Section: Respiratory Medicine

Original Research Article

EVALUATION OF MICROALBUMINURIA, SERUM ALBUMIN, AND PCO2 MARKERS IN COPD AND COR PULMONALE PATIENTS: IMPACT OF THERAPEUTIC INTERVENTIONS

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Received : 14/07/2024
Received in revised form : 12/09/2024
Accepted : 28/09/2024

Keywords:
COPD, Microalbuminuria, Serum albumin, pCO2, Cor pulmonale, Biomarkers, GOLD criteria

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DOI: 10.47009/jamp.2024.6.5.36

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (5); 194-199

Abstract

Background: Cor Pulmonale is a condition causing right ventricle hypertrophy, affecting 65 million COPD patients. Early detection is crucial, especially in COPD patients without significant PAH, with serum albuminuria and pCO2 levels as indicators. This study aimed to evaluate the biomarkers and compare the BMI associated with COPD, Cor pulmonale, and the effect of therapeutic measures. **Materials and Methods:** This prospective observational study included 82 COPD patients who attended the Government Hospital of Thoracic Medicine and Stanley Medical College between June 2018 and May 2019. Routine blood tests, arterial blood gases, microalbuminuria analysis, ECG, and 2D ECHO were performed. COPD was treated according to the GOLD guidelines and Cor pulmonale per the cardiologist's advice, with follow-up and repeat investigations at 6 months. **Result:** Microalbuminuria was more prevalent in males (83.1%), underweight patients (87.2%), and those with a smoking index of > 600 (93.54%), with significant differences in age, BMI, smoking index, and GOLD staging, acute exacerbation ($p<0.05$). The variations in serum albumin and pCO2 levels across age groups, gold-stage FEV1, and acute exacerbations were statistically significant ($p<0.001$). Overweight patients had slightly higher serum albumin (3.67±0.33) and pCO2 (50.91±7.96), while obese patients had lower serum albumin (3.38±0.72) and pCO2 (48.78±8.30). The differences in serum albumin and pC02 between baseline and follow-up were statistically significant ($p<0.05$). **Conclusion:** Microalbuminuria, serum albumin, and pCO2 are cost-effective markers for the early detection of Cor pulmonale in patients with COPD. Microalbuminuria remains unchanged post-therapy, and significant reductions in serum albumin and pCO2 levels indicate its utility in early diagnosis and treatment monitoring.

INTRODUCTION

Cor Pulmonale is defined by WHO as "hypertrophy of the right ventricle resulting from diseases affecting the function and structure of the lungs except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart" (WHO expert committee report 1963).[1] According to WHO estimates, nearly 65 million patients have modest to severe chronic obstructive pulmonary disease (COPD). More than 3 million people died of COPD in 2005, which is approximately 5% (estimated to be 1 in 20) of all deaths worldwide. The maximum evidence available on COPD occurrence, illness, and death comes from high-income and industrialized nations. Even in these nations, precise epidemiologic statistics on COPD are difficult and expensive to collect. Moreover, about 90% of COPD mortality occurs in low- and middle-income nations.[2] The global initiative for lung disease (GOLD) has projected that COPD is going to be the third cause of mortality worldwide by 2020.[3]

COPD is a heterogeneous disease with both pulmonary and extrapulmonary symptoms and is characterised by long-term airflow obstruction. Cardiovascular disease remains one of the leading causes of mortality and morbidity in patients with COPD, independent of the well-recognised risk factors, including age, sex, and smoking status.[4] An exacerbation of Chronic Obstructive Pulmonary Disease is defined as: "an acute, sustained worsening of the patient's condition from the stable state, beyond normal daily variations, requiring a change in regular

medication in a patient with underlying Chronic Obstructive Pulmonary Disease".[5]

RV dysfunction is common in patients with advanced COPD and is more pronounced in the presence of pulmonary arterial hypertension (PAH).[6] However, new research has shown that cardiac complications including RV dysfunction and hypertrophy start early in the course of the disease even at subclinical levels of PAH. This means that PAH is not the sole pathological determinant of cor pulmonale in COPD.[7] The cause of death in COPD patients is not solely due to respiratory failure. But also due to cardiovascular complications, lung cancer, or other reasons that often remain unrecognised.[8] Smoking is directly linked to RV dysfunction and remodelling, whereas hypoxemia causes RV hypertrophy. Furthermore, patient survival was more closely associated with right heart dysfunction than with PAH values. These findings underscore the critical need for early detection of RV dysfunction, which remains challenging in COPD patients, particularly those without significant PAH.[9]

Microalbuminuria (MAB) is a widely accepted marker of endovascular dysfunction and a predictor of cardiovascular events and all-cause mortality in the common population.[10] Serum protein levels are influenced by inflammation and calorie intake. Albumin, a negative acute-phase reactant, decreases during the acute-phase response due to increased catabolism.[11] Research indicates that hypoalbuminemia correlates with higher mortality rates and extended hospital stays in patients with COPD.[12] Another study identified serum albumin and pCO2 levels as indicators of Cor Pulmonale in AECOPD patients.[13]

Aim

This study aimed to evaluate the biomarkers and compare the BMI associated with COPD, Cor Pulmonale, and the effect of therapeutic measures on these markers.

MATERIALS AND METHODS

This prospective observational study included 82 COPD patients who attended the Department of Thoracic Medicine, Government Hospital of Thoracic Medicine, Tambaram Sanatorium, and Stanley Medical College between June 2018 and May 2019. This study was approved by the Institutional Ethics Committee before initiation, and informed consent was obtained from all patients.

Inclusion criteria

Patients diagnosed with COPD and Cor pulmonale were included in this study.

Exclusion criteria

Patients with renal disease, liver disease, diabetes mellitus, macroalbuminuria, ischemic heart disease, malignancy, symptoms of obstructive sleep apnoea, urinary tract infection in the previous week, persistent haematuria in the previous year, or unwillingness to participate in the study were excluded from the study.

Methods: All patients underwent a thorough history and clinical examination and were categorised according to the GOLD COPD staging system. Routine blood investigations, including renal function tests (RFT), liver function tests (LFT), and complete blood counts (CBC), were conducted. Arterial blood gases were measured via arterial puncture and a spot morning urine sample was collected for microalbuminuria analysis. ECG and 2D ECHO with colour Doppler were performed.

Body mass index (BMI) was calculated using the formula: weight in kilograms divided by the square of height in meters. Treatment for COPD was administered according to the GOLD guidelines, whereas management for Cor Pulmonale was provided based on the cardiologist's recommendations. The patient was followed up for 6 months, and the above-said investigations were repeated and analysed statistically.

Statistical analysis: Data were entered into an MS Excel sheet and analysed using SPSS software version 16. Descriptive statistics were used to summarize continuous and categorical variables. Chi-square tests were used to examine the associations between categorical variables using Fisher's exact test. McNemar's test compared baseline and follow-up categorical values. Independent t-tests and paired t-tests were used to compare baseline and follow-up numerical values, and ANOVA was used for comparisons across more than two groups. Statistical significance was set at $p>0.05$.

RESULTS

A total of 47.6% of patients were in the 61-70 age group, followed by 39% in the 51-60 years and 13.4% in the ≤ 50 years age group. Of these, 86.6% were males and 13.4% were females. Of the patients, 57.3% were underweight, 25.6% were normal weight, 11% were overweight, and 6.1% were obese. A total of 37.8% of the patients had a smoking index of > 600, followed by 24.4% of patients with a smoking index of 100-300 and 13.4% had never smoked. In the gold staging distribution, 61% of the patients had < 30% predicted FEV1, followed by 28% with 30-50% predicted FEV1. Acute exacerbation occurred in almost half of the patients (57.3%) and microalbuminuria occurred in 81.7% of the patients. 75.6% were alive at 6 months follow-up. 14.6% of patients died and 9.8% were lost to follow-up [Table 1].

Patients aged 61-70 years exhibited the highest prevalence of microalbuminuria (94.8%), followed by those aged 51-60 years (84.3%), and those aged < 50 years (27.2%). Underweight patients exhibited the highest prevalence of microalbuminuria (87.2%), followed by normal-weight (85.7%), obese (60%), and overweight patients (55.5%). Patients with a smoking index of > 600 exhibited a higher prevalence of microalbuminuria (93.54%) than those with a

ISSN (O): 2687-5365; ISSN (P): 2753-6556

smoking index of ≤ 600 (75%) and never-smokers (72.7%). In gold staging, those with < 30% predicted FEV1 had a higher prevalence of microalbuminuria (96%), followed by patients with 30-50% predicted FEV1 (73.9%), and those with 50–80% predicted FEV1 (22.2%). Microalbuminuria was more prevalent in patients with acute exacerbations (96%) than in those without exacerbations (60%). The differences in age (p<0.001), BMI (p=0.012), smoking index (p=0.001), gold-stage FEV1% (p=0.001), and acute exacerbation (p<0.001) with microalbuminuria were statistically significant.

Male patients exhibited a higher prevalence of microalbuminuria (83.09%) than female patients (72.7%), although the difference was not statistically significant (p=0.212) [Table 2].

Serum albumin levels decreased with age, with patients aged <50 years having the highest mean serum albumin (4.00±0.50) and the lowest pCO2 (46.68±6.86). Those aged 61-70 had the lowest mean serum albumin (3.18±0.26) and the highest mean pCO2 (56.60±6.58). Males and females had similar serum albumin levels, with males at 3.37±0.47 and females at 3.35±0.39. Males had a slightly higher mean pCO2 (53.25±7.69) compared to females (49.15±7.10).

Overweight patients had slightly higher serum albumin (3.67±0.33) and pCO2 (50.91±7.96), while obese patients had lower serum albumin (3.38±0.72) and pCO2 (48.78±8.30). Serum albumin varied slightly with smoking index, with those smoking 100-300 and 300-600 having higher mean serum albumin (3.52±0.51) compared to those with an index >600, who had the lowest serum albumin (3.18±0.36). pCO2 was highest in those who smoked <100 (55.89±7.67) and >600 (54.43±6.25).

Patients with FEV1% > 80% predicted had the highest mean serum albumin (3.70±0.46) and the lowest mean pCO2 (46.26±6.86). Patients in the 30-50% predicted group had a lower serum albumin (3.18±0.32) and a higher pCO2 (55.55±6.44). Patients without acute exacerbation had a higher mean serum albumin (3.64±0.52) and lower mean pCO2 (47.08±5.43) compared to those with acute exacerbation, who had a lower serum albumin (3.16±0.27) and higher pCO2 (56.88±5.43).

The variations in serum albumin and pCO2 levels across age groups, gold-stage FEV1, and acute exacerbations were statistically significant (p<0.001). The variations in serum albumin and pCO2 levels across sex (p=0.928, p=0.101), BMI (p=0.146, p=0.333), and smoking index (p=0.059, p=0.258) were not statistically significant [Table 3].

Table 1: Demographic details and clinical comparison of the patients.

		Frequency (%)
Age group in year	≤ 50	11 (13.4%)
	51-60	32 (39%)
	61-70	39 (47.6%)
Gender	Male	71 (86.6%)
	Female	11 (13.4%)
BMI	Underweight	47 (57.3%)
	Normal	21 (25.6%)
	Overweight	9 (11%)
	Obese	5 (6.1%)
Smoking index	Never smoked	11 (13.4%)
	< 100	4 (4.9%)
	100-300	20 (24.4%)
	300-600	16 (19.5%)
	> 600	31 (37.8%)
Gold staging in FEV1	> 80% predicted	0
	50-80% predicted	9 (11%)
	30-50% predicted	23 (28%)
	< 30% predicted	50 (61%)
Acute exacerbation	Yes	47 (57.3%)
	No	35 (42.7%)
Micro Albuminuria	Yes	67 (81.7%)
	No	15 (18.3%)
After 6 months	Expired	12 (14.6%)
	Lost to follow-up	8 (9.8%)
	Alive	62 (75.6%)

Table 2: Comparison of microalbuminuria with clinical characteristics

		Microalbuminuria		**P-value**
		Yes	**No**	
Age group in year	≤ 50	3 (27.27%)	8 (72.72%)	< 0.001
	51 - 60	27 (84.37%)	5 (15.62%)	
	61 - 70	37 (94.87%)	2 (5.12%)	
Sex	Male	59 (83.09%)	12 (16.9%)	0.212
	Female	8 (72.72%)	3 (27.27%)	
BMI	Underweight	41 (87.23%)	6 (12.76%)	0.012
	Normal	18 (85.71%)	3 (14.28%)	
	Overweight	5 (55.55%)	4 (44.44%)	

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	Obese	3 (60%)	2 (40%)	
Smoking index	Never smoked	8 (72.72%)	3 (27.27%)	0.001
	< 100	3 (75%)	1 (25%)	
	100-300	15 (75%)	5 (25%)	
	300-600	12 (75%)	4 (25%)	
	> 600	29 (93.54%)	2 (6.45%)	
Gold stage FEV1%	50-80% predicted	2 (22.22%)	7 (77.77%)	0.001
	30-50% predicted	17 (73.91%)	6 (26.08%)	
	< 30% predicted	48 (96%)	2 (4%)	
Acute exacerbation	Yes	46 (97.87%)	1 (2.12%)	< 0.001
	No	21 (60%)	14 (40%)	

Table 3: Comparison of serum albumin & pCO2 with clinical characteristics

		Mean			
		Serum Albumin	**P-value**	**pCO2**	**P-value**
Age group in years	< 50	4±0.50	< 0.001	46.68±6.86	< 0.001
	51 - 60	3.36±0.45		50.01±6.86	
	61 - 70	3.18±0.26		56.6±6.58	
Gender	Male	3.37±0.47	0.929	53.25±7.69	0.101
	Female	3.35±0.39		49.15±7.10	
BMI	Underweight	3.29±0.41	0.146	53.95±7.23	0.333
	Normal	3.39±0.52		51.6±8.40	
	Overweight	3.67±0.33		50.91±7.96	
	Obese	3.38±0.72		48.78±8.30	
Smoking index	Never smoked	3.3518±0.38958	0.059	49.1473±7.10226	0.258
	< 100	3.3675±0.62425		55.885±7.67365	
	100-300	3.521±0.50518		51.235±8.83983	
	300-600	3.5219±0.51350		52.805±8.75494	
	> 600	3.1842±0.35755		54.4345±6.25274	
Gold stage FEV1%	> 80% predicted	3.6956±0.45703	< 0.001	46.2589±6.86200	< 0.001
	50-80% predicted	3.63±0.52752		49.0265±7.71225	
	30-50% predicted	3.1814±0.32404		55.5454±6.43713	
Acute Exacerbation	Yes	3.16±0.27	0.001	56.88±5.43	0.001
	No	3.64±0.52		47.08±5.43	

Table 4: Comparison of Gold staging at baseline with at 6 months

Gold Stage at Baseline	**Gold Stage at follow-up**			**P-value**
	50-80% predicted	**30-50% predicted**	**<30% predicted**	
50 - 80% predicted	6 (100%)	0 (0%)	0 (0%)	0.09
30 - 50% predicted	4 (22.22%)	5 (27.77%)	9 (50%)	
< 30% predicted	1 (2.63%)	15 (39.47%)	22 (57.89%)	

Table 5: Distribution of microalbuminuria at baseline and 6 months follow up

Micro Albuminuria	**Microalbuminuria at follow-up**		**P- value**
	Yes	**No**	
Yes	50 (96.15%)	2 (3.84%)	0.453
No	5 (50%)	5 (50%)	

Table 6: Distribution of serum albumin and pCO2 at baseline and follow-up

		Mean	**P-value**
Serum Albumin (mg%)	Baseline	3.38±0.47	0.002
	Follow up	3.56±0.47	
pCO2 (mm Hg)	Baseline	52.52±7.75	0.001
	Follow up	49.58±6.19	

According to gold staging at follow-up, after six months of follow-up, six (100%) patients maintained 50-80% predicted. In the 30-50% predicted baseline, after six months of follow-up, nine patients (50%) showed deterioration to <30% predicted. In <30% predicted at baseline, after six months of follow-up, 22(57.89%) patients maintained <30% predicted. The differences in gold stage at baseline and gold staging at follow-up were not statistically significant(p=0.09) [Table 4].

In patients with microalbuminuria at baseline, two (3.84%) patients showed no microalbuminuria at follow-up. In patients who did not have microalbuminuria at baseline, five (50%) patients showed microalbuminuria after follow-up. The difference in microalbuminuria at baseline with microalbuminuria at follow-up was not statistically significant (p=0.453) [Table 5].

The mean serum albumin level at baseline was 3.38±0.47, which decreased after 6 months at follow-up (3.56±0.47). The mean pC02 at baseline was 52.52±7.75 mmHg which had decreased after 6 months at follow-up at 49.58±6.19 mmHg. The differences in serum albumin and pC02 between

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baseline and follow-up were statistically significant ($p<0.05$) [Table 6].

DISCUSSION

In our study, 86.6% of the patients were male and 13.4% were female. In all age groups, the distribution of males was 5-7 many times the number of females. Males were most numerous in the 61-70 age group and least numerous in the ≤ 50 years group. Sorheim et al. studied the gender differences in COPD and concluded that female gender was associated with lung function reduction and more severe disease in patients with COPD.[14]

In our study, male patients had a higher prevalence of microalbuminuria (83.1%) than women (72.7%). This can be explained by the high sample size and the presence of microalbuminuria due to other causes of endothelial injury and inflammation in males. A cross-sectional study by Shayo et al. of 104 patients with chronic obstructive pulmonary disease (COPD) patients revealed a 24% prevalence of albuminuria, rising to 100% in those with a history of cardiovascular disease (CVD). Albuminuria significantly increased with COPD severity, which was consistent with our findings. Age group differences in microalbuminuria distribution were statistically significant ($p < 0.05$).[15]

In our study, 57.3% of the subjects were underweight, 25.6% were normal weight, 11% were overweight, and 6.1% were obese. Underweight subjects had a higher prevalence of microalbuminuria (87.2%), followed by normal-weight (85.7%), obese (60%), and overweight (55.5%) subjects. The difference in the distribution of microalbuminuria among different levels of BMI was statistically significant ($p < 0.012$), which correlates with the study done by Karadag and Guo et al. did a meta-analysis which concluded that being overweight is associated with a reduced risk of all-cause mortality among patients with COPD while being underweight is associated with an increased risk of all-cause mortality in these patients.[16,17]

In our study population, 61% of the subjects had <30% predicted FEV1, 28% had 30 – 50% predicted FEV1, and 11% had 50-80% predicted, and patients with < 30% predicted FEV had a higher prevalence of microalbuminuria (96%). The difference in the distribution of microalbuminuria among the gold staging levels was statistically significant ($p < 0.05$). Casanova et al. found no association between microalbuminuria and spirometry severity in COPD,10 whereas Mehmood et al. found that COPD patients with microalbuminuria had significantly lower FEV1 levels. However, reduced FEV1 is not specific to COPD and may be manifested in other diseases such as congestive heart failure, asthma, cystic fibrosis, thoracic kyphosis, multiple sclerosis, and other conditions.[18]

In our study, more than half of the patients (57.3%) experienced acute exacerbations, and patients with acute exacerbations had a higher prevalence of microalbuminuria (96%) than those without acute exacerbations (60%). The difference in the distribution of microalbuminuria among subjects with acute exacerbations was statistically significant ($p < 0.05$). Kömürcüoglu et al. established an association with the exacerbations and microalbuminuria. Serum albumin on the first day of admission can predict respiratory failure in COPD patients with acute exacerbation.[19]

In our study, patients with acute exacerbation had low mean serum albumin levels (3.16±0.27 mg %), whereas the mean serum albumin level was high in patients without acute exacerbation (3.64±0.52 mg %). Mean pCO2 is higher in patients with acute exacerbation (56.88±5.43 mmHg) whereas mean pCO2 is low in patients without acute exacerbation (47.08±5.43 mmHg). Samaria and Utsav's study shows that the difference in the distribution of serum albumin & pCO2 among different acute exacerbations was statistically significant ($p < 0.05$), which is consistent with our study.[13]

In our study, at the 6-month follow-up, 75.6% of the subjects survived, 14.6% died, and 9.8% were lost to follow-up. Serum albumin and pCO2 levels significantly differed across age groups, BMIs, smoking index, GOLD stage, and presence of acute exacerbations. Older, underweight subjects, those with higher smoking indices, severe GOLD staging, and acute exacerbations exhibited lower serum albumin and higher pCO2 levels, suggesting more severe hypercapnia in malnourished patients with COPD and Cor Pulmonale. Kömürcüog˘lu et al. found no statistically significant difference in GOLD staging or microalbuminuria levels between baseline and 6-month follow-up, suggesting the irreversibility of pulmonary endothelial damage in COPD patients and the potential use of these markers to identify Cor Pulmonale.[19]

CONCLUSION

Microalbuminuria was significantly associated with age, BMI, smoking index, GOLD severity staging, and acute exacerbations. Microalbuminuria was not significantly associated with sex. Serum Albumin and pCO2 were not associated with the smoking index but were associated with GOLD severity staging and acute exacerbations. There was no significant change in microalbuminuria after therapeutic intervention. Serum albumin and pCO2 levels were significantly reduced at the follow-up. Measuring microalbuminuria, serum albumin, and pCO2 is straightforward and cost-effective, enabling the early diagnosis of Cor Pulmonale in COPD patients in resource-limited and emergency settings. Serum albumin and pCO2 levels can be used to monitor therapeutic intervention. Endothelial and microvascular mechanisms are promising targets for the early detection and management of Cor pulmonale.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

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ISSN (O): 2687-5365; ISSN (P): 2753-6556