

## Original Research Article

# Comparative study of some routinely measured Serum biochemical parameters between acute exacerbation of Chronic Obstructive Pulmonary Disease and stable Chronic Obstructive Pulmonary Disease patients in a tertiary care hospital of Kolkata: an attempt to make simple prognostic indicators

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### ABSTRACT

**Background:** Patients with COPD often have exacerbations which frequently require hospitalization, resulting in higher mortality rates and costs than patients managed at OPD. Some easily available blood parameters in both stable COPD and AECOPD patients are measured that can be done in every patient even in poor resource settings. Finally, Results were analysed statistically to find out if there is any presence of significant difference of biochemical profile in stable COPD patients and AECOPD patients with or without any prognostic significance.

**Methods:** In institution based observational case control study, authors measured 1. FBS and PPBS 2. Serum Urea and Creatinine 3. Serum Electrolytes- Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup> 4. LFT 5. Uric acid in both stable COPD(n=50) and AECOPD (n=50) patients. Finally, Results were analysed statistically to find out if there is any presence of significant difference of biochemical profile in stable COPD patients and AECOPD patients.

**Results:** AECOPD patients had statistically significant higher urea, uric acid levels and higher fasting hyperglycemia than stable COPD patients. Hyponatremia, hyponatremia and hyperkalemia, hypokalemia - all were significantly higher in AECOPD group. Low level of serum bilirubin and higher level of AST and ALP were common in AECOPD patients. AECOPD patients with high urea value (>50 mg/dl) (but not high creatinine) was associated with poor patient outcome in respect to ICU transfer, death and prolonged hospital stay. Low bilirubin, high ALP and AST level in AECOPD patients was associated with higher ICU transfer and mortality but only high ALP level was associated with prolonged hospital stay. High uric acid level (>6 mg/dl) was a major determinant of ICU transfer, mortality and prolonged hospital stay.

**Conclusions:** Predicting exacerbation by these parameters early in the course of disease can decrease morbidity and mortality as well as health care cost to great extent. By measuring the changes in it can also be predicted early who will need ICU support in future and who can be treated at ward.

**Keywords:** Chronic obstructive pulmonary disease, Urea, Creatinine, Electrolytes, Liver function tests, Uric acid

### INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the most common respiratory disorder encountered in clinical practice. It constitutes 30% of cases seen in chest clinics

and accounts for 1-2.5% admissions in hospitals all over India.<sup>1</sup> Acute exacerbation COPD showed a hospital mortality rate of 24% if the patient gets admitted in ICU. This mortality rate increased to 30% if the patient was above 65 years.<sup>2</sup>

Patients with COPD often have exacerbations which frequently require hospitalization, and these hospitalized patients have higher mortality rates and costs than patients managed at OPD. During exacerbation there is acute stress on the body either in the form of increased oxidative stress or systemic inflammation. Although oxidative stress has been studied in inflammatory airway diseases for decades, its reliable assessment in clinical practice has remained elusive. A number of local (lung-specific) and systemic (blood-based) oxidative stress markers have been suggested to serve as indicators of oxidant-induced tissue damage in the lungs, but unfortunately most of the markers are not easily amenable or used for research purpose.<sup>3-6</sup>

Some easily available blood parameters were measured in both stable COPD and AECOPD patients, like 1. FBS and PPBS 2. Serum Urea and Creatinine 3. Serum Electrolytes- Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup> 4. LFT 5. Uric acid - that can be done in every patient even in poor resource settings. Therefore, tried to correlate these parameters between these 2 groups and sorted out rise or fall of which parameters are statistically significant in acute exacerbation state. So, these parameters may become pretty useful in predicting exacerbation in COPD patients, if these parameters starts to rise or fall. Predicting exacerbation early in the course of disease by simpler method can decrease morbidity and mortality as well as health care cost to great extent. By measuring the changes in FBS, PPBS, serum electrolytes, LFT, Urea, Creatinine, uric acid author can also make such prognostic indicators after analysing the data, and later from these data authors can predict early who will need ICU support in future and who can be treated at ward.

## METHODS

This study was carried out at the Chest Department, NRS Medical College and Hospitals, during the period from October 2014 to September 2015 (One Year) with 50 AECOPD patients (cases) from indoor and 50 stable COPD patients from OPD (controls). AECOPD patients were diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, supported by spirometric evidence of airflow obstruction [FEV<sub>1</sub>/FVC <0.70] when clinically stable, with clinical criteria of exacerbation including increased dyspnea, increased sputum volume, or sputum purulence. Criteria for exclusion were as follows: 1) Bronchial Asthma / Lung Abscess/ Lung Cancer. 2) Subjects who were recently started on Antibiotic / Antioxidant Therapy. 3) Known case of Pulmonary Koch's. 4) Ischaemic Heart Disease. 5) Previously diagnosed Diabetic and

hypertensive patients. 6) Patients not giving informed consent for participating in the study.

The study began after receiving approval of the ethical committee of NRSMCH, Kolkata. Patients attending the Chest OPD and admitted in Indoor Wards were selected as given in the inclusion criteria and recruited after getting an informed consent in writing in accordance with the provisions of the Code of Ethics for research on human beings.

Relevant History and thorough clinical examination of those patients were done. Diagnosis of COPD and severity of airway obstruction was confirmed by Spirometry with bronchodilator reversibility testing (as per GOLD guideline 2014 and 2015). Chest X ray was done. Pulse Oxymeter was then used to determine SpO<sub>2</sub> at rest. Then 5 ml blood was drawn in a clot vial and sent for estimation of Blood for FBS, PPBS, Serum Urea, Creatinine, LFT, Uric acid, Serum Electrolytes - Sodium, Potassium and Chloride.

Finally, Results were analysed statistically to find out if there is any presence of significant difference of biochemical profile in stable COPD patients and AECOPD patients.

## Statistical analysis

The results were presented in mean±standard deviation and percentages. The Chi-square test was used to compare the categorical variables. The unpaired t-test was used to compare two discrete variables. The one-way analysis of variance was used to compare more than two discrete variables.

Pearson correlation coefficient was calculated to find the direction of association between two discrete variables. The p <0.05 was considered statistically significant. All the analyses were carried out using SPSS 16.0 version (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Demographic data

Age: In both AECOPD and stable COPD - most common age group is between 55-65 yrs, 28 patients (56%) and 21 patients (42%) in both groups respectively. Among 50 patients in each group 9 AECOPD patients (18%) were above age >75 yrs, whereas only 2 stable COPD patients (4%) were above that age. Median age in AECOPD group was 63.50 yrs(50-85 yrs) and stable COPD group was 62.0 yrs (47-85 yrs).

Sex: Among 50 AECOPD patients 38 patients (76%) were male and 12(24%) were female whereas among 50 stable COPD patients 42(84%) were male and 8(16%) were female.

**Table 1: Correlation between serum urea, creatinine, sugar profile, electrolytes and uric acid.**

Parameters	AECOPD (n=50)		Stable COPD (n=50)		p value
	Median	range	Median	range	
Urea	45.5	11.0-92	25.5	12.0-93	<0.001
Creatinine	1	0.5-2.2	0.8	0.5-2.1	0.034
FBS	83	40-190	83.1	43-146	0.06
PPBS	104.5	74-236	100.5	64-226	0.03
Sodium	138	112-153	138	124-145	0.664
Potassium	4.4	2.1-6.5	4.1	2.5-5.2	0.32
Chloride	99.5	84-115	99.7	85-112	0.989
Uric Acid	5.4	1.5-9.1	3	0.7-6.7	<0.001

**Table 2: Correlation between LFT**

LFT	AECOPD		Stable COPD		p value
	Median	Range	Median	range	
Bilirubin	1.2	0.3-2.5	1.7	0.4-2.6	0.003
Protein	6.8	5.4-7.9	6.8	5.5-7.6	0.968
Albumin	3.6	2.0-4.5	3.7	2.8-4.3	0.003
ALT	33.5	12-100	22	11.0-53.0	<0.001
AST	44.5	13-124	34	15-87	<0.001
ALP	101	45-578	55	28-255	<0.001

### **Correlation of different biochemical parameters in AECOPD and stable COPD patients**

From Table 1 and 2, it can be seen that among the parameters, median value of Serum Urea, Creatinine, PPBS, Uric Acid and among LFTs serum Albumin, AST, ALT, ALP - are statistically significantly higher in AECOPD group. Median Bilirubin value is significantly lower in AECOPD group. But, when the values were stratified in different ranges (i.e. - normal value, above normal and subnormal) more intensified picture was found.

### **Stratified data correlation**

#### **Urea**

It is found that 30 AECOPD patients (60%) were having urea level higher than 50 mg/dl, whereas only 5 (10%) stable COPD patients having urea value higher than that, which is statistically significant (p value 0.001).

Mean urea level in AECOPD and stable COPD patients were 46.5mg/dl and 30.3 mg/dl respectively. Range of urea level in AECOPD and stable COPD group were 11-92 mg/dl and 12-93 mg/dl respectively (Table 3).

#### **Creatinine**

Data wise 15 AECOPD patients (30%) were having higher creatinine level (>1.5 mg/dl), but only 4 stable

COPD patients (8%) having higher creatinine level than that, which is also statistically significant (p value 0.005).

Mean creatinine level in AECOPD and stable COPD were 1.2 mg/dl and 1 mg/dl respectively. Range of creatinine varies from 0.5-2.2 mg/dl in AECOPD group and 0.5-2.1 mg/dl in stable COPD group (Table 3).

#### **Sodium**

Hyponatremia (<135meq/L) was seen in 12 AECOPD patients (24%) and in only 4 stable COPD patients (8%). Hypernatremia (>150 meq/L) was found in 4 AECOPD patients (8%) but in none of the stable COPD patients. Values were statistically significant (p value 0.007)

Mean sodium level in both group was 136.3 meq/L and 136.9 meq/L. Sodium level ranges from 112-153 meq/L in AECOPD patients, and 124-145 meq/L in stable COPD patients (Table 4).

#### **Potassium**

Hypokalemia (<3.5 meq/L) was seen in 7 AECOPD patients (14%) and in 3 stable COPD patients (6%). Hyperkalemia (>5.3 meq/L) was seen in 4 AECOPD patients (8%) whereas in none of the stable COPD patients. Values were statistically significant (p value 0.04)

Mean potassium value was 4.3 and 4.1 meq/L in both groups whereas potassium value ranges from 2.1-6.5

meq/L in AECOPD patients and 2.5-5.2 meq/L in stable COPD patients. Values were statistically not significant (p value >0.5) (Table 4).

**Chloride**

Hypochloremia (<96 meq/L) was found in 12 patients (24%) in each group, whereas Hyperchloremia (>108

meq/L) was found in 7 AECOPD patients (14%) and in 5 stable COPD (10%) patients. Values were statistically not significant (p value >0.5).

Mean chloride level was 99.7 and 99.6 meq/L in both groups (Table 4).

**Table 3: Comparison of Urea and Creatinine level in AECOPD and stable COPD.**

Parameters		Group				p value
		AECOPD		Stable COPD		
		Count	Column N %	Count	Column N %	
Urea	<50 mg/dl	30	60.0%	45	90.0%	0.001
	>50 mg/dl	20	40.0%	5	10.0%	
Creatinine	<1.5 mg/dl	35	70.0%	46	92.0%	0.005
	>1.5 mg/dl	15	30.0%	4	8.0%	

**Table 4: Comparison of serum electrolytes in AECOPD and stable COPD.**

		Group				p value
		AECOPD		Stable COPD		
		Count	Column N %	Count	Column N %	
Sodium	<135 MEQ	12	24.0%	4	8.0%	0.007
	135-150 MEQ	34	68.0%	46	92.0%	
	>150 MEQ	4	8.0%	0	0.0%	
Potassium	<3.5 MEQ	7	14.0%	3	6.0%	0.042
	3.5-5.3 MEQ	39	78.0%	47	94.0%	
	>5.3 MEQ	4	8.0%	0	0.0%	
Chloride	<96 MEQ	12	24.0%	12	24.0%	0.82
	96-108 MEQ	31	62.0%	33	66.0%	
	>108 MEQ	7	14.0%	5	10.0%	

**Liver Function Test (LFT)**

Low normal serum bilirubin (<1 mg/dl), higher level of AST (> 48 IU/L), ALP (>115 IU/L) were more common in AECOPD patients. No statistical significance found in serum protein, serum albumin and ALT values in between these two groups.

Mean bilirubin, AST and ALP values were 1.2 and 1.7 mg/dl; 53.3 and 35.9 IU/L; 128 and 67.5 IU/L in AECOPD and stable COPD patients respectively. No statistical significance found in serum protein, serum albumin and ALT values in between these two groups (Table 5).

**Uric acid**

There was significant statistical difference in uric acid levels of AECOPD and stable COPD patients. AECOPD patients were having higher Uric acid level (>6 mg/dl) than stable COPD patients (p value <0.005).

Mean uric acid level in two groups were 5.3 and 3.0 mg/dl respectively, whereas highest value was 9.1 and 6.7 mg/dl respectively (Table 6).

**Blood sugar level**

AECOPD patients had higher Fasting hyperglycemia than stable COPD patients. Post prandial hyperglycemia was statistically insignificant in both the groups.

Mean FBS level in AECOPD and stable COPD were 95.3 and 83.1 mg/dl respectively, and mean PPBS were 125.3 and 108 mg/dl respectively (Table 7).

**Different patient outcome and correlation with blood parameters**

*Correlation of Blood sugar level with patient outcome*

Among the 9 AECOPD patients transferred to ICU, 8 patient (88.9%) had FBS value >110 mg/dl and 3 patient

had PPBS value >200 mg/dl. Among the 3 AECOPD patient died, all had FBS >110 mg/dl and 2 patient had PPBS >200 mg/dl. Results were statistically significant. Mean FBS and PPBS level in ICU transferred patient was 148.0 and 184.8 mg/dl. Mean FBS and PPBS level in those patients who died was 177.0 and 208 mg/dl (Table 8).

**Correlation of serum electrolyte and outcome in AECOPD**

Among 9 AECOPD patient shifted to ICU, 4 patient (44.4%) had hyponatremia and 2 patient (22.2%) had hypernatremia, which was statistically significant (p value 0.022). Among them 2 patients had hyperkalemia and 2 patients had hypokalemia (22.2% each) which was also statistically significant (p value 0.046) Among the 3 patient died, all had hyponatremia (100%) and 2 patient

had hypokalemia (66.6%), both of which are statistically significant (p value 0.017 and 0.025 respectively).

No statistically significant correlation found with serum hypo/hyperchloremia with ICU transfer or death in AECOPD patients (Table 9).

**Correlation of LFT and AECOPD patient outcome**

Low normal bilirubin level (<1mg/dl) was more frequently seen in ICU transferred (55.6%) patients and those patients who died also had low normal bilirubin level (66.7%). Higher AST (>48 IU/L) level was associated with higher ICU transfer (66.7%) and higher mortality (66.7%). Higher ALP (>115 IU/L) value was also associated with higher ICU transfer (88.90%) and higher mortality (100%). No statistical correlation found in serum protein, albumin or ALT level (p value >0.5) (Table 10).

**Table 5: Comparison of LFT in AECOPD and stable COPD.**

		Group				p value
		AECOPD		Stable COPD		
		Count	Column N %	Count	Column N %	
Bilirubin	<1 MG/DL	19	38.0%	6	12.0%	0.003
	>1 MG/DL	31	62.0%	44	88.0%	
Protein	<6GM/DL	4	8.0%	4	8.0%	1
	>6GM/DL	46	92.0%	46	92.0%	
Albumin	<3GM/DL	6	12.0%	2	4.0%	0.14
	>3 GM/DL	44	88.0%	48	96.0%	
ALT	<55 U/L	35	70.0%	42	84.0%	0.09
	>55 U/L	15	30.0%	8	16.0%	
AST	<48 IU/L	27	54.0%	40	80.0%	0.006
	>48 IU/L	23	46.0%	10	20.0%	
ALP	<115 IU/L	27	54.0%	45	90.0%	<0.005
	>115 IU/L	23	46.0%	5	10.0%	

**Table 6: Comparison of Uric acid level in AECOPD and stable COPD.**

		Group				p value
		AECOPD		Stable COPD		
		Count	Column N %	Count	Column N %	
Uric acid	<6 MG/DL	32	64.00%	48	96.00%	<0.005
	>6 MG/DL	18	36.00%	2	4.00%	

**Table 7: Comparison of FBS, PPBS in AECOPD and stable COPD.**

		Group				p value
		AECOPD		Stable COPD		
		Count	Column N %	Count	Column N %	
FBS	<110 mg/dl	34	68.0%	44	88.0%	0.016
	>110 mg/dl	16	32.0%	6	12.0%	
PPBS	<200 mg/dl	47	92.0%	49	98.0%	0.307
	>200 mg/dl	03	6.0%	1	2.0%	

**Table 8: Serum electrolytes and patient outcome.**

	ICU TRANSFER			DEATH	
		Count	Column N %	Count	Column N %
Sodium	<130 meq	4	44.4%	3	100.0%
	136-150 meq	3	33.3%	0	0.0%
	>150 meq	2	22.2%	0	0.0%
Potassium	<3.5 meq	2	22.2%	2	66.7%
	3.5-5.3 meq	5	55.6%	1	33.3%
	>5.3 meq	2	22.2%	0	0.0%
Chloride	<96 meq	4	44.4%	2	66.7%
	96-108 meq	4	44.4%	1	33.3%
	>108 meq	1	11.1%	0	0.0%

**Table 9: Serum LFT and patient outcome.**

	ICU transfer		Death		
	Count	Column N %	Count	Column N %	
Bilirubin	<1 mg/dl	5	55.60%	2	66.70%
	>1 mg/dl	4	44.40%	1	33.30%
Protein	<6gm/dl	2	22.20%	1	33.30%
	>6gm/dl	7	77.80%	2	66.70%
Albumin	<3gm/dl	1	11.10%	1	33.30%
	>3 gm/dl	8	88.90%	2	66.70%
ALT	<55 U/l	4	44.40%	1	33.30%
	>55 U/l	5	55.60%	2	66.70%
AST	<48 IU/l	3	33.30%	1	33.30%
	>48 IU/l	6	66.70%	2	66.70%
ALP	<115 IU/l	1	11.10%	0	0.00%
	>115 IU/l	8	88.90%	3	100.00%

**Table 10: Uric acid level and patient outcome.**

Parameter		ICU transfer				Death			
		Yes		No		Yes		No	
		Count	Column N %	Count	Column N %	Count	Column N %	Count	Column N %
Uric acid	<6 mg/dl	0	0.00%	31	75.60%	0	0.00%	31	66.00%
	>6 mg/dl	9	100.00%	10	24.40%	3	100.00%	16	34.00%

**Table 11: Serum urea, creatinine level and patient outcome.**

		ICU transfer		Death		p value
		Count	Column N %	Count	Column N %	
urea	<50 mg/dl	2	22.20%	0	0.00%	<.05
	>50 mg/dl	7	77.80%	3	100.00%	
creatinine	<1.5 mg/dl	3	33.30%	1	33.30%	>.05
	>1.5 mg/dl	6	66.70%	2	66.70%	

*Correlation of Uric acid level and AECOPD patient outcome*

Among the 9 AECOPD patient shifted to ICU and the 3-patient died, all had uric acid level >6mg/dl, which are statistically significant (p value 0.00 and 0.022). Mean

uric acid level in ICU transferred and general non-ICU patient was 7.9 and 4.7 mg/dl respectively (p value <0.001). Those patients who died had mean uric acid level 8.3 mg/dl (p value 0.006). Highest uric acid level observed in this group was 9.1 mg/dl (Table 11).

### *Serum Urea and Creatinine level and AECOPD patient outcome*

Among 9 AECOPD patients transferred to ICU, 7 patients (77.8%) had urea level >50 mg/dl and all the 3-patient died had urea level higher than that, which was statistically significant. (p value 0.011 and 0.029). Higher creatinine level (>1.5 mg/dl) was significantly associated with ICU transfer (p value 0.008) but not with patient death (p value 0.153).

### *Different biochemical parameters and correlation with duration of hospital stay.*

Higher serum urea level was associated with hospital stay >7 days, whereas no statistically significant correlation found between prolonged hospital stay and higher creatinine level. Both hypo and hypernatremia were significantly associated with prolonged hospital stay (>7 days), but no significant correlation was found with serum potassium and chloride level. Higher serum uric acid level was significantly associated with prolonged hospital stay (>7 days) Among LFT parameters only higher serum ALP (>115 IU/L) level was associated with prolonged hospital stay. No statistically significant association found with serum bilirubin, protein, albumin, ALT and AST level.

## **DISCUSSION**

In both case and control group male preponderance seen, 76% and 84% respectively, which corroborates the data of other workers.<sup>7</sup> Most common age group of presentation was between 55-65 yrs in both case and control arm, 56% and 42% respectively. This observation corresponds to other similar studies. This is because it was more commonly seen in patients with advanced lung disease as an expression of deterioration in host defenses at the bronchial mucosal level.<sup>8</sup> Second most common age of presentation was 65-75 yrs in both the groups. In AECOPD group 18% patients were above 75 yrs of age.

AECOPD patients had significantly higher values of serum urea, creatinine and uric acid than stable COPD patients. Hypernatremia, hyponatremia and hyperkalemia, hypokalemia - all were significantly higher in AECOPD group, but hypo/hyperchloremia not significantly related to AECOPD group. hyponatremia itself may be a predictor of poor outcome in patients of COPD. It may lead to central nervous system dysfunction; confusion, convulsions, coma, reversible cardiac conduction defect, secondary renal insufficiency even death (Suri et al, Porcel et al).<sup>9-11</sup>

AECOPD patients had lower bilirubin level than stable COPD group. Higher circulating bilirubin levels are associated with less airflow obstruction, slower longitudinal lung function decline, and less incident chronic obstructive pulmonary disease (COPD). Increased serum bilirubin in patients with moderate-to-

severe COPD is associated with decreased risk of acute exacerbations of COPD (AECOPD).<sup>12</sup>

Higher levels of serum AST and ALP were found in AECOPD patients. AECOPD patients had higher fasting hyperglycemia (FBS>110 mg/dl), but no relation was found with post prandial hyperglycemia (PPBS >200 mg/dl). Among AECOPD patient's high urea value (>50 mg/dl) was associated with poor patient outcome in respect to ICU transfer, death and prolonged hospital stay but no statistically significant association was found with poor patient outcome and creatinine level.

Serum uric acid, the final product of purine degradation, has been shown to be increased in the hypoxic state, including in patients with COPD.<sup>13-15</sup> In this study also, high uric acid level (>6mg/dl) was a major determinant of ICU transfer, mortality and prolonged hospital stay in this study (almost 100% association). In a study done by Lopez et al, a high significant correlation was noted between hypoxemia and uric acid levels in both stable and unstable COPD patients (p 0.05). Likewise, a direct relationship was noted between COPD severity and uric acid levels among stable COPD patients (p <0.001), i.e., the higher the COPD severity, the higher the uric acid levels.<sup>16</sup>

Low bilirubin, high ALP and AST level were associated with higher ICU transfer and mortality, but only high ALP level is associated with prolonged hospital stay.

## **CONCLUSION**

Among serum biochemical markers serum ALP, AST, Bilirubin have a promising impact on patient outcome. High ALP, AST and low normal bilirubin level can be an indicator of poor patient outcome. Fasting hyperglycemia can also be a good indicator for poor patient outcome. Serum uric acid level also can be a promising and easily available marker to detect poor patient outcome early in the course of hospital stay.

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