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Chest Heart Journal
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EDITORIAL

Pulmonary Menifestations of Dengue

S.M. Abdur Razzaque

[Chest Heart J. 2023; 47(1) : 1-3]
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Dengue is an arthropod-borne viral disease transmitted to humans through the bites of infected female mosquitoes of the Aedes genus. The dengue virus (DENV) belongs to the Flaviviridae family, and humans can be infected with any of the four antigenically distinct serotypes (DENV 1-4).[1] Around 50 million dengue infections are reported annually with 5 million cases of severe dengue in form of Dengue Hemorrhagic Fever (DHF) with annual mortality of 12,000.[2] lung disease is not common among general dengue patients, the symptoms are generally mild and affect mainly the upper airway. However, it is common and more prominent among severe dengue or fatal dengue cases. So, the problem can be various manifested and can lead to death.

Variable frequencies of respiratory symptoms have been reported in patients with dengue. The types of lung involvement include symptoms of cough, breathlessness, and hemoptysis.[3] Pulmonary complications are less common and can present as pleural effusion, pneumonitis, noncardiogenic pulmonary edema, acute respiratory distress syndrome, and pulmonary hemorrhage.[4]

Possible pathophysiology of lung disease in dengue:

The pathophysiology of lung disease in dengue is still not conclusive. There are many possible causes of lung disorders among dengue patients.

First, thrombocytopenia can directly cause spontaneous bleeding in any organs including lung in dengue patients. Diffuse alveolar hemorrhage is rare and is typically related to severe-often fatal-forms of the disease. Hemoptysis has been reported in 1.4% of DENV infections.

Second, plasma leakage during dengue infection can also be the causes of lung problems in dengue. This process proved to be a consequence of dengue immunopathology.

Third, the superimposed lung infections in dengue patients are also reported.

Some important lung diseases in dengue:

1. Pulmonary hemorrhage

Pulmonary hemorrhage is a severe lung disease in dengue. Pulmonary hemorrhage is a very rare complication of dengue infection. This condition presenting with hemoptysis has been reported in 1.4% of dengue infections.[5] This can be early detected by lung CT scan. The pattern is usually diffuse alveolar hemorrhage. In immunocompetent host, dengue must be a differential diagnosis in any cases with problem of diffuse alveolar hemorrhage. The other differential diagnoses are influenza A (H1N1), leptospirosis, malaria, and Staphylococcus aureus infection. The management is usually supportive and symptomatic.

2. Pleural effusion

As noted, pleural effusion is a sign of severe dengue. 1/3rd of dengue patients presented with PE and the frequency increased with severity and younger age.[6] It is noted that ultrasonography can help early diagnosis of effusion and can help the physician in charge to plan for management of pending severe clinical features of dengue. Conservative management is useful in cases with small effusion. However, in cases with large amount of effusion, the intercostal drainage placement is indicated. In some severe cases, hemothorax can be observed and the use of intercostal drainage placement is useful for management. Fluid replacement therapy and balancing of body fluid is required, which can be based on standard guideline for management of any dengue cases.

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3. Pneumonia

In fact, pneumonia is a common problem worldwide. The interrelationship between dengue and pneumonia is sporadically reported in several literatures. Staphylococcus pneumonia is an important concomitant problem seen in dengue patients. Cavity forming pneumonia might be observable. Also, the co-infection between dengue and influenza can result in exacerbation of pneumonia. In pediatric patients, the coinfection with Mycoplasma pneumonia is also reported.[4] Hence, the concurrent dengue and pneumonia is possible in clinical practice.

In case without coinfection, the severe form of dengue might also be prone to have pneumonia as complication and the pneumonia might be the cause of death in dengue patient.[5] The extremely rare type of pneumonia, pneumocystis pneumonia in non-HIV dengue patients is also reported.[7] To manage the problem, identification of the pathogen and assignment of proper antibiotic is required.

4.Pulmonary edema

Pulmonary edema can also be a problem in dengue. Pathophysiology is the same as the case of pleural effusion. Disturbance of colloid oncotic pressure is believed to be the main cause of the problem. Sometimes, the problem can also be seen in concordant with other dengue systemic problems such as dengue myocarditis. It should also be noted that pulmonary edema can sometimes be iatrogenic.[8]

5. Respiratory distress syndrome

Respiratory distress syndrome is the most serious lung disease in dengue, and this can result in respiratory failure. Sometimes, the problem can also be seen in concordant with other dengue systemic problems such as acute pancreatitis and myocarditis. Aggressive management is needed and can be helpful in increasing survival. Management of ARDS in dengue fever is similar to ARDS of any other etiology. Role of noninvasive ventilation in improving morbidity and mortality of dengue associated ARDS is proved. The supportive management for dengue also influences the outcome of the condition. Apart from respiratory support, minimizing nosocomial complications and preventing risk factors play prominent roles in its management.[9]

Chest imaging pattern in Dengue

The most observed chest imaging found in dengue is pleural effusion, which is often bilateral. When unilateral, it usually occurs on the right. CT thorax is a good modality for evaluation of dengue patients with respiratory complaints. Frequently detected findings on chest CT included pleural effusion, atelectasis, consolidation, and ground-glass opacification.[10] Parenchymal abnormalities are less common, have no specific distribution pattern, and can be accompanied by interlobular septal thickening and nodules, representing edema or pulmonary hemorrhage.

Conclusion:

Lung disease is not common among general dengue patients; however, it is common among severe dengue cases or fatal cases. The problem can be various manifested and can lead to death. The clinician must recognize the lung disease among the patient with dengue and manage it properly.

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ORIGINAL ARTICLE

Predictive Value and Cut Off Level of Fractional Exhaled Nitric Oxide (FENO) as an Inflammatory Biomarkers in Distinguishing Asthma –COPD Overlap (ACO) from COPD

Prodip Kumar Sarkar[1], Mushfiq Newaz Ahmed[2], Jewel Barai[1], Mohammad Ezazul Karim[3], Manoranjan Roy[4], SK Shahinur Hossain[5], Md. Khairul Anam[5], Bipul Kanti Biswas[5], Mohammed Shahedur Rahman Khan[6]

Abstract

Background*: Asthma–COPD overlap (ACO) is difficult to diagnose because it is characterized by persistent airflow limitation, and patients present with several manifestations that are usually associated with both asthma and COPD. ACO is a disease entity which warrants early screening and isolation from COPD for which FeNO is a useful tool.Asthma and COPD overlap isassociated with significant health status impairment increased execerbations, and increased hospitalizations.). Fractional exhaled nitric oxide (FeNO) is an easy, sensitive, reproducible and noninvasive marker for directly detecting eosinophilic airway inflammation*

Objective: *The aim of the study was to find out the performance of fractional exhaled nitric oxide (FeNO) for the differentiation of ACO and COPD.*

Methods: *This cross sectional observational study conducted at the Department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital from October 2019 to September 2020in collaboration with the Department of Pathology, Radiology and Respiratory Laboratory. A total of 102 patients with Asthma-COPD overlap (ACO) and COPD were enrolled in this study. . A receiver operating characteristic curve was constructed for identifying an optimal cut-off value of FeNO for ACO and COPD.*

Results: *Out of 102 patients with Asthma-COPD overlap (ACO) and COPD. Out of which 42 patients were asthma-COPD overlap (ACO) and another 60 were COPD group. Mean FVC and FEV_1 were significantly higher in ACO than COPD group. And also mean post-bronchodilator FEV_1/FVC was significantly higher in ACO than COPD group (65.0±2.8% vs 47.9±9.7%). Mean FEF 25-75 was found 1.77±0.23 L/sec in ACO group and 0.61±0.46 L/sec in COPD group, that was significant between two groups. (p<0.001). Mean FeNO was found 27.8±9.2 ppb in ACO group and 12.8±5.6 ppb in COPD group, which indicated mean FeNO level was significantly higher in ACO group than COPD group (p<0.001). Based on the receiver-operating characteristic (ROC) curves FeNO level had area under curve 0.913.*

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Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value ≥16.5 ppb, with 90.5% sensitivity and 71.7% specificity for prediction of ACO. The test of validity shows sensitivity of FeNO level ≥16.5ppbvs ACO was 90.5%, specificity 71.7%, accuracy 79.4%, positive and negative predictive values were 69.1% and 91.5% respectively.

Conclusion: *In conclusion, FVC, FEV_1, post-bronchodilator FEV_1/FVC, FEF 25-75 and FeNO were statistically significant when compared to ACO and COPD group. The results of this study provide evidence that inflammatory biomarkers of FeNO can be used to support the diagnosis of ACO.*

Keywords: *COPD, ACO, FeNO*

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Introduction

Asthma and COPD have been regarded as two distinct disease entities that often overlap[1]. Asthma and COPD overlap has a prevalence of 15%-20% in patients with obstructive airway disease (Asthma and COPD)[2]and associated with significant health status impairment, increased exacerbations, and increased hospitalizations[3].Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) issued a joint document describing that Asthma-COPD overlap (ACO) is characterized by persistent airway limitation with several features usually associated with both asthma and COPD[4].

The clinical phenotypes and underlying mechanisms of ACO have attracted interest during recent years. However ACO remains somewhat controversial and there is no consensus on the best definition of ACO[5]. The clinical phenotypes, including biomarkers of ACO remain elusive. Inflammatory biomarker such as fractional exhaled nitric oxide (FeNO) is sometimes used to distinguish between asthma and COPD (Global Initiative for Asthma, 2019). Fractional exhaled nitric oxide (FeNO) is an easy, sensitive, reproducible and noninvasive marker for directly detecting eosinophilic airway inflammation[6]. However, the exact role of FeNO in patients with ACO remains to be defined.[7,8]

In the present study, we performed a Cross sectional-observational study that aimed to evaluate the diagnostic performance of FeNO, which may be able to indicate airway eosinophilic inflammation in patients with COPD and to differentiate ACO from COPD.

Materials and methods

This cross sectional observational study conducted at the Department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital from October 2019 to September 2020in collaboration with the Department of Pathology, Radiology and Respiratory Laboratory.

Inclusion criteria:

- Asthma-COPD overlap (ACO) and COPD patients defined as per GOLD and GINA guideline.
- Age: ≥40 years

Exclusion criteria:

- Cystic fibrosis
- Bronchiectasis
- Hematological disorder
- Used any oral corticosteroid in the previous 4 weeks
- Receiving anti IgE therapy
- Exacerbation of COPD in previous 4 week

Study Procedure

Selections of patients with Asthma-COPD overlap (ACO), Asthma and COPD from NIDCH according to inclusion and exclusion criteria. Eligible participants were explained the study and written informed consent were obtained from all. Data were recorded by a standard proforma (History and clinical examination details). In first phase a written informed consent was obtained from the patients of obstructive airway diseases fulfilling the inclusion and exclusion criteria.The relevant socio-demographic characteristics and history of the smoking were collected by face to face interview using predesigned interveiw schedule. After complection of interview the patient was examined

physically all information and findings were recorded in the preformed proforma.Some base line investigations were done after diagnosis like-CBC, ECG, LFT, S. Creatinine, S. electrolytes, TSH. Chest x ray, Pure Tone Audiometry, Blood sugar. FeNO levels and blood eosinophil counts were measured in specimens from patients naïve to inhaled corticosteroids (ICS) and those using ICS. All patients underwent the following on the same day: FeNO, spirometry, BHR or bronchodilator reversibility, sputum induction and blood collection.

Observations & results

This cross sectional observational study was carried out in the Department of Respiratory Medicine, NIDCH, Dhaka from October 2019 to September 2020. One hundred and two patients with ACO and COPD were included in this study based on inclusion and exclusion criteria. Out of which 42 patients were asthma-COPD overlap (ACO) and another 60 were COPD group. All the information was collected by face to face interview of the patients. Value of $p < 0.05$ was taken as statistically significant. The findings were organized by descriptive and inferential statistics.

Table I

Distribution of the study patients by demographic characteristics (n=102)

Demographic characteristics	ACO (n=42) n	%	COPD(n=60) n	%	*P* value
Age (years)					
40-59	19	45.2	27	45.0	
60-79	20	47.6	31	51.7	
≥80	3	7.1	2	3.3	
Mean±SD	60.5	±12.8	61.6	±10.7	[a]0.614[ns]
Range min-max)	40.0	-82.0	40.0	-86.0	
Sex					
Male	32	76.2	50	83.3	[b]0.371[ns]
Female	10	23.8	10	16.7	
BMI (kg/m^2)					
<18.5	2	4.8	9	15.0	
18.5-24.9	37	88.1	43	71.7	
25.0-29.9	1	2.4	7	11.7	
≥30.0	2	4.8	1	1.7	
Mean±SD	22.5	±2.7	21.7	±3.1	[a]0.145[ns]
Range (min-max)	18.1	-30.8	16.5	-30.7	

ns= not significant
[a]P value reached from unpaired t-test
[b]P value reached from chi square test

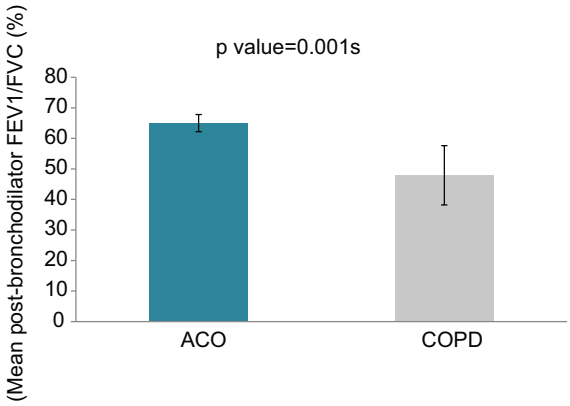

Fig.-1: *Bar diagram showing post-bronchodilator FEV_1/FVC of the study patients(n=102)*

s= significant
P value reached from unpaired t-test

Table II

Distribution of the study patients according to smoking (n=102)

Smoker	ACO (n=42) n	%	COPD (n=60) n	%	*P* value
No	7	16.7	5	8.3	0.165[ns]
Yes	35	83.3	55	91.7	
If yes					
<20 (pack/yr)	11	26.2	14	23.3	
≥20 (pack/yr)	24	57.1	41	68.3	

ns= not significant
P value reached from chi square test

Table III

Distribution of the study patients according to FVC and FEV_1 (n=102)

	ACO (n=42) Mean±SD	COPD (n=60) Mean±SD	*P* value
FVC (L)	2.52±0.49	1.89±0.91	0.001[s]
Range (min-max)	1.64-3.16	0.91-2.99	
FEV_1 (L)	1.53±0.28	0.91±0.37	0.001[s]
Range (min-max)	1.01-1.99	0.40-1.69	

s= significant
P value reached from unpaired t-test

Table IV

Distribution of the study patients according to FEF 25-75(n=102)

	ACO (n=42) Mean±SD	COPD (n=60) Mean±SD	*P* value
FEF 25-75 (L/sec)	1.77±0.23	0.61±0.46	0.001[s]
Range (min-max)	1.34-2.19	0.17-2.23	

s= significant

P value reached from unpaired t-test

Table V

Distribution of the study patients according to FeNO(n=102)

	ACO (n=42) Mean±SD	COPD (n=60) Mean±SD	*P* value
FeNO (ppb)	27.8±9.2	12.8±5.6	0.001[s]
Range (min-max)	13.0-42.0	3.0-23.0	

s= significant

P value reached from unpaired t-test

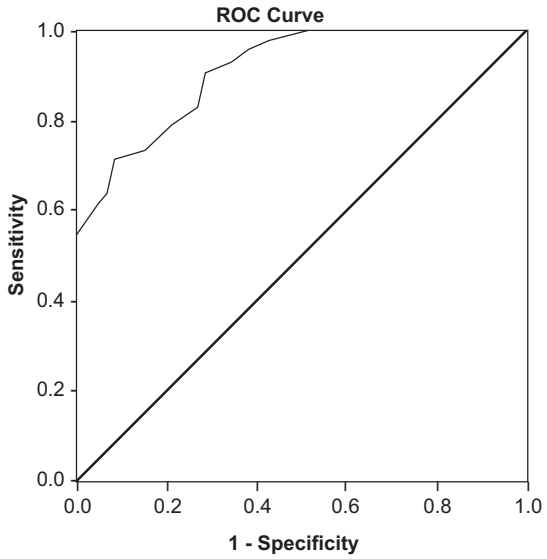

Fig.-2: *Receiver-operating characteristic (ROC) curve of FeNO level for prediction of ACO*

The area under the receiver-operating characteristic (ROC) curves for prediction of ACO is depicted in table VI. Based on the receiver-operating characteristic (ROC) curves FeNO level had area under curve 0.913. Receiver-operator characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value of ≥16.5 ppb, with 90.5% sensitivity and 71.7% specificity for prediction of ACO.

Table VI

Receiver-operating characteristic (ROC) curve of FeNO level for prediction of ACO

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI) Lower bound	Upper bound
FeNO level	≥14.5	95.2	63.3	0.913	0.862	0.965
	≥15.5	92.9	66.7			
	≥16.5	90.5	71.7			
	≥17.5	83.3	73.3			
	≥18.5	78.6	80.0			
	≥19.5	73.8	85.0			

Table VII

Comparison between ACO and FeNO level (n=102)

FeNO	ACO	
	Positive(n=42)	Negative(n=60)
≥16.5ppb (n=55)	38(True positive)	17(False positive)
<16.5ppb (n=47)	4(False negative)	43(True negative)

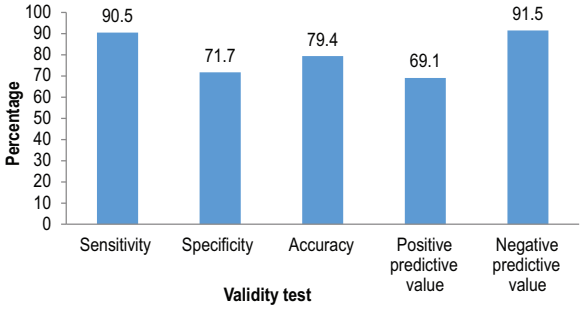

Figure 3: *Bar diagram showing ssensitivity, specificity, accuracy, positive and negative predictive values of the FeNO level.*

Discussion

This study it was observed that almost half (47.6%) patients belonged to age 60-79 years in ACO group and 31(51.7%) in COPD group. The mean age was found 60.5±12.8 years in ACO group and 61.6±10.7 years in COPD group. The mean age was not statistically significant (p>0.05) between two groups. In this present study it was observed that more than three fourth (76.2%) of the patients were male in ACO group and 50(83.3%) in COPD group. Whereas, female was 10(23.8%) and 10(16.7%) in ACO and COPD group respectively. The difference was not statistically significant (p>0.05) between two groups. Almost similar study conducted by Takayama et al.[9] where they observed male was 42(75.0%) in ACO group and 54(83.1%) in COPD group, the difference was not statistically significant (p=0.368).

We found in this study 35(83.3%) patients were smoker in ACO group and 55(91.7%) in COPD group. Majority 24(57.1%) in ACO group and 41(68.3%) of the patients in COPD group had smoked ≥20 pack per year. The difference was statistically significant (p<0.05) between two groups. In this current study it was observed that majority (88.1%) patients were BMI 18.5-24.9 kg/m^2 in ACO group and 43(71.7%) in COPD group. The mean BMI was found 22.5±2.7 kg/m^2 in ACO group and 21.7±3.1 kg/m^2 in COPD group. The mean BMI was not statistically significant (p>0.05) between two groups. Similarly Takayama et al.[9] consisted that mean BMI was 22.6±5.6 kg/m^2 in ACO group and 23.0±3.7 kg/m^2 in COPD group, that was not significant between two groups (p=0.679). Kobayashi et al.[10] reported that mean BMI was 24.0±3.8 kg/m^2 and 23.4±3.8 kg/m^2 in ACO group and COPD group respectively, the difference was not significant between two groups(p=0.331).In this study it was observed that mean FVC was found 2.52±0.49 L predicted in ACO group and 1.89±0.91 L predicted in COPD group. The mean FEV_1 was found 1.53±0.28 L predicted in ACO group and 0.91±0.37 L predicted in COPD group, which indicated mean FVC and FEV_1 were significantly higher in ACO than COPD group. Kobayashi et al.[10] consisted that the mean FVC was 3.32±0.99 L in ACO group and 3.09±1.73 L in COPD group, that was not significant between two groups (p=0.428). We found in this study mean post-bronchodilator FEV_1/FVC was found 65.0±2.8 percent in ACO group and 47.9±9.7 percent in COPD group. The differences was statistically significant (p<0.05) between two groups. Almost similarly study observed by de Llano et al.[8] where they found mean post-bronchodilator FEV_1/FVC was 62.2±19.8 percent in ACO group and 54.3±18.3 percent in COPD group. The differences was statistically significant (p<0.05) between two groups.

We found in this study mean FeNO was found 27.8±9.2 ppb in ACO group and 12.8±5.6 ppb in COPD group. The differences was statistically significant (p<0.05) between two groups. Manshadi et al.[11] study showed that ACO subjects have a higher mean level of FeNO than COPD-only; however, it was not statistically significant. In contrast, one study showed that ACO patients had a significantly higher level of FeNO than COPD (p< 0.01)[12]. Takayama et al.[9] reported that the FeNO levels were higher in patients with ACO (median 24.5 ppb with range 14.0–39.5 ppb) than in patients with COPD (median 16.0 ppb with range 12.0–20.0 ppb) *P*<0.01). Kobayashi et al.[10] consisted that mean FENO levels were significantly higher in patients with ACO than in those without ACO (38.5±28.6 ppb vs20.3±11.0 ppb, *P*<0.001). In this study it was observed that based on the receiver-operating characteristic (ROC) curves FeNO level had area under curve 0.913. Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value ≥16.5 ppb, with 90.5% sensitivity and 71.7% specificity for prediction of ACO. Manshadi et al.[11] reported that the significant optimal cut-off values to differentiate ACO from COPD-only was for Def 1 FeNO ≥36 ppb with the sensitivity of 39%,

specificity of 88% and AUC of 0.63, p=0.046, and Def 3 FeNO e"23.5 ppb with the sensitivity of 80% and specificity of 50%, and area under the curve (AUC) of 0.65, p=0.047[9]. More subjects with ACO definition 1 compared to COPD-only had FeNO values ≥36 ppb (33% vs. 12%; p=0.046) with sensitivity, specificity, and area under the curve (AUC) of 39%, 88%, and 0.63, respectively; with ACO definition 2, no FeNO cut-off values were statistically significant; and with ACO definition 3, FeNO values e" 23.5 ppb (80% vs. 51%; p=0.047) with sensitivity, specificity, and area under the curve (AUC) of 80%, 50%, and 0.65Higher levels of FeNO in ACO patients compared to those with COPD-only were observed in all studies. Chen et al.[12]; Alcazar-Navarrete et al.[13]; Kobayashi et al.[10] and Deng et al.[14] studies showed that FeNO can be useful to differentiate ACO from COPD and introduced optimal cut-off values of 19, 22.5, 23, and 29 ppb with a sensitivity of 68, 70, 73, 80%, and specificity of 75, 75, 68.2, and 73%, respectively. The area under the curve (AUC) for the cut-off 19, 22.5, 23 and 29 ppb was 0.79, 0.78, 0.74, and 0.85, respectively (Chen et al.[12]; Alcazar-Navarrete et al.[13]; Kobayashi et al.[10]; Deng et al.[14]).In this present study it was observed that FeNO e"16.5ppb, true positive 38 cases, false positive 14 cases, false negative 4 cases and true negative 43 cases in identification by ACO. The validity test shows sensitivity of FeNO level e"16.5ppbvs ACO was 90.5%, specificity 71.7%, accuracy 79.4%, positive and negative predictive values were 69.1% and 91.5% respectively. Manshadi et al.[11] consisted that when significant cut-off values for this purpose were FeNO e" 36 ppb with the sensitivity of 39% and specificity of 88% for definition 1. If applied in practice, this will mean that when the test is positive we will mostly be right, but we will be able to identify less than 50% of the patients or missing more than 50%. For definition 3, FeNO e" 23.5 ppb with the sensitivity of 80% and specificity of 50%, we will identify 80% of the patients with the disease, i.e., ACO, be missing only 20% but not be right with the ACO diagnosis in about 50% of the patients. One study conducted on 132 COPD and 57 ACO, showed that FeNO is a good predictor to differentiate ACO from COPD with AUC of 0.78. They introduced the cut-off value of 22.5 ppb with a sensitivity of 70% and a specificity of 75%. This variation in the results creates uncertainty and calls for studies to be done using same types of measuring tool for FeNO, describing the population selection and reference to a common definition of ACO[12].

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ORIGINAL ARTICLE

Histopathological Pattern of Bronchial Carcinoma among Women in Bangabandhu Sheikh Mujib Medical University

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Abstract

Background and Aims: *Bronchial carcinomas arise from the bronchial epithelium or mucous glands and carcinoma tissue material can be obtained by Computed Tomography (CT) guided biopsy or Fibre optic Bronchoscopy (FOB) with needle biopsy. Till now treatment of bronchial carcinoma is directed according to histological diagnosis. To observe histopathological pattern of Bronchial carcinoma and current clinico-pathological status of Bronchial Carcinoma among women in Bangabandhu Sheikh Mujib Medical University.*

Methods*: This observational study was conducted on cases of suspected bronchial carcinoma patients and previously diagnosed cases of bronchial carcinoma on management process using pre-designed data collection sheet. Lung biopsy was done under CT guidance in Department of Radiology, BSMMU and other centers or FOB with needle biopsy from lesion in Respiratory Medicine, BSMMU and biopsy material was sent for histopathological study for confirmation of diagnosis in Department of Pathology, BSMMU and also other centers in case of diagnosed patients.*

Results: *In this study the mean age of patient was 64.1±8.0 years for females. Maximum patients (57.9%) had age group 60-70 years followed by 23.7% patient's age 71-80 years. Considering histopathological findings, maximum patients had adenocarcinoma (39.5%), small cell carcinoma (21.1%), squamous cell carcinoma (13.2%) and others types (26.3%).*

Conclusions: *Adenocarcinoma now seems to be the most common histological subtype of lung cancer in this study. An in-depth understanding of the detrimental effects of various environmental exposures when combined with a comprehensive analysis of the molecular basis of lung cancer will lead to the establishment of new and efficacious strategies for the prevention and treatment of this devastating disease.*

Keywords: *Bronchial carcinoma, Lung biopsy, Histopathological sub-types*

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Introduction

Lung cancer is the most commonly diagnosed cancer worldwide[1] but its geographic distribution shows marked regional variation. Age-standardized incidence rates vary over a wide range, more than fourfold among men and fivefold among women[2]. This marked variation in rates cannot be explained on the basis of diagnostic practices and data quality alone. However, the lung cancer epidemic is on the rise in the developing world. Though smoking is single major determinant of lung cancer, in the past, rates tended to be highest in urban areas, which led to conjecture that air pollution might be a cause of the lung cancer epidemic[3].

Lung cancer manifests itself in multiple histologic types as classified by conventional light microscopy. The four major types, as traditionally identified by histologic appearance, include squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell undifferentiated carcinoma. Together these four types of lung cancer account for more than 90% of lung cancer. These primary bronchial carcinomas are composed of a family of epithelial tumors that represent a subset of a larger collection of lung and pleural tumors classified by the World Health Organization (WHO) in 2004[4].

Cigarette smoking increases risk for all major histologic types[5]. A few occupational exposures, such as chloromethyl ethers and radon have been linked to small cell lung cancer. Worldwide, adenocarcinoma tends to be the most common cell type seen in female lung cancer patients, accounting for approximately one-third of all lung cancer diagnoses in most regions[6]. The resulting evidence from studies that have tested these hypotheses indicates that the trend of increasing rates of adenocarcinoma is primarily due to changes in cigarette smoking behavior and features of cigarettes (etiologic or protective) agents and individual susceptibility to these agents.

Whether women are more or less susceptible than men to the carcinogenic effects of cigarette smoke is controversial. While lung cancer in never smoking women is more common than in never smoking men and up to 80% of lung cancer cases in women are related to smoking[7]. The proportion of never smoking lung cancer patients was more than twice as high for women than for men in a case-control study[8]. The gender differences in susceptibility may be related to differences in nicotine metabolism and in metabolic activation or detoxification of lung carcinogens; women have higher levels of DNA adducts than men, which may result in greater susceptibility to carcinogens[9]. Hormonal factors may also play a role in susceptibility. Conversely, early menopause (age 40 years or younger) was associated with a decreased risk for adenocarcinoma (odds ratio 0.3). More recent large randomized studies suggest that the use of hormonal therapies such as estrogen and progestin may be associated with an increased risk of lung cancer in women[10].

Lung cancer patients are investigated with several tests like sputum and pleural fluid. However for histopathological tissue diagnosis from Peripheral lung lesions CT guided FNAC or biopsy is investigation of choice.

Methods

This cross-sectional study was conducted in Bangabandhu sheikh Mujib Medical University (Indoor and OPD) of Bangladesh. A standardized field questionnaire was formulated in consonance with the British Medical Research Council (BMRC) questionnaire on Respiratory symptoms and then translated into Bangla for the convenience of data collection from the respondents. Before the commencement of actual data collection, the nature and intent of the study were explained to the participants in their vernacular language with the help of local collaborators. Non probability purposive sampling was the choice of sampling. Total of 30 women, all histopathologically proven lung cancer were selected as study subjects. Data were collected by face-to-face interviews taken one by one using a predesigned, pretested questionnaire.

Our questionnaire-based interview had three parts. The first part was based on the participant's socio-demographic profile, including name, age, sex, religion, marital status, educational status and monthly income. The second part included work-related history, including questions comprising all the details of present and past employment, including working time, working section, duration of employment, and use of personal protective equipment. Data were collected using a preformed data collection sheet (questionnaire). All

information regarding clinical features was recorded in a data collection sheet. Suspected new patients were selected for study as per inclusion and exclusion criteria. Diagnosis of Bronchial Carcinoma was based on physical findings, laboratory investigations and radiological imaging. After proper counseling an informed written consent was taken from every participant. Information about demographic and clinical profile and laboratory parameters were collected on the predesigned data sheet. Laboratory parameters were include complete blood counts, sputum for malignant cell, chest X-ray, CT scan of chest with contrast, Pleural fluid study (if present), USG of whole abdomen etc. Material was collected from suspected Lung lesion by various methods including CT guided core biopsy and by flexible Bronchoscopy with biopsy, brush, washing etc. Cytological or Histological specimen was examined under light microscopy for confirmation of diagnosis of histopathological pattern.

All the data were checked and edited after collection. Then the data were entered into computer and statistical analysis of the results being obtained by using windows based computer software devised with Statistical Packages for Social Sciences (SPSS-23) (SPSS Inc, Chicago, IL, USA).

The variables were expressed as mean and standard deviation. The qualitative data were analyzed by chi-square test and quantitative data were analyzed by ANOVA test. The correlation study was analyzed by Spearman's correlation test. Multiple comparison tests were analyzed by one way ANOVA test. P value of less than 0.05 was considered statistically significant.

The proposal of this study was approved at the 174th meeting of IRB (Institutional Review Board) of BSMMU (Bangabandhu Sheikh Mujib Medical University), Bangladesh (NO. BSMMU/2019/973) held on 19th January, 2019. Informed written consent was taken from every patient before enrollment.

Results

in the present study, maximum patients (57.9%) had age group 60-70 years followed by 23.7% patients age 71-80 years. The mean age of the respondents was 64.1±8.0 years, minimum age 46 and maximum 80 years (Table-1). Maximum patients (50.0%) had no exposure to any particle or smoke, 31.6% patients had exposure to particles (cooking fume) and 18.4% patients had history of passive smoking (Table-2). Regarding hormonal status of the female patients, most of the patients (71.1%) had history of menopause followed 21.1% patients had both history of menopause and history of OCP and 7.9% patients had no of history of menopause (Table-3). Most common clinical presentation was cough (55.5%), followed by weight loss (68.4%), anorexia (55.3%), SOB (47.4%), fever (34.2%), chest pain (34.2), Hemoptysis (18.4%), hoarseness (13.2%), dysphasia (13.2%) (Table-4). Clinical examination findings revealed maximum patients had anemia (36.8%) followed by lymphadenopathy (21.1%), clubbing (15.8%) and jaundice (10.5%). Chest examination findings were observed maximum patients had mass lesion (52.6%) followed by pleural effusion (26.3%), collapse (21.1%) and consolidation (13.2%) (Table-4).

Considering chest X-ray findings, maximum patients had mass lesion (68.4%) followed by effusion (26.3%), collapse (21.1%), hilar enlargement (13.2%), consolidation (13.2%) (Table-5). Regarding CT scan of chest contrast maximum patients had mass lesion (65.8%) followed by mediastinal LN (34.2%), effusion (28.9%), hilar LN (28.9%), consolidation (23.7%), collapse (23.7%), pleural thickening (5.3%) (Table-6). Considering histopathological findings, maximum patients had adenocarcinoma (39.5%), small cell carcinoma (21.1%), squamous cell carcinoma (13.2%) and others types (26.3%) (Figure-1)

In our study we found no significant association of histopathological findings among hormonal status of the study patients (p>0.05) (Table-7), smoking status of the study patients (p>0.05) (Table-8) and age of the study patients (p>0.05) (Table-9).

Table I

Age distribution of the study patients (n=38)

Age groups	Frequency	Percentage (%)
40-50	3	7.9
51-60	4	10.5
60-70	22	57.9
71-80	9	23.7
Total	38	100.0
Mean±SD	64.1±8.0	
Range	(46-80) yrs	

Table II

Distribution of the study patients by smoking status (n=38)

Smoking status	Frequency	Percentage (%)
Passive smoker	7	18.4
Exposure to particles (cooking fume)	12	31.6
No exposure to any particle or smoke	19	50.0
Total	38	100.0

Table-III

Distribution of the study patients by hormonal factor (n=38)

Hormonal factor	Frequency	Percentage (%)
History of menopause	27	71.1
Both H/O menopause and history of OCP	8	21.1
No history	3	7.9
Total	38	100.0

Table IV

Distribution of the study patients clinical presentation (n=38)

Clinical presentation	Frequency	Percentage (%)
Fever	13	34.2
Anorexia	21	55.3
Weight loss	26	68.4
Cough	28	73.7
Haemoptysis	7	18.4
Chest pain	13	34.2
SOB	18	47.4
Hoarseness	5	13.2
Dysphasia	5	13.2
Bone pain	2	5.3
Pleural effusion	10	26.3
Mass lesion	20	52.6
Collapse	8	21.1
Consolidation	5	13.2
Pneumothorax	2	5.3

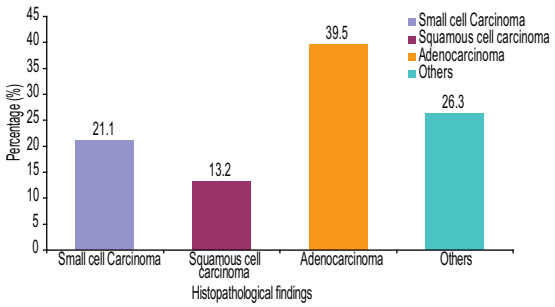

Fig.-1: *Bar diagram showing the histopathological findings*

Table V

Distribution of the study patients by chest X-ray PA view (n=38)

Chest X-ray findings	Frequency	Percentage (%)
Effusion	10	26.3
Mass Lesion	26	68.4
Collapse	8	21.1
Hilar enlargement	5	13.2
Consolidation	5	13.2
Cavitary lung lesion	1	2.6

Table VI

Distribution of the study patients by CT scan of chest with contrast (n=38)

CT scan of chest with contrast	Frequency	Percentage (%)
Effusion	11	28.9
Mass Lesion	25	65.8
Collapse	9	23.7
Mediastinal LN	13	34.2
Hilar LN	11	28.9
Consolidation	9	23.7
Cavitary lung lesion	1	2.6
Pleural thickening	2	5.3
Pericardial effusion	1	2.6
Lymphangitis carcinomatosa	1	2.6

Table-VII

Association of histopathological findings with hormonal factor (n=38)

Histopathological findings	n	Hormonal factor			p-value
		History of menopause	Both H/O menopause and history of OCP	No history	
Small cell carcinoma	8	7(87.5%)	0(0.0%)	1(12.5%)	0.242^{ns}
Squamous cell carcinoma	5	5(100.0%)	0(0.0%)	0(0.0%)	
Adenocarcinoma	15	9(60.0%)	4(26.7%)	2(13.3%)	
Others	10	6(60.0%)	4(40.0%)	0(0.0%)	
Total		27(71.1%)	8(21.1%)	3(7.9%)	

ns= not significant, Chi-square test was done

Table-VIII

Association of histopathological findings with smoking status (n=38)

Histopathological findings	n	Smoking status			p-value
		Passive smoker	Exposure to particles (cooking fume)	No exposure to any particle or smoke	
Small cell carcinoma	8	2(25.0%)	1(12.5%)	5(62.5%)	0.178^{ns}
Squamous cell carcinoma	5	2(40.0%)	3(60.0%)	0(0.0%)	
Adenocarcinoma	15	1(6.7%)	4(26.7%)	10(66.7%)	
Others	10	2(20.0%)	4(40.0%)	4(40.0%)	
Total	38	27(71.1%)	8(21.1%)	3(7.9%)	

ns= not significant, Chi-square test was done

Table-IX

Association of histopathological findings with age of the patients (n=38)

Histopathological findings	n	Age group (in years)				p-value
		40-50	51-60	60-70	71-80	
Small cell carcinoma	8	1(12.5%)	2(25.0%)	4(50.0%)	1(12.5%)	0.761^{ns}
Squamous cell carcinoma	5	0(0.0%)	0(0.0%)	3(60.0%)	2(40.0%)	
Adenocarcinoma	15	2(13.3%)	1(6.7%)	8(53.3%)	4(26.7%)	
Others	10	0(0.0%)	1(10.0%)	7(70.0%)	2(20.0%)	
Total	38	3(7.9%)	4(10.5%)	22(57.9%)	9(23.7%)	

ns= not significant , Chi-square test was done

Discussion

This cross sectional observational study conducted including thirty eight histopathologically proven lung cancer in case of woman admitted in Bangabandhu Sheikh Mujib Medical University, Dhaka to evaluate the prevalence and histopathological variation of Bronchial carcinoma and current demographic pattern of lung cancer among women. In this study the mean age of patient was 64.1±8.0 years for females. Maximum patients (57.9%) had age group 60-70 years followed by 23.7% patients age 71-80 years.

In present study most common clinical presentation was cough (55.5%), followed by weight loss (67.4%), dyspnea (55.3%), SOB (47.4%), fever (34.2%), chest pain (34.), Hemoptysis (18.4%), hoarseness (13.2%), dysphasia (13.2%). In agreement with our study, one study [11] reported the most common presenting symptom was cough, seen in 87.1% patients, weight loss 64.65%, dyspnoea 81.03%, hoarseness of voice 11.20%, fever 19.82%, and chest pain 70.68%.

In present study the clinical examination findings were observed maximum patients had anaemia (36.8%) followed by lymphadenopathy (21.1%), clubbing (15.8%) and jaundice (10.5%). Another study[11] reported peripheral lymphadenopathy was seen in 20 (17.2%) patients, pallor 47.4%, clubbing 29.3%. In present study, pleural effusion was seen in 26.3% of patients similar to that reported by another study[12]. An Indian study[13] reported it in 28% cases. Another study[14] found pleural effusion 28.0%.

Adenocarcinoma was the common lung cancer in our study (39.5%), followed by small cell carcinoma 21.1% and squamous cell carcinoma 13.2%. Houston et al. (2014) reported the same. Two Indian studies[12,15] reported squamous cell carcinoma to be the most common type. Our findings are in conformity with studies in other parts of the world where adenocarcinoma has replaced squamous cell carcinoma as the most common type of lung cancer[16]. However, two studies[17,18] had reported the commonest types to be adenocarcinoma and small cell carcinoma respectively, which is consistent with present study. A study[19] reported adenocarcinoma was the most common histological subtype found in 40.9% patients followed by squamous cell carcinoma (32.7%) and small cell carcinoma (20%). Our results were in concordance with three Indian studies[20,21,22] reporting adenocarcinoma as a commonest subtype. The shift in the incidence of squamous cell carcinoma to adenocarcinoma may be associated with the switch from non-filtered to filtered cigarettes and the depth of inhalation had been altered. Smoke from filtered milder cigarettes may be more deeply inhaled that result in deposition of carcinogen more peripherally, giving rise to adenocarcinomas[23].

In our patients, considering histopathological findings, maximum patients had adenocarcinoma (39.5%), small cell carcinoma (21.1%), and squamous cell carcinoma (13.2%) and others types (26.3%). Similar findings reported in many literatures. The four major histologic subtypes of lung cancer include squamous cell carcinoma (25%), adenocarcinoma (30%), large cell carcinoma (10%), and small cell carcinoma (20%). Contrary to previous reports, squamous cell carcinoma has the highest incidence among our cases (52%), while adenocarcinoma (27%), large cell carcinoma (6%), and small cell carcinoma (15%) have almost similar incidences[24,25,26]

In our study out 15 adenocarcinoma patients, 4(26.7%) patients' exposure to particles (cooking fume) and 1(6.7%) patients were passive smoker. Among 5 squamous cell carcinoma patients 3(60.0%) exposure to particles (cooking fume). Out 10 other type of histopathology 4(40.0%) had exposure to particles (cooking fume) and 2(20.0%) patients were passive smoker. An Iraninan study[27] reported the low percentage of smoker female patients. The reason for this could be due to passive smoking in women which was impossible to investigate because of the retrospective nature of the study, the passive smoking was leading to increased number of SCC cases in our study. Another Iranian study[28] showed the distribution of the histological types of lung cancer in patients. Histopathologically, 70 (28.9%) cases were adenocarcinomas, among them 57.9% female patients were passive smoker. 69 (28.5%) cases were small cell carcinomas, among the 7.9% female were passive smoker, and 12 (5.0%) cases were classified as other histologies among them 2.6% female patients were passive smoker.

In present study, no significant association of histopathological findings was found with hormonal status of the study patients. Out of 38 lung cancer patients 71.1% patients had history of menopause and 21.1% patients had history of both menopause and history of OCP. Among 15 adenocarcinoma patients 60% were menopausal and 40% had both menopausal and history of OCP. Out of 5 patients of squamous cell carcinoma 100% patients were menopaused. The effect of circulating estrogens is the most clinically relevant biological difference between NSCLC in both genders. Estrogen stimulation causes proliferation in NSCLC cell lines through the estrogen receptor (ER-alfa and

ERbeta). ERs are expressed in both normal lung tissue and lung tumors in both sexes. However, patterns of hormonal-receptor expression according to gender and smoking status or its prognostic factor remains undefined.

Adenocarcinoma was the most common lung cancer in our study (38.5%), followed by small cell carcinoma (21.1%), squamous cell carcinoma (13.2%). Our findings are in conformity with studies in other parts of the world where adenocarcinoma has replaced squamous cell carcinoma as the most common type of lung cancer.

Conclusion

Adenocarcinoma now seems to be the most common histological subtype of lung cancer in this study. The worldwide epidemic of lung cancer in women continues to trouble clinicians and researchers alike. An in-depth understanding of the detrimental effects of various environmental exposures when combined with a comprehensive analysis of the molecular basis of lung cancer will lead to the establishment of new and efficacious strategies for the prevention and treatment of this devastating disease.

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ORIGINAL ARTICLE

Association Between Serum Neutrophil Lymphocyte Ratio and Control of Asthma

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Abstract

Background: *Asthma is a serious global health issue. Assessment of disease control is essential in management of asthmatic patients. Recently, serum Neutrophil-Lymphocyte ratio have been evaluated in various chronic diseases and is also reported as a prognostic marker for future exacerbation in case of Chronic obstructive pulmonary disease. However, there are only limited knowledge regarding its association with asthma.*

Objective: *To find out the association of serum Neutrophil lymphocyte ratio (NLR) in assessment of asthma control.*

Methods: *This was a cross-sectional observational study in which 110 diagnosed cases of asthma were conveniently recruited from Respiratory medicine department of National Institute of Diseases of Chest and Hospital from June 2020 to September 2021. Asthma symptom control was assessed by asthma control test. FEV1 was measured by spirometry to detect level of airflow obstruction. Blood was collected from each subject and Complete blood count was performed by Autoanalyzer. Neutrophil lymphocyte ratio was calculated manually from CBC. All data were collected into a preformed questionnaire. After completion of data collection, analysis was done through Statistical Package for Social Science (SPSS) version 23.*

Results: *Mean age of the study subjects was 31.6±10.9 years with male (72.7%) predominance. The mean Neutrophil-Lymphocyte ratio was 2.72±0.69. The NLR was observed to increase with increasing severity of airflow obstruction and this difference was statistically significant (p=0.001). Again, mean NLR in those with uncontrolled asthma differed significantly from those with well controlled and partially controlled asthma (p<0.05). A moderate negative correlation (r= -0.762; p=0.001) was found between NLR and Asthma control. Multivariate regression analysis revealed an independent association between Neutrophil-Lymphocyte ratio and Asthma control status.*

Conclusion: *In this study, it was found that NLR was higher in patients with uncontrolled asthma and had a moderate association with asthma control status.*

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Introduction:

Asthma is a globally significant non-communicable disease with major public health consequences for both children and adults, including high morbidity and mortality in severe cases. According to Darwesh et al.[1] asthma is ranked as the 14th most important chronic disease. As per report of Global Asthma Network[2], around 300 million people have asthma worldwide, and it is likely that by 2025 a further 100 million may be affected. In 2016, the Global Burden of Disease (GBD) study estimated that there were 339.4 million people worldwide affected by asthma and this represents a 3.6% increase in age-standardized prevalence since 2006 (Global Asthma Report, 2018). In Bangladesh alone, the first national asthma prevalence study found that 5.2% or 7 million people suffer from asthma (National Guidelines-Asthma & COPD, 2016); current prevalence may be even higher.

There is good evidence that asthma can be controlled with appropriate treatment. However, despite the continuous development and readily available effective asthma management strategies, a lack of proper implementation of treatment guidelines results in asthma control that is far below optimum in the majority of patients (GINA, 2020)[3]. The consequences of suboptimal control are significant. Poorly controlled asthma can lead to irreversible airway remodeling that is less amenable to asthma treatment and episodes of exacerbation that may be life-threatening or even fatal. According to WHO[4] estimates, there were 417,918 deaths due to asthma at the global level and 24.8 million DALYS (disability adjusted life years) attributable to Asthma in 2016.

There are some parameters which are used to assess control of asthma. Asthma Control Test (ACT) is a useful clinical method in this regard, but it includes data of several clinical features which show subjective variations. Spirometry is another standard technique to measure current asthma status, but it needs special settings and adequate patient's education to perform. So, a simple and easily measurable biochemical marker for monitoring of asthma is needed. Inflammatory markers have an important place in the pathogenesis of asthma disease. Cytokines in the pathogenesis of asthma cause an increase in neutrophils, eosinophils and natural killer cells (Fu et al., 2014)[5] and lymphocytes have a central role as a conductor of the immune orchestra that contributes to asthma (Holgate, 2012)[6]. These two factors lead to elevated NLR in asthma. Recently, several studies have found association between NLR and disease severity of several other chronic diseases. In patients of COPD, NLR is reported as a prognostic marker for future exacerbation. This study was carried out to evaluate the role of NLR as a marker in asthma control in comparison with the other evaluating markers. Since measurement of serum NLR is simple and widely available, it may significantly aid in improving care of asthma patients.

Methods:

This was a Cross-sectional observational study carried out at Department of Respiratory Medicine, National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka from June 2020 to September 2021.

A total 110 asthma patients attending in outpatient department of NIDCH were selected as per inclusion & exclusion criteria

Inclusion criteria:

- Pre diagnosed case of Asthma (According to GINA, 2020)
- Age ≥12 years

Exclusion criteria:

- Smoking
- Other obstructive/restrictive lung diseases (COPD, Bronchiectasis, DPLD)
- Co-morbid conditions (DM, HTN, Ischemic Heart Disease)
- Chronic kidney disease
- Hepatic failure
- Active malignancies
- Inflammatory Bowel or musculoskeletal Disease
- Receiving systemic steroids within 4 weeks
- Having fever and cough with sputum complaints
- Pregnancy

Operational definitions:

Asthma: Patients fulfilling the following criteria (GINA 2020)[3] -

- One or more symptoms of wheeze, shortness of breath, chest tightness and cough which:

Occur variably over time and vary in intensity, often worse at night or on waking, often triggered by exercise, laughter, allergen, cold air & often appear or worsen with viral infections

- Post-bronchodilator FEV_1/FVC ≥0.75 and increase in FEV_1 >12% and >200 ml from baseline 10 minutes after nebulization with 200-400 micrograms of salbutamol or equivalent

Asthma control test (ACT)

Validated standardized self-administered 5-item questionnaire that are related to the asthma symptoms, use of rescue medications and the impact of asthma on the daily life.

Total score ranges from 5-25. Cutoff points for well controlled asthma ≥20 points, for partially controlled asthma: 16-19 points and for uncontrolled asthma ≤15 points (Nathan et al.)[7].

NLR- Ratio of neutrophil and lymphocyte using either absolute count or the percentage/relative count obtained from a Complete blood count with differentials. Normal level of NLR is 1-2 (Zahorec R, 2001)[8].

Severity of Airflow Obstruction in Asthma-

Level of Severity	FEV_1
Normal	≥80%
Mild	<80-65%
Moderate	<65-50%
Severe	<50-30%
Life-threatening	<30%

Results:

This cross-sectional study was carried out with an aim to find out the association between neutrophil lymphocyte ratio (NLR) & assessment of asthma control in patients attending in the outpatient department of NIDCH. A total 110 patients of asthma who fulfilled the inclusion and exclusion criteria during the period from June 2020 to September 2021 were included in this study. The results are shown below-

Table I

Distribution of the study population by age (n=110)

Age (years)	Number of patients	Percentage
d"20	22	20.0
21-30	32	29.1
31-40	39	35.5
41-50	10	9.1
51-60	6	5.5
>60	1	0.9
Mean ±SD	31.6	±10.9
Range (min-max)	15.0	-62.0

Table I shows that more than one-third 39(35.5%) of the participants belonged to age group 31-40 years. The mean age was 31.6±10.9 years.

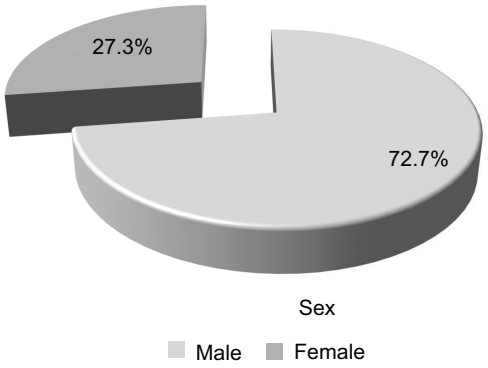

Figure 1: *Pie chart showing sex distribution of the study population (n=110)*

Figure 1 shows that Male patients were predominant 80(72.7%) over female 30(27.3%) with a male female ratio of 2.7:1.

Table II

Distribution of the study population according to severity of airflow obstruction (FEV_1% predicted) (n=110)

Severity of airflow obstruction	FEV_1 (% predicted)	Number of patients	Percentage (%)
Normal	≥80	21	19.1
Mild	<80-65	51	46.4
Moderate	<65-50	38	34.5
Severe	<50-30	0	0.0
Mean ±SD		69.4±10.0	

Table II shows that 51(46.4%) participants had mild airflow obstruction and 38(34.5%) had moderate airflow obstruction. 21(19.1%) respondents had normal FEV_1 (% predicted). The mean FEV_1 was 69.4±10.0%.

Table III shows that majority 66(60.0%) patients had partially controlled asthma (ACT score 16-19). The mean ACT score was 18.5±3.3.

Table IV shows that mean neutrophil was 71.7±9.1%, mean lymphocyte was 27.7±6.0%, mean NLR 2.72±0.69

Table V shows that mean NLR was significantly higher in patient with moderate airflow obstruction when compared less severe airflow obstruction.

Table III

Distribution of the study population according to asthma control status (n=110)

Asthma control status	ACT score	Number of patients	Percentage
Well controlled	≥20	37	33.6
Partially controlled	16-19	66	60.0
Uncontrolled	≤15	7	6.4
Mean ±SD		18.6±3.2	

Table IV

Determination of serum NLR of the study population (n=110)

Parameter	Neutrophil (%)	Lymphocyte (%)	NLR
Mean±SD	71.7±9.1	27.7±6.0	2.72±0.69
Range (min-max)	44.7-89.2	18.0-42.2	1.14-4.44

Table V

Association between Airflow obstruction and NLR (n=110)

FEV_1 percent predicted	NLR Mean±SD	F value	df	P value
Normal (n=21)	1.86±0.59			
Mild (n=51)	2.80±0.50	36.51	2	0.001[s]
Moderate (n=38)	3.09±0.54			

s= significant, P value reached from ANOVA test

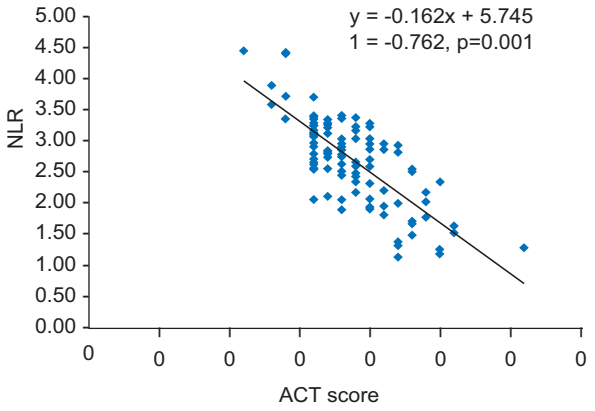

Fig.-2: *Scatter plot showing correlation between ACT and NLR*

A scatter plot of ACT score against NLR was plotted. A significantly negative Pearson correlation was found between ACT score and NLR of asthma patients (r = -0.762; p=0.001)

Table VI

Multivariate logistic regression analysis to predict ACT score (<15)

Parameters	Adjusted OR	95% CI for OR Lower	Upper	P value
Age	0.614	0.125	3.028	0.549[ns]
Sex	0.234	0.048	1.146	0.073[ns]
FEV_1 (% predicted)	15.351	1.882	69.450	0.016[s]
NLR	8.479	1.421	57.726	0.029[s]
Peripheral blood eosinophilia	0.171	0.180	7.609	0.097[ns]
H/O previous exacerbation within last 1 year	2.515	0.240	26.344	0.442[ns]
H/O previous hospitalization within previous 2 years	3.667	0.323	41.590	0.294[ns]

s= significant, ns= not significant

p-value reached from multivariate analysis by binary logistic regression analysis. OR=Odd's Ratio

In multivariate analysis, FEV_1 and NLR were found to be independent predictors for uncontrolled asthma. However, age, sex, peripheral blood eosinophilia, H/O previous exacerbation and H/O previous hospitalization failed to add statistically significance to the model (p>0.05). It is evident from Table VI that among the predictors, the strongest one was FEV_1 (p=0.016, adjusted OR 15.351) followed by NLR (p=0.029, adjusted OR 8.479).

Discussion:

The mean age of the participants was 31.6±10.9 years with an age range of 15-62 years. In a study of Hendy et al.[9], their observed mean age was 35.44±13.0 years. More than 1/3rd of the participants 39(35.5%) of the current study belonged to age group of 31-40 years. Similarly, a study conducted by Bishwajit et al.[10] over the south Asian people (n=35,929) having asthma, where they found that majority of the participants belonged to the age group of 30–44 years.

Among 110 participants, male was 80(72.7%) and female was 30(27.3%). Male female ratio was 2.7:1. Abdulnaby et al.[11] also found male predominance (67 out of 120 participants) in their study. On the other hand, Darwesh et al.[1] observed that male was 48.0% and female was 52.0%. Hendy et al.[9] also reported that out of 90 subjects, 40% were male and 60% were female. Even in the National Asthma Prevalence Study (Hassan et al.[12]), the male-female ratio was 0.9:1 in the adult population. The male predominance in the present study sample could be due to ours being a hospital-based study with a greater proportion of male patients visiting the hospital OPD in our socio-cultural context.

Majority of the respondents (69 out of 110; 62.7%) had normal body weight, mean BMI was 21.5±2.2 kg/m^2. Similarly, Zhong et al.[13] demonstrated that 51.9% participants had normal BMI. Furutate et al.[14] documented that mean BMI was 22.4±2.89 kg/m^2.

The current study observed that mean neutrophil was 71.7±9.1%, mean lymphocyte was 27.7±6.0% and mean NLR was 2.72±0.69. Hendy et al.[9] also found mean NLR was 2.77±1.87 among 90 asthmatics included in their study. Similar finding was observed by Gungen and Aydemir[15], where they found the mean NLR was 2.2±1.2 among 142 participants. Recent Japanese study by Mochimaru et al.[16] also found that NLR level was elevated among asthmatic adults (2.48±0.14).

Regarding risk factors of poor asthma control, 24(21.8%) participants had H/O previous exacerbation within last one year and 12(10.9%) had H/O previous hospitalization within previous 2 years. We observed that 4(57.1%) out of 7 uncontrolled cases and 20(30.3%) out of 66 partially controlled cases had H/O previous exacerbation within last one year. No H/O exacerbation was found in well controlled asthma. The LIAISON study conducted on 8111 asthmatics of 12 European countries reported similarly that the percentage of patients reporting exacerbations in the last 12 months was lower in patients with controlled asthma compared to those with partially controlled and uncontrolled disease (Braido et al.[17]). Among 110 participants, majority 72(65.5%) had normal serum eosinophil count (50-400/mm^3) and 38 had high eosinophil count. Although, high serum eosinophilia is thought to be a factor for poor asthma control (GINA), we did not find any significant relationship among them.

The mean FEV_1 % predicted of the respondents in the current study was 69.4±10.0%. The greatest proportion 51(46.4%) of the participants had mild air flow obstruction (FEV_1<80-65%). 38(34.5%) respondents had moderate airflow obstructions (FEV_1 <65-50%) and 21(19.1%) were found to have normal FEV_1 (e"80%). A study conducted on 50 adult patients having asthma (Darwesh et al.[1]) reported that the mean FEV_1 was 62.7±18.1% which was consistent with present work. Patients with severe airflow obstructions (FEV_1 <50%) could not be included into the study as they were experiencing severe exacerbation due to either lower respiratory tract infections &/or currently on systemic steroid.

We observed that mean NLR was significantly higher in moderate airflow obstruction when compared with mild obstruction and normal airflow (3.09±0.54, 2.80±0.50 and 1.86±0.59 respectively). Darwesh et al.[1] reported that the mean NLR of asthmatic cases was significantly increased to 3.7 with increase of severity of airflow obstruction (p<0.001). Huang et al.[18] performed a systemic review and meta-analysis of studies to investigate the relationship between the NLR and asthma,

where they found that mean NLR was higher (2.02) in stable asthma and larger NLR values were associated with uncontrolled asthma.

Regarding asthma control status according to ACT score, majority 66(60.0%) of the participants had partially controlled asthma (ACT score 16-19) followed by 37 had well controlled (33.6%) and 7 had uncontrolled asthma (6.45%). The mean ACT score was 18.5±3.3. Gungen and Aydemir[15] also found that mean ACT was 18.3±5.1. Hendy et al.[9] documented that the number of well controlled cases (ACT e"20) was 20 (44.4%) and partially controlled & uncontrolled cases were 25 (55.5%). A study done by Yan et al.[19] based on ACT scores also found good asthma control in 31.61% of patients with asthma, partial asthma control in 40.27%, and poor asthma control in 28.12%. Current study had very small number of uncontrolled asthma patient which was quite opposite to international studies. The cause might be the exclusion of patients experiencing severe asthma attack as they could not perform spirometry properly.

The current study observed that mean NLR was significantly higher in uncontrolled asthma in comparison to partially and well controlled asthma (3.97±0.45, 2.91±0.41 and 2.15±0.63 respectively). Darwesh et al.[1] reported that the mean NLR of asthmatic cases was significantly increased to 3.7 with no control of asthma ($p<0.001$) which was in concert to the present study. Again, the study done by Hendy et al.[9] found mean neutrophil/ lymphocyte percentage was higher in asthmatics with ACT less than 20 versus those having ACT at least 20 (with statistically significant difference), which means that neutrophil/lymphocyte ratio increases as asthma becomes uncontrolled.

The present study observed that, there was a negative correlation ($r= -0.756$; $p=0.001$) between ACT score and NLR in asthma patients. Hendy et al. (2019) also found similar significant negative correlation between NRL and ACT score ($p=0.028$). Similarly, Gungen and Aydemir[15] also determined a statistically significant correlation between NLR and ACT ($r=0.206$, $p=0.042$).

In multivariate analysis, FEV_1 % predicted and mean NLR were found to be independent predictors for ACT score. Among the predictors, the strongest one was FEV_1 % predicted as it could predict uncontrolled asthma more accurately (adjusted OR=15.351, $p=0.016$) than NLR (adjusted OR=8.479, $p=0.029$). However, age, sex, peripheral blood eosinophilia, H/O previous exacerbation and H/O previous hospitalization failed to add statistically significance to the model ($p>0.05$).

So, in present study, we found that, the increment of mean NLR (2.72±0.69) of asthma patients was occurred according to reducing level of asthma control (mean ACT score 18.6±3.2) and had a statistically moderate significant negative correlation between serum NLR and ACT score.

Conclusion:

So, we concluded that serum neutrophil-lymphocyte ratio was independently associated with ACT score and thus could predict the control status of asthma. Increased NLR in a patient with apparently stable asthma should alert us about loss of control of asthma and risk of future exacerbation. We should assess the patient more thoroughly and initiate appropriate management In future, this finding should be validated by calculating the cut-off value of NLR along its sensitivity, specificity, PPV and NPV to predict control of asthma through further studies.

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ORIGINAL ARTICLE

Differentiating Pulmonary Tuberculosis with COPD from COPD alone by Platelet Lymphocyte ratio

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Abstract

Background*: Pulmonary tuberculosis, is a frequent comorbid condition in patients of chronic obstructive pulmonary disease, which is associated with significantly increased morbidity and mortality. It is often difficult to distinguish acute exacerbation of chronic obstructive pulmonary disease from development of pulmonary tuberculosis in patients of chronic obstructive pulmonary disease, at an earlier stage. Platelet–lymphocyte ratio, raised in inflammatory conditions, obtained from complete blood count. Whether platelet lymphocyte ratio as a potential marker can identify patients of chronic obstructive pulmonary disease complicated with pulmonary tuberculosis, is yet to be verified.*

Objective: *The purpose of the study was to assess the validity of platelet–lymphocyte ratio for differentiation of patients between pulmonary tuberculosis with chronic obstructive pulmonary disease from patients of chronic obstructive pulmonary disease alone.*

Methods: *This cross-sectional analytical study was conducted in department of Respiratory Medicine of National Institute of Diseases of the Chest and Hospital, Mohakhali, Dhaka from November 2019 to March 2021. Forty (40) patients of known chronic obstructive pulmonary disease suspected of having pulmonary tuberculosis were investigated with platelet–lymphocyte ratio. A receiver operating characteristic curve was constructed for identifying an optimal cut-off value for PLR, which compared later on with Sputum for X pert MTB/RIF assay result.*

Results: *In this study, the mean platelet lymphocyte ratio of patients of chronic obstructive pulmonary disease withpulmonary tuberculosis (or X pert positive group) (295.41 ± 124.88) was higher than respondents of chronic obstructive pulmonary disease withoutpulmonary tuberculosis (or X pert negative group) (197.70± 64.36).Platelet lymphocyte ratio >197.25 is best cut-off value in distinguishing patients between pulmonary tuberculosis with chronic obstructive pulmonary disease from patients of chronic obstructive pulmonary disease alone. At Platelet–lymphocyte ratio>197.25, sensitivity, specificity, positive predictive value, negative*

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predictive value, accuracy is 79.3%, 81.8%, 92%, 60% and 80% respectively. Area under the curve for platelet lymphocyte ratio was 0.804, 95% confidence interval [CI], 0.662-0.946; p <0.003).

Conclusion: *This study showed that platelet lymphocyte ratio was significantly higher in chronic obstructive pulmonary disease complicated with pulmonary tuberculosis from chronic obstructive pulmonary disease alone. So, Platelet–lymphocyte ratio could be developed as a useful marker for identifying tuberculosis infection in chronic obstructive pulmonary disease patients.*

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INTRODUCTION

Chronic obstructive pulmonary disease is a systemic inflammatory disease that is common, preventable and treatable. It is one of the leading causes of death globally[1]. Global COPD statistics (2018), according to the Global Burden of Disease (GBD), COPD is already the third leading cause of death worldwide. Most national data show that<6% of the adult population have COPD and prevalence & burden of COPD are projected to increase over the coming decades due to continued exposure to COPD risk factors[2]. In recent decades, morbidity and mortality have been found to be significantly increased in patients with COPD complicated with PTB[3].

The interrelationship between TB and COPD is very complex. A substantial number of patients develop TB-associated COPD[4,5,6,7]. This is the most commonly reported relationship. However, many different associations have also been published. COPD patients are at high risk of developing pulmonary TB. COPD is a common comorbidity in patients with TB, second only to diabetes[8,9,10]. History of TB negatively impacts the long-term course of COPD with early mortality and increased frequency of exacerbations[11]. COPD also alters the clinical presentation of TB and is a risk factor for increased morbidity and mortality from TB[12,13]. Early diagnosis of PTB in COPD patients could contribute to prevent further disease progression and transmission of TB within the community, which could be an important public health issue[14]. Simultaneously, after completing treatment for pulmonary TB, about two-thirds of patients have pulmonary function abnormalities, with obstructive defect being the main abnormality[15].

So, it is necessary to keep a high suspicion on the development of PTB in COPD patients[16]. It is difficult to diagnose PTB in COPD patients due to similar clinical features of acute exacerbation of COPD and classical radiological findings often absent, at an earlier stage of PTB. Moreover, tests for confirmation of the diagnosis of PTB, not routinely performed in all COPD patients. So, a need raised for searching out of an indicator or marker that could readily provide a clue or guidance, for earlier screening of the COPD patients whether they complicated with PTB or not.

Inflammatory markers derived from routine blood examination, are extensively used for differential diagnosis and prognostic evaluation in several situations, such as inflammatory diseases, cancer & cardiovascular diseases. The importance of platelet lymphocyte ratio (PLR) has been emphasized as a marker in some disorders like non-small-cell lung cancer, acute coronary syndrome, end stage renal disease & so on[17-19]. Like that - Platelet lymphocyte ratio (PLR) an easily obtainable inflammatory marker whether could act as a potential aid for diagnosis of PTB in COPD, is unclear.

Materials and methods

This study was conducted in the Department of Respiratory Medicine of National Institute of the Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh from December 2019 to March 2021. It was a cross-sectional analytical study.

Inclusion criteria of sample

Patients of known COPD (diagnosed by spirometry) Suspected of having PTB (based on history, clinical examination and X-ray Chest).

Exclusion criteria of sample

1. History of past tuberculosis.
2. Presence of known haematological disorders (CML, Myelofibrosis) or known malignancy.

3. Currently under oral-steroid therapy and or history of steroid use (within last 3 month), NSAID, antiplatelet medications.
4. History of radio therapy or chemo therapy within 4 weeks before enrolment.
5. History of recent (within 30 days) COPD exacerbation with or without hospitalization.

Study Procedure

Patients of known COPD suspected of having PTB attending OPD and admitted inpatient department of Respiratory Medicine, NIDCH, Mohakhali, Dhaka. Purposive sampling was done in this study. Enrolment of patients of known or previously diagnosed COPD patients suspicious of having PTB (based on spirometry), according to inclusion and exclusion criteria. Eligible participants were being explained about the study and written informed consent obtained from all participants. Enrolled patients were then evaluated properly by taking history, physical examination and investigations like full blood count, Chest X ray, sputum for AFB, sputum for X pert MTB/RIF assay. All data were recorded systematically in a preformed data collection sheet. Data were then analyzed using appropriate statistical formula. After collection, data were checked manually by data collection sheet and relevant investigations of the patients. Statistical analysis was done by using SPSS (Statistical Package for Social Sciences) software version 22. Mean with standard deviation, frequency & their percentage were calculated to express descriptive part of the study. Descriptive analysis was shown in table, graph, chart and curve. For inferential statistics, categorical data were analyzed with Chi-Square test and quantitative data were analyzed with student "t" test. All statistical tests were performed at 5% levels of significance and level of $p < 0.05$ were considered significant.

Operational Definitions

PLR ratio

PLR defined as ratio obtained by dividing absolute count of platelet by absolute lymphocyte count in complete blood count. PLR are 36.63~149.13 and 43.36~172.68, respectively in Male and female[20]

OBSERVATIONS & RESULTS

This cross-sectional study was carried out among 40 COPD patients, suspicious of having PTB, who attended OPD and admitted inpatient department of Respiratory Medicine, National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka. The study was performed to find out, whether Platelet lymphocyte ratio can differentiate between patients of COPD with PTB from patients of COPD alone. Value of $p < 0.05$ was taken as statistically significant. The findings were organized by descriptive and inferential statistics.

Table-I

Demographic characteristics of the study subjects (n=40)

Characteristics	Frequency (number of the patients)	Percentage (%)
Age (years)		
40 - 49	8	20.0
50 - 59	16	40.0
60 - 69	10	25.0
≥70	6	15.0
Mean ± SD	58.07 ± 9.28	
Min – max	40 - 75	
Residence		
Rural	30	75.0
Urban	10	25.0
Occupation		
Cultivator	14	35.0
Businessman	8	20.0
Service holder	6	15.0
Shopkeeper	4	10.0
Housewife	2	5.0
Fisherman	2	5.0
Driver	2	5.0
Carpenter	2	5.0

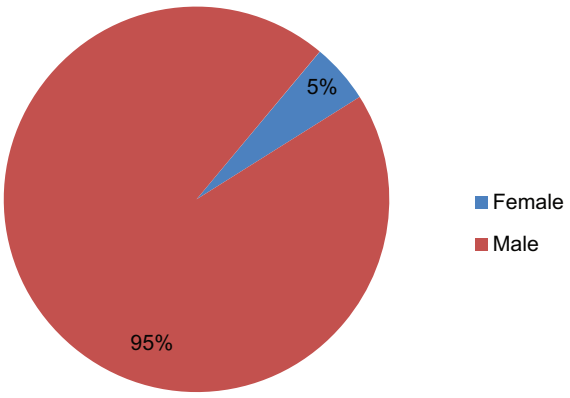

Fig.-1: *Distribution of the study subjects according to gender (n=40)*

Table-II

Distribution of the study subjects according to co-morbidity (n=40)

Co-morbidities	Frequency (n)	Percentage (%)
Diabetes mellitus	25	62.5%
Hypertension	5	12.5 %
Anaemia	10	25%

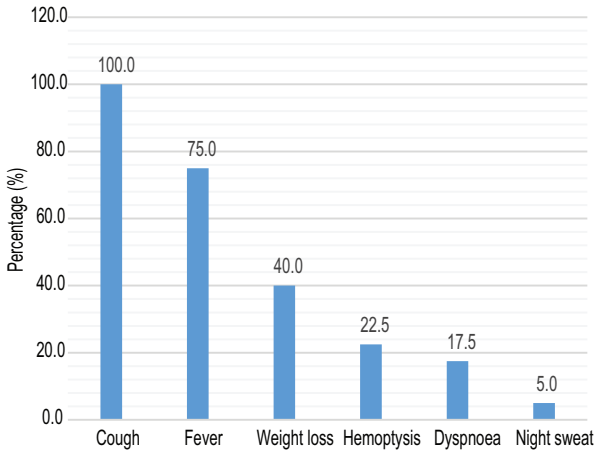

Fig.-2: *Distribution of the study subjects according to symptoms (n=40)*

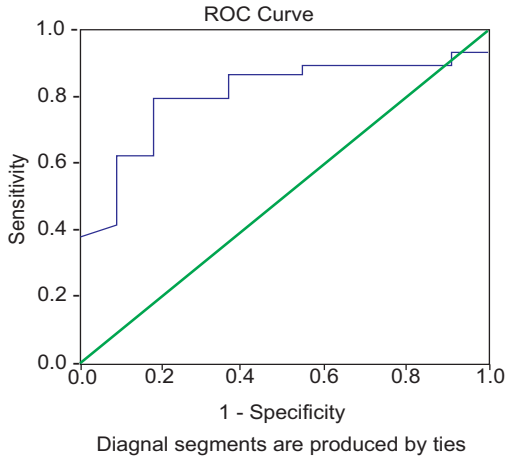

Fig.-3: *ROC curve of PLR in differentiating patients between PTB with COPD from patients of COPD alone*

Table-III

Lab finding of the study subjects (n=40)

Lab findings	COPD with PTB (Mean ± SD) (n=29)	COPD without PTB (Mean ± SD) (n=11)	p-value t, df
PLR	301.19 ± 125.56	191.35 ± 48.49	0.008* 2.80, 38

Table IV

AUC of PLR in differentiating PTB with COPD from patients COPD alone (n=40)

Variable	Area	SE	p-value	95% CI	
				Lower Bound	Upper Bound
PLR	0.804	0.072	0.003	0.662	0.946

Table-V

Youden index of PLR in differentiating between patients of PTB with COPD from patients of COPD alone

PLR	Sensitivity	Specificity	Youden Index J= Max (SEN+SPE-1)
170.57	0.862	0.455	0.317
171.48	0.862	0.545	0.408
179.97	0.862	0.636	0.498
192.00	0.793	0.636	0.429
197.25	0.793	0.818	0.611
199.00	0.759	0.818	0.577
199.80	0.724	0.818	0.542
200.32	0.690	0.818	0.508
200.82	0.655	0.818	0.473

Table VI

Association of PTB in COPD patient with PLR at cut off value 197.25 (n=40)

	PLR	PTB (X pert positive)	Total (X pert negative)	p-value	χ^2, df
χ197.25	23 (79.3)	2 (18.2)	25 (62.5)	0.001*	12.71,
< 197.25	6 (20.7)	9 (81.8)	15 (37.5)		1
Total	29 (100.0)	11 (100.0)	40 (100.0)		

Table VII

Sensitivity, specificity, PPV and NPV of PLR (at cut off value 197.25) in differentiating PTB with COPD from patients of COPD alone (n=40)

PLR (Cut off value)	Sensitivity	Specificity	PPV	NPV	Accuracy
197.25	79.3	81.8	92.0	60.0	80.0

Table VIII

Sensitivity, specificity, PPV and NPV of PLR at different cut off value in differentiating between PTB with COPD from patients of COPD alone (n=40)

PLR (Cut off value)	Sensitivity	Specificity	PPV	NPV	Accuracy
179.97	86.2	63.6	86.2	63.6	80.0
192.00	79.3	63.6	85.2	53.8	75.0
197.25	79.3	81.8	92.0	60.0	80.0
199.00	75.9	81.8	91.7	56.3	77.5
200.32	72.4	81.8	91.3	52.9	75.0

Discussion

This cross sectional study was carried out to investigate the validity of the platelet-lymphocyte ratio in discriminating between patients of COPD with pulmonary TB from those with COPD alone. Data were collected from Department of Respiratory Medicine of National Institute of the Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh. All the data were analyzed with SPSS version 22.0.

The platelet-lymphocyte ratio (PLR), reflect ratio of cells in innate immunity, a readily calculable laboratory marker, has attracted attention as a new inflammatory marker, has been used for several diseases such as cancer, cardiovascular disease and inflammatory diseases.

Platelet lymphocyte ratio (PLR) could be used as a marker for differential diagnosis between COPD patients complicated with PTB from patients of COPD alone. The findings of the study carried out by Chen et al.[21] included the following;

1) A PLR >216.82 was the optimal cut-off value for differentiating patients COPD with pulmonary TB from patients COPD without PTB;

2) The diagnostic ability of the PLR was superior to that of NLR, ESR & CRP for distinguishing patients of COPD with pulmonary TB from patients of COPD alone.

This was the first study to demonstrate the diagnostic ability of the platelet -lymphocyte ratio for differentiating COPD patients with and without PTB. In this retrospective study, 87 respondents were COPD complicated with PTB and the rest 83 had COPD. The platelet lymphocyte ratio of the patients of COPD without PTB with a mean of (130.21 ±45.30) and with PTB was 287.05 ± 32.76)).

In present study a total 40 patients from NIDCH, who fulfilled the inclusion criteria were enrolled.

Among them thirty-eight (95%) of them were men and 2 (5%) were female. The mean age was 58.07 ± 9.28 years. The demographic characteristics of the study subjects are summarized in (Table-I). In the Present study, there is significant difference in patients of known COPD with or without PTB in terms of PLR. The mean Platelet lymphocyte ratio of COPD with PTB or in X pert for MTB/RIF positive group (295.41 ± 124.88) was higher than respondents of COPD without PTB or in X pert for MTB/RIF negative group (197.70± 64.36).

Present study also showed sensitivity and specificity at different cut-off value of platelet lymphocyte ratio in differentiating between patients of COPD with PTB from patients of COPD alone, by generating a receptor operating curve (Figure 3). Among these cut-off values of platelet lymphocyte ratio in differentiating patients of COPD with PTB from COPD alone, platelet lymphocyte ratio >197.25 is best cut-off value in distinguishing patients of COPD with PTB from COPD alone. At PLR >197.25, sensitivity, specificity, positive predictive value, negative predictive value and accuracy is 79.3%, 81.8%, 92%,60% and 80% respectively. The AUC for PLR was 0.804, 95% confidence interval [CI], 0.662-0.946; p <0.003), which was statistically significant.

The findings of the study conducted by Cheng et al.[21] revealed that, optimal cut-off value of PLR for the Chinese, was >216.82, identified for differentiating patients of COPD with pulmonary TB from patients COPD without PTB.

At PLR >216.82, sensitivity, specificity, positive predictive value, negative predictive value was 92.4%, 84.5%, 91.6%, 86.2%. Area under curve (AUC) in ROC curve for platelet lymphocyte ratio in differentiating COPD complicated with PTB was 0.87 (AUC, 0.87; 95% confidence interval [CI], 0.73-0.91; p <0.05).

Conclusion

Present study suggests that, PLR a useful diagnostic marker which is higher in COPD patients with PTB than patients of COPD alone. Cut off value of >197.25 is identified as optimal cutoff value with a sensitivity, specificity, positive predictive value, negative predictive value and accuracy 79.3%, 81.8%, 92%, 60% and 80% respectively.

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ORIGINAL ARTICLE

Association between Serum Uric Acid and Severity of Airflow Obstruction in Asthma

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Abstract

Background and objectives: *Asthma is a globally significant non-communicable disease with major public health consequences. Objective of this study was to find out the association between serum uric acid levels and severity of airflow obstruction, to measure the serum uric acid in asthma patients and to determine the severity of asthma by FEV1.*

Methodology: *This cross sectional study was done in the National Institute of Diseases of the chest & Hospital (NIDCH), Mohakhali and total 110 study population who fulfilled the GINA 2019 criteria for the diagnosis of asthma in adults with e" 18 years were included. Patient with smoking, other obstructive lung diseases, gout or F/H of hyperuricemia, chronic kidney disease, hepatic failure, active malignancies or acute gastrointestinal bleeding, IHD, patients treated with diuretics and xanthine derivatives (e.g. theophyline) and pregnancy were excluded.*

Results: *Mean serum uric acid level 6.76 mg/dl (±0.53 mg/dl) is found significantly higher among obese patient than non-obese patients. The most common trigger was ongoing URTI. Among the participants, 24 (21.8%) had well controlled symptoms. 59 (53.6%) had partly controlled symptoms and 27 (24.6%) had uncontrolled symptoms. Significantly higher serum uric acid level was also observed in patient with partially controlled and uncontrolled asthma when compared with well controlled asthma. Significantly higher serum uric acid level was found in patient with more severe airflow obstruction when compared less severe airflow obstruction*

Conclusions: *Higher serum uric acid levels are associated with higher severity of asthma and poor asthma control.*

Keywords: *Asthma, Serum uric acid, Airflow obstruction*

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Introduction:

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow inflammation[1].There is a large geographical variation in asthma prevalence, severity and mortality. While asthma prevalence is higher in high income countries, most asthma-related mortality occurs in low-middle income countries[2]. In Bangladesh alone, the first national asthma prevalence study conducted in 1999 found that 5.2% or 7 million people suffer from asthma[3,4] , current prevalence may be higher.

Many cells and elements play a role in the pathogenesis of asthma, in particular, mast cells, eosinophil, T lymphocytes, macrophages, neutrophils and epithelial cell[6]. In particular, the subjects poly sensitized and with food allergy may present more severe asthma[7]. It has also noted recently that obesity is a risk factor for asthma because it causes an increase of leptin, TNF-á, and IL-6, which exert a pro-inflammatory non-eosinophil action[8]. In addition, the lack of physical activity, for weight gain, contributes to the determinism of the disease[9]. The vitamin D modulates the effects of glucocorticoids and also has a role in bronchial remodeling, as it regulates the expression of genes of bronchial smooth muscle[10]. In infants at risk viral respiratory infections can cause wheezing, which in turn can evolve later in asthma particularly in individuals with atopic predisposition[11].

European studies have shown little apparent improvement in the levels of symptom control[12]. Poor asthma control is associated with increased risk of exacerbations, debilitation, impaired quality of life, increased health-care utilization and reduced productivity[12]. Importantly, a history of asthma exacerbations is a risk factor for future exacerbations; hence, understanding predictive factors is important[13]. Other risk factors include poor asthma control and poor adherence [13,14]. Serum Uric Acid is the final product of purine degradation, which increases significantly during hypoxia [15]. Increased UA levels occur in the airways of allergen-challenged asthmatic patients[16]. Furthermore, strategies targeting inhibiting UA synthesis with allopurinol or the UA degrading enzyme-urease led to a decrease in proTh$_2$ cytokines production, lung inflammation, repair, and fibrosis[17]. Previous studies focused on the signaling pathway and the mechanism underlying UA- induced Th$_2$ cell immunity and airway inflammation[16] but evidence of increased levels of serum UA during asthma exacerbation is uncertain.

To find out the association between serum uric acid levels and severity of airflow obstruction in asthma is general objective and to measure the serum uric acid in asthma patients, to determine the severity of asthma by FEV1 and to find out the association between serum uric acid and severity of airflow obstruction in asthma are the specific objectives of this study. By doing so, it may lay the ground for further research on newer measures to improve asthma control in a resource-limited setting such as in the Bangladeshi population.

Methodology:

This Cross sectional observational study was conducted from December 2019 to March 2021in the National Institute of Diseases of the chest & Hospital (NIDCH), Mohakhali. Purposive sampling was done and total 110 study population who fulfilled the GINA 2019 criteria for the diagnosis of asthma in Adults with e" 18 years of age were included. Patient with smoking, other obstructive lung diseases, gout or F/H of hyperuricemia, chronic kidney disease, hepatic failure, active malignancies or acute gastrointestinal bleeding, IHD, patients treated with diuretics and xanthine derivatives (e.g.theophyline) and pregnancy were excluded. Statistical analysis was performed using SPSS 22.0 for Windows. A p value of < 0.05 was considered statistically significant. One way ANOVA test was employed to compare mean serum uric acid levels between those with normal, mild, moderate, and severe airflow obstruction. Pearson correlation was used to assess correlation between

serum uric acid and FEV_1. Multivariate regression analysis was performed to determine the association between serum uric acid and all the independent variables together.

Results

The mean age of the participants was 33.4 ±9.6 years. The lowest age was 18 years and the highest age was 70 years. 66 (60%) of participants were male and 44 (40%) were female, 88(80%) are married and 71 (64.5%) of the participants are residing in urban residence. Obesity underweight, normal BMI and overweight are found in 5 (4.5%), 24 (21.8%), 67 (60.9%) and 14 (12.7%) participants respectively (Table I).

The distribution of the participants according to severity of airflow obstruction, graded from normal to severe, is shown in Table II. The mean pre-bronchodilator FEV_1 % of predicted of the respondents was 61.2 ± 12.8%. The lowest was 32% and the highest was 87% of predicted. Most of the participants are in moderate severity group (Table II).

Among the participants, 47 (42.7%) had an ongoing upper respiratory tract infection. 23 (20.9%) of the participants identified recent exposure to cold weather as a trigger while in 08 (7.3%) the trigger was dust. Allergic food and fumes are found as triggering factor in 2 (1.8%) and 3(2.7%) respectively. 27 (24.5%) could not specify any exposure to triggers (Table III).

Table I

Demographic Characteristics of Participants (n=110).

Characteristics	Frequency	Percentages
Marital status		
Unmarried	22	20.0
Married	88	80.0
Residence		
Rural	39	35.5
Urban	71	64.5
Educational status		
Below primary	22	20.0
Primary	17	15.5
Secondary	33	30.0
Higher secondary	27	24.5
Bachelor and above	11	10.0
Occupation		
Housewife	31	28.2
Services	25	22.7
Student	23	20.9
Business	19	17.3
Unemployed	03	2.7
Others	09	8.2
BMI		
Underweight	24	21.8
Normal	67	60.9
Overweight	14	12.7
Obese	05	4.5

Table II

Distribution of the Participants According to Severity of Airflow Obstruction (n=110)

Severity	Pre bronchodilator FEV_1 % predicted	Frequency	Percentages	FEV_1 %predicted Mean (±SD)
Normal	e”80	10	9.1	82.9 ± 2.1
Mild	<80-65	24	21.8	73.8 ± 4.0
Moderate	<65-50	56	50.9	58.0 ± 3.6
Severe	<50-30	20	18.2	42.8 ± 5.5
Life-threatening	<30	0	0	0
Total	87-32	110	100	61.2± 12.8

Table III

Distribution of Participants According to Recent/Ongoing Exposure to Triggers (n=110)

Triggers	Frequency	Percentages
URTI	47	42.7
Cold exposure	23	20.9
Allergic food	02	1.8
Dust	08	7.3
Gas/fumes	03	2.7
Pollen	0	0
Carpets/blankets/cloth	0	0
Pet animal	0	0
Cockroaches	0	0
Drugs	0	0
Exercise	0	0
None	27	24.5

Significant higher serum uric acid level was also found in patient with more severe airflow obstruction ($p<0.001$) (Table IV).

Significant higher serum uric acid level was also observed in patient with partially controlled and uncontrolled asthma when compared with well controlled asthma ($p>0.001$) (Table V).

Table IV

Comparison of Serum Uric Acid According to Severity of Airflow Obstruction (n=110)

Severity of airflow obstruction	Serum Uric Acid (mg/dl) Mean (±SD)	F	p
Normal (n=10)	5.74±0.44	31.180	<0.001
Mild (n=24)	6.57±0.42		
Moderate (n=56)	6.91±0.40		
Severe (n=20)	7.09±0.33		

Table V

Comparison of Serum Uric Acid According to Level of Control of Asthma (n=110)

Level of control Uric of asthma	Acid Serum (mg/dl) Mean (±SD)	F	p
Well controlled (n=24)	6.15±0.52	33.981	<0.001
Partially controlled (n=59)	6.86±0.41		
Uncontrolled (n=27)	7.08±0.36		

It is evident that the strongest predictor is Pre bronchodilator FEV_1, followed by use of ICS, and peripheral blood eosinophilia (Table VI).

Table VI

Multiple Regression Analysis to Predict Square root of Serum Uric Acid (n=110)

Variables	Unstandardized Coefficients		Standardized Coefficients	t	p*
	B	Std. Error	Beta		
Age	-0.007	0.004	-0.122	-1.688	0.095
Sex	0.026	0.079	0.024	0.335	0.738
Pre bronchodilator FEV_1	-0.025	0.004	-0.583	-6.896	<0.001
Improper use of ICS	0.270	0.114	0.194	2.363	0.020
Exposure to trigger	0.087	0.100	0.070	0.876	0.383
Blood eosinophilia	-0.176	0.083	-0.163	-2.124	0.036

*p value reached from multiple linear regression analysis FEV_1 =Forced Expiratory Volume in 1st second

Discussion

This cross sectional study was done in NIDCH, Mohakhali, Dhaka with the aim to find out the association between serum uric acid level and severity of airflow obstruction in asthma. A total of 110 patients were included in this study according to inclusion and exclusion criteria.

The mean age of the participants was 33.4 (±9.6) years. The lowest age was 18 years and the highest age was 70 years. Study over the south Asian people (n=35,929) where they found that majority of the participants belonged to the age group of 30–44 years[18]. Among 110 participants, 66 (60%) of participants were male and 44 (40%) were female. The male to female ratio was 1.5:1. Abdulnaby et al.[19] also found male predominance in their study. In the National Asthma Prevalence Study conducted by Hassan et al.[20], the ratio was 0.9:1 in the adult population.

In the present study, only 5(4.5%) participants had obesity. Underweight, normal BMI and overweight were found in 24(21.8%), 67(60.9%) and 14(12.7%) participants respectively. Mean serum uric acid level was found significantly higher among obese patient than non-obese patients. Ali N et al.[21] also found higher serum uric acid level ($p< 0.01$) among the obese persons of their study subjects (n=260).

Asthmatic individuals with normal FEV_1 or mild airflow obstruction tend to visit the OPD accounting for 10(9.1%) and 24(21.8%) respectively. FEV_1 was 54.1±16% predicted in adult asthma patient in an Egyptian study Abdulnaby et al.[19] which was consistent with present study. The most common trigger was found to be an ongoing URTI (47 out of 110). This was in concordance with the study conducted by Hassan et al[20] in Dhaka and coastal areas ofBangladesh in 2001 where common cold was identified as the most prevalent trigger. A study was conducted in a tertiary hospital in Northeastern Thailand over 73 asthmatic patients by Mairiang D et al.[22] where they also found URTI as the most common trigger (38.81%) of asthma exacerbation.

Mairiang D et al.[22] observed that poor adherence to ICS was a significant cause of asthma exacerbation (16.42%).Peripheral blood eosinophilia was detected in 48 (43.6%) participants. The remainder 62 (56.4%) had normal eosinophil counts. A study by Abdulnaby et al.[19] revealed higher sUA in severe asthma patients compared with moderate asthma patients ($P<0.001$) which was consistent with the present study. Similar findings were also observed by Li et al[23].

A scatter plot of pre-bronchodilator FEV_1 against serum uric acid was plotted. A significantly negative Pearson correlation is found between serum uric acid and pre-bronchodilator FEV_1 ($r=0.615$, $p<0.001$) which was consistent with the study of Li et al[23] ($r = 0.507$, $p< 0.001$). Negative correlation between serum uric acid and FEV_1 was also observed by Abdulnaby et al.[19].

In the present study, it is evident from regression analysis that pre-bronchodilator FEV_1, improper use of ICS, and peripheral blood eosinophilia significantly predict serum uric acid level. That means severity of air flow obstruction is a predictor for the serum uric acid. Degree of asthma severity was found significant predictors of high serum uric acid ($r^2=0.43$, $p<0.001$) in multiple linear regression by Abdulnaby et al.[19] which was consistent with the present study.

Conclusion

Serum uric acid is independently associated with severity of airflow obstruction in asthma. Higher serum uric acid levels are associated with higher severity of asthma and poor asthma control.

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ORIGINAL ARTICLE

The Usefulness of Pleural Fluid ADA to Serum CRP Ratio in Differentiating between Tubercular and Malignant Pleural Effusion

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Abstract

Background: *Tubercular pleural effusion (TPE) and malignant pleural effusion (MPE) are usually distinguished by pleural fluid cellular predominance, cytology and adenosine deaminase (ADA) level although both diseases may show similar cytological and biochemical picture including ADA. In such cases, differentiating TPE and MPE is challenging and needs histopathology of pleural tissue following closed needle biopsy of pleura, pleuroscopy, VATS (Video Assisted Thoracoscopic surgery). Unfortunately, diagnostic yield of closed needle pleural biopsy is not satisfactory and latter procedures are not widely practiced.*

Objective: *To assess the usefulness of pleural fluid ADA to serum CRP ratio in differentiating between tubercular and malignant pleural effusion.*

Materials and Methods: *This cross-sectional, method validation study was conducted in the National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka from July 2021 to September 2022 on diagnosed case of tubercular pleural effusion (TPE) and malignant pleural effusion (MPE). Ratio of pleural fluid ADA to serum CRP was estimated in all cases and compared between patient with TPE and MPE. A receiver operating characteristic curve (ROC) was constructed for identifying TPE. A value of p<0.05 was considered statistically significant for all tests.*

Results: *A total of 59 patients were enrolled in this study, of which 31 patients had TPE and 28 patients had MPE. Pleural fluid ADA level was significantly higher in patient with TPE but there was no significant difference in serum CRP level between patients with TPE and MPE. Pleural fluid ADA to serum CRP ratio was also higher in TPE group compared to MPE group and the difference was statistically significant. At cut off value of e"1.28, pleural fluid ADA to serum CRP ratio had a sensitivity of 90.3%, specificity of 82.1%, accuracy of 86.4%, positive predictive value of 84.8%, negative predictive value of 88.5%, positive likelihood ratio of 5.06 and negative likelihood ratio of 0.12 in diagnosis of TPE and area under curve (AUC) was 0.921 on receiver operating characteristic curve (ROC).*

Conclusion: *This study demonstrated that pleural fluid ADA to serum CRP ratio was significantly higher in tubercular pleural effusion comparing with malignant pleural effusion.*

Keyword: *pleural fluid ADA, Serum CRP, ADA to CRP ratio.*

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Introduction:

Pleural effusion is one of the most common challenging problems for the physicians worldwide. It is known as abnormal accumulation of fluid within the pleural space. It is not a disease itself rather an important clinical manifestation of systemic and pleural diseases. Internationally the incidence of pleural effusion is 320/1000,000 in industrialized countries and only in USA it is at least 1.5 million cases annually[1,2].

When it comes to differentiating benign and malignant causes of pleural effusion, it often creates a challenge to the physicians. In addition, differentiating between tubercular and malignant effusion has important therapeutic and prognostic implication. Bangladesh is listed among the 30-high burden countries for TB. It continues to be among the top 8 countries accounting for two-thirds of the Global TB burden[3]. According to the Global TB Report 2020, 292,942 TB patients were notified to the National Tuberculosis Control Programme (NTP) in 2019. The incidence rate for all from of tuberculosis is 221 per 100,000 population per year with mortality of 24 per 100,000 population per year which is accounted for over 38,000 deaths annually[3]. For extra pulmonary TB, one of the most common presentations is tubercular pleural effusion. It may be represented as either primary or post primary form of TB. It is the result of sequential immunological reaction when pleural cavity is exposed to mycobacterial antigen. Therefore, direct smears of pleural effusion or effusion cultures are often negative. Pleural fluid AFB smears is positive in only <5% of cases and culture is positive in only 10-20% of cases[4]. Although pleural biopsy for histopathology is 80-100% sensitive in diagnosing tubercular pleural effusion and 42-97% sensitive in diagnosing malignant pleural effusion, the procedure itself is invasive in nature, thereby, requires expert and trained manpower[4]. Moreover, setup of this procedure is expensive to install widely across all level of health care facility therefore, making it inconvenient to adopt as a routine investigation in pleural diseases.

In case of tubercular pleural effusion, one of the commonly explored investigation tools is adenosine deaminase (ADA) which is a polymorphic enzyme that catalyzes the deamination of adenosine to inosine and ammonia. It is related to lymphocytic differentiation and proliferation, showing a significant increase in its values during antigenic response of lymphocyte, hence, regarded as a marker of cell mediated immunity. Several isoforms of ADA are known but the most explored in diagnostic purposes are ADA1 and ADA2. ADA1 isoenzyme is present in all cells, predominant in lymphocytes, while ADA2 is predominant in monocytes and macrophages. ADA2 accounts for 80% of total ADA activity in tubercular pleural effusion. However, determination of this isoenzyme in the evaluation of tubercular pleural effusion has shown to be clinically insignificant[5]. Burgess et al.[6] found sensitivity and specificity of ADA to be 90% and 89%, respectively, at the cutoff value of 50 U/L in an area with high TB prevalence. But ADA level can also be raised in malignancy, lymphoma and collagen vascular disease. Some studies demonstrate ADA level in malignant pleural effusion and tubercular pleural effusion is not significantly different which is quite confusing to reach diagnosis. It is reported that ADA activity in effusion is age-dependent, being more accurate in the younger population than in elderly patients. The accuracy and the cutoff value of ADA in differential diagnosis of tubercular pleural effusion are dependent on the incidence of tuberculosis in a specified region. Only meta-analyses of new studies from various regions with various incidences of tuberculosis and study population of different ages will confirm the utility of ADA in tubercular pleural effusion diagnosis.

C-reactive protein (CRP) was discovered in 1930 and is widely used as a sensitive, but nonspecific marker of systemic inflammation. It is an acute phase protein synthesized mainly by hepatocytes in response to tissue injury or inflammation. The induction of CRP synthesis is triggered by a number of cytokines, which are released in the inflammatory region, chiefly the pyrogenic cytokine, interleukin-6, which is released mainly from macrophages and monocytes. Increased serum C-reactive protein levels have been reported in many pulmonary disorders, including pneumonia, malignancies, and pulmonary thromboembolism. Although few studies reported significant difference in serum CRP level between tubercular and malignant effusion, serum CRP alone is not a reliable marker to differentiate between these two types of effusion.

Swetha et al.[7] demonstrated that pleural fluid ADA to serum CRP ratio d+1.2 is 78% sensitive and 83% specific in differentiating malignant from tubercular pleural effusion. But the ratio is a new tool that is not explored widely in previous studies. So, the aim of the present study is to evaluate the utility of this new parameter to discriminate between tubercular and malignant pleural effusion.

Materials and Methods:

This cross-sectional, method validation study was carried out on admitted patient under the Department of Respiratory Medicine of the National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh from July 2021 to September 2022.

Inclusion Criteria:

1) Patients with tubercular pleural effusion diagnosed on the basis of histopathology of pleural biopsy or,
2) Patients with malignant pleural effusion diagnosed on the basis of pleural fluid cytology for malignant cell or histopathology of pleural biopsy
3) Patients who give informed written consent

Exclusion criteria:

1) Patient with transudative pleural effusion
2) Patient with congestive heart failure, chronic liver disease, chronic kidney disease, connective tissue diseases

Purposive sampling was done in this study. Newly admitted patients to NIDCH with unilateral pleural effusion as evident from history, clinical examination and CXR P/A view were selected. Full information regarding nature of study was provided to the patient and written informed consent was obtained from eligible patient. Then, pleural fluid was aspirated followed by pleural fluid study including physical appearance, biochemistry (protein and glucose), cytology, exfoliative cytology for malignant cell, Gene Xpert for MTB and ADA. Pleural biopsy was performed using Abrams pleural biopsy needle with all aseptic precaution followed by histopathological examination. Those who fulfilled the inclusion and exclusion criteria were finally enrolled as sample whose blood was then collected and sent for serum CRP. Pleural fluid ADA, serum CRP and pleural fluid ADA to serum CRP ratio were recorded systematically in preformed data collection sheet. Data was analyzed using appropriate statistical formula.

Results:

Table I shows that mean age was found 35.7±20.3 years in TPE group and 53.9±15.8 years in MPE group. Almost one third (32.3%) patients were service holder in TPE group and majority (39.3%) of the patients in MPE group were farmer. Majority (67.7%) patients in TPE group and 8 (28.6%) in MPE group were from urban area which was statistically significant ($p<0.05$).

Figure 1 shows that among the 59 respondents, majority i.e. 31 (52.5%) had tubercular pleural effusion and the rest 28 (47.5%) of the respondents had malignant pleural effusion.

Table II shows that median WBC total count was found 750.0 (200.0-1850.0) cell/cmm in TPE group and 155.0 (57.5-387.0) cell/cmm in MPE group with statistically significant ($p<0.05$) difference between two groups. Majority of the patients in both groups had lymphocyte predominance.

Table III shows that median pleural fluid ADA was found 57.0 (43.6-75.0) U/L in TPE group and 17.1 (12.1-22.6) U/L in MPE group that was statistically significant ($p<0.05$). The median serum CRP was found 30.0 (18.2-34.7) mg/L in TPE group and 34.0 (14.3-64.0) mg/L in MPE group that was not statistically significant. The median pleural fluid ADA to serum CRP ratio was 2.16 (1.49-3.35) in TPE group and 0.48 (0.24-1.14) in MPE group which was statistically significant ($p<0.05$) between two groups.

Figure 2 shows Receiver operating characteristic curve which was graphically plotted to represent comparative relationship between sensitivity (True positive rate) and specificity (True negative rate) of pleural fluid ADA to serum CRP ratio, at all possible cut-off points and to determine best cut-off value of the ratio.

Table IV shows that area under curve of pleural fluid ADA to serum CRP ratio in differentiating tubercular pleural effusion was 0.921, meaning that 92.1% of the total subjects had been diagnosed correctly. As 95% CI did not include the value 0.5 and p value 0.001, so result was statistically significant.

Table V shows that according to Youden index, the best cut off value was found to be 1.28, denoting sensitivity 90.3% and specificity 82.1%.

Table VI shows association of diagnosed case tubercular pleural effusion based on histopathology with pleural fluid ADA to serum ratio at cut off value e"1.28. Out of 59 cases, 28 cases were true positive, 5 cases were false positive, 3 cases were false negative and 23 cases were true negative. The difference was statistically not significant between two groups.

Table VII shows that at cut off value of e"1.28, pleural fluid ADA to serum CRP ratio had sensitivity 90.3%, specificity 82.1%, accuracy 86.4%, positive and negative predictive values were 84.8% and 88.5% respectively, positive and negative likelihood ratio were 5.06 and 0.12 respectively, to differentiate tubercular from malignant pleural effusion.

Table I

Association between demographic characteristics and pleural effusion (n=59)

Demographic characteristics	TPE (n=31)		MPE (n=28)		P value
	f	%	*f*	%	
Age (years)					
d+10	2	6.5	0	0.0	
11-20	6	19.4	1	3.6	
21-30	7	22.6	2	7.1	
31-40	6	19.4	3	10.7	
41-50	3	9.7	3	10.7	
51-60	2	6.5	6	21.4	
61-70	3	9.7	13	46.4	
>70	2	6.5	0	0.0	
Mean ±SD	35.7	±20.3	53.9	±15.8	[a]0.001[s]
Range (min-max)	9.0	-80.0	13.0	-70.0	
Sex					
Male	21	67.7	19	67.9	[b]0.992[ns]
Female	10	32.3	9	32.1	
Occupational status					
Farmer	4	12.9	11	39.3	
House wife	6	19.4	9	32.1	
Service	10	32.3	0	0.0	[b]0.002[s]
Business	3	9.7	6	21.4	
Retired	1	3.2	1	3.6	
Unemployed	7	22.6	1	3.6	
Residence					
Rural	10	32.3	20	71.4	[b]0.003[s]
Urban	21	67.7	8	28.6	

s= significant; ns= not significant
[a]P value obtained from unpaired t-test
[b]P value obtained from chi square test

Table II

Association between pleural fluid cytology and pleural effusion (n=59)

Pleural fluid cytology	TPE (n=31) Median (IQR)		MPE (n=28) Median (IQR)		P value
WBC total count (cell/cmm)	750.0 (200.0-1850.0)		155.0 (57.5-387.0)		[a]0.008[s]
Cellular predominance	*f*	%	*f*	%	
Lymphocyte	27	87.1	25	89.3	[b]0.795[ns]
Neutrophil	4	12.9	3	10.7	

s= significant; ns= not significant

[a]P value reached from Mann-Whitney U test

[b]P value reached from chi square test

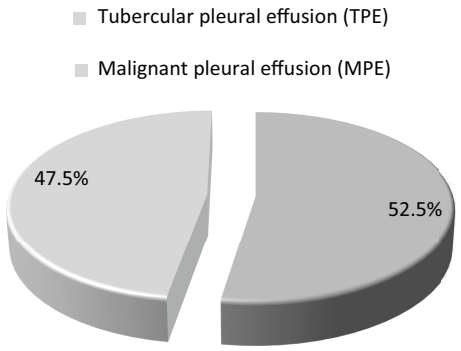
Table III

Association of pleural fluid ADA, serum CRP, pleural fluid ADA to serum CRP ratio with pleural effusion (n=59)

Variables	TPE(n=31) Median (IQR)	MPE(n=28) Median (IQR)	P value
Pleural fluid ADA (U/L)	57.0 (43.6-75.0)	17.1 (12.1-22.6)	0.001[s]
Serum CRP (mg/L)	30.0 (18.2-34.7)	34.0 (14.3-64.0)	0.316[ns]
Pleural fluid ADA to serum CRP ratio	2.16 (1.49-3.35)	0.48 (0.24-1.14)	0.001[s]

s= significant; ns= not significant

P value reached from Mann-Whitney U test



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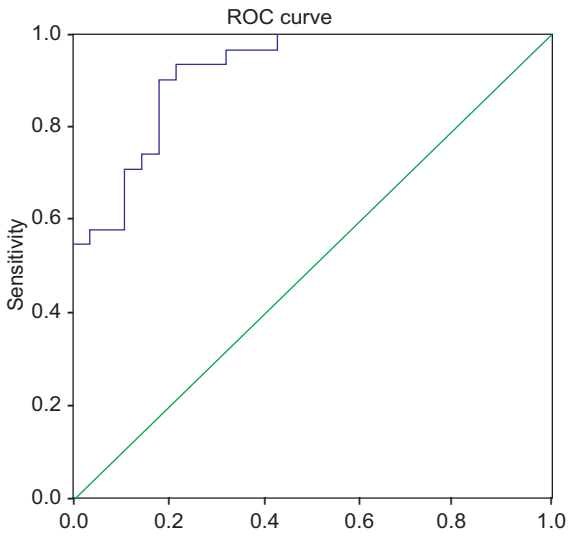

Fig.-2: *Receiver operating characteristic (ROC) curve of pleural fluid ADA to serum CRP ratio*

Table IV

Area under curve (AUC) of pleural fluid ADA to serum CRP ratio for differentiating tubercular pleural effusion

Variables	Area under the ROC curve	SE	P value	95% Confidence interval (CI) Lower bound	Upper bound
Pleural fluid ADA to serum CRP ratio	0.921	0.034	0.001[s]	0.855	0.987

s= significant

Table V

Youden index of pleural fluid ADA to serum CRP ratio in differentiating between patients with tubercular and malignant pleural effusion

Pleural fluid ADA to serum CRP ratio	Sensitivity	Specificity	Youden index J= Max (SEN+ SPE-100)
1.04	93.5	71.4	64.9
1.12	93.5	75.0	68.5
1.19	93.5	78.6	72.1
1.24	90.3	78.6	68.9
1.28	90.3	82.1	72.4
1.31	87.1	82.1	69.2
1.35	83.9	82.1	66.0
1.38	80.6	82.1	62.7

Table VI

Association between diagnosed case of tubercular pleural effusion and pleural fluid ADA to serum ratio at cut off value e+1.28 (n=59)

Pleural fluid ADA to serum CRP ratio (≥1.28)	Diagnosed case of TPE (on histopathology) Positive (n=31)	Negative (n=28)	P value
Positive (n=33)	28 (True positive)	5 (False positive)	0.727^{ns}
Negative (n=26)	3 (False negative)	23 (True negative)	

s= significant
P value calculated from McNemar's test

Table VII

Validity tests of pleural fluid ADA to serum CRP ratio at cut off value of ≥1.28 to differentiate tubercular from malignant pleural effusion

Validity test	Percentage	95% CI
Sensitivity	90.3	74.3-98.0
Specificity	82.1	63.1-93.9
Accuracy	86.4	75.0-94.0
Positive predictive value	84.8	71.5-92.6
Negative predictive value	88.5	72.1-95.8
Positive likelihood ratio	5.06	2.27-11.29
Negative likelihood ratio	0.12	0.04-0.35

Discussion:

This cross-sectional, method validation study was carried out to assess the validity of pleural fluid ADA to serum CRP ratio for differentiation of tubercular from malignant pleural effusion. Data were collected from the Department of Respiratory Medicine of National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh. All the data were analyzed with SPSS version 23.0. Data were presented through different tables and graphs.

In this study, mean age of patient with tubercular and malignant pleural effusion was 35.7±20.3 years and 53.9±15.8 years, respectively, which was statistically significant($p<0.05$) and was in concordance with a study conducted by Mohamed et al.[8] who reported mean age for tubercular and malignant pleural effusion patients was 34.68±14.72 years and 57.65±10.03 years respectively, which was highly significant.

Among the 59 respondents, 31 (52.5%) patients had tubercular pleural effusion and 28 (47.5%) had malignant pleural effusion. Tubercular pleural effusion was diagnosed on basis of demonstration

of caseating granuloma on histopathology of pleural biopsy. On the other hand, malignant pleural effusion was diagnosed if malignant cell was found in pleural fluid exfoliative cytology or pleural biopsy for histopathology demonstrated malignancy.

Among the respondent, two thirds were male (40, 67.8%) and one third were female (19, 32.2%). Although majority (50.8%) patients came from rural area, higher proportion of tubercular pleural effusion patient (21, 67.7%) came from urban area. Patients came from urban area constituted predominantly by urban slum dwellers who were exposed to overcrowding and poor environmental condition and were more vulnerable to TB (Banu et al).[9]

Our study showed lymphocyte predominance in pleural fluid in 87.1% patients with tubercular and 89.3% patient with malignant pleural effusion. These correlates with the findings of Liam et al.[10] who reported 90% patient with tubercular pleural effusion had lymphocyte predominance and Verma et al.[11] also demonstrated 90.5% of their patient with malignant pleural effusion had lymphocyte predominance. The predominance of lymphocytes in tubercular and malignant pleural effusions probably reflects the role of T lymphocytes in the cellular immune reaction against M. tuberculosis and neoplasia. However, neutrophils tend to predominate in pleural fluid when the disease is of short duration, and lymphocytes tend to prevail when symptoms have lasted longer[12]. Moreover, Bielsa et al.[13] showed that high neutrophil levels in MPE, an indicator of intense pleural inflammation are significantly associated with adverse overall survival.

In this study, significantly higher level of pleural fluid ADA was found in TPE in comparison to MPE (median 57 U/L vs 17.1 U/L, $p<0.05$). These findings are supported by Ernam et al.[14] who demonstrated higher pleural fluid ADA in TPE in contrast to MPE (Median 75.41 vs 22.09, $p<0.001$). Pleural fluid ADA has high sensitivity and specificity in diagnosis of TPE. A retrospective study[15] over 2100 patient revealed that at cutoff value of >35 U/L, pleural fluid ADA had 93% sensitivity, 90% specificity, a positive likelihood ratio (LR) of 10.05 and a negative LR of 0.07 in diagnosing TPE. Elevated pleural fluid ADA is a hallmark of TB effusions, whether lymphocytes or neutrophils predominate in the pleural fluid. Although neutrophils are the predominant cells in the early stages of TPE, they release chemokines that attract monocytes and macrophages with subsequent release of ADA 2 isoenzyme which is major contributor to the high total ADA activity in TPE.

However, conflicting data were obtained by Zariæ et al.[16] who reported, poor specificity (70.4%), despite acceptable sensitivity (89.2%) of ADA at cutoff value of 49 U/L in diagnosing TPE. Another study showed that at cut off value of e+30 U/L, pleural fluid ADA is 70.8% sensitive and 95.2% specific to diagnose TPE. It is speculated that population ethnicity might have an influence on diagnostic value of ADA as better ADA diagnostic performance was observed in studies conducted in Europe, whereas performance was poorer in studies from East Asia than from other regions[17].

Ogata et al.[18] also demonstrated that although ADA activity in pleural fluid is highly sensitive (85.5%) and specific (86.5%) in the diagnosis of TPE, lung cancer or mesothelioma may show high ADA activity. This finding is corroborated by Kim et al.[19] who also reported elevated ADA in both TPE and lymphoma associated MPE with no statistically significant difference between two groups (median 84 vs 73, $p=0.47$).

CRP is an acute phase protein, predominantly secreted from hepatocytes when triggered by variety of cytokines, chiefly IL-6, at the sites of inflammation. It reflects ongoing inflammation or tissue damage much more accurately than other parameters of the acute phase response. In this study, the median (IQR) of serum CRP in tubercular and malignant pleural effusion were 30.0 (18.2-34.7) mg/L and 34.0 (14.3-64.0) mg/L respectively, which were elevated in both groups but the difference was not significant ($p=0.316$). The findings were substantiated by a prospective study conducted by Mohamed et al.[8] who reported raised CRP in TPE and MPE with no significant difference (mean 28.34±14.41 and 27.87±13.21 respectively, $p=0.916$). In MPE, the reasons for CRP elevation were not completely understood. One possible explanation was due to cytokine production by tumor tissue and elevated CRP values might indicate a higher tumor burden. It was reported

to have a catabolic effect on metabolism which was associated with an increase in resting energy expenditure and loss of lean tissue in patients with lung cancer, key factors in determining cancer survival[20].

In contrast, Chierakul et al.[21] showed that the difference of serum CRP level was significant between the patients with TPE and MPE although it was raised in both groups (mean 106.93±9.54 vs 49.66±8.84, p<0.01). They also reported significantly higher pleural fluid CRP level in TPE group compared to MPE. Two mechanisms were proposed behind that significantly higher level of pleural fluid CRP in TPE. First, a local production of CRP in the pleural space of TPE patients enhanced by inducer cytokines, especially IL-6. Alternatively, it might result from leakage of plasma CRP via the inflamed pleura because a correlation between serum and pleural fluid CRP levels was demonstrated.

In view of the limitations of using pleural fluid ADA and serum CRP level alone as biomarkers for differentiating TPE and MPE, Swetha et al.[7] combined the two parameters in an attempt to develop a predictor of MPE with acceptable sensitivity and specificity. Their findings revealed a significantly lower pleural fluid ADA to serum CRP ratio in MPE group in comparison to TPE group (mean 1.36±1.28 vs 6.96±7.32, p<0.001). A concordant finding was also found in the present study. Patients with TPE have significantly higher level of pleural fluid ADA to serum CRP ratio comparing to patients with MPE (median 2.16 vs 0.48, p<0.05).

In this study, sensitivity and specificity at different cut-off value of pleural fluid ADA to serum CRP ratio in differentiating patients with TPE from patients with MPE were demonstrated by generating a receiver operating curve (ROC) (Figure 2). Among these cut-off values to differentiate TPE patients from MPE patients, e+1.28 was regarded as best cut-off value on the basis of Youden's index with sensitivity 90.3%, specificity 82.1%, accuracy 86.4%, positive predictive value 84.8%, negative predictive value 88.5%, positive likelihood ratio 5.06 and negative likelihood ratio 0.12. The area under curve (AUC) was 0.921(95% confidence interval [CI], 0.855-0.987), which was statistically significant (p <0.05). These findings were corroborated by the findings of Swetha et al. (2020) who reported that at cut off value of d+1.2, pleural fluid ADA to serum CRP ratio was 78.95% sensitive and 83.33% specific in differentiating patients with MPE from TPE yielding an AUC of 0.789 on ROC.

Pleural fluid ADA to serum CRP ratio can be obtained on OPD basis or on the day of inpatient admission. It is an easier & less expensive method compared to pleural biopsy and doesn't introduce additional workload for both the clinician and patient. Therefore, it can provide an opportunity to distinguish TPE patients from MPE patients at an earlier stage and to provide timely treatment with anti-TB drugs.

Conclusion:

The current study suggested that pleural fluid ADA to serum CRP ratio is a useful tool in differentiating between tubercular and malignant pleural effusion. Cut off value of e+1.28 is identified as optimal cut off value with sensitivity 90.3%, specificity 82.1%, accuracy 86.4%, positive predictive value 84.8%, negative predictive value 88.5%, positive likelihood ratio 5.06 and negative likelihood ratio 0.12.

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ORIGINAL ARTICLE

Utility of Serum Uric Acid and Serum Uric Acid to Creatinine Ratio in the Assessment of Severity in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract:

Background: *Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) lead to multiple hospital admissions, longer hospital stays as well as increased morbidity and mortality. Currently, no effective biomarker exists that can assess disease severity and activity in acute conditions. Serum uric acid is increased in the hypoxic state as well as in systemic inflammation like COPD.*

Objective: *To determine the utility of serum uric acid and serum uric acid to creatinine ratio to assess the severity of acute exacerbation of COPD.*

Methods: *This cross-sectional study was conducted in the Department of Respiratory Medicine, NIDCH, Mohakhali, Dhaka from June 2020 to August 2021. A total of 139 diagnosed COPD patients (both acute exacerbation of COPD and stable COPD) were enrolled. Blood sample was collected for serum uric acid, serum creatinine and arterial blood gas analysis. Results were obtained from the student t- test, ANOVA, Chi-square tests. ROC curve was prepared to see the efficacy of uric acid and uric acid to creatinine ratio in the assessment of severity.*

Results: *Among 139 patients, 48 patients had stable COPD and 91 patients had acute exacerbations; among AECOPD patients, 50(54.9%) were labeled as severe and 41 (45.1%) were non-severe based on their ABG findings. Serum uric acid to creatinine ratio and uric acid levels were found to be significantly higher in exacerbation patients. Serum uric acid to creatinine ratio was found to be significantly higher in severe exacerbation patients. The area under the ROC curve of serum uric acid to creatinine ratio and serum uric acid was 0.654 and 0.610 in assessing the severity of AECOPD. The sensitivity, specificity, PPV and NPV of serum uric acid were 0.660, 0.610, 0.853 and 0.595 in assessing the severity of acute exacerbation at a cut off value of 6.85. The sensitivity, specificity, PPV and NPV of serum uric acid to creatinine ratio were 0.800, 0.537, 0.678 and 0.688 in assessing the severity of acute exacerbation at cut off value of 6.32.*

Conclusion: *In the absence of spirometry and arterial blood gas analysis, serum uric acid and serum uric acid to serum creatinine ratio cannot be used to assess the severity of AECOPD.*

Keyword: *COPD, Serum uric acid, Serum uric acid to creatinine ratio*

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Introduction:

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of mortality, morbidity, and economic burden around the world. COPD is a significant and underdiagnosed public health issue in Bangladesh, owing primarily to the high prevalence of smoking and biomass fuel use, and it is frequently underdiagnosed among patients. COPD affects approximately 12.5% of Bangladeshi adults[1].

During exacerbations, reduced respiratory functions reduce oxygen intake, resulting in cellular hypoxia. This causes increased purine turnover and adenosine metabolism, which results in increased uric acid levels[2]. Raised serum uric acid levels have been linked to gout, hypertension, and cardiovascular disease. As a result, it is thought to be a predictor of various diseases[3].

Despite being one of the leading causes of prompt death worldwide, no effective biomarkers have been developed to predict severity, risk of exacerbations, and guide treatment, despite ongoing research[4]. We know that spirometry is required for diagnosis and severity assessment, as well as the mMRC scale and CATs score. In Bangladesh, spirometry is not always available in rural areas, can be expensive, and patients with acute exacerbations cannot blow effectively. In an emergency, we measure arterial blood gas levels to determine the severity and need for noninvasive ventilation.

However, because both of this test is expensive and requires specialized knowledge, it is not available in every hospital, particularly in rural areas. As a result, we should seek out less expensive and more effective means for evaluating severity. The primary goal of this study is to assess the utility of serum uric acid and serum uric acid to creatinine ratio in assessing severity in acute exacerbations of COPD, which may be useful for patients in our country.

Materials and Methods:

This cross-sectional study was conducted in the Department of Respiratory Medicine, NIDCH, Mohakhali, Dhaka from June 2020 to August 2021.

Inclusion criteria

1. Patients diagnosed as COPD, both acute exacerbations and stable cases.
2. Age above or equal to 40 years.

Exclusion criteria

1. Patients with other lung diseases like asthma, bronchiectasis, DPLD.
2. Patients with CKD or CLD.
3. Pregnancy or lactation.
4. Patients with raised serum uric acid levels for example gout or family history of hyperuricemia, active malignancies, acute gastrointestinal bleeding, myeloproliferative or lymphoproliferative disorders, IHD, LVF, alcoholism.
5. Patients who were receiving medications that may affect serum level of uric acid or creatinine such as allopurinol, ethambutol, pyrazinamide, cyclosporine, probenecid, heparin, low dose aspirin, diuretics, fenofibrate, losartan, etc.

A total of 139 diagnosed COPD patients (acute exacerbations and stable) were enrolled in this study. Each patient was categorized into GOLD stages of severity according to their post-bronchodilator FEV_1. Acute exacerbations of COPD patients were further labeled into severe and non-severe based on their arterial blood gas findings (No respiratory failure vs. acute respiratory failure, both non-life-threatening and life-threatening)[5]. Blood sample was collected for serum uric acid, serum creatinine and arterial blood gas analysis. Serum uric acid to creatinine ratio was calculated from uric acid and creatinine levels. All the data obtained were documented in a preformed data questionnaire and analyzed by using the Statistical Package for Social Sciences (SPSS) version 22.

Results and Observations:

Among 139 patients, male patients were 119 (85.6%) and females were 20 (14.4%). 119 (85.6%) patients were above 50 years of age. The current smoker was 100 (71.9%), ex-smoker was 15 (10.8%) and non-smoker was 24 (17.3) patients. The mean pack-year of the current and ex-smokers was 19.1 ± 7.2. 48 (34.5%) patients had stable COPD and 91 (65.5%) patients had an acute exacerbation. Among AECOPD patients, 50(54.9%) were labeled as severe and 41 (45.1%) were labeled non-severe based on their arterial blood gas findings (no respiratory failure vs. acute respiratory failure).

ABG analysis revealed, PO_2 was significantly lower in acute COPD patients (56.09 ± 12.47) than stable

COPD patients (65.54 ± 8.90); PCO_2 was found significantly higher in acute COPD patients (52.12 ± 11.90) than stable COPD patients (43.10 ± 3.60) and FEV1 was found significantly lower in acute COPD patients (35.72 ± 12.29) than stable COPD patients (43.44 ± 8.55).

The mean value of serum uric acid level was 6.77 ± 1.32 and 5.37 ± 1.74 in acute and stable COPD patients respectively. The mean value of serum uric acid to creatinine ratio was 7.28 ± 1.94 and

6.50 ± 2.04 in both acute exacerbation of COPD and stable COPD patients respectively. The mean value of serum creatinine was 0.96 ± 0.20 and 0.84 ± 0.14 in both acute and stable COPD patients respectively. Serum uric acid, serum creatinine and serum uric acid to creatinine ratio both were found significantly higher in acute than stable COPD patients. Serum uric acid to creatinine ratio was found significantly higher in severe acute COPD patients than non-severe acute COPD patients (7.78 ± 2.23 vs 6.67 ± 1.29; $p<0.05$).PO_2 was found significantly lower in severe acute exacerbation patients than non-severe acute exacerbation patients (53.46 ± 13.16 vs 59.31 ± 10.88; $p<0.05$). But PCO_2 was found significantly higher in severe acute exacerbation patients than non- severe exacerbation patients (55.72 ± 13.35 vs. 47.73 ± 8.02; $p<0.05$).

There was a significant difference in serum uric acid among the GOLD grading in severe acute exacerbation patients but the change was not gradual according to the grading of GOLD staging.

Serum uric acid had a significant negative correlation with pH in severe and non-severe acute exacerbation patients; also serum uric acid had a significant positive correlation with PCO_2 in severe exacerbation patients. Serum uric acid to creatinine ratio had a significant negative

Correlation with pH in severe acute exacerbation patients, also serum uric acid to creatinine ratio had a significant positive correlation with PO_2 in stable COPD patients.

The area under the ROC curve of serum uric acid to creatinine ratio and serum uric acid was 0.654 and 0.610 respectively in predicting the severity of acute COPD. The best cut off value of serum uric acid was 6.85 in predicting the severity of acute COPD according to Youden Index. The sensitivity, specificity, PPV and NPV of serum uric acid were 0.660, 0.610, 0.853 and 0.595 respectively in predicting the severity of acute COPD at a cut off value of 6.85. The best cut off value of serum Uric Acid to serum creatinine ratio was 6.32 in predicting the severity of acute COPD according to Youden Index. The sensitivity, specificity, PPV and NPV of serum uric acid to serum creatinine ratio were 0.800, 0.537, 0.678 and 0.688 respectively in predicting the severity of acute COPD at a cut off value of 6.32.

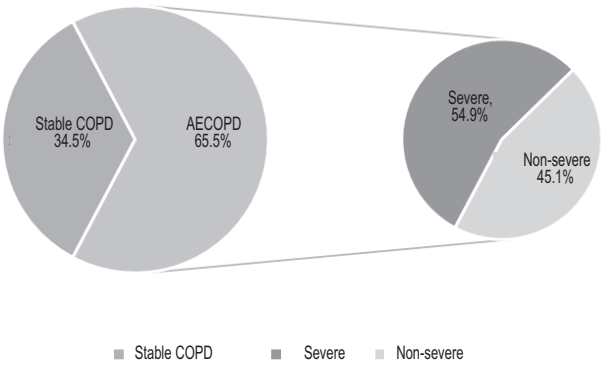

Fig.-1: *Pie chart showing distribution of COPD patients*

Table I

Comparison of laboratory findings between acute and stable COPD patients (N=139)

Characteristics	Acute COPD (N=91) (mean±SD)	Stable COPD (N=48) (mean±SD)	t-value	df	p-value
pH	7.39 ± 0.07	7.40 ± 0.04	-0.77	137	0.438^{ns}
PCO_2	52.12 ± 11.90	43.10 ± 3.60	5.11	137	$<0.001^{s}$
PO_2	56.09 ± 12.47	65.54 ± 8.90	-4.65	137	$<0.001^{s}$
FEV1 (%predicted)	35.72 ± 12.29	43.44 ± 8.55	-3.88	137	$<0.001^{s}$

(Unpaired t-test was done; s – Significant, ns – non-significant)

Table II

Comparison of laboratory findings between acute and stable COPD patients (N=139)

Characteristics	Acute COPD (N=91) (mean±SD)	Stable COPD (N=48) (mean±SD)	t-value	df	p-value
Serum uric acid	6.77±1.32	5.37±1.74	5.30	137	<0.001[s]
Serum Creatinine	0.96 ± 0.20	0.84 ± 0.14	3.86	137	<0.001[s]
Serum uric acid to creatinine ratio	7.28±1.94	6.50±2.04	2.20	137	0.029[s]

(Unpaired t-test was done; s – Significant, ns – non-significant)

Table III

Laboratory findings of the acute exacerbation of COPD patients according to severity (N=91)

	Acute COPD		t-value	df	p-value
	Severe (mean ± SD)	Non-severe (mean ± SD)			
pH	7.38 ± 0.07	7.40 ± 0.06	-1.18	89	0.239[ns]
PO_2	53.46 ± 13.16	59.31 ± 10.88	-2.28	89	0.025[s]
PCO_2	55.72 ± 13.35	47.73 ± 8.02	3.36	89	0.001[s]
FEV1	36.13 ± 13.54	35.22 ± 10.71	0.34	89	0.728[ns]
Serum uric acid	6.98 ± 1.60	6.51 ± 0.81	-1.56	89	0.092[ns]
Serum creatinine	0.93 ± 0.23	1.00 ± 0.13	1.70	89	0.121 [ns]
Uric acid to creatinine ratio	7.78 ± 2.23	6.67 ± 1.29	2.81	89	0.006[s]

(Unpaired t-test was done; s – Significant, ns – non-significant)

Table IV

Serum uric acid and uric acid to creatinine ratio according to Gold staging in severe and non- severe acute exacerbation of COPD patients (N=91)

Gold staging of COPD	Severe		Non-severe	
	Serum uric acid (mean ± SD)	Uric Acid to Creatinine ratio (mean ± SD)	Serum uric acid (mean ± SD)	Uric Acid to Creatinine ratio (mean ± SD)
Stage 2	6.43 ± 0.53	8.39 ± 2.72	6.28 ± 0.00	7.73 ± 0.45
Stage 3	6.39 ± 1.17	7.15 ± 1.90	6.24 ± 0.76	6.24 ± 1.32
Stage 4	7.78 ± 1.90	8.23 ± 2.34	6.84 ± 0.85	6.88 ± 1.23
p-value	0.008[s]	0.212[ns]	0.066 [ns]	0.069 [ns]
F-value	5.30	1.60	2.92	2.87
df	2	2	2	2

(ANOVA test was done ; s – Significant , ns – non-significant)

Table V

Correlation of serum uric acid with pH, PO_2 and PCO_2 in severe & non-severe acute exacerbation and stable COPD patients (N=139)

	Acute exacerbation of COPD				Stable COPD	
	Severe		Non-severe			
	r	p-value	R	p-value	R	p-value
pH	-0.681	<0.001[s]	-0.485	0.001[s]	-0.023	0.878[ns]
PO2	-0.172	0.231[ns]	0.100	0.535[ns]	0.160	0.276[ns]
PCO2	0.463	0.001[s]	-0.028	0.862[ns]	0.192	0.192[ns]

(Pearson's correlation was done; s – Significant, ns – non-significant)

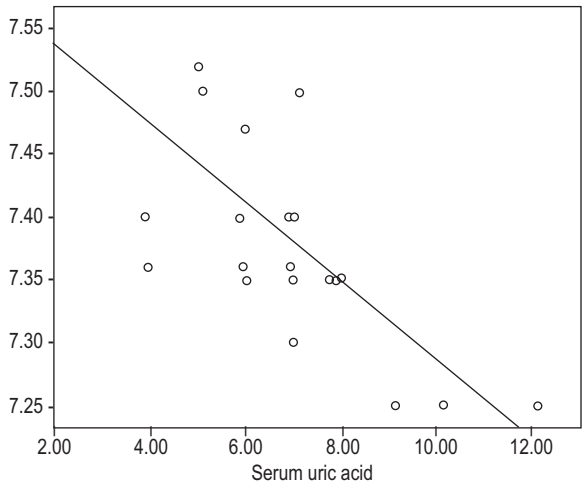

Fig.-2: *Scatter diagram showing correlation of serum uric acid with pH in severe acute COPD patients*

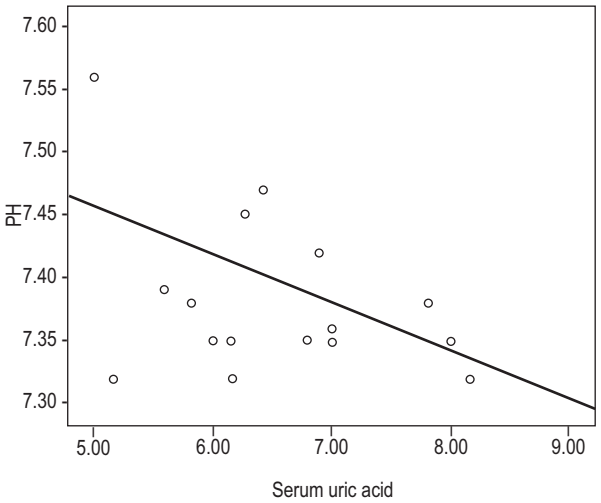

Fig.-3: *Scatter diagram showing correlation of serum uric acid with pH in non-severe acute COPD patients*

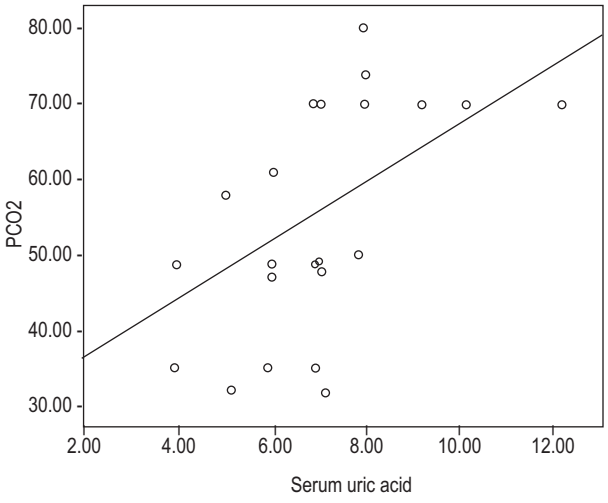

Fig-4: *Scatter diagram showing correlation of serum uric acid with PCO_2 in severe acute COPD patients*

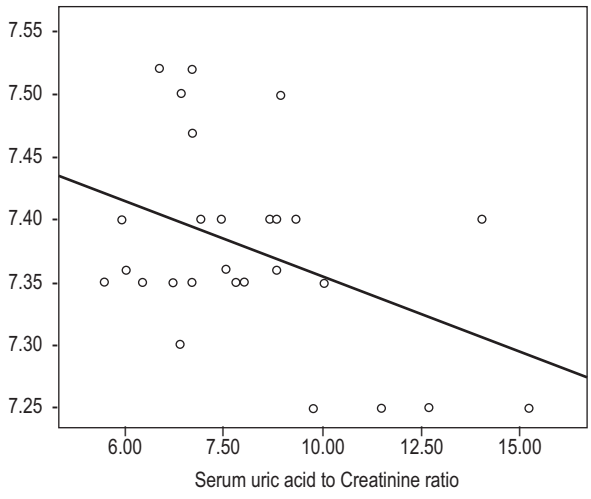

Fig.-5: *Scatter diagram showing correlation of serum uric acid to creatinine ratio with pH in severe acute COPD patients*

Table VI

Correlation of uric acid to creatinine ratio with pH, PO_2 and PCO_2 in severe & non-severe acute exacerbation and stable COPD patients (N=139)

	Acute COPD				Stable COPD	
	Severe		Non-severe			
	r	p-value	R	p-value	r	p-value
pH	-0.368	0.009[s]	-0.287	0.069	0.238	0.103 [ns]
PO_2	-0.179	0.214 [ns]	0.190	0.235	0.338	0.019[s]
PCO_2	-0.070	0.630 [ns]	-0.146	0.363	0.087	0.556 [ns]

(Pearson's correlation was done; s – Significant, ns – non-significant)

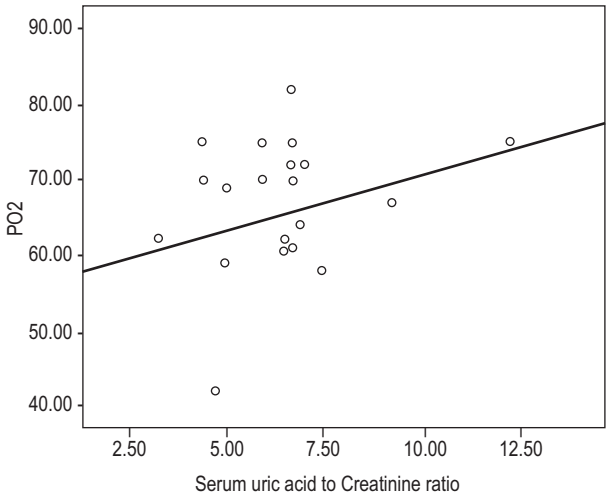

Fig.-6: *Scatter diagram showing correlation of serum uric acid to creatinine ratio with PO_2 in stable COPD patients*

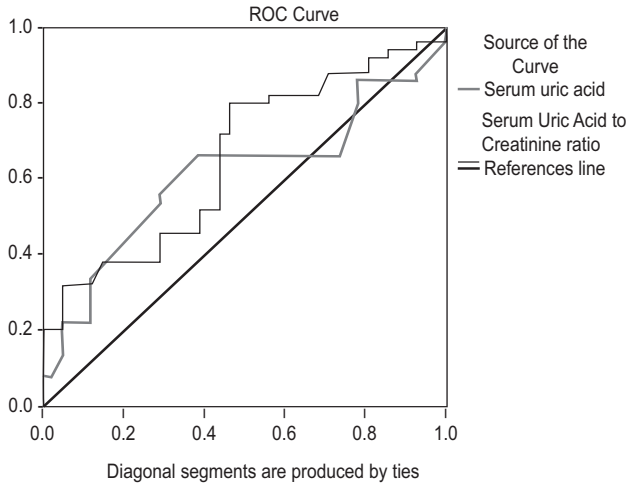

Fig.- 7: *ROC curve of serum uric acid and serum uric acid to serum creatinine ratio in predicting the severity of acute COPD*

Table VII

Sensitivity, specificity, PPV and NPV at different cut-off values of serum uric acid in predicting the severity of acute COPD (N=139)

Serum Uric Acid	Sensitivity	Specificity	PPV	NPV	Youden Index
5.86	0.860	0.220	0.795	0.563	0.080
5.98	0.800	0.220	0.806	0.474	0.020
6.16	0.660	0.293	0.794	0.414	-0.047
6.35	0.660	0.415	0.830	0.500	0.075
6.85	0.660	0.610	0.853	0.595	0.270
6.98	0.540	0.707	0.835	0.558	0.247
7.45	0.300	0.878	0.738	0.507	0.178
7.87	0.220	0.951	0.687	0.500	0.171
8.08	0.080	0.976	0.463	0.465	0.056

Table VIII

Sensitivity, specificity, PPV and NPV at different cut-off values of serum uric acid to serum creatinine ratio in predicting the severity of acute COPD (N=139)

Serum Uric Acid to serum creatinine ratio	Sensitivity	Specificity	PPV	NPV	Youden Index
5.83	0.880	0.220	0.579	0.601	0.100
5.94	0.820	0.317	0.594	0.591	0.137
6.16	0.820	0.390	0.621	0.640	0.210
6.19	0.820	0.439	0.641	0.667	0.259
6.32	0.800	0.537	0.678	0.688	0.337
6.47	0.720	0.537	0.655	0.611	0.257
6.69	0.600	0.561	0.625	0.535	0.161
6.98	0.520	0.561	0.591	0.489	0.081
7.11	0.520	0.585	0.604	0.500	0.105

Discussion:

There is a growing curiosity about the use of biomarkers in the assessment of COPD. But such facts are difficult to establish, mainly due to weak associations and lack of reproducibility in various studies among different parameters of COPD[6].

In this study, 48 (34.5%) patients had stable COPD and 91 (65.5%) patients had an acute exacerbation of COPD. Among acute exacerbation of COPD patients, 50(54.9%) patients were labeled as severe and 41(45.1%) patients were labeled as non-severe based on their arterial blood gas findings (No respiratory failure vs. acute respiratory failure, both non-life-threatening and life- threatening)[5]. Serum uric acid to creatinine ratio was found significantly higher in severe acute COPD patients than non-severe acute COPD patients (7.78±2.23 vs. 6.67±1.29; $p<0.05$). Serum uric acid was also found higher in severe acute COPD patients (6.98 ± 1.60) than non-severe exacerbation patients (6.51 ± 0.81) but the difference was not statistically significant ($p>0.05$).

In this study, Serum uric acid (6.77±1.32 vs. 5.37±1.74; $p<0.05$), serum creatinine (0.96±0.20vs 0.84±0.14;$p<0.05$) and serum uric acid to creatinine ratio (7.28±1.94 vs. 6.50±2.04;$p<0.05$) was found significantly higher in acute exacerbation of COPD patients than Stable COPD patient. A similar study by Antus et al.[7] found a significantly higher level of serum uric acid in acute exacerbation of COPD patients than stable COPD patients (342.0±26.8 ìmol/l vs. 319.5±19.5 ìmol/l; $p<0.05$). These results were in agreement with those obtained by Bartziokas et al.[8] who found that serum uric acid levels were higher in patients with more severe airflow limitation, cardiovascular comorbidity, frequent exacerbations, and prolonged hospitalization.

We observed that serum uric acid level was significantly higher ($p=0.001$) in acute COPD GOLD stage 4(7.34±1.56) compared to stage 2 (6.37±0.42) and 3 (6.32±0.99) but uric acid to creatinine ratio was significantly higher in COPD stage 2 (8.15±2.14 in stage 2 vs. 6.73±1.69 in stage 3 vs. 7.60±2.00 in stage 4, $p=0.035$). Serum uric acid level was 3.97±0.90 and 5.69±1.73 in Gold stage 2 and 3 respectively in stable COPD, it was statistically significant ($p=0.006$). Serum uric acid to creatinine ratio was 4.96±1.49 and 6.85±1.99 in GOLD stage 2 and 3 respectively in stable COPD, which was also statistically significant ($p=0.010$). In the study of Bartziokas et al.[8] serum uric acid levels increased with the severity of acute exacerbation of COPD. In contrast, Nicks et al.[9] found that COPD patients with GOLD stages 1 and 2 had higher levels of uric acid than did severe COPD patients (GOLD stages 3–4) and stated that a higher level of uric acid was associated with better lung function9.

Here we have found that serum uric acid had significant negative correlation with pH in severe($r=-0.681$,$p=<0.001$) and non-severe (r=-

0.485,p=0.001) acute exacerbation patients, also serum uric acid had significant positive correlation with PCO_2 in severe exacerbation patients (r=0.463,p=0.001). Serum uric acid to creatinine ratio had significant negative correlation with pH in severe acute exacerbation patients(r=-0.368,p=0.009), also serum uric acid to creatinine ratio had significant positive correlation with PO_2 in stable COPD patients (r=0.338,p=0.019).A positive correlation with PO_2 may be because PaO_2 at rest or even during an exacerbation may not inevitably reflect the whole spectrum of hypoxemia in COPD patients as tissue hypoxia is determined by the balance between arterial oxygen transport and oxygen demands in tissue. Antus et al. (2017) found a significant inverse correlation between serum uric acid levels and PaO_2 (r=- 0.393, $p<0.05$)[7].

The area under the ROC curve of serum uric acid to creatinine ratio and serum uric acid was 0.654 and 0.610 respectively in predicting the severity of acute exacerbation of COPD. The ROC analyses were done by Kocak et al.[10] indicated that serum uric acid to creatinine ratios can be a better convenient marker than serum uric acid levels in predicting exacerbation risk (AUC,

0.586 vs. 0.426) and disease severity (AUC, 0.560 vs. 0.475) particularly at higher cut-off values, but with low specificity. In the study of Abdel Halim et al.[11] both serum uric acid and uric acid to creatinine ratios had higher prediction levels for the severity of acute COPD (being in the category C or D); AUC=0.819, the cut-off value was 4.25 (sensitivity: 0.97, specificity: 0.87) for uric acid and AUC=0.847, the cut-off value was 7.92 (sensitivity: 0.99, specificity: 0.85) for uric acid to creatinine ratio.

We have found in this study that the best cut-off value of serum uric acid was 6.85 in predicting the severity of acute COPD according to the Youden Index. The sensitivity, specificity, PPV, and NPV of serum uric acid were 0.660, 0.610, 0.853, and 0.595 respectively in assessing the severity of acute COPD at the cut-off value of 6.85. The best cut-off value of uric acid was 6.85 in assessing the severity of COPD. At 6.85 cut-off value of serum uric acid, sensitivity and specificity were 0.218 and 0.714 respectively.

In this study, the best cut-off value of Serum uric acid to serum creatinine ratio was 6.32 in assessing the severity of acute COPD according to the Youden Index. The sensitivity, specificity, PPV, and NPV of serum uric acid to serum creatinine ratios were 0.800, 0.537, 0.678, and 0.688 respectively in assessing the severity of acute COPD at cut-off value 6.32. At 6.32 cut-off value of serum uric acid to creatinine ratio, sensitivity and specificity were 0.704 and 0.413 respectively.

Conclusion:

In conclusion, it can be said that in the absence of spirometry and arterial blood gas analysis, serum uric acid and serum uric acid to serum creatinine ratio cannot be used to assess the severity of acute exacerbation of COPD. In future, different subgroup of population with defined characteristics (smoker, non-smoker etc.) can be studied to further evaluate the utility of serum uric acid and serum uric acid to serum creatinine ratio to assess the severity of acute exacerbation of COPD.

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ORIGINAL ARTICLE

Demographic Profile And Clinical Outcome of Pediatric COVID-19 Patients Admitted In Dhaka Medical College Hospital

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Abstract

Background*: Corona Virus Disease 19 (Covid 19) is a global pandemic. Children of all ages are infected but had less severe outcome than adults. Infants were more vulnerable and case fatality is higher in this age group. Most patients experience milder symptoms but patients with co-morbid disease had moderate to severe disease.*

Method: *This is a descriptive study of 400 patients which was conducted at Department of Pediatrics of Dhaka Medical College Hospital, during the period from May 2020 to August 2021.*

Results: *Patients in the second wave were younger. The disease severity, complications and case fatality rate were higher than those in the first wave. In the second wave, there were more neonates, younger children and adolescent. The most frequent signs and symptoms in both waves were fever, dyspnea and cough, and the most relevant comorbidities were malignancy, renal, cardiovascular diseases and chronic neurological diseases. Patients from the second wave more frequently presented renal and gastrointestinal symptoms, were more often treated with conventional oxygen therapy, anticoagulants and corticoids and non- invasive mechanical ventilation and less often with invasive mechanical ventilation. These results might help to understand the characteristics of the second wave and the behavior and danger of SARS-CoV-2 in Bangladesh and surrounding countries. Further studies are needed to confirm our findings.*

Conclusion: *The results of the present study shows higher number of infants are infected and higher domestic contact history and history of travel is observed in second wave. These results might help to understand the characteristics of this second wave. We think that COVID-19 will not disappear soon. New variants of the virus may appear, the vaccination process can predictably last all year 2023 or more, until a sufficiently high percentage of the population is protected. We must remain vigilant in the constant study and disseminate our results to the scientific community to formulate strategies and guidelines for prevention and treatment of future waves.*

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Introduction:

Coronavirus disease-19 (COVID-19) caused by Severe Acute Respiratory Syndrome Corona Virus -2 (SARS CoV-2), a global pandemic, has become a serious health threat since first detection in December 2019. Several waves are seen in the pattern of reported cases worldwide, making it difficult for public health workers. In Bangladesh, we observed the first wave in May 2020 up to October 2020 and a second in February 2021 to August 2021[1]. As a consequence of the first outbreak, the Bangladesh Government introduced a series of strict prevention measures, including-home confinement, decreasing social interaction and commercial activity, work from home ,online school, limitation of transportation and banning of international travel which reduced the disease activity significantly. Introduction of vaccination programme, mandatory wearing of a face mask and maintaining a safe social distance was the key to prevention. Unfortunately, the number of cases of patients with COVID-19 began to increase towards the end of February 2021 and showed up with rapidly increasing cases with higher case fatality and had rapidly spread to peripheral districts[2]. As the number of cases in Bangladesh has continued to grow, it was named as the second wave. Since then the Government was forced to re-impose serious restrictive measures, including local and regional lockdowns, banning of social gathering, cultural and sports activities, restriction in movements. The second wave of COVID-19 had been predicted months earlier as our neighbouring countries. Europe and The United States are currently suffering the consequences of this second wave and are taking similar restrictive measures. Empirical data would suggest that this second wave differs from the first in such factors as age range and severity of the disease[3]. The similarities and differences between the characteristics of the two waves remain largely unknown. Population comparison is difficult because the technological and logistical capacity is limited, detection and diagnosis of asymptomatic patients are difficult, mild cases were reluctant to hospital visits.

This study compared the severity and characteristics of the two waves in hospitalized patients in the COVID unit of the department of Paediatrics at Dhaka Medical College Hospital. We evaluated and compared age, gender, severity, complication and the outcome of the patient.

Materials and methods

We conducted a descriptive study in Dhaka Medical Hospital between May 2020 and August 2021. All patients admitted up to October 2020 were considered to be in the first wave and all those admitted from March, 2021 till October, 2021 in the second wave. The only inclusion criterion was to be a hospitalized patient, 0-15 years of age, who have RT PCR positive for COVID 19 infection. We excluded those with suspected SARS-CoV-2 infection but had no laboratory confirmation and those who came to the hospital with symptoms compatible with COVID-19 but did not comply with our criteria, duration of admission was <24 hours, SARS-CoV-2 infection was confirmed by RT-PCR using swab samples from the upper respiratory tract (nasopharyngeal swab). Tests were carried out with the SARS-CoV-2 Real Time PCR Detection Kit. This study was approved by the Ethical Review Board of Dhaka Medical College, Dhaka.

Total 436 patients were admitted during study period. Among them 400 children were enrolled who fulfilled our criteria and were willing to participate. Among them, 175 patients were enrolled during the first wave and 225 in the second wave. Data was given as numbers and percentages or means and standard deviations. Statistical comparisons between two groups were made using the ÷2 test (categorical variables) or the unpaired t test. Statistical significance was set at p value is< 0.001. Logistic regression models were used to identify the combined effect of the selected variables on mortality. All calculations were made using the SPSS 22 statistical package.

Results

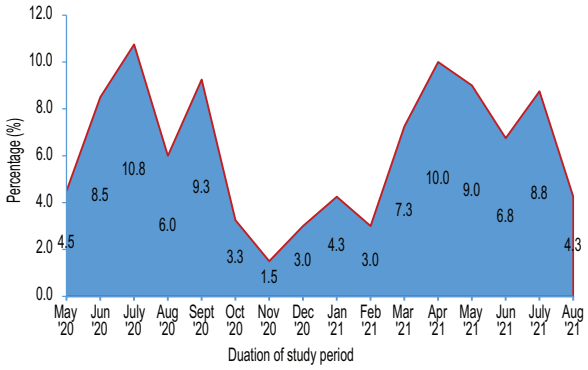

Fig.-1: *Percentage of patients with COVID-19 admitted per month*

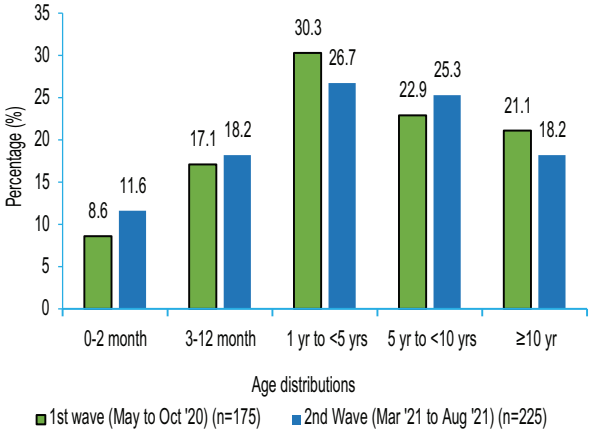

Fig.-2: *Distribution by age intervals of the patients admitted for COVID-19 during 1st and 2nd wave*

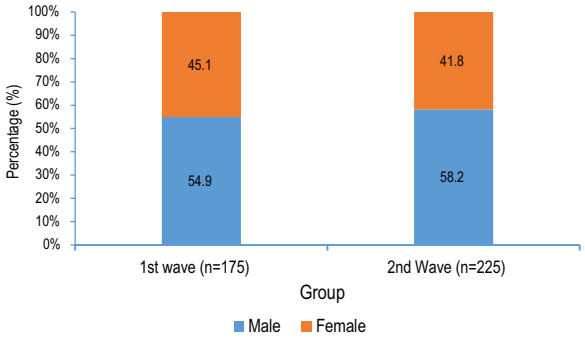

Fig.--3: *Bar diagram shows distribution by sex during 1st wave and 2nd wave*

Male: Female ratio = 1.2: 1 [1st wave (May to Oct '20) (n=175)]
Male: Female ratio = 1.4: 1 [2nd Wave (Mar '21 to Aug '21) (n=225)]

Table I

Epidemiological characters of patients

Variables	1st wave (n=175)	2nd Wave (n=225)	p-value
Age (years)	4.86±3.96	4.76±4.10	0.811
Gender, male	96(54.9%)	131(58.2%)	0.500
Any contact to COVID-19 patients within 14 days	127(72.6%)	197(87.6%)	<0.001
Family member affected	26(14.9%)	60(26.7%)	0.004

Table II

Classification of disease severity

Disease severity	1st wave (n=175)	2nd Wave (n=225)	p-value
Asymptomatic	10(5.7%)	9(4.0%)	0.429
Mild	14(8.0%)	13(5.8%)	0.772
Moderate	59(33.7%)	84(37.3%)	0.454
Severe	85(48.6%)	91(40.4%)	0.104

Table III

Complications of COVID-19 in children

Complications	1st wave (n=175)	2n wave (n=225)	p-value
MIS-C	1(0.6%)	3(1.3%)	0.447
ARDS	7(4.0%)	9(4.0%)	1.000
Respiratory failure	16(9.1%)	23(10.2%)	0.718
Heart failure	5(2.9%)	7(3.1%)	0.882
Bleeding manifestations	12(6.9%)	19(8.4%)	0.081
Others	35(20.0%)	41(18.2%)	0.653

Chi-square test was done

Results

During the study period, 436 children with COVID 19 infection, confirmed by RT-PCR, were admitted to the hospital. The monthly distribution of hospital admissions is shown in Fig 1. The first wave peaked at the June- August 2020 and was followed by a progressive decline in detection with very few patients being admitted in November to February 2020. The number of cases fluctuated upward from March 2021 until mid-August. Distributions of patients of both waves by age intervals were shown in Figure 2, which shows no significant difference. Figure 3 shows higher no of male children were admitted in both waves (1.2:1 in 1st and 1.4:1 in 2nd wave). The relation between epidemiological variables with COVID 19 was shown in Table1 which shows there is significant higher no of children in 2nd wave had contact with COVID 19 patients [127(72.6%) vs. 197(87.6%); p value <0.001] and had significantly higher no of history of travelling or residing in a pandemic area [124(70.9%) vs. 196(87.1%): p value <0.001] Severity was classified according to guideline of BPA guideline. Most of the children presented with severe (48.6% in 1st wave and 40.4% in second wave) disease. The most serious complications were respiratory failure (9.1% and 10.2%respectively), ARDS, multi-system inflammatory syndrome in children (MIS-C), bleeding manifestations, heart failure. Most of the patients recovered in both the waves.

Discussion:

To our knowledge, this observational study is the first study in Bangladesh. Similar studies were conducted in neighbouring countries like India and Asian countries like China[4] and Hong Kong [5] during waves .The incidence rate of covid 19 infection among Bangladeshi children is 7%in both waves[6]. Case detection rate was lower in winter season when influenza virus causes more respiratory tract infection[7]. More patients were admitted during 2nd wave due to increase awareness among general population and increasing case detection rate. In both the waves, 1 to 5 years old children are predominant. male patients are predominant in number in both waves similar results were found in Iran[8] (50.9%) and in Spain[9].Most patients admitted with moderate to severe disease and a few critical cases. In our study we found symptomatic neonates who were Covid positive, followed by their mothers being confirmed with Covid 19 infection. The patients of second wave had significantly higher frequency of cough, nasal congestion, dyspnoea and diarrhoea. Most children in our study classified as severe disease (48.6% and 40.4% respectively), only a few critical patients were admitted (4.0% in first wave vs 12.4% in second wave) who needed advanced life support for higher rate of Mechanical ventilation and respiratory support. A retrospective cohort study conducted in April 2021 in Bronx, New york found similar results[10]. Hence there is no definite or clearcut treatment guideline for pediatric covid positive patients, we followed our national guidelines and guideline of Bangladesh Pediatrics Association[11] Common complications in both the waves were respiratory failure (9.1% and 10.2%respectively),ARDS, bleeding manifestations, heart failure. There were 4 patients who experienced multisystem inflammatory Syndrome in children (MIS-C) after 3 -4 weeks of diagnosis, which manifested as high fever, rash, cervical lymphadenopathy, bilateral conjunctival injection, cracked lip, bleeding manifestations. Globally, the first case of MIS-C as a complication of pediatric Covid 19 was reported in Europe[12]. Multiple pediatric studies in Asia have reported MIS-C as rare, although this study found few cases in both first and second wave. Mortality rate was 4.6% and 6.7% respectively. A comparative study in Reus, Spain showed similar results[3].

Conclusion:

The results of the present study shows higher number of infants are infected and higher domestic contact history and history of travel is observed in second wave. These results might help to understand the characteristics of this second wave. We think that COVID-19 will not disappear soon. New variants of the virus may appear, the vaccination process can predictably last all year 2023 or more, until a sufficiently high percentage of the population is protected. We must remain vigilant in the constant study and disseminate our results to the scientific community to formulate strategies and guidelines for prevention and treatment of future waves.

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REVIEW ARTICLE

A Systematic Review on the Role of Diffusing capacity of the lung for carbon monoxide (DLCO) in Chronic Obstructive Pulmonary Disease (COPD) Assessment

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Abstract

The measurement of diffusing capacity of the lung for carbon monoxide (DLCO) is not included in most common used models of COPD assessment. Here, the goal of this Systematic Review to evaluate the role of DLCO in COPD assessment. We conducted a systematic literature search in Pubmed, Google Scholar, and Scopus using a search strategy PICO model on "diffusing capacity or diffusing capacity for carbon monoxide "or" DLCO and COPD and "assessment" were included. The search yielded thousands of papers, of which 11 publications came into light for full review. This review led to that DLCO % predicted might be an important measurement for COPD patients in terms of severity, exacerbation risk, mortality, emphysema domination, and presence of pulmonary hypertension. As diffusion capacity reflects pulmonary ventilation and perfusion at the same time, the predictive value of DLCO or DLCO combined with other criteria worth further exploration.

***Keyword**: Diffusing capacity, DLCO % predicted, COPD assessment.*

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Introduction:

Chronic obstructive pulmonary disease (COPD) affects more than 328 million people[1] and is the third leading cause of death worldwide.[2] To evaluate the severity of COPD, a number of measurements are required. Spirometry has been the cornerstone of COPD assessment, including forced expiratory volume during the first second (FEV1), forced vital capacity (FVC), and the ratio between these two measurements (FEV1/FVC). Recently, to achieve a multidimensional evaluation, the spirometry measures are supplemented by assessment of symptoms, risk of exacerbations, as well as quantitative assessment of emphysema by CT imaging.[3,4] However, one noninvasive and widely available tool is not included in commonly used prognostic models of COPD assessment, the measurement of diffusing capacity of the lung for carbon monoxide (DLCO).

Diffusing capacity of the lung for carbon monoxide is a measure of gas exchange reflective of the

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complex interactions occurring at the alveolar–capillary interface.[5] It reflects changes in functional lung volume and gas transport across the alveolar–capillary membrane at the same time. Pathological changes characteristic of COPD are found in the airways, lung parenchyma, and pulmonary vasculature.[6] Airflow limitation is the basic characteristic of COPD, and correlates with the reduction in the FEV_1 and FEV_1/FVC ratio. The peripheral airway limitation progressively traps gas during expiration, resulting in hyperinflation. Pulmonary hypertension may develop late in the course of COPD because of vasculature loss due to hyperinflation and hypoxic vasoconstriction of the small pulmonary arteries. Hyperinflation and pulmonary hypertension both influence the lung diffusing capacity, resulting in decrease of DLCO and DLCO/VA (DLCO divided by the alveolar volume). Thus, DLCO provides more information regarding respiratory physiology than spirometry alone.

However, the importance of DLCO in COPD assessment has not been paid enough attention. A few studies suggested an association between decreased DLCO and frequent exacerbation, but the sample size was relatively small.[7,8]

Here, we conducted a systematic review of observational studies to explore the relation of DLCO and COPD severity, exacerbation, and mortality, the most important three factors of COPD assessment.

Methods:

This systematic review was tried according to Preferred Reporting Items for Systematic Review (PRISMA) 2020.

Search strategy:

We performed a comprehensive search of database named Pubmed, Google Scholar, Scopus without language restriction. We searched by the keyword "diffusing capacity" OR "diffusing capacity for carbon monoxide" or "DLCO" AND "COPD" AND "assessment". Among thousands of searched papers, we kept 11 papers for review by some selection criteria. Case reports and small sample sized articles were excluded.

Study selection:

High-quality observational studies investigating DLCO in patients with COPD were included. The studies were selected in agreement with the previously mentioned criteria, and any difference in opinion about eligibility was resolved by consensus.

Discussion:

Among the 12 most validated prognostic models (ADO index, APACHE II, BOD index, BODE index, BODEx index, CODEX index, COTE index, CURB-65, DOSE index, LACE index, updated ADO index, and updated BODE index), none of them included DLCO or DLCO % predicted. Diffusing capacity of the lung for carbon monoxide (DLCO) is inconsistently obtained in patients with COPD, and the added benefit of DLCO testing beyond that of more common tools is unknown.

It is well known that DLCO is related to emphysema. Our review also showed a great degree of decrease in DLCO % predicted in emphysema dominant COPD patients, when compared to non-emphysema dominant COPD patients. Impairment in DLCO was associated with increased COPD symptoms, reduced exercise performance, and severe exacerbation risk even after accounting for spirometry and CT evidence of emphysema. These findings suggest that DLCO should be considered for inclusion in future multidimensional tools assessing COPD. [9]

Reduced exercise capacity in patients with DL_{CO} <LLN was related to higher ventilatory requirements, a faster rate of decline in dynamic Inspiratory reserve volume and greater dyspnoea during exercise. These simple measurements should be considered for the clinical evaluation of unexplained exercise intolerance in individuals with ostensibly mild COPD. [10]

In GOLD I COPD patients, a DLCO < 60% predicted is associated with increased risk of death and worse clinical presentation. [11]

It is important to assess the prognosis of patients with chronic obstructive pulmonary disease (COPD) and acute exacerbation of COPD (AECOPD). Recently, it was suggested that DLCO should be added to multidimensional tools for assessing COPD.DLCO was likely to be as good as or better prognostic marker than FEV_1 in severe AECOPD. [12]

Patients with COPD have an accelerated decline in DLCO compared with smokers without the

disease. However, the decline is slow, and a testing interval of 3 to 4 years may be clinically informative. The lower and more rapid decline in DLCO values in women, compared with men, suggests a differential impact of sex in gas exchange function. [13]

Diffusing capacity was the strongest predictor of exercise capacity in all subjects. In addition to FEV_1, DLCO and Inspiratory capacity provided a significantly higher predictive value regarding exercise capacity in COPD patients. This suggests that it is beneficial to add measurements of diffusing capacity and inspiratory capacity when clinically monitoring COPD patients. [14]

Patients with reduced DLCO, particularly when d" 20% of predicted, are more likely to have reduced Pao_2 at rest and are more likely to require supplemental oxygen with low levels of activity. Thus, DLCO is useful in evaluating whether supplemental oxygen is required for exercise. [15]

Current and former heavy smokers with lower baseline *DLCO* values show a significantly greater progression of CT-quantified emphysema and decline in FEV_1/FVC. These results show that the *DLCO* may be a useful measurement in the evaluation and follow-up of heavy-smoking subjects, with or without airflow obstruction. [16]

Even though an association is seen between DLCO%, and SpO_2, and $ÄCO_2$ in COPD patients at rest, a stronger association was seen between DLCO% and GOLD score. This suggests that DLCO is more descriptive of systemic deconditioning than gas exchange status in COPD patients at rest. [17]

Pulmonary hypertension is one of the most common vascular comorbidities in COPD patients. We found that DLCO % predicted was significantly lower in COPD patients with PH compared to COPD patients without PH. A subset of COPD-PH patients deemed the "vascular phenotype" is defined as those patients who have minimal airflow obstruction but severe hemodynamic derangement. This subset of patients was characterized with lower DLCO and worse mortality compared to COPD patients without PH. And study showed that DLCO % predicted was an independent predictor for survival in COPD patients with PH. [18,19]

Conclusion:

The current review showed that DLCO % predicted was an important measurement for COPD patients in terms of severity, exacerbation risk, mortality, emphysema domination, presence of pulmonary hypertension and requirement of O2 supplementation. Although current prognostic models assessing mortality and morbidity do not include DLCO % predicted, findings from this study suggest that inclusion of DLCO % predicted in such models should be considered.

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CASE REPORT

Microscopic Polyangiitis with Concurrent Autoimmune Hemolytic Anemia in a Middle-Aged Female: A Case Report and Literature Review

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Abstract

A 50-year-old female came to us with cough, dyspnea and severe pallor. Subsequently her renal impairment was found and ground glass opacity was noted on both lung fields in Computed Tomography of Chest. Work up of autoimmunity and anemia was done. P-ANCA and DAT (Direct Agglutination Test) came positive and patient was diagnosed as microscopic polyangiitis with autoimmune hemolytic anemia with renal and pulmonary involvement.

Key words: *Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis; Microscopic Polyangiitis; Autoimmune Hemolytic Anemia.*

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Background

Microscopic polyangiitis (MPA) is a pauci-immune-type necrotizing systemic vasculitis affecting small blood vessels. It is associated with the presence ofantineutrophil cytoplasmic antibodies (ANCA). ANCA-associated vasculitis can be differentiated into disease with or without granulomas comprising granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA)and eosinophilic granulomatosis with polyangiitis (EGPA)[1] all these have different frequencies of ANCA-positivity.[2,3] The major target antigens in ANCA associated vasculitis are proteinase3 (PR3) and MPO (myeloperoxidases). PR3-ANCA presents as C-ANCA pattern and arepredominantly seen in patients with GPA while MPO-ANCA are associated with a P-ANCApattern and are mainly associated with seen in patients with MPA.[4] It is a multisystem disorder mostly affecting kidney, respiratory tract, skin, gastrointestinal tract, and peripheral nerves. Patients with ANCA-associated vasculitis may present with a variety of constitutional symptoms such as fatigue, fever, weight loss and systemic symptoms according to involvement.[5]

Anemia is a common complication of ANCA associated vasculitis or Microscopic polyangiitis (MPA). Many cases have been reported to have

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anemia of varying degree in association with MPA. Renal impairment, anemia of chronic disease (ACD), blood loss (through urine and into the alveoli), nutritional anemia, immunosuppressive drugs, hemolysis (in the microvasculature) and all potentially contributed to the rapid development of anemia. But very few reported cases yet mentioned the concomitantoccurrence of autoimmune hemolytic anemia and Microscopic polyangiitis (MPA).[6]

Here in this article, we have reported a case of female of 50 years of age who was diagnosed with Microscopic polyangiitis (MPA) and Autoimmune hemolytic anemia (AIHA) concurrently.

Case presentation

A married female patient of 50 years of age who was normotensive, non-diabetic, non-smoker and non-alcoholic presented to the hospital on 26thJuly 2022 with the complaints of shortness of breath for 15 days, fever with cough for 7 days which started gradually and were increasing progressively. Initially shortness of breath exacerbated on moderate to severe exertion but later it was affecting daily activities and was associated with orthopnoea and nocturnal dypnoea. The symptom was partially relieved by taking rest and was not associated with facial or leg swelling. The fever was intermittent in nature having no diurnal variation with highest recorded temperature 101° F. It was subsided by taking paracetamol and not associated with burning micturition, abdominalpain,swelling, joint pain or skin rash. Cough was dry in nature with occasional mucoid sputum and persisted throughout day and night with no diurnal variation. There was no associated hemoptysis. Patient also complained of pallor, palpitation, dizziness, loss of appetite and severe prostration. There was no history of blood loss, pulmonary tuberculosis (PTB) or contact with known PTB patients. Her bowel and bladder habit were normal. She had no other significant past history except that she had been handling pigeon for 6 months and history of biomass fuel exposure for more than 20 years. Her age of menarche was 13 years with regular menstrual cycle and average menstrual flow. She had no significant family history. She was Immunized during her childhood according to schedule and also vaccinated against COVID-19. As per general examination patient was severely anemic and temperature was 101°F. Oxygen saturation (SpO_2) at rest was 94% in Room air and SpO_2 after 1-minute sit-to-stand test was 90% in Room air. Nothing else significantly contributing findings were there.

Examination of respiratory system revealed to have bilaterally restricted chest movementand total chest expansion was 2 cm. Respiratory rate was 18/minute. There were no significant abnormalities in tracheal position, apex beat, percussion note or vocal fremitus. Breath sound was vesicular and fine end-inspiratory crepitations which was unaltered by cough noted over both lung fields but were more marked on the left side. Vocal resonance was normal in all 3 lines on both sides of the chest. Other systemic examinations revealed nothing significant finding.

The initial complete blood count reported significant anemia (Hemoglobin: 5.8 mg/dl) with high ESR (Erythrocyte Sedimentation Rate) 110 and elevated white blood cell count (12,200/ mm3) and serum creatinine was 3.21 mg/dL. Urine R/E revealed presence of albumin, Red Cells and pus cell in significant amount. C-reactive protein (CRP) was 60 mg/dL.Chest X-ray revealed inhomogeneous opacity with air bronchogram in the lower zone of right lung and lower, mid and part of upper zones of left lung (Figure-1) and CT scan of chest reported soft tissue density with air- bronchogram within and diffuse ground glass opacity (GGO) are noted in all lobes of both lungs (Figure-2). RT-PCR for COVID-19 came out to be negative.Sputum for AFB (Acid Fast Bacillus) came out negative in 2 samples, MTB (*Mycobacterium tuberculosis*) was not found in GeneXpert But fungal stain in sputum reported to have *Candida* sp. Both sputum and Blood C/S (culture & sensitivity) showed negative result for any bacterial growth. Taking all investigation reports into account, work-up for autoimmunity and connective tissue disease was done and only P-ANCA came significantly positive >100 U/mL. In this stage, for evaluation of anemia, peripheral blood film was analyzed and it suggested having hemolytic anemia. Further work up for hemolytic anemia revealedincreased reticulocyte count (3.5%), elevated unconjugated serum bilirubin(3.1 mg/dL) and positive direct Coomb's test which confirmed autoimmune hemolytic anemia (Table I).

Table-I
Laboratory Parameters of the Patient

Parameters	Date	Patient Values†	Reference Values
Hemoglobi n%	24.07.2022	5.8 gm/dl	12.4 to 16.4gm/dl
	26.07.2022	5.4 gm/dl	
	02.08.2022	8.7 gm/dl	
Erythrocyte Sedimentation Rate	24.07.2022	110 mm in 1st hour	20mm in 1st hour
	26.07.2022	136 mm in 1st hour	
	02.08.2022	69 mm in 1st hour	
White Blood Cell Count	24.07.2022	12,200/cmm	4,000 to11,000/cmm
	26.07.2022	14,600/cmm	
	02.08.2022	17,600/cmm	
Platelet Count	24.07.2022	1,60,000/cmm	1,50,000 to 4,00,000/ cmm
	26.07.2022	5,84,000/cmm	
	02.08.2022	2,64,000/cmm	
RT-PCR for COVID-19	24.07.2022	Negative	-
S. Creatinine	24.07.2022	3.21 mg/dL	0.70 to 1.30 mg/dL
	02.08.2022	2.2 mg/dL	
Urine R/E	24.07.2022	• Albumin (++) • RBC - plenty • Pus cell - 4-6/HPF	-
Sputum for AFB	24.07.2022	Negative (Two samples)	-
ECG	25.07.2022	Sinus tachycardia	-
Echocardiography-2D, M-mode and color doppler	25.07.2022	Tricuspid Regurgitation, Grade-I with mild pulmonary hypertension (PASP-32 mm Hg)	-
USG of whole abdomen	24.07.2022	Mild Hepatic fatty change	-
Peripheral blood	27.07.2022	• RBC- Anisochromia and anisocytosis including spherocytosis, polychromatic cells and nucleated cells • WBC- Mature with increased total count with neutrophil predominance • Platelets- Increased in Number and showing marked anisocytosis and many giant platelets	-
Reticulocyte	28.07.2022	3.5%	0.5-2%
Serum Bilirubin	28.07.2022	Total: 4.2 mg/dL Direct: 1.1mg/dL Indirect: 3.1 mg/dL	Total: 0.3 to 1 mg/dL Direct: 0.1 to 0.3 mg/dL Indirect: 0.2 to 0.7 mg/dL
Coomb's Test	28.07.2022	DAT positive	-
Sputum for X-pert MTB/Rif	01.08.2022	MTB Not detected	-
Sputum for C/S	01.08.2022	No growth	-
Sputum for fungal stain	01.08.2022	*Candida Sp.*	-
Blood C/S (FAN method)	02.08.2022	No growth	-
C-reactive protein	02.08.2022	60 mg/L	< 5 mg/L
S. electrolytes	02.08.2022	Sodium:142 mmol/L Potassium: 3.40 mmol/L	Sodium:135-145 mmol/L Potassium: 3.5 to 5 mmol/L
S. Troponin-I	02.08.2022	0.031 ng/mL	<0.06 ng/mL
p-ANCA	02.08.2022	>100 U/mL	<5 U/mL
c-ANCA	02.08.2022	1.0 U/mL	<30 U/ mL
Complement C3	02.08.2022	1.35 g/L	0.90-1.80 g/L
Complement C4	02.08.2022	0.22 g/L	0.10-0.40 g/L
ANA	02.08.2022	60 mg/L	< 5 mg/L

ANA, antineutrophil cytoplasmic antibodies; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibodies; PASP, pulmonary arterial systolic pressure; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies;
†Abnormal patient values are in bold

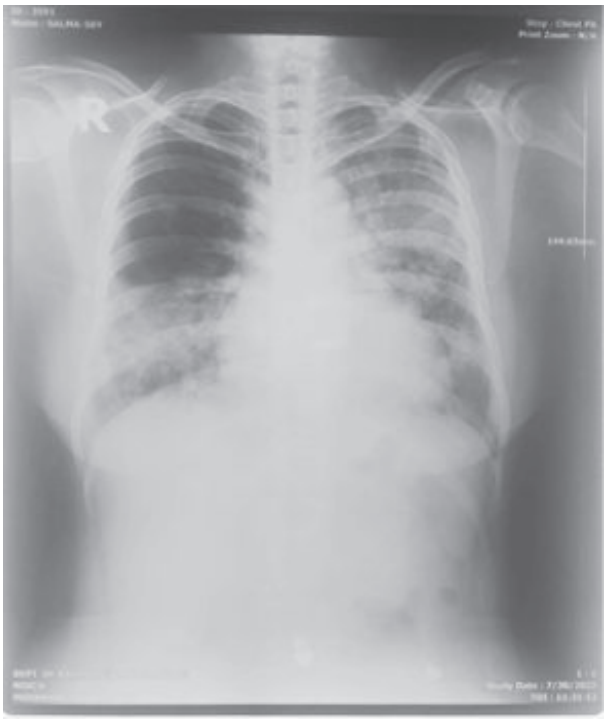

Fig.-1: *Chest X-ray of the patient*

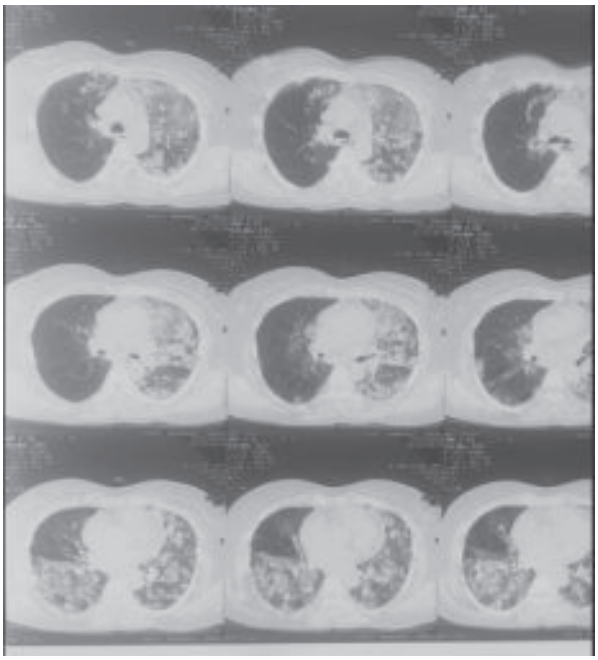

Fig.-2: *HRCT Chest of the patient*

Patient was treated conservatively with oxygen, nebulization, bronchodilator, IV antibiotics, antifungal initially. Then IV methylprednisolone was started. After the confirmatory diagnosis of MPA was made, pulse cyclophosphamide along with IVIG was planned to be started. But unfortunately, patient got hemodynamically unstable with severe hypoxia.The patient's attendant requested DNAR (do not attempt resuscitation) and despite all the reasonable efforts, patient expired on the following day. Post mortem and organ assessment was planned which would require consent of first degree relative by the local law, but they did not give consent into this matter.

Discussion

Microscopic polyangiitis is an ANCA-associated vasculitis (AAV) characterized by small vessel necrotizing vasculitis (arterioles, capillaries, venules). The availability of ANCA testing may have contributed to an increase in MPA incidence over the past 20 years. It has a little male preponderance (male: female ratio of 1.8:1) and typically manifests between the ages of 50 and 60.[7–9]

In a study by Yann Nguyen et al., they analyzed 378 MPA patients in France between 1966 and 2017 and showed how the disease presented clinically upon diagnosis and how it progressed over the course of a five-year follow-up period. The predominant clinical characteristics at diagnosis included renal impairment in 74% of cases, arthralgias in 45% of cases, skin in 41%, lungs in 40%, and mononeuritis multiplex in 32%, Alveolar hemorrhage in 5% of cases, cardiomyopathy in 5%, and severe gastrointestinal symptoms in 4% of cases. The average serum creatinine level was 217 mol/L. ANCA was found in 86% of patients.[10,11]

A prominent characteristic of renal symptoms rapidly progressive glomerulonephritis (RPGN). Various studies also reported 80–100% renal manifestationsamong MPA patients, ranging from no symptoms to end-stage renal disease requiring dialysis.[12,13] Most common urinary findings include proteinuria, microscopic hematuria, and granular or red cell casts.[14]25-55% of patients experience pulmonary symptoms.[15] Diffuse alveolar hemorrhage due to pulmonary vasculitis is the standard pulmonary symptom of MPA. Hemoptysis, dyspnea, coughing, and pleuritic chest discomfort are often reported symptoms.[16,17] Common Radiologicalfinding in computed tomography in these cases are ground-glass opacity which denotes alveolar hemorrhage, chronic interstitial inflammation of the alveolar septa, andcapillaries.[18,19]

Histological confirmation of vasculitis is still thegold-standard in the diagnosis of MPA.[15,20]ANCA is 50–75% sensitive in MPA diagnosis.[8,12]Enzyme-linked immunoassays (ELISA) has greater specificity for diagnosing ANCA associated with MPA, which detects perinuclearstaining pattern(P-ANCA) caused by antibodies against myeloperoxidase (MPO-ANCA).

Our patient a middle-agedfemale of 50 years of age who presented with pulmonary symptomslike dyspnea, fever and pallor. After gradual evaluation and investigations, her blood inflammatorymarkers (CRP and ESR) came to be high with leukocytosis, thrombocytosis and severe anemia. Her renal function test, S. creatinine was 3.21 mg/dl with proteinuria and hematuria in urinalysis. Consequently, her chest imaging was done and Computed topography showed Soft Tissue Density Areas with air bronchogram within and diffuse GGO are noted in all lobes of both lungs. In the mean time she was negative for COVID-19,tuberculosis, blood and sputum culture. Considering all factors,autoimmunity work-up was done and P-ANCA came positive with significantly high titer (>100 U/mL with normal range <5 U/mL). It indicates that patient had antibodies against myeloperoxidase (MPO) of neutrophil that is MPO-ANCA which is predominantly seen in Microscopic polyangiitis. Simultaneously patient being investigated for severe anemia and diagnosed with Autoimmune Hemolytic anemia with positive Direct Coombs test. Patient was diagnosed as Microscopic polyangiitis with pulmonary and renal involvement with AIHA.

Anemia has been reported to be closely associated with MPA where most of them were associated with anemia of chronic disease, low erythropoietin level due to renal impairment, iron deficiency anemia due to chronic hemorrhage via lung or urinary system. Many cases found hemolytic anemia but these were due to extravascular hemolysis of alveolar hemorrhage where Direct Coomb's test came negative[21] But none of the cases of MPA or ANCA related vasculitis yet mentioned the association of MPA with Autoimmune Hemolytic anemia.

Autoimmune hemolytic anemia is immune mediated destruction of RBC and many conditions have been reported as risk factors for the AIHA such as lymphoproliferativediseases, immunodeficiencies, infections, solid tumors and other autoimmune diseases. Among the other autoimmune conditions, Systemic Lupus Erythematosus (SLE) has been reported to be a significant one but several cases of Systemic Sclerosis or Sjogren Syndrome, Hashimoto's thyroiditis and Graves' disease, ulcerative colitis, and autoimmune hepatitis have also been reported to be associated with AIHA. But none of the study yet demonstrated the association between AIHA and Microscopic polyangiitis or any ANCA related vasculitis.[22,23]

As our patient didn't have any previous history of anemia, jaundice or any kind of autoimmune diseases before the diagnosis of MPA and the symptoms of respiratory manifestations of MPA and severe anemia evolved and diagnosed within the same time frame, an assumption can be postulated that AIHA can be associated with MPA still further research and investigation should be conducted to evaluate the association.

Key Clinical Message

Microscopic polyangiitis (MPA) is an autoimmune disorder causing necrotizing vasculitis of small blood vessels targeting multiple systems. Though anemia has been a common complication of MPA or ANCA associated vasculitis, yet autoimmune hemolytic anemia associated with MPA is very rare. Nevertheless, it should be kept in consideration.

Funding Statement

The study didn't receive any funding.

Ethical Approval

The study is exempt from ethical approval in our institution.

Consent

Written informed consent was obtained from the patient or the publication of this case report and the accompanying images.

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