine were included. An institution Ethics Committee approval was obtained and the respective Proforma and interview questionnaire were approved. The patients were divided into two groups. Group-A COPD patients consisted of those with pneumonic signs and symptoms. Group B COPD patients were those with and non-pneumonic clinical features. All the patients were subjected to the assays of biomarkers such as White Blood cell count (WBC count), C reactive protein, plasma proadrenomedullin (ProADM), and procalcitonin (PCT). The ProHOSP index hospitalization was also included. Inclusion Criteria: Patients with COPD with both pneumonic signs and non-pneumonic signs were included. Patients age between 40 and 70 years were included. Patients of both the genders were included. Patients with serial ProADM assays at the time of admission, 30 day and 180 day intervals were included. Patients with clear cut clinical signs were included in both the groups. Patients with one of the following features of COPD alone were included: i) Spirometry values indicating FEV_1/FVC <70% during the last two year period either pre or post hospitalization. ii) Global Initiative for Chronic Obstructive Lung Disease (GICOPD) staging with or without spirometry values; iii) COPD reported, without spirometry values or staging, in charts/by patients at presentation. In this study Non-pneumonic COPD exacerbation was considered when dyspnea, sputum production with increasing purulent nature above normal day-to-day variation requiring change in their medical management, but without new/increased chest radiographic infiltrate. Whereas the Pneumonic exacerbation was considered when there was lung infiltration accompanying one of the following signs and symptoms: i) cough, sputum production, dyspnea, tachypnea, or pleuritic pain and ii) auscultatory or infectious signs/symptoms: rales, crepitation, temperature 38.0°C, shivering, white blood cell count [WBC] < 4 or > 10 cells ´ 10^9/L, each lasting < 28 days. Exclusion Criteria: Patients with Dementia, failure to give consent, patients on IV sedative drugs and other medical co-morbidities. Patients who are on corticosteroids were excluded. Patients with immune-compromise were excluded. All the Patients were clinically evaluated thoroughly on admission and periodically throughout hospitalization. Demographic data, laboratory measurements, vital signs, radiological results, and medications/interventions were recorded. Non-COPD comorbidities were identified through chart review and patient report. Health status was obtained on telephone, in a fixed interview by trained health personnel at the intervals of at 360, and 540 days post-discharge. Patients or their family members/ health care providers were contacted. Patients whose health status could not be elicited by this method were labeled as indeterminable survivors and their latest hospital discharge date showed in medical records was used to calculate survival.

Statistical Analysis:

The categorical variables were expressed as mean, SD and percentages. 95%CI was provided for all the calculations. Frequency comparison was done by chi-square test, two-group comparison by Mann–Whitney U-test. The primary and secondary endpoints were all-cause mortality at the follow-up and 1 and 3 years after discharge. Associations with these endpoints were assessed via Cox regression analyses and significance levels for chi-square (Wald test).

Results

Characteristics of the cohort and 5–7-year survivors or non-survivors appear in Table 1. Documented COPD stages, NYHA dyspnea classifications, advanced age, co-morbidity burden, smoking history, and hospitalization for the index exacerbation suggest that at ProHOSP admission, the cohort predominantly had COPD of moderate or greater severity.

Table 1:

Variables	Total Number (N =96)	12 months survivors (n = 89)	12 to 18 months survivors (n = 79)	p value
Age				
40 to 50	25 (26.04%)	29 (30.20%)	23 (23.95%)	
50 to 60	47 (48.95%)	40 (41.66%)	37 (38.54%)	.001
60 to 70	24 (25%)	20 (20.83%)	19 (19.79%)	
Gender				

Male Female	58 (60.41%) 38 (39.58%)	54 (56.25%) 35 (36.45%)	45 (46.87%) 34 (35.41%)	0.195
GOLD grade I II III IV	 20 (20.83%) 33 (34.37%) 31(32.29%) 12 (12.5%)	 18 (18.75%) 30 (31.25%) 28 (29.16%) 13 (13.54%)	 17 (17.70%) 28 (29.16%) 26 (27.08%) 08 (08.33%)	0.021
BMI, kg/m ^{2} Mean	23.4 (21.2–30.5)	22.6 (21.3–29.10)	23.1 (23.8–29.1)	0.001
NYHA dyspnea class I II III IV	 13 (13.54%) 41 (42.70%) 21 (21.87%) 21 (21.87%)	 14 (14.58%) 37 (38.54%) 18 (18.785%) 20 (20.83%)	 13 (13.54%) 35 (36.45%) 16 (16.66%) 15 (15.62%)	 0.001
Smoking Yes No Former smokers	 24 (25%) 56 (58.33%) 16 (16.66%)	 22 (22.91%) 55 (57.29%) 12 (12.5%)	 20 (20.83%) 53 (55.23) 16 (16.66%)	 0.001
Co-morbidities Coronary heart disease Congestive heart failure Chronic renal failure Diabetes mellitus	 12 (12.5%) 09 (09.37%) 11 (11.45%) 27 (28.12%)	 14 (14.58%) 11 (11.45%) 14 (14.58%) 28 (29.16%)	 15 (15.62%) 13 (13.54%) 16 (16.66%) 29 (30.20%)	 0.00 0.14 0.14 0.17
Clinical history Cough Chills Fever	 58 (60.41%) 31 (32.29%) 27 (28.12%)	 52 (54.16%) 27 (28.12%) 22 (22.91%)	 49 (51.04%) 24 (25%) 18 (18.54%)	 0.002
Clinical findings Confusion Body Temp. Systolic BP Arterial PH Hear rate	 08 (08.33%) 41 (42.70%) 21 (21.87%) 25 (26.04%) 55 (57.29%)	 06 (06.25%) 38 (39.58%) 18 (18.54%) 22 (22.91%) 49 (51.04%)	 05 (05.20%) 37 (38.54%) 15 (15.62%) 22 (22.91%) 49 (51.04%)	 0.002
Mean Arterial pH	7.43(07.39–7.46)		7.43(97.40–7.46)	7.42(7.38–7.450)	.018
Laboratory findings Blood or sputum culture Positive culture ProADM, nmol/L Initial Discharge time PCT- µg/L Initial Discharge time CRP, mg/dL Initial Discharge time WBC count Initial Discharge time Hospital Stay Mean value in Days	 54 (56.25%) 16 (16.66%) 1.10 0.85 0.87 1.0 103 19 11.52 09.55 08.35±1.26	 2 (02.08%) 13 (13.54%) 1.07 0.89 0.90 1.01 109 20 10.72 09.25 09.15±1.76	 54 (56.25%) 16 (16.66%) 1.10 0.85 0.87 1.0 103 19 11.52 09.55 09.31±1.06	 0.001	
Outcome Mean Length-of-stay in days	9 [6–13]	9.21 [6–13]	11 [9–17]	<.001	

Table 1: Showing the long-term vital status of the subjects (n-96)

Mortality: During the period of study for 18 months 07/96 (%) died during the first 12 months of follow up. Another 10/ 89 (%) pod the remaining patients died within 06 months of follow up.

The mortality rate for the entire period of study was 17.70% (17/96 patients). The one year survival rate was 93% (n-96) and survival rate at the end of 18 months was 88.76% (n-89). Cox regression analyses were used to assess the association of blood biomarker values with all-cause mortality of discharge alone or combined with demographic/clinical variables in Table 2. Regarding blood biomarkers alone, univariate analysis was found to have significant associations of ProADM ($p < .001$) and PCT ($p < .001–.001$). But it was not significant association with CRP ($p \geq .451$) or WBC ($p \geq 0.371$), with primary and secondary outcomes. The prognostic value of ProADM after 12 months and 18 months' time intervals was observed. For ProADM, it was highest within the first 12 months; 15.15 (95%CI; 6.3–35.37), initially it was 16.98 (7.15 to 38.55). It remained significant after 18 months period also with value of 10.5 (95%CI; 5.7–19.6). In the case of PCT, the prognostic value was initially 11.25 (95%CI; 5.85-25.68) and decreased by 12 months with a value of and, at 18 months it was 1.2 (0.9-1.6). The Bivariate analysis of prognostic accuracy of the biomarkers of COPD patients plus age or each biomarker plus age, smoking status, BMI, NYHA dyspnea class, exacerbation type, and individual co-morbidities was analyzed and found that the ProADM or PCT values independently predicted 12 months and 18 months mortality. (Table 2)

Table 2:

Biomarkers	12 months follow up	18 months follow up	P value
ProADM			0.001
Univariate model	15.15 (6.3–35.37)	10.5 (5.7–19.6)	
Prognostic Accuracy	0.718 (7.1- 31.24)	0.651 (0.610-0.710)	
Demographic/ Clinical model	0.731 (0.676–0.786)	0.671 (0.610- 0.731)	
PCT			
Univariate model	0.712 (0.654–0.721)	0.712 (0.654–0.721)	0.001
Prognostic Accuracy	0.589 (0.515–0.663)	0.6218(0.543–0.657)	
Demographic/ Clinical model	0.731 (0.676–0.786)	0.652(0.613–0.709)	
CRP			
Bivariate model	1.31 (1.0–2.4)	1.23 (0.89–1.05)	
Prognostic Accuracy	1.5 (1.0-2.4)	1.2 (0.9-1.6)	0.451
Demographic/ Clinical model	1.48 (1.0–2.13)	1.2 (0.9–1.21)	
WBC Count			
Univariate model	1.0(0.3-4.51)	0.8 (0.3-1.87)	
Prognostic Accuracy	0.521 (0.421-0.548)	1.2 (0.3- 2.21)	0.371
Demographic/ Clinical model	0.731 (0.676–0.786)	0.474 (0.430-0.542)	

Table 2: Showing the Bivariate, prognostic accuracy of the biomarkers in the study (n-96)

Discussion

The present study is an analysis of 96 patients with COPD of varying degrees of exacerbation of pneumonia and non-pneumonias with index hospitalization revealed three main issues. The biomarker ProADM values from the index hospitalization were strong and independent in 12 months mortality. This observation was also expressed by three published studies [3, 4 and 5] which used ProADM accuracy to predict medium-term non-survival in patients with COPD. Even though the follow up period in this study was small to use the biomarker as a predictor of COPD, a preliminary setting was accomplished as a protocol for the Institute. This study also combined ProADM with demographic/clinical variables and other biomarkers like CRP and PCT, significantly by augmenting the follow up of all-cause mortality prediction accurately when compared to that of the multivariate model alone. Such a finding is also supported by Celli et al. (%%%) From their study the authors found that interleukin-6 alone, or in combination with blood biomarkers like WBC and CRP, age, BODE, and hospitalization history, accurately improved their three year mortality prediction in stable COPD patients using just the demographic/clinical variables. A multicenter observation by Stolz et al. [4] found that by combining ProADM values measured during stable COPD with BODE significantly improved the 1-year and 2-year all-cause mortality prediction relative to applying BODE alone. In this study also the data of non-COPD patients with lower respiratory tract infections was predictable. [16, 26 and 27] The present study also included demographic data including age [25, 28 and 29], smoking status [28], positive X-ray for consolidation [30], and co-morbidity burden]30 and 31] in assessing the predictability of mortality.

Conclusions:

It is of interest to note that ProADM as a biomarker seem to be associated with vital status in COPD patients. ProADM in addition to other biomarkers like PCT and CRP improved the predictability in assessing the morbidity and mortality in COPD patients with or without pneumonia. The discharge ProADM values alone or in combination with a multidimensional demographic/clinical model accurately predicted the mortality in patients hospitalized for pneumonic or non-pneumonic COPD exacerbation.

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