

## Role of Cystatin c and N-terminal pro-BNP in Hospitalized COPD patients with preserved left ventricular ejection fraction

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**Abstract:** Preventive medicine and early disease detection is a gold standard medicine, Chronic obstructive pulmonary diseases (COPD) is independent risk factor for cardiovascular diseases, estimated to be third leading of disability and death by 2020. Cardiovascular diseases may be unrecognized when co-exist with COPD and portend poor prognosis. Since the two shared some clinical presentation, it's a challenge for clinicians to accurately identify and differentiate patients with isolated COPD and COPD with left ventricular systolic dysfunction at early stages. Left ventricular systolic dysfunction in COPD patients is associated with poor prognosis. Cystatin c and NT-proBNP showed promising and emerged markers for early identification and ascertain prognosis of different diseases. The combined roles of the two biomarkers in COPD are subtle. We aim to find out combined role of cystatin c and NT-proBNP in COPD patients with preserved left ventricular ejection fraction. **Methods:** A retrospective study analyzed data of 1999 hospitalized COPD patients, categorized into Acute exacerbation COPD (AECOPD)  $n=1637$  (81.7%) and Stable COPD (SCOPD)  $n=362$  (18.1%). Furthermore, COPD was categorized with reduced ejection fraction 91 (10.3%) and preserved ejection fraction 795 (89.7%).

**Results:** Both Cystatin c and NT-proBNP increased with decreased left ventricular ejection fraction  $p$ -value  $<0.044$ ,  $p <0.001$  respectively. NT-proBNP found elevated in AECOPD (mean  $1420 \pm 3419$  pg/mL) than SCOPD ( $1015 \pm 2514$  pg/mL),  $p <0.039$ . Cystatin c and NT-proBNP increased with duration of admission  $p <0.003$ ,  $p <0.001$  respectively. **Conclusion:** In this study, results show that Cystatin c and NT-proBNP which may be helpfully to the clinicians even in limited resourced area to differentiate the two clinical conditions at early stages and to ascertain prognosis and treat accordingly to prevent further disease progression.

**Keywords;** Acute exacerbation chronic obstructive pulmonary disease; stable chronic obstructive pulmonary disease; cystatin c; NT-proBNP; Left ventricular ejection fraction.

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### I. Introduction

Chronic obstructive pulmonary diseases are chronic inflammatory diseases that is characterized by airflow limitation due to chronic airway remodeling and inflammations that occurred and lead to progressive irreversible obstruction of airway and destruction of lung parenchyma [1]. Is a major global burden causing disability and death worldwide with its prevalence significantly upsurges every year [2], it's estimated that by 2020 chronic obstructive pulmonary diseases (COPD) will be 3<sup>rd</sup> leading cause of morbidity and mortality worldwide [3]. Several studies showed that managing COPD patient is associated with extra cost of living and burden to the family [4-6].

COPD is independent risk factor for cardiovascular diseases and associated with two-fold increase risk of cardiovascular disability and mortality globally [7, 8]. Studies have demonstrated that patient with COPD has 4.5-fold increased risk of developing heart failure [9], heart failure in COPD patients is the leading cardiovascular causes of hospital re-admission, prolongation of hospitalization and is associated with poor prognosis [10]. However, COPD may co-exist with cardiovascular diseases and potentiate disease progression [11]. Co-existence of COPD with cardiovascular diseases portend poor short term and long term outcome [12]. Several studies showed that COPD progression if untreated may lead to left ventricles dysfunction

associated with poor outcome and increased mortality[13, 14].In COPD, inflammatory cells play a key role in commencement and progression of the disease[15].Environmental factors, life style(smoking), recurrent childhood airway infections and occupational hazards such as inhalation of noxious particles and end product fumes from industries together with/without genetic variation factors have been linked as the risk factors that causes COPD.[16]

Progressive exposure to oxidative stress and imbalance between antioxidant and oxidants causes direct and indirect injury to the lungs cell's deoxyribonucleic acid (DNA), protein and lipids, also may lead to release and transcription of inflammatory proteins , activation of proteases, down regulation of anti-protease and consequently induce apoptosis[15].Through this etiopathogenic mechanism several biomarkers including cystatin c and brain natriuretic peptides (BNP)has been found significantly raised in patient with COPD[17, 18].

The rise of Cystatin c and pro BNP biomarkers and other inflammatory markers explain the link and their biopathophysiology between COPD and cardiovascular diseases [18]. The two cardio-renal biomarkers (cystatin c and NTproBNP) are investigative test that aid clinician to determine progress ,severity of different diseases and stratifying the risk and further may be used in planning and follow up for individual treatments in COPD patients[19, 20].Cystatin c as muscle independent renal bio-makers is reported to rise in cardiovascular diseases and Chronic obstructive pulmonary diseases with left ventricular systolic dysfunction[21]. Elevated serum biomarkers cystatin c was associated with increase mortality during twelve months' follow-up in hospitalized patient with heart failure and COPD[22].

Patient with emphysema and chronic bronchitis in different studies showed to have elevated cystatin c level and more marked in severe Global initiative for chronic obstructive lung disease (GOLD) stages and in patients with smoking history[21]. Cystatin c was significant prominent in heart failure patient and is associated with poor prognosis[23]. Serum N-Terminal pro-BNP is inactive cardiac biomarker resulted from cleavage of active pro-BNP ,found substantial elevated in patient with severe COPD independent of left ventricular diastolic dysfunctions[24].In heart failure patients N-terminals pro-BNP is used as a prognostic marker for survival and disease progression and may be used to determine disease outcome and progression of the disease[25].Hawkins et al study showed that NT-proBNP is the powerfully indicator and predictor of morbidity and mortality in COPD and heart failure patients in both symptomatic and asymptomatic patients[26].

Association of N-terminal proBNP in COPD and cardiovascular diseases or Cystatin c in COPD and left ventricular systolic dysfunction has been reported by several studies, however there is striking paucity of data concerning combined role of Cystatin c andNTproBNP in COPD patient with preserved left ventricular ejection fraction. We aimed to find out the existing gap.

## **II. Method**

Its cross-section retrospective study, analyses data of admitted patients at our hospital in the respiratory department diagnosed with COPD from January 2013 to November 2017. We defined COPD as ratio of force expiratory volume in one second /force vital capacity (FEV1/FVC) less than 70% after bronchodilator test based on ICD 10 criteria /American thoracic society criteria. Furthermore, COPD was categorized in two major groups 'acute exacerbation COPD (AECOPD) and stable COPD (SCOPD). We defined AECOPD as new onset or worsening respiratory symptoms (wheezing, difficult breathing, sputum purulent, fever) which require addition of new drug/s as per GOLD definition, whereas we define stable COPD as patient with known COPD but with no new symptoms that require new addition of drug.

Baseline data were obtained including demographic data age, sex, weight. Serum biomarkers Cystatin c, N-terminal pro BNP and echocardiographic finding on left ventricular ejection fraction from the hospital data pool were retrieved. We define normal ejection fraction(EF) as preserved ejection fraction or normal left ventricular systolic function when EF is equal or above 50%, we set cut off value for concentration level of NT-proBNP and cystatin c of >900pg/mL and 0.9mg/L respectively. Other blood tests including serum creatinine, cholesterol, Low density lipoprotein (LDL), triglyceride, blood cell counts and high density lipoprotein (HDL) were also obtained from the hospital data pool and analyzed. We further transform NT-pro BNP into log-transformed data to reduce extreme values. Ethical clearance was requested and approved by the institution research administrative committee.

### **Sample size**

Our Initial sample size was 4038 patients but due to exclusion and inclusion criteria we analyzed 1999 COPD patients. Our inclusion criteria were age above 18 years, admitted patient with diagnosis of COPD based on ATS criteria. Patients admitted with other diagnoses includes renal failure, malignancy, interstitial lung diseases, asthma, recently stroke and myocardial infarction where excluded from our study.

### **Statistical analysis**

Data were analyzed using SPSS version 16. Kolmogorov-smirnov was used to confirm data normality. Data that

were normally distributed were expressed in as mean  $\pm$  standard deviation (SD) and median (range) was used to express non-normal distributed data. Mann-Whitney test or Independent sample t test was used to compare difference between two groups, chi square was used for frequency data test. Correlations between cystatin c, log-transformed NTproBNP and left ventricular ejection fraction, hospital admission (days), age, and other laboratory blood results were analyzed using the spearman correlation test and liner regression model also was used to find relationship between dependent variables (log-transformed NTproBNP, cystatin c). We regarded p value of  $\leq 0.05$  statistical significant.

### III. Results

A total of 1999 patients with Chronic obstructive lung diseases were studied,1387 (69.2%)were male and 612(3.6%) were female, giving male to female ratio of 2.3/1. Patients with acute exacerbation COPD (AECOPD) were 1637 cases (81.7%) and stable COPD (SCOPD) were 362(18. 1%).The mean weight of  $52\pm 24.7$  and mean age of the study was  $72.60\pm 10.196$ , other demographic features and parameters were as recorded in the

Parameters	AECOPD(N=1637)	SCOPD(N=362)	P-value
Age(years)	72.51 $\pm$ 10.27	92.97 $\pm$ 9.83	=0.437
Sex (male/female)	1138/499	248/114	=0.706
Hospitalization (days )	11.73 $\pm$ 5.94	12.25 $\pm$ 6.67	=0.146
NTproBNP (pg/mL)	1420.50 $\pm$ 3419.11	1015.80 $\pm$ 2514.97	<0.092*
Cystatin c (mg/L)	1.21 $\pm$ 0.47	1.18 $\pm$ 0.471	=0.450
Ejection fraction%	60.28 $\pm$ 11.09	61.90 $\pm$ 9.24	=0.730
Hemoglobin (mg/dL)	13.22 $\pm$ 20.70	13.07 $\pm$ 21.25	=0.222
Creatinine (um/L)	59.46 $\pm$ 37.30	55.88 $\pm$ 26.13	<0.084*
Neutrophils (cells/mm <sup>3</sup> )	6.23 $\pm$ 3.96	4.94 $\pm$ 2.79	<0.001*
White Blood cell (x 10 <sup>9</sup> )	7.94 $\pm$ 4.98	6.77 $\pm$ 3.10	<0.001*
LDL (mmol/L)	2.62 $\pm$ 0.82	2.64 $\pm$ 0.76	=0.640

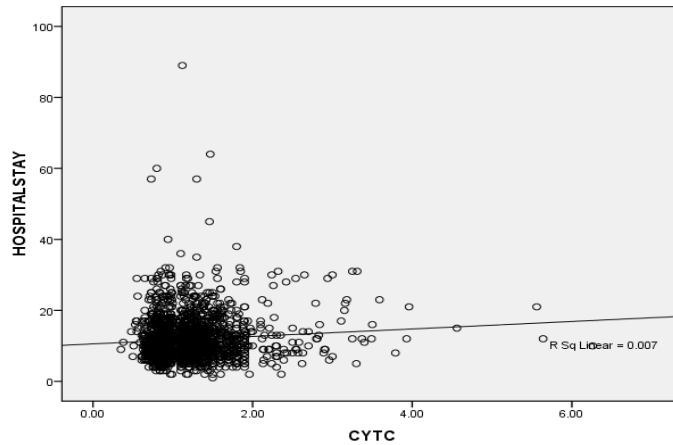
\*Statistically significant. LDL-low density lipoproteins;AECOPD-acute exacerbation COPD;SCOPD-stable COPD

**table 1.** We found, based on seasonal admission, winter season has high incidence of admission of COPD patients (33.6%), followed by summer (28.0%), and there was no admission difference between autumn and spring, whereby in autumn incidence of admission was (19.7%), spring has lowest admission incidence (18.5%). The mean days of hospital stay was  $12\pm 6$  days, with minimum duration of hospital admission of 1 day and maximum duration spent by admitted patient was 64 days. From retrieved data, left ventricular ejection fraction results of 886 COPD patients was obtained, whereby 795 patients (89.7%) had preserved ejection fraction and 91 (10.3%) patients had reduced left ventricular ejection fraction.

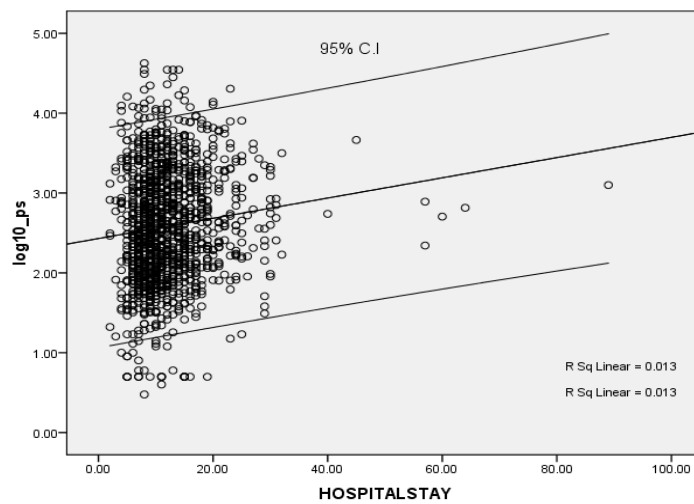
#### Cystatin c and COPD in relation to NT-pro BNP

In this study, we found that cystatin c level increases significantly with the increased NTproBNP ,correlation coefficient  $r=0.042$ ,  $p<0.001$ ,C.I 95%, however there was no difference between cystatin c in AECOPD and SCOPD( $1.206\pm 0.47, 1.180\pm 0.47$ )  $P=0.45$ , The level of NTproBNP was significant higher in AECOPD (mean  $1420\pm 3419$ pg/mL) than SCOPD ( $1015\pm 2514$ pg/mL) ( $p<0.039$ ).Based on sex preference, there was no sex difference between AECOPD and SCOPD ( $p<0.76$ ), relationship between creatinine and cystatin c was positive  $0.320$  ( $p<0.001$ ).hospital admission was prolonged in COPDpatients with higher level of Cystatin c  $p<0.003$  (**figure 1**), and log-transformed NTproBNP level $<0.001$ (**figure 2**)The mean LV ejection fraction was of AECOPD and SCOPD were ( $60.28\pm 11.09\%$ ), ( $60.19\pm 9.24\%$ )respectively .Serum biomarker cystatin c showed weak negative correlation with LV ejection fraction  $-0.068$ ( $p<0.044$ ) ,however there is moderate negative correlation coefficient between log-transformed NTproBNP with LV ejection fraction  $-0.303$ ( $p<0.001$ )(**figure 3** ).Cystatin c level and NTproBNP were significantly positive correlated with age (correlation coefficient  $r=0.262$   $p<0.001$ ), (correlation coefficient  $r=0.252$ ), $p<0.001$  respectively .Furthermore

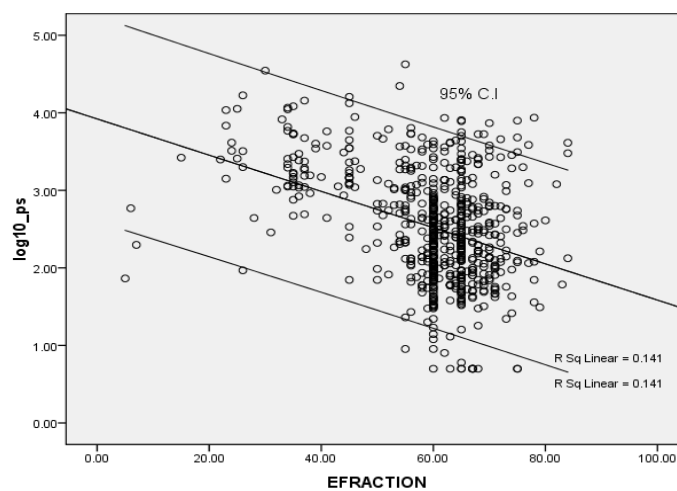
we found that elevated neutrophils and white blood cell correlate with exacerbation COPD ( p-value <0.001, p<0.001 respectively)



**Figure ;** correlation between cystatin and hospitalization (days)



**Figure 1;** relation between logNTproBNP and hospital (days)



**Figure 2;** Left ventricular ejection fraction was found inverselyproportion with logNTproBNP

#### **IV. Discussion**

Inthis study, our results explain the possibility of using combined biomarkers cystatin c and NTproBNP for early detection of COPD changes involving left ventricular systolic function and prevent further progression of the disease ,including reduction of exacerbation rate and improve quality of life .since the two diseases

shared some characteristic apart from age and risk factor such as smoking they have shared symptoms such as dyspnea which occurred later in left ventricular dysfunction and associated with poor prognosis in COPD patients. Furthermore, the two biomarkers can be used during individualization and follow-up and monitoring outcome of the given treatment.

Despite COPD being independent risk factors for cardiovascular diseases, several studies showed cardiovascular manifestation including left ventricular systolic dysfunction are the extra pulmonary manifestation of COPD(18,24). Etiopathological mechanisms explained genetic and environmental factors are the major player on initiation and progression of COPD, Hawkins NM explained the theory of genetic variabilities and development of COPD, whereby they found only 20% of individuals who had smoking history developed COPD. Different studies done showed that presences of genetic factors has contributed to the initiation and progression of COPD to individuals when exposed to environmental factors such as noxious gases, inhaled irritants or early childhood infections by stimulation of inflammatory cells of the airways (12,13).

Other factors such as hypoxia and oxidative stress showed to induce systemic inflammations by activation of airway epithelia cells, macrophages and cause reduction of numbers of cilia in the airway, results into impaired mucus clearance and airway dilation in response to stimuli(25). As systemic inflammatory process, several inflammatory cytokines IL 6,17, TNF  $\alpha$ 1 and C-reactive protein are released into the system and cause injury to the lungs, blood vessels, kidneys and heart (26,27). The release of inflammatory cytokines has been accompanying with release of biomarkers(cystatin c and NT-proBNP), study done by Erick Knight et al found that elevated level of cystatin c were independently connected with smoking, age and C-reactive protein(28). One study showed release of cystatin linked with inflammatory process, Gerald Luc et al found that elevated level of inflammatory markers tumor necrotic alpha(TNF $\alpha$ ), fibrinogen and interleukin 6 (IL-6) were strongly positive correlated with level of plasma cystatin c(29).

Regarding COPD patients, our study Cystatin c level and NTproBNP were elevated with the duration of hospitalization  $p < 0.003$ ,  $p < 0.001$  respectively. As explained by Zhang et al showed that, cystatin c may be used as a tool for evaluation and predictor of hospital admission in COPD (16). Our result differ from study done by Koyner JL showed decrease cystatin c was associated with increase hospital stay in patient COPD but associated with increase mortality(30).

In a normal individual's macrophages play a key role of body immunity and they are in large number in airways and alveoli, changes of the normal physiology of airways and lung parenchyma caused by smoking or noxious particle lead to extremely increase of this body defense line (macrophages and neutrophils) and level its significant lofty during exacerbation of COPD. In additional Viral infections may trigger increase level of cystatin c, in our study we found white blood cells and neutrophils were significant elevated in AECOPD than stable COPD  $p < 0.001$ ,  $p < 0.001$  respectively, and there was more admission during winter season (31%) than all other seasons followed by summer (28%). Wilkinson et al and others showed there were more admission of patients with AECOPD during winter season(31), and exacerbation of COPD was more due to viral infections (32), same result was found by fanny W.S et al that further exacerbation rate of COPD occurred due to common virus (33). In present study we found no sex difference on ejection fraction and exacerbation rate, apart from exacerbation rate, Wenqiao Wang et al had different results, he found male gender was independent risk factor for exacerbation of COPD but we had similar results on winter season as independent risk factor for acute exacerbation chronic obstructive pulmonary diseases exclusive of environmental factors (34)

However, we found no significant difference on the level of cystatin c between two groups (AECOPD and COPD)  $p = 0.45$ . There was significant increase of NTproBNP in AECOPD than SCOPD with  $p$  value  $< 0.092$ , study done by Huang et al compared level of NTproBNP from patients with AECOPD and control group, they found significant increase NTproBNP in AECOPD group than control group (35). COPD patients with increased NT proBNP level they had poor prognosis if not intervened, Arne Didrick Hoiseith et al found NTproBNP was significant elevated in AECOPD than SCOPD patients and found to be independent risk factors portend long term prognosis in COPD(36). Furthermore Chris P Gale et al found that NTproBNP level was significant higher in COPD patients with cardiovascular complications includes right ventricles dysfunction, left ventricle dilatation(36). In our study, we found that increases level of serum Cystatin c was inversely correlated with left ventricular ejection fraction  $p < 0.04$ , shows that cystatin c may be used as predictor of left ventricular systolic function. NTproBNP also may be used as determinant of severity of left ventricular systolic dysfunction, we further showed increase level of NTproBNP was inversely correlated with left ventricular ejection fraction  $p < 0.001$ , as explained by Francisco Javier carrasco-sanchez et al found that cystatin c was independent predictor of mortality and is associated with re-admission and prolongation of admission(37).

## V. Conclusion

Serum Cystatin c and NTproBNP found to be independent usefully biomarker used in COPD patients, used at for determine early changes of COPD with involvement of left ventricular changes and may predict duration of hospitalization and exacerbation rate. Cystatin c may be used as reliable markers for determining progression and outcome of AECOPD and SCOPD but with limited on differentiate the two. Further prospective studies with large sample size may be done to determine role of cystatin c in COPD based on right ventricular involvement and severity of COPD including lung function test as per GOLD definition.

## Study limitation

The present study is retrospective cross sectional study, we have missed data for some variables from retrieved hospital data. Therefore, we cannot exclude missed data as possible alternative justifications of our study results, secondly small number group of patients with reduced ejection fraction also make it difficult to give strong conclusions, thirdly some confounder was not included in the study such as drugs history and risk factors such smoking, occupational history and treatment given to the patients during admission, we questionable they may interfere with our results. Further prospective studies are looked-for with required patient risk factors, drug history, right ventricles studies and with further categorization of severity COPD based on lung function test as per GOLD criteria.

Conflict of interest We declare no conflict of interest

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## Abbreviations

SCOPD; Stable chronic obstructive pulmonary diseases; NTproBNP; N-terminal pro b-type natriuretic peptides; AECOPD; Acute exacerbation chronic obstructive pulmonary diseases; LVEF; left ventricular ejection fraction; CVD; Cardiovascular diseases; GOLD; Global initiative for chronic obstructive lung disease: ATS; American thoracic society

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