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EDITORIAL

Nontuberculous Mycobacteria in Port Site Infection Following Laparoscopic Surgery: Challenges for Doctors

Bipul Kanti Biswas

[Chest Heart J. 2022; 46(2) : 48-49]
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Laparoscopic surgery, also called "minimally invasive surgery," was developed in the 18th century and quickly became the preferred way to do many operations[1]. Philips Mouret reported the first laparoscopic cholecystectomy. Since then, the technique has been used and improved for many other surgeries. Laparoscopy has its own set of unique complications. Besides significant complications like bowel or vascular injury, Port site infection (PSI) caused by NTM is an infrequent but well-documented complication that can occur following laparoscopic surgeries. Depending on the reporting area and type of surgery, the PSI rate varies from 3.3% to 8%.

PSIs, based on the timing of their presentation, are classified into two categories: Early onset PSI (within a week of the surgical procedure) is often caused by Gram-positive or Gram-negative bacteria. Delayed or Late onset PSI (presents between three to four weeks after surgical procedure) is mainly caused by atypical mycobacteria[2]. Most outbreaks of NTM infections are caused by problems with sterilization, reuse of disposable devices without proper sterilization, and disinfection of reusable laparoscopes with 2% glutaraldehyde as a substitute for sterilization.

The most frequent NTM species responsible for skin/soft tissue infections are M. abscessus, M. fortuitum, M. marinum, M. ulcerans, and M. chelonae.Females are more likely to be affected. The exact reason for this is unknown, but it may be because laparoscopic procedures are more commonly done on women[3]. Identifiable comorbidities were rare, but diabetes mellitus and hepatitis B were identified as possible risk factors. NTM infections can affect one or more port sites, with the umbilical port being the most common one. Port-site NTM infections usually show up as nodule formation, pus pockets, wounds that won't heal, and subcutaneous nodules.

There are five clinical stages of the non-tuberculous or atypical mycobacterial port-site infection[4].

Stage 1: A small tender nodule near the port site.

Stage 2: Increase in size and tenderness with a sign of inflammation, a nodule, followed by discharge of white pus.

Stage 3: Reduced pain with continuously discharging sinus and necrosis of the overlying skin.

Stage 4: Chronic sinus with white or serous discharge.

Stage 5: Hyperpigmentation with necrosed skin and appearance of nodules at the other site.

The definitive diagnosis of NTM infections can be made by ZN staining of the pus, wound swab, or aspirated fluid. The sample should be simultaneously sent for NTM culture. The culture can be performed in solid egg-based (Lowenstein-Jensen), agar-based, or liquid medium (Middle brook). The bacterial growth will appear in two to five days of incubation for rapid growers, while slow growers may take two to eight weeks.The mycobacterial species can be identified by biochemical reactions, PCR, line probe assays, 16S

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or 23S ribosomal RNA DNA sequencing, or matrix-assisted laser desorption ionization-time of flight mass spectrometry. Pan-mycobacterial polymerase chain reaction (PCR) test can also be used for diagnosis.

Deep structures can be evaluated using ultrasound or computed tomography images, which can then be used to guide decisions about surgical excision or drainage.If surgical excision of the port site is performed, the tissue must be sent for histopathology and culture.

NTM are resistant to many antimicrobials. Hence, culture and sensitivity must be obtained whenever possible. As NTM shows a limited response to isoniazid, rifampicin, pyrazinamide, and ethambutol, DST should include additional drugs such as macrolides, quinolones, oxazolidinones, tetracyclines, and aminoglycosides, as well as broad spectrum beta lactam antibiotics. Susceptibility data suggest that several newer antibiotics (bedaquiline, linezolid, telithromycin, and tigecycline) may have activity against NTM. Still, their role in treatment remains to be defined. Current American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) guidelines recommend the use of combination therapy with different classes of agents, as rapidly growing NTM can develop resistance by mutation while on therapy. Inducible macrolide resistance has been demonstrated in M. fortuitum and M. abscessus.It is recommended to use a macrolide (clarithromycin or azithromycin) combined with parenteral medications such as amikacin, cefoxitin, or imipenem for skin and soft tissue infections caused by Mycobacterium abscesuss. In contrast, imipenem is preferred for M. chelonae, as it is uniformly resistant to cefoxitin.The suggested treatment for M. fortuitum infection is combination therapy with at least two active agents as guided by DST results. There is no consensus regarding the correct duration of therapy, except that prolonged treatment is required to prevent disease relapse. ATS/IDSA guidelines recommend a minimum of 4 months of therapy with at least two agents with in vitro activity.[5]

Although prolonged treatment with antimicrobial drugs alone can cure in some cases, good outcomes often require extensive debridement and removal of prosthetic material.Surgical debridement is reserved for cases with extensive tissue necrosis, abscess formation, or poor response to appropriate antimicrobial therapy.

In conclusion, NTM port site infection is a frustrating complication of laparoscopic surgery. Proper cleaning and sterilization of laparoscopic instruments and solutions used to disinfect the skin are essential to prevent infections. Most patients respond well to treatment. However, DST-guided multidrug regimens must be given for a long time.

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ORIGINAL ARTICLE

Role of Bronchial Brush and Bronchial Wash Cytology in the Diagnosis of Lung Cancer: A Comparative Study

S M Abdur Razzaque[1], Md. Khairul Anam[1], Bipul Kanti Biswas[1], Manoranjan Roy[2], Md. Serazul Islam[2], Golam Sarwar Liaquat Hossain Bhuiyan[2], Mousumi Podder[3], Goutam Sen[4]

Abstract:

Background: *Lung cancer is one of the most common cancer around the world which is associated with significant mortality. Cytological techniques are used as first-line diagnostic tools in suspected lung tumors, based on which crucial management decisions are made. Bronchial brush (BB) and bronchial wash (BW) are two commonly employed techniques with variable diagnostic yield of lung cancer.*

Objective: *The main objective of the present study was to compare cytological pattern of Bronchial Wash and Bronchial Brush in diagnosing Lung Cancer.*

Methods: *This cross-sectional comparative study was conducted in the admitted patients under Department of Respiratory Medicine, National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka, between January 2022 and December 2022. A total of 55 patients, clinically suspected of lung cancer and had a positive report on bronchial biopsy were included in the study. After written informed consent, a rapid diagnostic workup was made by clinical history, thorough physical examinations and necessary investigations. Bronchial biopsy was considered as a gold standard and cytology samples of bronchial brush (BB) and bronchial wash (BW) were obtained for the prediction of lung cancer. Sensitivity, specificity, accuracy, positive predictive value and negative predictive value were calculated separately for BB and BW. Collected data were compiled and appropriate analyses were done by using computer-based software, Statistical Package for Social Sciences (SPSS) version 25.0.*

Results: *In this study, out of 55 patients, male patients were predominant (65.5%), the male to female ratio was 1.9:1 with mean age was 54.7±12.1 years. More than two third (69.1%) patients were smoker. Among the bronchial brush specimens squamous cell carcinoma was found in 28(50.9%) cases, adenocarcinoma in 9(16.4%), small cell carcinoma in 7(12.7%), carcinoid lung cancer in 2(3.6%) and remaining 9(16.4%) cases were normal. Histological cell type in bronchial wash were 10(18.2%) squamous cell carcinoma, 4(7.3%) adenocarcinoma, 13(23.6%) small cell carcinoma, 1(1.8%) carcinoid lung cancer and 27(49.1%) normal finding. Sensitivity of bronchial brush was 82.8% in squamous cell carcinoma, 66.7% in adenocarcinoma, 55.6% in small cell carcinoma and 40.0% in carcinoid. Sensitivity of bronchial wash was 34.5% in squamous cell carcinoma, 33.3% in adenocarcinoma, 88.9% in small cell carcinoma and 20.0% in carcinoid.*

Conclusion: *Our results show that bronchial brush is a much superior technique in diagnosing lung cancer, as it demonstrates far better sensitivity in comparison to bronchial wash. So, this study concluded that the diagnostic yield of bronchial brush cytology is higher than that of bronchial wash cytology in the lung. Bronchial brush has better efficacy in typing squamous cell carcinoma followed by adenocarcinoma, carcinoid while bronchial wash is superior in typing small cell carcinoma.*

Key words: *Bronchial brush, bronchial wash, bronchial biopsy, lung.*

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Introduction:

Lung cancer is one of the most common cause of death from cancer worldwide and causing 1.4 million deaths per year[1]. It's the leading cause of cancer deaths in developed countries and is also rising at intimidating rates in developing countries[2]. In Bangladesh, the circumstance of lung cancer is 16.7% of all cancers[3]. The most common cancer (25%) among male cancer patients with a 6.1:1 male-female ratio[3]. Prognosis of lung cancer is explosively related the stage of cancer at the time of diagnosis. Time survival rate ranges from 5% for IV stage and 80% for stage I cancers.[4] So early diagnosis is essential for improving the prognosis of lung cancer. The only hope of combating the disease successfully remains in diagnosing the disease at the earliest possible stage.[5] Procedures used to diagnose lung tumors should be accurate as far as possible and should provide an optimal characterization of tumor type. Endoscopic examination of the tracheobronchial tree is the most proven valuable method in diagnosing lung cancer. Its advent revolutionized respiratory cytology as techniques like a bronchial brush (BB), bronchial wash (BW), bronchoalveolar lavage and bronchial biopsy became more easy, accessible and more popular[6]. Cytological diagnosis of respiratory samples obtained by flexible fiberoptic bronchoscope is the most commonly used technique and is safer, economical and provides quick results. Both BW and BB used concurrently are effective in the diagnosis of lung tumor as it preserves both cells and architectural arrangement. The best result can be obtained by combining these techniques with radiological and histological findings[7]. The role of bronchial washings and brushings under bronchoscopic control for the cytological diagnosis of lung cancer has been reported by various studies. Since it is a cost-effective and dependable way of showing for early lung cancer it can be extensively applied especially in developing countries. Presently, bronchial washing and brushing studies are routinely employed for the diagnosis of pulmonary neoplasm in different parts of the globe as well as in Bangladesh[8]. This technique can be used in conjunction with radiological and histological findings to give 100% accuracy in the diagnosis of lung cancer. Most of the authors agree that bronchial washings do not add significant information to that obtained from the brushings and that the preparations are of inferior quality[9]. The common symptoms of presentation were cough of long duration and chest pain. Very few cases presented with hemoptysis, change of voice and difficulty in swallowing. Shortness of breath was seen only in patients having an associated chronic obstructive pulmonary disease or advanced disease[10].

The availability of a reliable cytological investigative tool will enable us to diagnose lung cancer at an early stage making it amenable to treatment regimens that will ultimately affect the patient's survival. Therefore, the present study is based on the cytologic evaluation of bronchial brush and bronchial wash for the diagnosis of lung cancer. It will also provide the relative incidence of various cytological types of bronchogenic carcinoma diagnosed by these procedures in our population.

Materials and methods:

This cross-sectional comparative study was conducted in the admitted patients under Department of Respiratory Medicine, National Institute of Diseases of the Chest & Hospital, Mohakhali, Dhaka, between January 2022 and December 2022. A total of 55 patients, clinically suspected for lung cancer and had a positive report on bronchial biopsy were included in the study. Radiological lesion (Chest X-ray) suggestive of centrally placed malignancy, prominence of a hilar shadow with whiskering appearance, hilar/ parahilar masses, mediastinal widening, complete or partial collapse of lung, central bronchial cancer on endoscopic findings visible by fibreoptic bronchoscopy, age more than 20 years and both sexes were included in the study. All bronchial carcinoma approaching carina, all peripheral lung lesion, significantly disabled patients due to poor general condition and patient who refused to enroll in this study were excluded from the study. Consecutive convenient (purposive) sampling was done. Data were collected in a pre-designed data collection sheet designed for the study. Informed written consent was obtained from the patients or attendants after full explanation of the details of the disease process. After admission, a rapid diagnostic work up was made by clinical history, through physical examinations and necessary investigations. Demographic information like age,

sex, occupation, smoking status, etc. were obtained. All patients were investigated for Blood for CBC and ESR, X-ray chest P/A and Lateral view, Sputum for AFB, Bleeding time and Clotting time ECG and Bronchoscopy considering. Bronchial biopsy as a gold standard, cytology samples of bronchial brush (BB) and bronchial wash (BW) were obtained for prediction of lung cancer.

Cytological and histological specimens were obtained by fibreoptic bronchoscopy under local anaesthesia. In bronchial washing sterile isotonic saline introduced into the bronchi bronchoscopically and washings from different broncho-pulmonary segments are reaspirated, then smears are made from centrifuged deposits. Few slides were air dried and fixed in 100% methanol for May-Grunwald Giemsa (MGG) staining. Few slides were immediately fixed in a 95% ethanol for Papanicolaou's staining. Bronchial brushing can be done following washings. The area of suspected malignancy was brushed two or three times; smears was immediately fixed in 95% alcohol and stained by Papanicolaou's method. Then a single specimen was taken for histological examination from the same area by forceps and stained with haematoxylin and eosin after being processed. The slides were examined under the microscope first with low power objectives (10X) and then the areas in the slides having cells were focused under the high-power objectives (40X) to confirm the cytological features. Specimens that showed malignant characteristics were classified as positive, while those with appearances suggestive.

Collected data were compiled and appropriate analyses were done by using computer based software, Statistical Package for Social Sciences (SPSS) version 25.0. Qualitative variables were expressed as percentage. Quantitative variables were expressed as mean±SD. Sensitivity, specificity, accuracy, positive predictive value and negative predictive value were calculated for BB and BW in diagnosing lung tumors. Sensitivity was the percentage of cases in which biopsy proved cancer cases were rightly diagnosed by cytology. Specificity was percentage of cases that were not malignant on biopsy which were correctly diagnosed negative on cytology. Accuracy means fraction of patients whose conditions were correctly diagnosed by cytology. Chi square test was used for qualitative variables as shown cross tabulations. P value of less than 0.05 was considered as significant.

Results:

In this study, out of 55 patients, more than one third (34.5%) cases belonged to age >60 years. Mean age was found 54.7±12.1 years with range from 25 to 72 years. Almost two third 36(65.5%) cases were male and 19(34.5%) were female. Male to female ratio was 1.9:1. More than one fourth 15(27.3%) cases were service holder and housewives respectively (Table-1). More than two third (69.1%) cases were found smoker among them 21(55.3%) were smoked >20 pack/yr and 17(44.7%) were smoked <20 pack/yr (Table-2). Histological finding in bronchial biopsy were 29(52.7%) cases of squamous cell carcinoma (SCC) followed by 12(21.8%) adenocarcinoma (AC), 9(16.4%) small cell carcinoma (SCLC) and 5(9.1%) carcinoid lung cancer (Figure-1). Among the bronchial brush specimens squamous cell carcinoma was found in 28(50.9%) cases, adenocarcinoma in 9(16.4%), small cell carcinoma in 7(12.7%), carcinoid lung cancer in 2(3.6%) and remaining 9(16.4%) cases were normal. Histological cell type in bronchial wash were 10(18.2%) squamous cell carcinoma, 4(7.3%) adenocarcinoma, 13(23.6%) small cell carcinoma, 1(1.8%) carcinoid lung cancer and 27(49.1%) normal finding(Table-3). In squamous cell carcinoma of lung tumors, bronchial brush detected 24 out of 29 cases and bronchial wash detected 10 out of 29 cases. Thus bronchial brush showed better sensitivity and accuracy regarding typing of squamous cell carcinoma. In adenocarcinoma of lung tumors, bronchial brush detected 8 out of 12 cases and bronchial wash detected 4 out of 12 cases. Thus bronchial brush showed better sensitivity regarding typing of adenocarcinoma. In small cell carcinoma of lung tumors, bronchial brush detected 5 out of 9 cases and bronchial wash detected 8 out of 9 cases. Thus bronchial wash showed better sensitivity and accuracy regarding typing of small cell carcinoma. In carcinoid of lung tumors, bronchial brush detected 2 out of 5 cases and bronchial wash detected 1 out of 5 cases. Thus bronchial wash showed better sensitivity and accuracy regarding typing of carcinoid.

Sensitivity of bronchial brush was found 82.8% in squamous cell carcinoma, 66.7% in

adenocarcinoma, 55.6% in small cell carcinoma and 40.0% in carcinoid. Sensitivity of bronchial wash was found 34.5% in squamous cell carcinoma, 33.3% in adenocarcinoma, 88.9% in small cell carcinoma and 20.0% in carcinoid (Table 4 & 5).

Table-I

Demographic characteristics of the study patients (n=55)

Variables	Frequency	Percentage
Age (years)		
≤30	2	3.6
31-40	10	18.2
41-50	8	14.5
51-60	16	29.1
>60	19	34.5
Mean±SD	54.7	±12.1
Range (min-max)	25.0	-72.0
Sex		
Male	36	65.5
Female		19
34.5		
Occupational status		
Service	15	27.3
Housewife	15	27.3
Farmer	14	25.5
Businessman	10	18.2
Retired	1	1.8

Table-II

Distribution of the patients according to smoking status (n=55)

Smoking status	Frequency	Percentage
Smoker	38	69.1
Non smoker	17	30.9

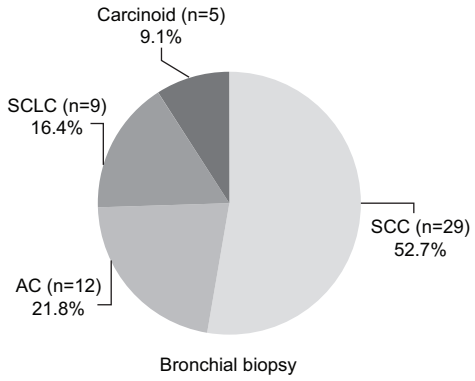

Fig.-1: *Pie chart showing bronchial biopsy of the patients (n=55)*

Table-III

Findings of bronchial brush and wash of the patients (n=55)

	Frequency	Percentage
Bronchial brush		
Squamous cell carcinoma	28	50.9
Adenocarcinoma	9	16.4
Small cell carcinoma	7	12.7
Carcinoid	2	3.6
Normal	9	16.4
Bronchial wash		
Squamous cell carcinoma	10	18.2
Adenocarcinoma	4	7.3
Small cell carcinoma	13	23.6
Carcinoid	1	1.8
Normal	27	49.1

Table-IV

Role of bronchial brush in subtype of lung cancer (n=55)

Bronchial brush	Validity test					P value
	Sensitivity	Specificity	Accuracy	PPV	NPV	
Squamous cell carcinoma	82.8	84.6	83.6	85.7	81.5	0.001
Adenocarcinoma	66.7	97.7	90.9	88.9	91.3	0.003
Small cell carcinoma	55.6	95.7	89.1	71.4	91.7	0.003
Carcinoid	40.0	100.0	94.5	100.0	94.3	0.007

P value reached from chi square test

Table-V

Role of bronchial wash in subtype of lung cancer (n=55)

Bronchial wash	Validity test					P value
	Sensitivity	Specificity	Accuracy	PPV	NPV	
Squamous cell carcinoma	34.5	100.0	65.5	100.0	57.8	0.001
Adenocarcinoma	33.3	100.0	85.5	100.0	84.3	0.001
Small cell carcinoma	88.9	89.1	89.1	61.5	97.6	0.001
Carcinoid	20.0	100.0	92.7	100.0	92.6	0.091

P value reached from chi square test

Discussion:

In the present study 55 patients, clinically suspected for carcinoma lung and had a positive report on bronchial biopsy are evaluated with bronchial brush and bronchial wash cytology, especially to determine the overall diagnostic yield of cytological techniques compared to histological diagnosis. Since the magnitude of carcinoma lung among various populations are still rising and the deadliest risk factor of cigarette smoking is still persisting, the control of the mortality due to carcinoma lung is possible only through early detection, advanced histological classification and specific treatment. Cytological techniques are getting more relevant especially with the bronchoscopic techniques and is a cost-effective screening method.

In this study it was observed that more than one third (34.5%) cases belonged to age >60 years. Mean age was found 54.7±12.1 years with range from 25 to 72 years. In a study done in Bangladesh by Sultana et al.[11] obtained that the mean age of 59.65±12.95 years with range from 34 to 90 years. Zainudeen et al.[12] reported that mean age of patients with lung cancer is 62.65 years ranging from 39 to 86 years. Jayakrishnan and Kamala[13] observed that the age of the patients ranged from 35-84 years with a mean age of 64.14 years. Majority of patients were in the age group 60 -79 (75.6%). Mrudula et al.[14] also revealed that majority (44%) cases belonged to age 41-70 years. Their studies finding were consisted with present study.

Present study observed that almost two third 36(65.5%) cases were male and 19(34.5%) were female. Male to female ratio was 1.9:1. More than one fourth 15(27.3%) cases were service holder and housewives respectively. Choudhury et al.[15] where they showed male to female ratio was 3.3:1. Zainudeen et al.[16] documented that out of total 154 cases of lung cancer 96.1% were males (148 cases) and 3.9% were females (6 cases). Male to female ratio was 24.6:1. Almost similar study conducted by Mrudula et al.[17] demonstrated that 65% cases were male and 35% were female. Male female ratio was 1.6:1. Sultana et al.[18] also documented that 35 (94.6%) patients were male and 2 (5.4%) patients were female with a ratio of male to female of 17.5:1. The above mentioned studies finding were almost consisted with this study.

This study observed that 38(69.1%) cases were found smoker among them 21(55.3%) were smoked >20 pack/yr and 17(44.7%) were smoked <20 pack/yr. This finding is similar to result which was observed by Jayakrishnan and Kamala[19] found their study out of 82 patients, smoking was present in 55 patients (67.1%). Choudhury et al.[20] also obtained that 25 cases (71.4%) were smokers and 10 were non smokers with a smokers to non-smokers ratio of 2.5:1, that was support with present study.

This study observed that in bronchial biopsy 29(52.7%) cases were squamous cell carcinoma (SCC) followed by 12(21.8%) adenocarcinoma (AC), 9(16.4%) small cell carcinoma (SCLC) and 5(9.1%) carcinoid lung cancer. In a study conducted by Zainudeen et al.[21] reported that histological cell types (Bronchial biopsy diagnosis for comparison as gold standard) were as follows- 92/176 cases (52.3%) SCC; 30/176 cases (17%) AC; 18/176 cases (10.2%) SCLC; 14/176cases (8%) poorly differentiated carcinoma and non neoplastic lesions constituted 22/176 cases (12.5%). In our country a study documented by Sultana et al.[22] observed that endobronchial biopsy and histopathology revealed bronchial carcinoma in 25 (67.6%) patients and 12 (32.4%) had no malignancy detected. Squamous cell carcinoma was diagnosed in 18 (48.6%) patients, adenocarcinoma in 4 (10.8%) patients and small cell carcinoma in 3 (8.1%) patients. This result was consistent with the study of Santos-Martínezet al.[23] that the most common histological types were squamous cell carcinoma (33.2%) and adenocarcinoma (29.8%). Choudhury et al.[24] reported squamous cell carcinoma was the most common malignancy constituting 85.7% of cases, followed by small cell carcinoma 9.5% and adenocarcinoma in 4.7% of cases as confirmed by histological examination. Chrabanska et al.[25] described that in 429 (67.8%) patients, and thus in 643 (59.3%) cytological specimens histopathology was considered as the gold standard method. Among them, 243 (56.6%) patients were positive and 186 (43.4%) patients were negative for malignancy. The presented study showed the highest number of patients were with squamous cell carcinoma (SCC) (34.57%) and adenocarcinoma

(AC) (34.57%), followed by small cell carcinoma (SCLC) (9.47%).

Present study observed that findings in bronchial brush were 28(50.9%) cases of squamous cell carcinoma, 9(16.4%) of adenocarcinoma, 7(12.7%) of small cell carcinoma, 2(3.6%) of carcinoid lung cancer and 9(16.4%) cases were normal. Histological cell type in bronchial wash were 10(18.2%) cases of squamous cell carcinoma, 4(7.3%) of adenocarcinoma, 13(23.6%) of small cell carcinoma, 1(1.8%) of carcinoid lung cancer and 27(49.1%) of normal finding. In a study conducted by Sultana et al.[26] reported that bronchial brush cytology revealed bronchial carcinoma in 33 (89.2%) patients of which squamous cell carcinoma was in 25 (67.6%), adenocarcinoma in 4 (10.8%) and small cell carcinoma in 4 (10.8%) patients. Agarwal et al.[27] reported that bronchial brush cytology showed squamous cell carcinoma in 50.0%, adenocarcinoma in 10.0% and large cell carcinoma in 40.0% of cases. The above mentioned studies finding were almost similar in this study.

This study observed that in squamous cell carcinoma of lung tumors, bronchial brush detected 24 out of 29 cases and bronchial wash detected 10 out of 29 cases. Thus bronchial brush showed better sensitivity and accuracy regarding typing of squamous cell carcinoma. In adenocarcinoma of lung tumors, bronchial brush detected 8 out of 12 cases and bronchial wash detected 4 out of 12 cases. Thus bronchial brush showed better sensitivity regarding typing of adenocarcinoma. In small cell carcinoma of lung tumors, bronchial brush detected 5 out of 9 cases and bronchial wash detected 8 out of 9 cases. Thus bronchial wash showed better sensitivity and accuracy regarding typing of small cell carcinoma. In carcinoid of lung tumors, bronchial brush detected 2 out of 5 cases and bronchial wash detected 1 out of 5 cases. Thus bronchial wash showed better sensitivity and accuracy regarding typing of carcinoid. Sensitivity of bronchial brush was found 82.8% in squamous cell carcinoma, 66.7% in adenocarcinoma, 55.6% in small cell carcinoma and 40.0% in carcinoid. Sensitivity of bronchial wash was found 34.5% in squamous cell carcinoma, 33.3% in adenocarcinoma, 88.9% in small cell carcinoma and 20.0% in carcinoid. Zainudeen et al.[28] reported that in typing of lung tumors, BB detected 22 out of 32 cases while, BW correctly typed only 30 out of 92 cases.6 cases of SCC were diagnosed as dysplastic cells by BB and 22 cases were typed to this category by BW. Thus BB showed better sensitivity and accuracy regarding typing of SCC. BW detected 8 out of 30 cases of AC. 4 cases showed dysplastic cells. While BB rightly typed 10 of 22 cases of AC and dysplastic cells seen in 12 cases. Sensitivity of BB was significantly higher (77.8%) when compared with BW (51.9%). But specificity on the other hand was higher for BW (90.9%) compared to BB (80%). Positive predictive value of BW was 97.6% compared to 93.3% obtained by BB. Negative predictive value of BB was 50% and of BW was 21.3%. Regarding accuracy, BB showed better result 78.3% compared to 56.8% with BW. This finding is similar to result which was observed by Sareen and Pandey[29]; Bodh et al.[30]. Both researchers obtained sensitivity of BB as 77.78. In AC BB showed higher sensitivity and accuracy than BW. BW typed 10 of 18 cases of SCLC and 6 of 12 cases by BB Thus in typing SCLC, BW seems to be slightly more sensitive than BB. BB showed maximum sensitivity and accuracy in typing SCC (61.1%), followed by SCLC (50%) and AC (45%). While BW showed highest sensitivity in typing SCLC (50%) followed by SCC (32.6%) and AC (27.7%). The diagnostic value of BB was highest in those with SCC followed by SCLC. Jayakrishnan and Kamala[31] also observed that in cases of squamous cell carcinoma bronchial brushing revealed sensitivity -19.6%, specificity -100%, positive predictive value -100%, negative predictive value-49.4% and accuracy-54.9%. In cases of adenocarcinoma, bronchial brushing revealed sensitivity -28.6%, specificity -92.6%, PPV-44.4%, NPV-82.9%, and accuracy-81.7%. Bronchial washing revealed sensitivity 7.1%, specificity -98.5%, PPV-50%, NPV-83.7%, and accuracy-82.9%. In cases of small cell lung carcinoma, bronchial brushing, bronchial washing and when both combined revealed similar values. Sensitivity -28.6%, specificity - 100%, positive predictive value -100%, negative predictive value-93.8%, and accuracy-94%.

The limitation is small sample size, there by analysing variety of cases was minimal of bronchial biopsy specimen for the validation of cytological techniques and absence of other confirmative tests

like surgical biopsy, biopsies of extrapulmonary metastatic lesions and autopsy.

Conclusion:

This results show that bronchial brush is a much superior technique in diagnosing lung cancer, as it demonstrates far better sensitivity in comparison to bronchial wash. So, this study concluded that the diagnostic yield of bronchial brush cytology is higher than that of bronchial wash cytology in lung. Bronchial brush has better efficacy in typing squamous cell carcinoma followed by adenocarcinoma, carcinoid while bronchial wash is superior in typing small cell carcinoma.

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ORIGINAL ARTICLE

Detection of Sensitivity and Specificity of Serum Adenosine Deaminase as A Diagnostic Marker of Extra Pulmonary Tuberculosis

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Abstract

Background: *The diagnosis of Extra Pulmonary Tuberculosis(EPTB) is difficult due to its nonspecific signs and symptoms and presence of few organisms in the involved site. Diagnosis of extra pulmonary TB is usually done by direct or indirect methods. Direct methods includes TB bacilli found by microscopy, culture or molecular methods. Indirect methods involve detection of humoral or cell mediated immune response of host to mycobacterial antigen or detection of biomarkers like Adenosine deaminase (ADA), Interferon ã (IFN ã) etc. By considering the importance of rapid and accurate diagnosis in TB treatment and control, the present study is planned to investigate the sensitivity and specificity of serum adenosine deaminase for diagnosis of EPTB.*

Objectives: *The main objectives of the study was to detect sensitivity and specificity of serum ADA level in the diagnosis of extra pulmonary tuberculosis.*

Methods: *This cross-sectional observational study was conducted in the Respiratory Medicine Department, NIDCH, Mohakhali, Dhaka in between October 2018-March 2020. Patients of clinically presumptive EPTB were taken(65 patients) according to selection criteria. Biopsy taken from EPTB involved site (pleura, Lymph node, Skin). Based on histopathological study, all of the patients were divided into two groups: Group A is histopathologically confirmed extra pulmonary tuberculosis and Group B is histopathologically not confirmed extra pulmonary tuberculosis.Blood sample was collected from all participants and send for serum ADA measurement by ADA-MTB KIT and compared with both groups. Data were analyzed using appropriate statistical formula.*

Results: *In this study, Most of the study subjects were in age group between 30–39 years (Group A-36.2%, Group B -27.8%) and 40-49 years (Group A -29.8%, Group B -22.2%). Among Group A, 20 (42.6%) were male and 27 (57.4%) were female and among Group B (histopathologically not confirmed extra pulmonary tuberculosis), 10 (55.6%) were male and 8 (44.4%) were female. Pleural effusion(55.3%), lymphadenopathy(38.3%) were observed higher in Group A than Group B. according to histopathological study, majority (55.3%) of Group A*

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patients had pleural TB, 40.4% had lymph node TB and 4.3% had skin TB. In group B patients, 50.0% had pleural TB, 38.9% had lymph node TB and 11.1% had skin TB. Serum ADA had sensitivity 91.5%, specificity 83.3%, PPV 93.5%, NPV 78.9% and accuracy 89.2% respectively in diagnosis of extra pulmonary TB at the cut- off value of 43U/L.

Conclusion: *This study revealed that serum ADA is significantly higher in histopathologically confirmed extra pulmonary tuberculosis patients than histopathologically not confirmed extra pulmonary tuberculosis patients.Serum ADA estimation are a useful tool for diagnosis of extra pulmonary tuberculosis particularly pleural TB, lymph node TB and skin TB.It could be used as a supporting tool for diagnosis of all presumptive EPTB patients.*

Keywords: *Serum ADA,extra pulmonary tuberculosis,sensitivity,specificity etc.*

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Introduction:

Tuberculosis (TB) remains a major global problem and a public health issue of considerable magnitude. It is one of the leading causes of death from infectious diseases worldwide usually caused by the bacterium Mycobacterium tuberculosis[1]. Presently, one-third of the world's population is thought to be infected with TB. New infections occur in about 1% of the population each year. There are two types of clinical manifestation of tuberculosis (TB) includes pulmonary TB (PTB) and extra pulmonary TB (EPTB). EPTB is the TB involving organs other than the lungs such as pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges. EPTB constituted about 20% of all cases of TB. In HIV-positive patients, EPTB accounts for more than 50% of all cases of TB[2]. Extra pulmonary TB (EPTB) results from the hematogenous and lymphatic spread of M. tuberculosis bacilli. Patients with EPTB may manifest constitutional symptoms such as fever, anorexia, weight loss, malaise and fatigue. Patients with EPTB especially may present with pyrexia of unknown origin (PUO) which may arise the diagnostic clue for EPTB[3]. Tuberculous lymphadenopathy is the most common form of EPTB, constitutes 35% of all cases of EPTB. Cervical lymph nodes the most common site of tuberculous lymphadenopathy constitute about 60%–90% of cases, classically termed as "scrofula[4]. TPE predominates in men, with an overall male-to-female ratio of 2:1. The gold standard for the diagnosis of tuberculous pleural effusion (TPE) remains the detection of mycobacterium tuberculosis in pleural fluid or pleural biopsy specimens either by microscopy and/or culture or the histological demonstration of caseating granulomas in the pleura along with acid fast bacilli [5]. Cutaneous tuberculosis is a relatively uncommon, comprising 1-1.5% of all extra pulmonary tuberculosis manifestations, which manifests only in 8.4-13.7% of all tuberculosis cases. The main etiological agent of the cutaneous tuberculosis is mycobacterium tuberculosis occasionally M. bovis or BCG vaccine[6]. The diagnosis of EPTB is difficult due to its nonspecific signs and symptoms and presence of few organisms in the involved site[7]. Diagnosis of extra pulmonary TB is usually done by direct or indirect methods. Direct methods includes TB bacilli found by microscopy, culture or molecular methods. Indirect methods involve detection of humoral or cell mediated immune response of host to mycobacterial antigen or detection of biomarkers like Adenosine deaminase (ADA), Interferon ã (IFN ã) etc. Low sensitivity of microscopy and staining(0-40%), prolonged diagnostic time(6-8 weeks)of culture method (gold standard) and invasiveness of histological techniques makes EPTB diagnosis more problematic. Nucleic acid amplification techniques (NAAT) are costly and not available everywhere. Antibody based tests and cell mediated immunity based tests gives only supportive evidence. So, it is essential to develop a test which is rapid, cost effective, non invasive, easy to perform in a resource poor country[8]. ADA(Adenosine deaminase) is an enzyme that catalyze the deamination reaction from adenosine to inosine. It is a indicator of active cellular immunity[9]. ADA helps in the differentiation of lymphoid cells and the maturation of monocytes

to macrophages[10]. The ADA found more in lymphocyte than erythrocyte [11]. ADA estimation in serum is an indirect biochemical test. Population of T lymphocyte increases in tuberculosis due to antigenic stimulation. Measurement of ADA level is very simple. It is a rapid test for early diagnosis of tuberculosis[12]. By considering the importance of rapid and accurate diagnosis in TB treatment and control, the present study is planned to investigate the sensitivity and specificity of serum adenosine deaminase for diagnosis of EPTB.

Materials and methods:

This cross-sectional observational study was conducted in the Respiratory Medicine Department, NIDCH, Mohakhali, Dhaka in between October 2018-March 2020. Patients of clinically presumptive EPTB were taken (65 patients) by history, clinical examination and appropriate investigations according to selection criteria. Written informed consent was obtained from eligible participants. Biopsy taken from EPTB involved site (pleura, Lymph node, Skin). Based on histopathological study, all of the patients were divided into two groups: Group A is histopathologically confirmed extra pulmonary tuberculosis and Group B is histopathologically not confirmed extra pulmonary tuberculosis.Blood sample was collected from all participants and send for serum ADA measurement by ADA-MTB KIT and compared with both groups. Data were analyzed using appropriate statistical formula. All statistical tests were performed at 5% levels of significance and level of $p < 0.05$ were considered significant. The summarize data were present in the table and chart.

Results:

In this study, Most of the study subjects were in age group between 30–39 years (Group A-36.2%, Group B -27.8%) and 40-49 years (Group A -29.8%, Group B -22.2%) (Table I). Among Group A, 20 (42.6%) were male and 27 (57.4%) were female and among Group B (histopathologically not confirmed extra pulmonary tuberculosis), 10 (55.6%) were male and 8 (44.4%) were female (Figure 1). Pleural effusion(55.3%), lymphadenopathy(38.3%)and skin TB (4.1%) were observed higher in Group A than Group B(Figure 2). According to histopathological study, majority (55.3%) of Group A patients had pleural TB, 40.4% had lymph node TB and 4.3% had skin TB. In group B patients, 50.0% had pleural TB, 38.9% had lymph node TB and 11.1% had skin TB (Table II). According to the ROC curve, a cut-off value 43U/L of serum ADA was found which can differentiate EPTB patients with 91.5% sensitivity and 83.3% specificity(Figure 3).

Table-I

Distribution of study population of both groups according to age (N=65)

Age (years)	Group A (n=47)	Group B (n=18)	p-value
18 - 29	7 (14.9)	2 (11.1)	
30 - 39	17 (36.2)	5 (27.8)	
40 - 49	14 (29.8)	4 (22.2)	
50 and above	9 (19.1)	7 (38.9)	
Mean±SD	31.49±11.54	36.50±14.26	0.148 n.s

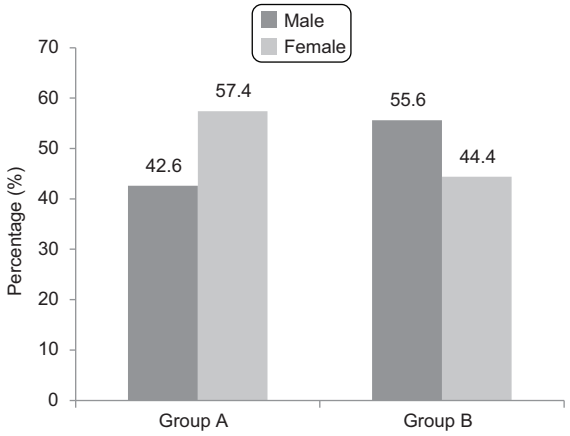

Fig.-1: *Distribution of study population of both groups according to gender (N=65)*

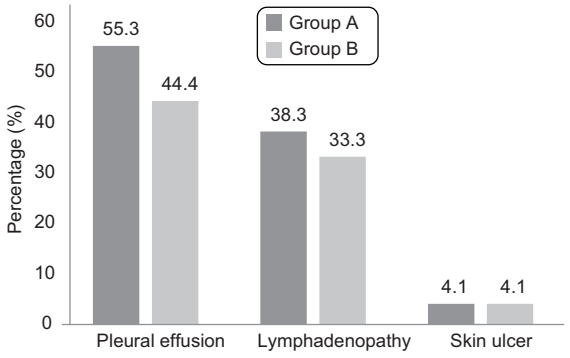

Fig.-2: *Clinical presentation of both groups (N=65)*

Considering 43U/L as the cut-off value of serum ADA, e™ 43 U/L was considered test positive and <43 U/L was considered test negative. Screening results of extra pulmonary tuberculosis among 65 patients, true positive were 43 cases and false positive were 3 cases, false negative were 4 cases and true negative were 15 cases (Table IV). Serum ADA had sensitivity 91.5%, specificity 83.3%, PPV 93.5%, NPV 78.9% and accuracy 89.2% respectively in diagnosis of extra pulmonary TB at the cut- off value of 43U/L (Table V).

Table-II

Distribution of study population according to histopathological study (N=65)

	Group A (n=47)	Group B (n=18)
Pleural TB	26 (55.3)	9 (50.0)
Lymph node TB	19 (40.4)	7 (38.9)
Skin TB	2 (4.3)	2 (11.1)

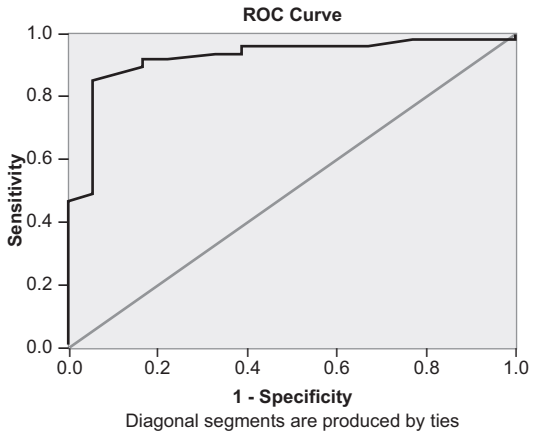

Fig.-3: *Receiver operating characteristic curve showing performance of serum ADA in differentiating EPTB patients (N=65)*

Table-IV

Screening results of extra pulmonary tuberculosis (N=65)

Screening for ADA	Group A (n=47)	Group B (n=18)	Total
≥43 U/L	43	3	46
<43 U/L	4	15	19
Total	47	18	65

Table-V

Serum ADA for diagnosing extra pulmonary TB (N=65)

Serum ADA	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
ADA (≥43 U/L)	91.5	83.3	93.5	78.9	89.2

Discussion:

In this cross-sectional observational study total 65 patients who were clinically presumptive as extra pulmonary tuberculosis were included. Majority of Group A patients had pleural TB (55.3%) and among rest, 40.4% had lymph node TB & 4.3% had skin TB. Among Group B patients 50.0% had pleural TB, 38.9% had lymph node TB and 11.1% had skin TB. Most studies found that lymph nodes, pleura, abdomen, bones, joints and genitourinary system as most common sites of involvement by EPTB[13]. One study found pleural TB as the most common form of extra pulmonary TB in adults though other study observed lymph node as most common site of involvement by EPTB and skin as the least common site of involvement[14,15].

In our study, pleural TB is the most common form of EPTB may be because our study was conducted in a tertiary level hospital, specialized for TB and most patients were referred from primary health care center for respiratory related diseases. Though there is no age predilection for EPTB and it is known to affect all age groups, majority of the patients of our study belonged to age group 30-49 years (61.5%) with a mean 32.88±12.45 years of age. Female preponderancies generally noticed by various studies including this study (53.8%) and other study owing to illiteracy, social exclusion, malnutrition and economic dependency with little access to health care[16,17]. There was no significant difference in age and gender distribution of our study patients between Group A and Group B as p-value >0.05 which is consistent with other studies[18].

The meta-analysis of 11 studies that included 2,251 patients and used different cut-off values of ADA activity showed a sensitivity of 99% and a specificity of 89%[19]. Recently published 3 meta-analyses showed a sensitivity of 91.8% to 92% and a specificity of 88.4% to 90%[20]. In our study Receiver Operating Characteristic Curve analysis found highly significant cut-off value (43U/L) of serum

ADA with sensitivity 91.5%, specificity 83.3%, PPV 93.5%, NPV 78.9% and accuracy 89.2% respectively in diagnosis of extra pulmonary TB.

ADA was equal to or greater than 47U/L in 100% of patients with TB pleurisy, but only in 5% of the patients with non-TB pleurisy (sensitivity 100% and specificity 89%)[21]. Serum ADA levels were done for 54 cases in the study of Antin et al, of which 45 (83.33%) cases showed elevated levels with the cut off value 50U/L[22]. In our sample, we had a relatively low but satisfactory resulting sensitivity and specificity. The negative predictive value of this test is high and this gives it a place as a widely usable screening test to exclude EPTB.

Although histopathology is an inexpensive and reliable tool for detecting extra-pulmonary TB cases in resource limited settings, studies have highlighted the limitations of associating specific histopathological features with TB. Furthermore, histopathology can be invaluable in arriving at specific tissue diagnosis in diseases clinically mimicking TB such as lymphomas. Although the conventional methods (smear microscopy/culture) were used as a reference standard, these methods are not sufficient to detect all EPTB . Besides, regarding our limitation that we could not determine whether a higher value of adenosine deaminase correlated with particular localization, as we included relatively small number of individual cases in our study. Nevertheless, the present study suggests to use serum ADA estimation as the biochemical marker in the diagnosis of EPTB highlighting it as simple, rapid, cheaper and accurate diagnostic test.

Conclusion:

This study revealed that serum ADA is significantly higher in histopathologically confirmed extra pulmonary tuberculosis patients than histopathologically not confirmed extra pulmonary tuberculosis patients. Overall sensitivity, specificity, PPV, NPV and accuracy for detecting EPTB of serum ADA were 91.5%, 83.3%, 93.5%, 78.9% and 89.2% respectively at the cut off value of 43U/L. Serum ADA estimation are a useful tool for diagnosis of extra pulmonary tuberculosis particularly pleural TB, lymph node TB and skin TB.

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ORIGINAL ARTICLE

Eosinopenia and Neutrophil to Lymphocyte Count Ratio as a Predictor of Outcomes in Patients Admitted with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract:

Background: *Acute exacerbation of chronic obstructive pulmonary disease (COPD) is a frequent cause of hospital admission and is associated with high resource utilization. Several biochemical markers have been studied as outcome predictors in patients admitted with acute exacerbation of COPD, but their measurement often requires significant resources. Neutrophil to lymphocyte count ratio and eosinophil count is easily obtained from a complete blood picture. Whether eosinopenia and neutrophil to lymphocyte count ratio (NLR), as a potential marker, can predict outcomes in patients admitted with acute exacerbation of COPD is yet to be verified.*

Materials and methods: *This cross-sectional observational study was conducted in the Department of Respiratory Medicine at the National Institute of Diseases of the Chest and Hospital from April 2021 to May 2022. A total of 116 diagnosed cases of COPD, admitted to the hospital with acute exacerbation, were enrolled in this study. NLR was calculated, and eosinopenia was observed from a complete blood count at admission. All data were collected in a performed questionnaire. NLR and eosinopenia (individually and in combination) were evaluated to predict non-invasive and invasive ventilation requirements. Statistical analysis of the findings was carried out using the Statistical Package for Social Sciences version 23. In addition, the Receiver Operating Characteristics (ROC) curves were constructed to identify an optimal cut-off value of NLR for predicting hospital outcomes.*

Result: *In this study, NLR e"9.6 was significantly associated with predicting the need for non-invasive ventilation (AUC of 0.824, sensitivity of 83.9%, specificity of 70.6%) and NLR e"12.95 with predicting the need for invasive ventilation (AUC of 0.864, the sensitivity of 92.3%, specificity of 75.7%,). The sensitivity and specificity of eosinopenia for predicting non-invasive ventilation were 54.8% and 94.1%; for invasive ventilation, 69.2% and 87.4%, respectively. For the combined eosinopenia and NLR, the sensitivity and specificity for predicting non-invasive ventilation were 54.8% and 98.8%; for invasive ventilation, 69.2% and 94.2%, respectively.*

Conclusion: *NLR and eosinopenia from peripheral blood can be used to predict hospital outcomes in patients admitted with AECOPD. However, combined eosinopenia and NLR rather than individual are good predictors of the need for mechanical ventilation.*

Keywords: *Neutrophil to lymphocyte count ratio, eosinopenia, acute exacerbation of COPD(AECOPD)*

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Introduction:

COPD is a complex and heterogeneous disease. It is a disabling condition characterized by poorly reversible airflow limitation and inflammation[1]. It is a leading cause of morbidity and mortality worldwide that induces an economic and social burden that is both substantial and increasing[2]. The worldwide prevalence of COPD is 10.1% in people 40 or older. It is the third leading cause of death worldwide, caused 3.23 million deaths in 2019. With the increasing prevalence of smoking in developing countries and ageing populations in high-income countries, the prevalence of COPD is expected to rise over the next 40 years. By 2060 there may be over 5.4 million deaths annually from COPD and related conditions[3]. For the diagnosis of COPD, spirometry is necessary. A post-bronchodilator FEV1/FVC ratio <0.70 confirms persistent airway limitation. In Bangladesh, the prevalence of COPD was estimated at around 12.5% and outdoor air pollution, smoking habit, and indoor air pollution from biomass fuel burning are known factors contributing to the high prevalence of COPD in Bangladesh[4]. Exacerbation of COPD is responsible for a significant impact on patients. Exacerbations are associated with a negative effect on health status, increasing hospitalisation rate, readmission, and disease progression[5].

On average, COPD patients generally experience 0.5 to 3.5 times the acute exacerbations of COPD per year. Acute exacerbation of COPD is the leading cause of death in COPD patients, with death rates of 6.7% in the hospital[6]. Accurately assessing the severity of an acute exacerbation of COPD and predicting the outcome of hospitalization is crucial for clinical care and the efficient use of scarce medical resources. It is difficult to predict the clinical behaviour of these individuals during an exacerbation. Kawamatawong, Apiwattanaporn and Siricharoonwong conducted a study showing that procalcitonin and CRP are not statically significant in predicting mechanical ventilation and mortality in AECOPD.[7] In a study, Gomez- Rosero et al. estimate the clinical utility of C Reactive Protein (CRP), Mean Platelet Volume (MPV), eosinophil count, and neutrophil/lymphocyte ratio (NLR) as in-hospital prognostic factors in patients with acute exacerbation of COPD.[8] After multivariate analysis adjusted for confounding variables, the NLR ratio was the only marker significantly associated with the risk of dying or being admitted to the ICU. IL-6 and TNF-á also studied as a predictor of hospital outcomes in AECOPD, but their use in routine clinical practice has limitations. In one study, copeptin and neutrophil CD64 (nCD64) were found to be significant predictors of short- and long-term prognosis among patients with acute exacerbations of COPD[9]. But these are not feasible in our community. A prediction scale (DECAF) is developed for patients hospitalized with acute exacerbation of COPD, which is practically difficult to apply in rural areas. So, we need a simple, readily available, and cost-effective parameter to predict the clinical outcomes of patients with acute exacerbation of COPD. The inflammatory status of COPD exacerbation involves various factors, such as immune cells, including neutrophils and lymphocytes, whose activity permanently damages the pulmonary tissue. Since inflammation is an integral part of COPD, circulating biomarkers that show inflammation status, such as the Neutrophil to Lymphocyte count ratio (NLR), can be considered a potential predictor of outcomes in patients admitted with an acute exacerbation of COPD.

Moreover, total leukocyte and neutrophil count have historically been used as a marker of infection. An association has also been found between infection and lymphocyte count. An increased peripheral blood NLR is an independent marker of mortality in patients with bacteremia that is related to acute exacerbation of COPD[10].

Eosinopenia is already proposed as a marker of infection, differentiating infectious from non-infectious causes of elevated CRP and identifying sepsis or bacteremia. In a study, Partouche et al. showed that persistent eosinopenia with the diagnosis of bacterial infection predicted hospital mortality in older patients[11]. Eosinopenia is also proposed as a predictor of short- and long-term prognosis in some diseases, including acute exacerbation of COPD. However, Emami Ardestani and Alavi-Naeini observed no statistically significant link between eosinophil count and in-hospital outcomes in acute COPD exacerbation cases[12]. In another research, in acute exacerbation of COPD, outcomes were similar between the eosinophilic and non-eosinophilic groups when they were followed up for six months after hospitalization.

Both these parameters' role in the acute exacerbation of COPD remains ambiguous and controversial. So, it needs further evaluation. Therefore, it is imperative to conduct this research to determine whether eosinopenia has a significant role in predicting hospital outcomes in patients

admitted with acute exacerbation of COPD. Additionally, to determine the cut-off value of NLR for our socioeconomic background to properly distribute our limited treatment facility resources to the patients with acute exacerbations of COPD.

Methods:

This cross-sectional observational study was conducted in the Department of Respiratory Medicine of the National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, from April 2021 to May 2022. The study protocol was approved by the Institutional Review Board (IRB) of NIDCH. Patients admitted to NIDCH with acute exacerbation of COPD were enrolled in this study. The exclusion criteria were any other known chronic lung disease, any haematological disorder-active or in the past medical history, active malignancy, and worsening of respiratory symptoms associated with other acute causes. We also excluded patients with clinically and radiologically confirmed pneumonia. Finally, 116 cases were selected according to inclusion and exclusion criteria. Eligible participants were being explained about the study, and written informed consent obtained from all participants. Enrolled subjects were given a predesigned questionnaire in locally understandable language. Clinical examinations were done, and BMI was calculated. ABG, CBC, and other relevant biochemical tests were done. Eosinophil count and NLR were calculated from the CBC report. All the data were recorded systematically in a preformed data collection sheet. Statistical analyses were conducted using the Statistical Package for Social Science version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA. Data were presented in frequency, percentage, mean, and standard deviation as applicable. The chi-square test was used to assess categorical data. Sensitivity, specificity, positive predictive value, and negative predictive value of eosinopenia (An absolute eosinophil count $\leq 0.04\times10^3/\mu l$) and NLR(The ratio of absolute neutrophil and lymphocyte count) were calculated for validity as a predictor of hospital outcomes in patients admitted with acute exacerbation of COPD. The Receiver Operating Characteristic (ROC) curve with area under the ROC curve was performed to measure the accuracy of NLR to predict the hospital outcomes and to identify its cut-off values for further analysis. All statistical tests were performed at 5% levels of significance. A p-value of <0.05 was considered statistically significant.

Results:

Table-I

Demographic characteristics of the study populations (n=116)

Demographic characteristics	Frequency (Number of patients)	Percentage
Age (years)		
41-50	6	5.2
51-60	46	39.7
61-70	47	40.5
71-80	15	12.9
>80	2	1.7
Mean±SD	63.1	±8.0
Range (min-max)	48.0	-86.0
Sex		
Male	109	93.97
Female	7	6.03
Residence		
Rural	68	58.6
Urban	48	41.4

Table-II

Distribution of the study population according to Smoking status and biomass exposure(n=116)

Smoking status and biomass exposure	Frequency (Number of patients)	Percentage
Smoker	113	97.4
Current smoker	9	7.8
Ex-smoker	104	89.65
Never smoker	3	2.55
Biomass exposure		
Yes	3	2.6
No	113	97.4

Table-III

Clinical presentation of the study population (n=116)

Clinical presentation	Frequency (Number of patients)	Percentage
Increased breathlessness	112	96.6
Increased cough	97	83.6
Increased sputum production	87	75.0
Fever	21	18.1
Fatigue	78	67.2

Table-IV

Baseline laboratory profile (complete blood count, biochemical test, and arterial blood gas analysis) of the study population (n=116)

	Mean±SD
CBC	
Hb (g/dl)	12.4±1.5
ESR (mm/1st hr)	36.1±18.9
T/C of WBC (K/µl)	11.7±3.4
T/C of Platelet (K/µl)	302.0±92.9
Neutrophils (K/µl)	9.9±3.3
Lymphocyte (K/µl)	1.30±0.83
NLR	9.8±5.7
Eosinophil (K/µl)	0.20±0.25
Biochemical test	
RBS (mmol/L)	6.6±2.4
Serum creatinine (mg/dL)	1.15±0.41
Serum bilirubin (mg/dL)	0.67±0.28
Serum SGPT (IU/L)	40.9±9.5
ABG	
P^H	7.4±0.1
PCO_2 (mmHg)	54.4±19.5
PO_2 (mmHg)	69.4±23.4
HCO_3 (mmHg)	32.1±9.5

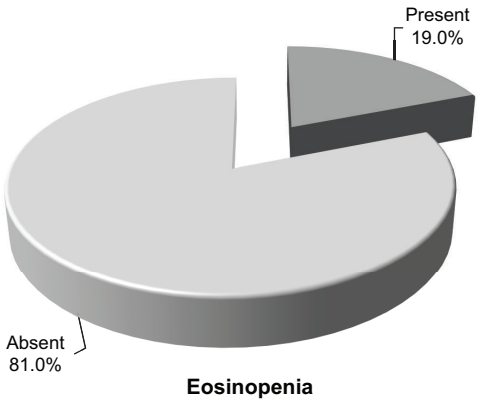

Fig.-1: *Pie chart diagram showing cases with eosinopenia of the study populations (n=116)*

Table-V

Hospital outcomes of the study populations (n=116)

Outcomes	Number of patients	Percentage
Need for Non-invasive ventilation		
Yes	31	26.7
No	85	73.3
Need for Invasive ventilation		
Yes	13	11.2
No	103	88.8

Table-VI

Association of eosinopenia with hospital outcomes of the patients admitted with acute exacerbation of COPD (n=116)

Eosinopenia	Non-Invasive Ventilation				df	Chi value	P value
	Yes (n=31)		No (n=85)				
	N	%	N	%			
Present	17	54.8	5	5.9	1	35.42	0.001s
Absent	14	45.2	80	94.1			
	Invasive Ventilation						
	Yes (n=13)		No (n=103)				
	N	%	N	%			
Present	9	69.2	13	12.6	1	24.07	0.001s
Absent	4	30.8	90	87.4			

s= significant

P value reached from chi-square test

Table-VII

Sensitivity, specificity, accuracy, positive and negative predictive values of the eosinopenia for prediction of hospital outcomes in the patients admitted with acute exacerbation of COPD

Validity test	Non-Invasive Ventilation	Invasive Ventilation
Sensitivity	54.8	69.2
Specificity	94.1	87.4
Accuracy	83.6	85.3
Positive predictive value	77.3	40.9
Negative predictive value	85.1	95.6

Table-VIII

Receiver-operator characteristic (ROC) curve of NLR for prediction of non-invasive ventilation in the patients admitted with acute exacerbation of COPD.

	Cut of value	Sensitivity	Specificity	Std. Error	Area under the ROC curve	95% Confidence interval (CI)		P value
						Lower bound	Upper bound	
NLR	≥9.6	83.9	70.6	0.043	0.824	0.740	0.909	0.001

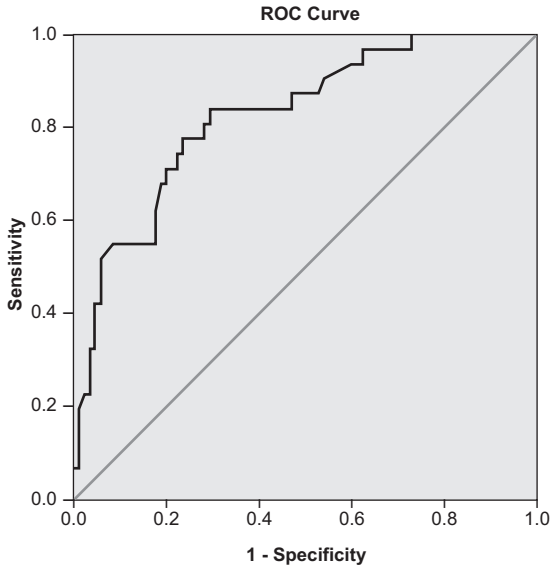

Fig 2: *Receiver-Operating Characteristics curve of NLR for predicting non-invasive ventilation in the patients admitted with acute exacerbation of COPD*

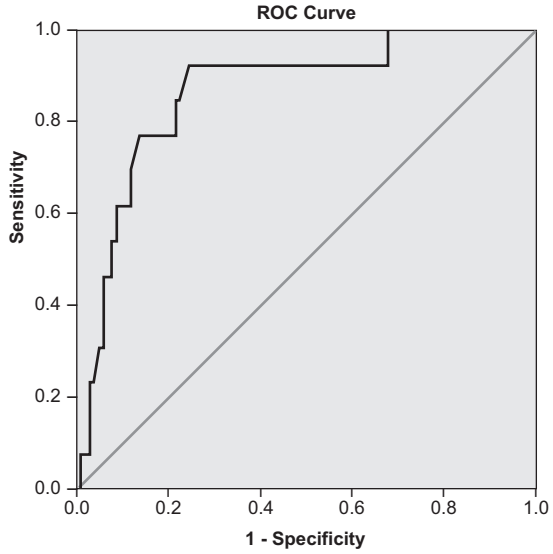

Fig. 3: *Receiver-operating characteristics curve of NLR for predicting invasive ventilation in the patients admitted with acute exacerbation of COPD.*

Table-IX

Receiver-operator characteristic curves of NLR for predicting invasive ventilation in the patients admitted with acute exacerbation of COPD.

	Cut of value	Sensitivity	Specificity	Std. Error	Area under the ROC curve	95% Confidence interval (CI)		P value
						Lower bound	Upper bound	
NLR	≥12.95	92.3	75.7	0.052	0.864	0.763	0.966	0.001

Table-X

Association between NLR with hospital outcomes of the patients admitted with acute exacerbation of COPD (n=116)

NLR	Non-Invasive Ventilation				df	Chi value	P value
	Yes (n=31)		No (n=85)				
	N	%	N	%			
≥9.6	26	83.9	25	29.4	1	27.35	0.001[s]
<9.6	5	16.1	60	70.6			
	Invasive Ventilation						
	Yes (n=13)		No (n=103)				
	N	%	N	%			
≥12.95	12	92.3	25	24.3	1	24.60	0.001[s]
<12.95	1	7.7	78	75.7			

s= significant

P value reached from chi squire test

Table-XI

Sensitivity, specificity, accuracy, positive and negative predictive values of NLR for prediction of hospital outcomes in the patients admitted with acute exacerbation of COPD

Validity test	Non-Invasive Ventilation	Invasive Ventilation
Sensitivity	83.9	92.3
Specificity	70.6	75.7
Accuracy	74.1	77.6
Positive predictive value	51.0	32.4
Negative predictive value	92.3	98.7

Table-XII

Association between combined eosinopenia and NLR with hospital outcomes (n=116)

Eosinopenia and NLR ≥9.6	Non-Invasive Ventilation				df	Chi value	P value
	Yes (n=31)		No (n=85)				
	N	%	N	%			
Present	17	54.8	1	1.2	1	49.90	0.001[s]
Absent	14	45.2	84	98.8			
Eosinopenia and	Invasive Ventilation						
NLR ≥12.95	Yes (n=13)		No (n=103)				
	N	%	N	%			
Present	9	69.2	6	5.8	1	41.22	0.001[s]
Absent	4	30.8	97	94.2			

s= significant

P value reached from chi squire test

Table-XIII

Sensitivity, specificity, accuracy, positive and negative predictive values of the combined eosinopenia and NLR predicting hospital outcomes in the patients admitted with AECOPD.

Validity test	Non-invasive Ventilation	Invasive Ventilation	Death
Sensitivity	54.8	69.2	51.0
Specificity	98.8	94.2	91.5
Accuracy	87.1	91.4	87.9
Positive predictive value	94.4	60.0	35.7
Negative predictive value	85.7	96.0	95.1

Discussion:

This cross-sectional study was conducted to assess the usefulness of the eosinopenia and neutrophil to lymphocyte count ratio as a predictor of outcomes in patients admitted with acute exacerbation of Chronic Obstructive Pulmonary Disease.

The present study observed that the majority (40.5%) of the cases are 61 to 70. The mean age was 63.1±8.0 years. Biradar, Teli, and N[13] also described a similar finding, where the mean age of the study population was 62.06 ±10.783 years. Among the 116 cases, 109 (93.97%) were male, and 7 (6.03%) were female. Similar findings were observed by Lee et al. where males were 91.4%, and females were 8.6% in their study population.[14] In the current study, 97.5% were a smoker. Among them, 9 (7.8%) were current smokers, and 104 (89.65%) were ex-smokers. In this study, three subjects (2.6%) were found to have been exposed to biomass.

Regarding the baseline laboratory profile, this study showed that the mean neutrophil count, lymphocyte count, and NLR were 9.9±3.3(K/µl), 1.30±0.83(K/µl), and 9.8±5.7, respectively. In addition, the mean eosinophil count was 0.20±0.25(K/µl).

In the present study, among the 116 cases, peripheral blood eosinopenia was present in 22 (19%) cases. On the other hand, in a study in Poland, Karauda et al. observed eosinopenia in 36% of the study population, and Biradar, Teli and N. in India observed 46% eosinopenia in their study group. Geographical location, ethnic variation, and phenotypic variation may cause such differences.

According to the current study, non-invasive ventilation was required by 26.7% (31 cases) of the total participants (n=116). However, the demand for non-invasive ventilation was 23% in a prior study[15]. Which is comparable to this one. In the present study necessity for invasive ventilation was 11.2% (13 cases). In a study in China, Teng, Ye and Xue observed that invasive ventilation was needed by 5% of the study population[16].

In the present study, 17 from the eosinopenic group (n=22) and 14 from the non-eosinopenic group (n=94) required non-invasive ventilation, where the difference was statistically significant ($p< 0.05$ from the chi-square test). The sensitivity, specificity, accuracy, PPV, and NPV of eosinopenia for the prediction of non-invasive ventilation were 54.8%, 94.1%, 83.6%, 77.3%, and 85.1%, respectively. Furthermore, regarding mechanical ventilation, Iranian population data also demonstrated statistical significance, where eosinopenia was discovered to be 69.57% sensitive, 63.64% specific, 36.36% PPV, and 87.5% NPV predicting the need for non-invasive ventilation.

In the current study, 9 out of 22 cases from the eosinopenic group needed invasive ventilation, whereas 4 from the non-eosinopenic group (94 cases) required invasive ventilation. Again, a statistically significant difference ($p< 0.05$ from the chi-square test) was observed between them. This study found eosinopenia to be 69.2% sensitive, 87.4% specific, 85.3% accurate, 40.9 % PPV, and 95.6 % NPV to predict the need for invasive ventilation.

In the present study, Receiver Operating Characteristics (ROC) with the area under the ROC curve analysis were performed to measure the accuracy of NLR for predicting the need for non-invasive and invasive ventilation and to identify its cut-off values for further research.

Based on the ROC curves, for non-invasive ventilation, NLR had an area under curve 0.824 (95% CI 0.740-0.909; p<0.05). NLR was used to develop Receiver Operating Characteristics (ROC), which provided a cut-off value of 9.6 with 83.9% sensitivity, 70.6% specificity, 74.1% accuracy, 51.0% PPV, and 92.3% NPV for predicting non-invasive ventilation. In the prediction of non-invasive ventilation requirements, elevated NLR was identified when the value was ≥9.6, and the difference was statistically significant (p<0.05). In a study done by Rajasurya and Gudivada (2019), the authors showed that NLR at the time of admission in patients with acute exacerbation of COPD was a reliable biomarker to predict the use of mechanical ventilation, which is consistent with the findings of the current study[17].

For invasive ventilation, Receiver Operating Characteristic (ROC) was constructed using NLR, which gave a cut-off value of 12.95, with 92.3% sensitivity, 75.7% specificity, 77.6% accuracy, 32.4% PPV, and 98.7% NPV for predicting invasive ventilation. NLR had an area under the ROC curve of 0.864 (95 % CI 0.763-0.966; p<0.05). In predicting invasive ventilation requirements, elevated NLR was identified when the value was ≥12.95 and the difference was also statistically significant (p<0.05). Teng, Ye and Xue (2018) in their study observed that the AUC of the NLR for predicting invasive ventilation was 0.732 (95 % CI 0.656-0.807; p<0.05). The sensitivity and specificity were 54.3% and 84.8 %, respectively, when 10.345 was used as the critical NLR value. In a study in China, the author observed that increased NLR was significantly associated with a higher risk of worse outcomes in the patients admitted with acute exacerbation of COPD. Furthermore, ROC analysis revealed that with a cut-off value of 10.23, NLR could predict in hospitals worse outcomes of severe acute exacerbation of COPD (sensitivity 62.1%, specificity 92.0%, AUC 0.833)[18].

In the present study, combined eosinopenia and NLR ≥9.6 were present in 18 (representing 15.5%) out of the 116 cases; among them, 17 cases needed non-invasive ventilation. Whereas 14 from the non-eosinopenic and NLR < 9.6 group required non-invasive ventilation. A statistically significant difference (P< 0.05 from the chi-square test) was also observed between them. The sensitivity, specificity, accuracy, PPV, and NPV of combined eosinopenia and NLR ≥9.6 for predicting non-invasive ventilation were 54.8%, 98.8%, 87.1%, 94.4%, and 85.7%, respectively.

In this study, 15 cases (12.9 %of the study group) had combined eosinopenia with NLR ≥12.95, and 9 of those 15 needed invasive ventilations. Whereas 4 (representing 3.96%) from the non-eosinopenic and NLR <12.95 group required invasive ventilation. The difference was statistically significant (p <0.05 from the chi-square test). Eosinopenia and NLRe" 12.95 had sensitivity, specificity, accuracy, PPV, and NPV of 69.2%, 94.2%, 91.4%, 60.0%, and 96.0%, respectively, for the prediction of invasive ventilation.

Any published research data was not found regarding combined eosinopenia and NLR (at a specific cut-off value) with sensitivity, specificity, PPV, and NPV to predict mechanical ventilation (invasive or non-invasive). So current studies in this aspect could not be compared with others.

Conclusion:

In acute exacerbation of COPD, combined eosinopenia and NLR rather than individual are good predictors of mechanical ventilation (invasive and non-invasive ventilation) requirement.

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ORIGINAL ARTICLE

Persistence of Fatigue and its Covariates after COVID-19 Infection: A Hospital-Based Study

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Abstract:

Background: *COVID-19 can cause symptoms that last for weeks or even months after recovery from acute illness. Persistent fatigue has been reported as a prominent symptom in recovering COVID-19 patients. The level of fatigue varies by country. In this study, we tried to evaluate the persistence of fatigue in patients after COVID-19 infection in our country and possible covariates of fatigue.*

Objective: *To find out the persistence of fatigue and its covariates after COVID-19 infection.*

Materials and Methods: *This cross-sectional observational study was conducted on 117 RT-PCR positive COVID-19 patients at National Institute of Diseases of the Chest and Hospital from July 2020 to June 2021. Patients were evaluated on an average of 105.4 (SD, 28.7) days after acute COVID-19 infection. Chalder Fatigue Scale (CFQ-11) was used to assess fatigue. Moreover, participants' dyspnoea was assessed by mMRC scale and other clinical parameters were also recorded. All data collected were analyzed using appropriate statistical formula and SPSS programme.*

Results: *Out of 117 patients (mean age 52.7 years [SD, 13.6]), fatigue was found in 64(54.7%) patients and dyspnoea in 49 (41.9%) patients. Diabetes mellitus 44(37.6%) and cardiovascular disease 38(32.5%) were commonly reported co-morbidities and were significantly higher in fatigued patients (51.6% and 48.4%, respectively). Seventy eight (66.7%) patients had severe COVID-19 and they were more fatigued (92.2% vs 35.8%). In multivariate analysis, diabetes mellitus (adjusted OR 7.6, 95% CI 1.8-32.4), cardiovascular disease (adjusted OR 23.0, 95% CI 4.1-96.2) and severe COVID-19 (adjusted OR 17.2, 95% CI 2.9-92.6) were found to be independent predictors for fatigue.*

Conclusion: *More than half of the patients suffer from persistent fatigue after COVID-19 infection. Diabetes mellitus, cardiovascular disease and severe COVID-19 are independent predictors for fatigue.*

Keywords: *COVID-19, Fatigue, Dyspnoea.*

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Introduction:

In December 2019, the novel coronavirus disease 2019 (COVID-19) outbreak occurred in Wuhan, Hubei Province, China[1]. It has spread quickly across China and beyond, resulting in total confirmed cases 181,665,251 and 3,941,411

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confirmed deaths across the world, as of June 30, 2021, according to World Health Organization. Until June 30, 2021, the number of confirmed cases in Bangladesh has risen to 9, 13,258, of which 14,503 have died[2].

81% of people with COVID-19 in China presented with mild symptoms; 14% presented with symptoms of severe respiratory dysfunction; and 5% developed a critical illness[3]. The medium and long-term problems faced by COVID-19 survivors after discharge from the hospital are currently unknown, but there's some emerging evidence.

A recent study- conducted in Italy shows that an overwhelming 87.4% of patients recovered from COVID-19 reported persistence of at least one symptom, particularly fatigue and dyspnoea, even two months after hospital discharge[4]. Another study in UK shows that new illness-related fatigue was the most commonly reported symptom by 72% participants in ICU group and 60.3% in ward group after an average 48 days discharge from hospital[5]. In early reports on the clinical features of infected patients, 44-69.6% listed fatigue as a presenting complaint[6].

A meta-analysis found that one fourth of the hospitalized survivors of SARS and MERS had decreased lung function and exercise capacity at 6 months after discharge[7]. It suggested that the impact of COVID-19 is probably going to be similar.

Fatigue is common in patients with symptomatic COVID-19 infection. Fatigue is measured in different ways, and its level varies by country. However, it is not known whether COVID-19 results in persistent fatigue in individuals recovered from an acute infection.

There are very limited studies in our country concerning the long-term health effects of COVID-19 and the on-going medical, psychological, and rehabilitation needs of these patients. That's why this study aims to evaluate the persistence of fatigue in patients after COVID-19 infection and possible covariates of fatigue.

This study will try to find out whether patients recovering from COVID-19 have persistent fatigue after their physical recovery, and to investigate whether there is a relationship between persistent fatigue and a variety of clinicopathological parameters.

It also emphasizes the importance of assessment of post-COVID symptoms that may identify a group worthy of further study and early intervention. This will help trials of clinical care strategies including personalised treatments to enhance long-term outcomes for current and future COVID-19 survivors.

Materials and methods:

This cross-sectional observational study was conducted in the department of respiratory medicine of National Institute of Diseases of the Chest and Hospital, Mohakhali, Dhaka during the period from July 2020 to June 2021.

Inclusion criteria were:

1. Age ≥18 years
2. All symptomatic patients diagnosed as COVID-19 by reverse transcriptase-polymerase chain reaction (PCR) test
3. After 6 weeks of symptom onset

Exclusion criteria were:

1. Asymptomatic individuals with COVID-19 positive
2. Patients with Thyroid disorders
3. Patients with active Tuberculosis
4. Patients undergoing Chemotherapy or Radiotherapy
5. Dementia, Psychiatric disorders, or unable to attend hospital visits due to frailty or severe disease.

Hundred and seventeen (117) patients were included in the study using purposive sampling method. After informing full information regarding the nature of the study, possible outcome, and importance of follow-up, written consent was obtained. In order to be considered for inclusion in the current study, patient was evaluated at least 6 weeks after the date of last acute COVID-19 symptoms. Enrolled patients were given a pre-designed questionnaire. Information was collected from the patient after exploration of different complaints. Fatigue was assessed by using Chalder Fatigue Scale (CFQ-11). Briefly, participants were asked to answer these questions with particular reference to the past month in comparison to their pre-COVID-19 baseline, with responses measured

on a Likert scale (0-3). Dyspnoea was assessed by modified Medical Research Council (mMRC) scale. Besides, routine socio-demographic information, the time intervals between initial symptom onset, oxygen saturation (SpO2) at rest by pulse oximetry and investigation reports were recorded with a structured questionnaire. All information regarding the clinical features and investigations was recorded in a data collection sheet.

Results:

Out of 117 patients majority 31(26.5%) belonged to the age group 61 to 70 years with mean age was 52.7±13.6 years. Male was 90(76.9%) and female was 27(23.1%) with male-female ratio was 3.9:1. Most of the patients had diabetes mellitus 44(37.6%) and cardiovascular disease 38(32.5%). Rest had hypertension 26(22.2%), chronic lung disease 21(17.9%), chronic kidney disease 8(6.8%), and cancer 6(5.1%). The patients were followed up for a mean duration of 105.4±28.7 days from the onset of acute COVID-19 symptoms.

Fatigue was found in more than half 64(54.7%) of the patients. Among the patients, the mean Chalder fatigue score was 4.12±2.44, total score was 15.0±6.6, mean physical fatigue score was 10.8±4.7 and mental fatigue score was 4.2±2.1.

Forty Nine (41.9%) patients were found to be dyspnoeic. Among them, mMRC score was 0 in 32.5%, 1 in 25.6% and e"2 in 41.9% patients. Majority 75(64.1%) of the patients had a SpO2 >94%.

Age, sex, BMI, and smoking status were not statistically significant (p>0.05) when compared between fatigued and non-fatigued patients.

Diabetes mellitus and cardiovascular disease were significantly higher in fatigued patients than non-fatigued patients (p<0.05). Dyspnoeic patients were more fatigued when compared with non-fatigued patients (p<0.05). Severe COVID-19 patients were more fatigued (92.2% vs 35.8%, p<0.05) than non-severe patients.

In multivariate analysis diabetes mellitus, cardiovascular disease and severe COVID-19 were found to be independent predictors for fatigue as here p value was low (p <0.05). However, dyspnoea was not found to be independent predictor for fatigue as p value was high (p >0.05).

Table-I

Demographic characteristics of the study population (n=117)

Demographic characteristics	*f*	%
Age (years)		
≤30	2	1.7
31-40	29	24.8
41-50	23	19.7
51-60	21	17.9
61-70	31	26.5
>70	11	9.4
Mean ±SD	52.7±13.6	
Range (min-max)	28.0-75.0	
Sex		
Male	90	76.9
Female	27	23.1

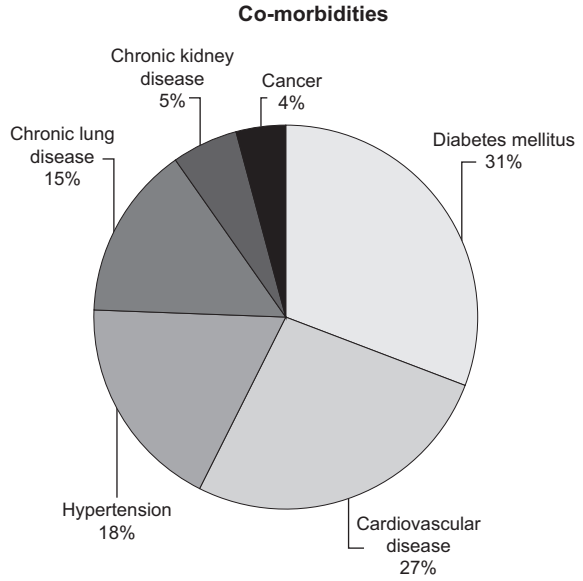

Fig.-1: *Pie chart showing co-morbidities of the study patients (n=117)*

Table-II

Distribution of the study population according to duration of follow up from the onset of acute COVID-19 symptoms (n=117)

Onset of acute COVID-19 symptoms to follow-up (days)	*f*	%
≤60	3	2.6
61-90	36	30.8
91-120	47	40.2
120-150	26	22.2
>150	5	4.3
Mean ±SD	105.4±28.7	
Range (min-max)	54.0-199.0	

Table- III

Distribution of the study population according to fatigue (n=117)

	f	%
Fatigue		
Yes	64	54.7
No	53	45.3
Chalder fatigue score (Bimodal Scoring)	4.12	±2.44
Range (min-max)	0.0	-9.0
Total score (Likert Scoring)	15.0	±6.6
Range (min-max)	4.0	-29.0
Physical fatigue score (CFQ-11 items 1-7)	10.8	±4.7
Range (min-max)	3.0	-20.0
Mental fatigue score (CFQ-11 items 8-11)	4.2	±2.1
Range (min-max)	1.0	-9.0

Table-IV

Distribution of the study population according to dyspnoea (n=117)

		f	%
Dyspnoea at rest	Yes	49	41.9
	No	68	58.1
mMRC scale	0	38	32.5
	1	30	25.6
	≥2	49	41.9

Table-V

Distribution of the study population according to SpO2 (n=117)

SpO2 (%)	*f*	%
<94	42	35.9
>94	75	64.1

Table-VI

Association between socio-demographic characteristics with fatigue (n=117)

Socio-demographic characteristics	Fatigue (n=64)		Non- fatigue(n=53)		χ^2 value	P value
	f	%	*f*	%		
Age (years)						
d 30	2	3.1	0	0.0		
31-40	12	18.8	17	32.1		
41-50	15	23.4	8	15.1	5.33	0.378^{ns}
51-60	12	18.8	9	17.0		
61-70	18	28.1	13	24.5		
>70	5	7.8	6	11.3		
Sex						
Male	53	82.8	37	69.8	2.76	0.097^{ns}
Female	11	17.2	16	30.2		
BMI (kg/m^2)						
<25.0	38	59.4	34	64.2	0.28	0.597^{ns}
≥25.0		26	40.6	19	35.8	
Smoking status						
Smoker	7	10.9	11	20.8	2.15	0.143^{ns}
Non-smoker	57	89.1	42	79.2		

ns= not significant

P value reached from chi square test

Table-VII

Association between co-morbidities with fatigue (n=117)

Co-morbidities	Fatigue (n=64)		Non- fatigue (n=53)		χ^2 value	P value
	f	%	*f*	%		
Diabetes mellitus	33	51.6	11	20.8	11.73	[a]0.001[s]
Cardiovascular disease	31	48.4	7	13.2	16.41	[a]0.001[s]
Hypertension	18	28.1	8	15.1	2.85	[a]0.091[ns]
Chronic lung disease	9	14.1	12	22.6	1.45	[a]0.229[ns]
Chronic kidney disease	6	9.4	2	3.8	1.43	[b]0.206[ns]
Cancer	5	7.8	1	1.9	2.09	[b]0.153[ns]

s= significant, ns= not significant

[a]P value reached from chi-square test

[b]P value reached from Fisher exact test

Table-VIII

Association between dyspnoea with fatigue (n=117)

	Fatigue (n=64)		Non- fatigue (n=53)		χ^2 value	P value
	f	%	*f*	%		
Dyspnoea at rest						
Yes	39	60.9	10	18.9	21.08	0.001[s]
No	25	39.1	43	81.1		
mMRC scale						
0	8	12.5	30	56.6		
1	17	26.6	13	24.5	29.66	0.001[s]
≥2	39	60.9	10	18.9		

s= significant

P value reached from chi-square test

Table-IX

Association between severity of COVID-19 with fatigue (n=117)

Severity of COVID-19	Fatigue (n=64)		Non- fatigue (n=53)		χ^2 value	P value
	f	%	*f*	%		
Non-severe	5	7.8	34	64.2	41.41	0.001[s]
Severe	59	92.2	19	35.8		

s= significant

P value reached from chi-square test

Table-X

Multivariate logistic regression analysis prediction for fatigue after COVID-19 infection

Parameters	Adjusted OR	95% CI for OR		P value
		Lower	Upper	
Diabetes mellitus	7.661	1.809	32.440	0.006[s]
Cardiovascular disease	23.070	4.150	96.253	0.001[s]
Dyspnoea	3.381	0.960	11.912	0.058[ns]
Severe COVID-19	17.259	2.988	92.672	0.001[s]

s= significant, ns= not significant

P value reached from multivariate analysis by binary logistic regression analysis

OR=Odd's Ratio

Discussion:

This cross-sectional observational study was carried out with an aim to assess the persistence of fatigue and its covariates after COVID-19 infection. One hundred and seventeen (117) symptomatic patients diagnosed as COVID-19 by polymerase chain reaction (PCR) test during the period from July 2020 to June 2021 were included in this study. The present study findings were discussed and compared with previously published relevant studies.

In this study, it was observed that most 31(26.5%) of the patients belonged to the age group 61 to 70 years with mean age was 52.7±13.6 years. Age was not statistically significant (p>0.05) when compared between fatigued and non-fatigued patients. An almost similar study was done by Carfi et al.[4] and Townsend et al.[9] that found mean age was 56.5±14.6 years and 49.5±15 years and age was not statistically significant when compared between fatigued and not-fatigued patients. Their study findings were also consistent with this study.

In this present study, it was observed that the majority 90(76.9%) patients were male with male-female ratio was 3.9:1. Sex difference was not statistically significant (p>0.05) when compared between fatigued and non-fatigued patients. Townsend et al.[9] reported that female patients were significantly higher in fatigued patients than non-fatigued patients (67.2% vs 39.3%). Their results also show a distinct female preponderance in the development of fatigue. This was in keeping with previous CFS findings done by Faro et al.[10]. We did not find any significant difference in fatigue between male and female patients. The possible reason might be female patients were less in number in our study.

Regarding co-morbidities, in this study it was observed that most of the patients had diabetes mellitus 44(37.6%) followed by cardiovascular disease 38(32.5%), hypertension 26(22.2%), chronic lung disease 21(17.9%), chronic kidney disease 8(6.8%), and cancer 6(5.1%). Diabetes mellitus and cardiovascular disease were significantly higher in fatigued patients than non-fatigued patients. Our findings suggested that patients with multiple co-morbidities had suffered from more fatigue.

In this present study we observed that fatigue was found in 64(54.7%) patients. Mean Chalder fatigue score was found 6.0±1.5 in fatigue group and 1.8±1.0 in non-fatigue group. The mean total score was found 20.0±4.1. The mean physical and mental fatigue score was found 14.4±2.9 and 5.6±1.8. The difference was statistically significant ($p<0.05$) between the two groups. Townsend et al.[9] reported that more than half reported persistent fatigue (52.3%), at 10 weeks (median) after initial COVID-19 symptoms. Fatigue was assessed using the CFQ-11 in all participants and the mean (±SD) score was 15.8±5.9 across the study population. The mean physical and psychological fatigue score (±SD) was 11.38±4.22 and 4.72±1.99. Qi et al.[11] and Carfi et al.[4] also found fatigue was 53.6% and 53.1%, respectively. Another study in UK done by Halpin et al.[5] where they reported new illness-related fatigue was the most common reported symptom by 72% participants in ICU group and 60.3% in ward group after a mean 48 days discharge from the hospital. However, post-SARS fatigue has been reported in 40% of individuals one year after initial infection, with 1 in 4 meeting CFS diagnostic criteria at that time point[12]. The levels of both physical and psychological fatigue seen in post-COVID are higher than those of the general population, but do not reach the levels of those seen in chronic fatigue syndrome[13,14]. Rates of fatigue seen in our cohort are roughly equivalent to those reported in chronic disease states by Coetzee et al.[15] and Jeon et al.[16]. Findings of the current study supported that the burden of post-COVID fatigue in our country might be higher than other chronic disease states.

In this current study dyspnoea at rest was found in 49(41.9%) patients. Among the dyspnoeic patients, more than sixty percent (60.9%) patients were found in fatigue group and 18.9% in non-fatigue group. The difference was statistically significant ($p<0.05$) between the two groups. Mandal et al.[8] found that 53% patients reported persistent dyspnea after a median 54 days post-discharge. These findings matched with our study.

Regarding severity of COVID-19, it was observed that the majority of the patients 78(66.7%) had suffered from severe COVID-19. Among patients diagnosed with severe COVID-19, 92.2% had fatigue and 35.8% were not fatigued. The difference was statistically significant ($p<0.05$) between the two groups. Townsend et al.[9]

demonstrated that there was no association between COVID-19 severity (need for inpatient admission, supplemental oxygen, or critical care) and fatigue following COVID-19. Their study findings do not match with our study. The possible explanation may be levels of fatigue may vary in populations as our study demonstrated that patients with co-morbidities were more fatigued.

In multivariate analysis, diabetes mellitus, cardiovascular disease and severe COVID-19 were found to be independent predictors for fatigue as here p value was low (p <0.05). In a study done by Townsend et al.[9] showed that overall, there was no association, either using unadjusted models, or models adjusted for age and sex, between COVID-19 disease-related characteristics (days since symptom onset, need for inpatient admission/ supplemental oxygen/critical care, length of hospital stay), routine laboratory markers of inflammation, cell turnover and fatigue post COVID-19. These results suggested that fatigue post-COVID-19 might be influenced by several factors.

This study highlighted the burden of fatigue, the impact on return to work, and the importance of follow-up of all patients diagnosed with COVID, not merely those who required hospitalization. A lengthy post-infection fatigue burden will impair quality of life and will have a significant impact on individuals, employers, and healthcare systems. These findings should be used to form management strategies for convalescent patients and allow intervention to occur in a timely manner.

Conclusion:

More than half of the patients suffer from persistent fatigue after COVID-19 infection. Diabetes mellitus, cardiovascular disease and severe COVID-19 are independent predictors for fatigue. Longer follow-up studies in a larger population are required to understand the full spectrum of health consequences after COVID-19 disease. A multidisciplinary post-COVID rehabilitation program should be established with special attention to people who had diabetes, cardiovascular disease and severe COVID-19.

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ORIGINAL ARTICLE

Prediction of the Need for NIV in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Comparative Study between DECAF and Modified DECAF Score

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Abstract

Background: *Exacerbation of chronic obstructive pulmonary disease (COPD) lead to multiple hospital admissions, longer hospital stays, increased treatment costs as well as increased morbidity and mortality. Currently, no optimal scoring system exists that can predict need for NIV in patients with acute exacerbation of COPD. Accurate prognostic tool can help physicians to select the appropriate level of care and preparedness.*

Objective: *To compare DECAF [(D) dyspnea, (E) eosinopenia, (C) consolidation, (A) acidemia, (F) atrial fibrillation] and modified DECAF score [(D) dyspnea, (E) eosinopenia, (C) consolidation, (A) acidemia, (F) frequency of hospital admission] in predicting the need for NIV in patients with acute exacerbation of chronic obstructive pulmonary disease.*

Materials and Methods: *This cross-sectional study was conducted in the Department of Respiratory Medicine, NIDCH, Mohakhali, Dhaka from April 2021 to May 2022. A total of 91 patients with acute exacerbation of COPD were enrolled in this study. All patients were subjected to complete medical history taking, chest examination, dyspnea assessment by extended modified Medical Research Council Dyspnea(eMRCD), complete blood count, chest radiograph, ECG, and arterial blood gas analysis. Both DECAF and modified DECAF score were calculated and the need for NIV was documented. All collected data were analyzed using appropriate statistical formula and SPSS programme.*

Results: *Out of 91 patients, 20 patients (21.97%) required non-invasive ventilation. The area under the ROC curve of DECAF and modified DECAF score was 0.973 and 0.974 respectively in predicting the need for NIV. The sensitivity, specificity, PPV and NPV of DECAF score were 84.21%, 94.44%, 80.00% and 95.77% respectively at a cut off value of 3. The sensitivity, specificity, PPV and NPV of modified DECAF score were 84.52%, 100%, 100% and 96.51% respectively at a cut off value of 4*

Conclusion: *Both DECAF score and the modified DECAF score are practical and can be calculated easily using simple questions and routine investigations available during the initial admission. Both were good predictors, but modified DECAF was superior in predicting need for NIV in patients with acute exacerbation of COPD*

Keywords: *COPD, DECAF score, modified DECAF score*

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Introduction:

Globally, Chronic obstructive pulmonary disease (COPD) is one of the significant causes of morbidity and mortality, resulting in a substantial and growing economic and social burden[1]. It is currently the third leading cause of death worldwide, causing 3.23 million deaths in 2019, with nearly 90% of deaths under the age of 70 occurring in low and middle income countries[2]. The prevalence of COPD is predicted to increase over the next 40 years and may even result in 5.4 million deaths annually by 2060 due to COPD and allied conditions[3].

GOLD defines Chronic obstructive pulmonary disease (COPD) as a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction[4]. Chronic bronchitis, small airway disease, and parenchymal destruction are the main components of chronic obstructive pulmonary disease (emphysema). It is considered in people over the age of 40 who have progressive persistent shortness of breath, chronic and recurrent cough, sputum production, and/or a history of recurrent exposure to risk factors. Spirometry is required to confirm the diagnosis clinically; the presence of post-bronchodilator FEV1/FVC less than 0.70 confirms the diagnosis[5]. COPD is a lung disease that increases the risk of cardiovascular, metabolic, skeletal muscle dysfunction, osteoporosis, depression, anxiety, and lung cancer[6].

Exacerbation of COPD can be defined as the deterioration of symptoms that essentially need management with antibiotics, oral corticosteroids, or both[4]. It generally includes an acute change in one or more of the following cardinal symptoms: (1) Dyspnea increases (2) cough increases in frequency and severity (2) Sputum production increases in volume and/or changes character. Acute Exacerbation can be divided into mild (presence of one out of three cardinal symptoms), moderate (presence of two out of three cardinal symptoms) and severe (presence of three cardinal symptoms)[7]. Exacerbations play an essential role in COPD prognosis, and individuals with recurrent exacerbations have been associated with worse outcomes[8]. Early recovery was found to be a significant factor in determining the long-term prognosis of COPD patients[9].

A robust clinical prediction tool could assist decisions regarding: location of care, early escalation of care, appropriateness for end-of-life care, and suitability for early supported hospital discharge and therefore could help to reduce morbidity and mortality and direct the most efficient use of resources during exacerbation period. In stable COPD, multiple prognostic tools were applied to predict mortality risk, but during the time of exacerbation, limited prognostic scores were found to identify exacerbation at risk of morbidity and mortality. Different scoring systems which were used previously in patients with acute exacerbation of COPD requiring hospital admission, were shown to be suboptimal[10]. The Dyspnea, Eosinopenia, Consolidation, Acidemia and Atrial Fibrillation (DECAF) score is a risk stratification tool initially designed to predict mortality during exacerbations. A modified DECAF score was subsequently designed with the frequency of hospital admissions in the previous year, replacing atrial fibrillation[11].

Our study aims to compare the effectiveness of modified DECAF over DECAF score in predicting the need for NIV in patients with acute exacerbation of COPD to determine which would be a better indicator for Bangladesh.

Materials and methods:

This cross-sectional observational study was conducted in the department of respiratory medicine of National Institute of Diseases of the Chest and Hospital, Mohakhali, Dhaka during the period from April 2021 to May 2022.

Inclusion criteria were:

Patients with diagnosed case of acute exacerbation of COPD admitted into NIDCH.

Exclusion criteria were:

1. COPD patients on domiciliary ventilation
2. Presence of other obstructive lung diseases like Asthma or bronchiectasis
3. Primary reason for admission is other than acute exacerbation of COPD (acute respiratory distress due to other reasons)

4. Patients with active malignancy
5. Patients with multisystem failure

Ninety-One (91) patients were included in the study using purposive sampling method. After informing full information regarding the nature of the study, possible outcome, and importance of follow-up, written consent was obtained. Relevant clinical history was taken through face-to-face interviews. The eMRCD grading and collected data were put on a structured questionnaire. CBC, Chest x-rays, ECG, and arterial blood gas analysis were done to calculate DECAF and Modified DECAF score. Data was collected regarding the need for non-invasive ventilation. All information regarding the clinical features and investigations was recorded in a data collection sheet.

Results:

Out of 91 patients, most patients were above 50 years of age (82.5%) with male predominance (89.0%). Most patients had lower socioeconomic status (72.5%). Of the admitted patients, about 65.9 % were current-smokers and 25.6% were ex-smokers. Severe exacerbations were most common in admitted patients and were noted to be 49 % in the study population. Moderate exacerbations were seen in 40 % and mild exacerbations in 11%. Severity of acute exacerbation of COPD had a significant relationship ($p<0.05$) with both the DECAF and modified DECAF score Among the study population, 49.4 % have co-morbidities. Among those with co-morbidities, HTN was most common at 18.7 %, followed closely by DM (15.3%), then IHD (9.9%) and Pulmonary HTN (5.5%). Both the DECAF and modified DECAF score were not significantly affected by the presence or absence of comorbidities ($p >0.05$).

There were 31 cases (34.06%) who presented with score 0 (eMRCD 0–4), 38 cases (41.76%) with score 1 (eMRCD 5a) and 22 cases (24.18%) presented with score 2 (eMRCD 5b). 15.39% of study patients presented with eosinopenia (<50 cells/mm3), 14.29% with consolidation, 18.68% with acidemia (pH <7.30), 5.50% with Atrial Fibrillation and 58.25% with the history of hospitalization for 2 or more times in last one year due to acute exacerbation of COPD. There was a statistically significant relation($p<0.05$) with the need for non-invasive ventilation and grade of dyspnea (eMRCD), eosinopenia, consolidation, acidemia and frequency of hospital admission (2 or more times in last year), but atrial fibrillation showed no significant relationship ($p>0.05$) with the need for non-invasive ventilation.

Out of 91 patients, 20 patients (21.97%) needed non-invasive ventilation where mean DECAF score was 3.3±0.825 and mean modified DECAF score was 4.5±0.825. The area under the ROC curve of DECAF score and modified DECAF score were 0.973 and 0.976, respectively, predicting need for non-invasive ventilation in patients with acute exacerbation of COPD. The DECAF score had a sensitivity of 85.00%, a specificity of 95.77%, and an accuracy of 93.41 %. In comparison, the modified DECAF score had a sensitivity and accuracy at 85.00% and 94.50%, respectively with a higher specificity at 97.18%.

Table-I

Demographic profile of the study population (n=91)

	Frequency (n)	Percentage
Age (years)		
40-50	16	17.6
51-60	33	36.3
61-70	37	40.6
Above 70 years	5	5.5
Gender		
Male	81	89.0
Female	10	11.0
Socio-economic status*		
Lower	66	72.5
Upper Lower	8	8.8
Middle Lower	13	14.3
Upper Middle	2	2.2
Upper	2	2.2

*Socioeconomic Status Scale-Modified Kuppuswamy Scale,2022

Table-II

Distribution of the study population by smoking status (n=91)

Smoking status	Frequency	Percentage
Current smoker	60	65.9
Ex-smoker	26	28.6
Never smoker	5	5.5
Average pack per year	20.16±5.54	

Table-III

Distribution of the study population by severity of acute exacerbation of COPD (n=91)

Severity of exacerbation	Frequency (n)	Percentage
Mild	10	11
Moderate	36	40
Severe	45	49
Total	91	100.0

Table-IV

Distribution of the study population by co-morbidities (n=91)

Comorbidities	Frequency (n)	Percentage
DM	14	15.3
HTN	17	18.7
IHD	9	9.9
Pulmonary HTN	5	5.5
None	46	50.6
Total	91	100.0

Table-V

Distribution of study population by the components of DECAF and modified DECAF score (n=91)

Components		Score	Frequency (n)	Percentage
Dyspnoea(eMRCD)	eMRCD 0-4	0	31	34.06
	eMRCD 5a	1	38	41.76
	eMRCD 5b	2	22	24.18
Eosinopenia(<50 cells/mm3)	No	0	77	84.61
	Yes	1	14	15.39
Consolidation	No	0	78	85.71
	Yes	1	13	14.29
Acidemia(pH<7.3)	No	0	74	81.32
	Yes	1	17	18.68
Atrial Fibrillation	No	0	86	94.50
	Yes	1	5	5.50
Frequency of Hospitalization	No	0	38	41.75
(2 or more times in last year)	Yes	1	53	58.25

Table-VI

Relationship between need for non-invasive ventilation and each component of DECAF & modified DECAF score among study population (n=91)

Components	Score	Need for Non-invasive Ventilation		Test of significance	p value
		Yes	No		
Dyspnoea(eMRCD)	0	1	30	χ^2=53.8263df 2	<0.00001*
	1	2	36		
	2	17	5		
Eosinopenia(<50 cells/mm3)	0	2	75	χ^2=62.8666df 1	<0.00001*
	1	12	2		
Consolidation	0	9	69	χ^2=35.1796df 1	<0.00001*
	1	11	2		
Acidemia(pH<7.3)	0	4	70	χ^2=63.4455df 1	<0.00001*
	1	16	1		
Atrial Fibrillation	0	19	67	χ^2=0.0121df 1	0.912511 ns
	1	1	4		
Frequency of Hospitalisation	0	1	37	÷2=14.2412df 1	0.000161*
	1	19	34		

p-value reached from Chi-Square test, *significant, ns= not significant

Table-VII

Comparison of DECAF score and modified DECAF score among study population by severity of acute exacerbation of COPD (n=91)

Severity of COPD		N	Mean±SD	Range (min-max)	F value	p-value
DECAF score	Mild	10	.48±.572	0–2	17.302	<0.001*
	Moderate	36	2.10±.968	1–4		
	Severe	45	3.53±.915	2-5		
	Total	91	1.34±1.384	0–5		
Modified	Mild	10	.80±.903	0–3	20.562	<0.001*
DECAF score	Moderate	36	3.10±.968	2–5		
	Severe	45	4.47±.915	3-6		
	Total	91	1.91±1.730	0–6		

p-value reached from ANOVA test, *significant

Table-VIII

Comparison of DECAF score and modified DECAF score among study population by the presence or absence of comorbidities (n=91)

Comorbidities	N	Mean±SD	Range (min-max)	F value	p-value	
DECAF score	DM	14	1.00±1.044	0–3	1.329	0.247^{ns}
	HTN	17	1.53±1.375	0–4		
	IHD	9	1.50±1.604	0–4		
	Pulmonary HTN	5	2.50±1.732	1–4		
	None	46	1.22±1.381	0–5		
	Total	91	1.34±1.384	0–5		
Modified	DM	14	1.67±1.435	0–4	1.114	0.344^{ns}
DECAF score	HTN	17	2.24±1.751	0–5		
	IHD	9	2.00±2.00	0-5		
	Pulmonary HTN	5	3.50±1.732	2–5		
	None	46	1.74±1.744	0–6		
	Total	91	1.91±1.730	0–6		

p-value reached from ANOVA test, ns= not significant

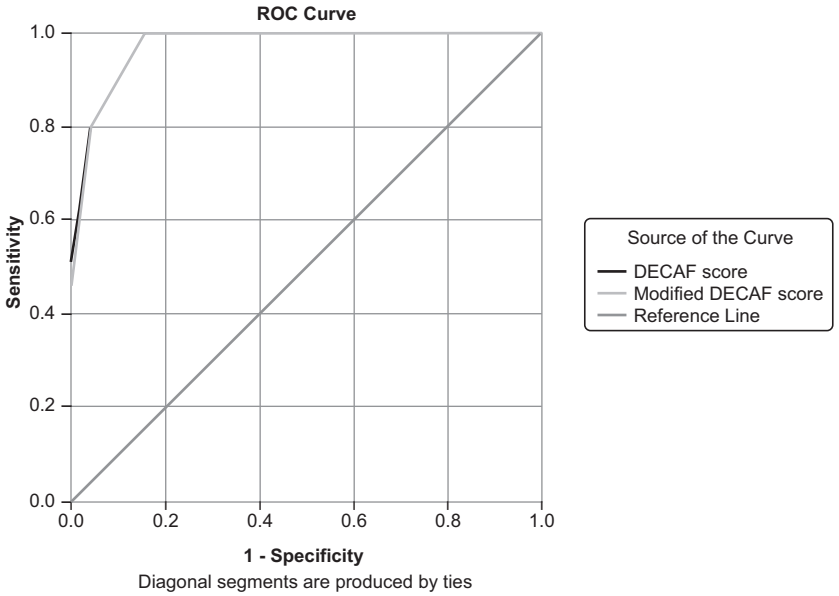

Fig.-1: *ROC curve of DECAF score and modified DECAF score in predicting the need for non-invasive ventilation in patients with acute exacerbation of Chronic Obstructive Pulmonary Disease (n=91)*

Table-IX

Test Result Variable(s)	AUC	Std. error	p-value	95% CI	
				Lower	Upper
DECAF score	.973	.014	<0.0001	.947	1.000
Modified DECAF score	.976	.014	<0.0001	.946	1.000

Table-X

Sensitivity, Specificity, PPV and NPV of DECAF score and modified DECAF score in predicting the need for non-invasive ventilation in patients with acute exacerbation of Chronic Obstructive Pulmonary Disease (n=91)

Test ResultVariable(s)	Cut off value*	Sensitivity	Specificity	PPV	NPV	Accuracy
DECAF score	3	85.00%	95.77%	85.00%	95.77%	93.41%
ModifiedDECAF score	4	85.00%	97.18%	89.45%	95.83%	94.50%

*cut off value reached from Youden Index

Discussion:

The hospital-based cross-sectional study was conducted on 91 patients admitted with AECOPD to determine whether the modified DECAF score was a superior prognostic score over the DECAF. Most patients were within the 50 to 70 age brackets, consistent with increased age being a risk factor for COPD. Gender-wise distribution revealed that 89% of the patients were male, representing an increased smoking prevalence in males. Among the participants, about 65.9 % were current smokers, and 25.6% were ex-smokers signifying the importance of smoking in the development of COPD. These findings reflect those from the study carried out by Islam et al. in 2013, where increasing age, male sex and smoking duration were regarded as independent risk factors for COPD in Bangladesh[12].

The DECAF Score: Dyspnea, Eosinopenia, Consolidation, Acidemia, and atrial Fibrillation was derived by Steer et al. 2012 to predict exacerbators with mortality risk during the hospital stay. DECAF score was primarily the prognostic tool used to stratify patients with AECOPD requiring hospital admission at risk of dying and to predict the outcomes[11]. The DECAF score was applied in patients with acute exacerbation of COPD at Alexandria University Hospital in 2014 by Zidan et al. and confirmed the strong prediction of DECAF score in expecting the in-hospital mortality and suggested the new modified DECAF score replacing atrial fibrillation with frequency of hospital admission in the previous year.

Extended Medical Research Council Dyspnoea (eMRCD) grading was incorporated in both DECAF and modified DECAF score as it includes degree of breathlessness along with functional dependence. Grade 5 of mMRC dyspnoea scale comprises of patients who are dyspneic even at rest. In eMRCD, grade 5 was divided into Grade 5a and 5b. Patients with Grade 5a could manage self-care independently, whereas in Grade 5b required assistance for basic self-care like bathing and dressing[13].

The study group selected had a varying presence of co-morbidities except for an underlying respiratory condition. On analyzing the data, it was seen that their presence or absence had no significant effect on the DECAF or the modified DECAF score, scoring a p-value above 0.05 in both instances (Table-VIII)

There were 31 cases who presented with dyspnea (eMRCD 0–4) with score 0, 38 cases presented with dyspnea (eMRCD 5a) with score 1 and 22 cases presented with dyspnea (eMRCD 5b) with score 2. There were 77 cases whose eosinophil count was >0.05 × 109 /L with score 0 and for 14 cases their eosinophil count was <0.05 × 109 /L with sore 1. There were 78 cases whose chest x-ray did not

show consolidation with score 0 and 13 cases whose chest x-ray showed consolidation with score 1. There were 17 cases in our study with their ABG showing acidemia (pH <7.30) with score 1 while the remaining 74 cases were (pH > 7.30) with score 0. There were 5 cases of atrial fibrillation in ECG with score 1 and remaining 86 cases did not show atrial fibrillation in ECG with score 0. There were 38 cases who had past history with less than 2 times of previous admission in the last year by acute exacerbation of COPD with score 0. There were 53 cases who had past history with more than or equal to 2 times of admission in the last year with score 1.

Incidence of need for non-invasive ventilation was 20 (21.97%). The difference in the components between these two-scoring system is atrial fibrillation in DECAF score and frequency of hospitalization for 2 or more times in the last one year due to acute exacerbation of COPD in modified DECAF score. It was found that atrial fibrillation was not significantly related ($p<0.05$) to the need for non-invasive ventilation, but frequency of hospital admission for 2 or more times in the last year was significantly related to the need for non-invasive ventilation scoring a p-value below 0.05 in all instances. This is in line with the findings of the study carried out by Zidan et al. in 2014 where atrial fibrillation was not significantly related to the need for NIV ($p>0.05$), but there was significant relationship between the frequency of admission with the need for NIV with a p value of < 0.001. Though a study conducted by Malik Sangwan in 2017 reflected significant relationship between mortality and atrial fibrillation ($p<0.05$)[13].

The severity classification of acute exacerbation of COPD was found to be significantly correlated with the DECAF and the modified DECAF score, having a p-value of less than 0.001.

The ROC curve for the DECAF and modified DECAF score for the prediction of the need for non-invasive ventilation were both above the reference line, making them good predictors for suitability. Their sensitivities were same (85.00%) and accuracy were also very similar, with DECAF score at 93.41 % and modified DECAF at 94.50%. The modified DECAF score was more specific at 97.18% compared to the 95.77% DECAF score.

As seen from the study, both the DECAF and modified DECAF Scores are good predictors for the need for non-invasive ventilation in acute exacerbation of COPD, having very similar sensitivities, specificities, and accuracy. But modified DECAF had a slightly higher edge, making it more specific and accurate than the DECAF score. This is in line with the findings of the study carried out by Zidan et al. in 2020, which showed both the scores to be an easy and practical method for predicting mortalities and the need for mechanical ventilation but suggested the use of modified DECAF scores in clinical settings due to its higher specificity[14].

Though the systemic review and meta-analysis carried out by Huang et al. (2020) concluded the DECAF score to have a better prognostic score and stable clinical values, it is important to note that they had mentioned that there was no significant difference between the DECAF and modified DECAF score and further study was needed to compare the two scores[15].

In this study, according to Youden index, the best cut-off value of DECAF score for the prediction of need for non-invasive ventilation was 3 On the other hand, the best cut-off value of modified DECAF score for the prediction of need for non-invasive ventilation was 4.

Conclusion:

In this study, we can see that increasing age, male gender and smoking are at a greater risk of exacerbations of COPD in Bangladesh. The DECAF and modified DECAF score were both found to be practical and helpful bedside prognostic score for the determination of need of non-invasive ventilation. But modified DECAF score has better specificity and accuracy than the DECAF score.

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REVIEW ARTICLE

COPD and Obstructive Sleep Apnea (OSA) - The Overlap Syndrome

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Abstract

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) are highly prevalent disorders and the co-existence of both disorders, termed the overlap syndrome (OS). Patients with OS have a substantially greater risk of morbidity and mortality, compared to those with either COPD or OSA alone. Keeping in mind the risk of mortality, it is crucial for clinicians to clinically evaluate the patients with OSA or COPD for the occurrence of overlap syndrome and provide effective treatment options for the same. This review aims to highlight the pathophysiology and the risks associated with the OS along with early detection and appropriate management protocols to reduce the mortality associated with it.

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Introduction and Background

The term overlap syndrome (OS) was coined by David C. Flenely in 1985 to describe the association between obstructive sleep apnea (OSA) with breathing disorders like chronic obstructive pulmonary disease (COPD) in a patient[1].

The prevalence of overlap syndrome varies among geographic regions and populations[2]. Shawon et al reported incidences of COPD coexisting with OSA ranging from 2.9% to 65.9% in a systematic review.

During sleep, patients with COPD experience nocturnal hypoxemia and hypoventilation mainly during the rapid eye movement (REM) phase of the sleep due to relaxation of intercostal muscles and reduced chest wall mobility. On the other hand, patients with OSA experience episodes of apnea and hypopnea mainly through upper airway collapse, reduced intrathoracic pressures, and activation of the sympathetic nervous system resulting in nighttime arousals and excessive daytime sleepiness[3]. These episodes of nocturnal oxygen desaturation (NOD) with hypercapnia and hypoxemia are more profound in patients with overlap syndrome in comparison to COPD or OSA alone. The overlap syndrome may further increase the risk of cardiovascular events particularly pulmonary hypertension and atrial fibrillation, thereby resulting in poor outcome and increased risk of mortality than in patients with COPD or OSA alone.

Factors in COPD that influence the potential for OSA

Complex interaction between sleep, bodymass index, and COPD may either prevent or promote development of OS. Patients with COPD with

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predominant emphysema and severe airflow obstruction may be protected against developing OSA. This is because the hyperinflated emphysematous lungs reduce the collapsibility of the upper airways by a caudal traction effect. Patients with severe COPD and emphysema also have lower body mass indices (BMIs), which is also protective against OSA[4]. In contrast, patients with relatively mild COPD who have a higher BMI tend to develop OSA, leading to the OS at a younger age[5]. These patients may be heavy smokers with higher cumulation of pack-years, which contributes to upper airway inflammation and OSA[6]. Furthermore, they often develop right heart failure at an earlier age. These patients experience rostral fluid shifts at night which worsens obstructive events due to edema of neck structures.

Clinical consequences of overlap syndrome

Patients with OS have increased risk of mortality due to cardiovascular events . Hypoxic drive results in oxidative stress and stimulates the release of systemic inflammatory mediators like TNF-á, IL-6, IL-8, CRP which ultimately results in endothelial dysfunction and atherosclerotic plaque formation[7].

OS also results in metabolic dysfunction including insulin resistance and abnormal lipid metabolism. OS is also associated with systemic hypertension which increases the risk of coronary artery disease, congestive heart failure, arrhythmias and stroke[8].

Patients with OS have increased risk of pulmonary hypertension and right heart failure. Hawrylkiewicz et al. observed in their study that 86% subjects with OS had pulmonary hypertension as compared to 16% subject with OSA alone[9].

Diagnosis of overlap syndrome

There is no formal guidance for the indications of performing a sleep study in patients with COPD. Extrapolating from the ATS guidelines for hypercapnic COPD patients, it is reasonable to consider diagnostic testing in COPD patients with an intermediate-to-high risk for OSA using the STOP-BANG questionnaire score[10]. Furthermore, COPD patients with pulmonary hypertension and borderline or nocturnal hypoxemia can be considered for sleep study. In-lab attended polysomnography with PAP titration is the gold standard for the diagnosis and treatment of OS.

Overlap syndrome is amenable to phenotyping

Figure 1 shows that patients with COPD may suffer from a spectrum of sleep related breathing disorder (SRBD), the exact nature of which depends on the relative severity of the emphysema and obesity. Patients with emphysema have higher sleep-related hypoventilation due to the mechanically disadvantaged downwardly displaced diaphragm, but they are protected against OSA because of low

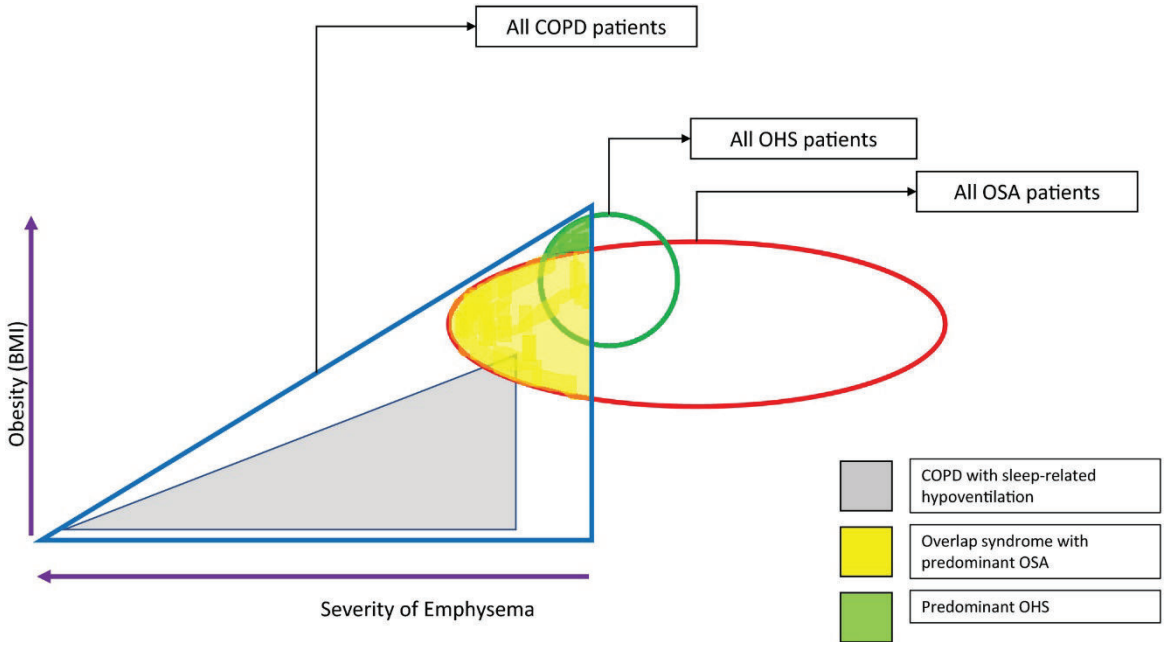

Fig.-1: *Proposed phenotypic classification of sleep-related breathing disorders (SRBD) in Chronic Obstructive Pulmonary Disease.*

BMI and caudal traction on the upper airways. In contrast, patients with obesity tend to have predominant OSA or OHS.

Management

Treatment of the overlap syndrome largely does not differ from treatment of the constituent diseases. The goal of treatment is to maintain adequate oxygenation at all times and to prevent sleep-disordered breathing disorder.

EVIDENCE FOR THE USE OF PAP THERAPY IN OVERLAP SYNDROME

To date, only observational studies of PAP therapy in OS patients have been conducted. PAP therapy in OS patients has been found to reduce pro-inflammatory markers implicated in cardiovascular disease, including C-reactive protein (CRP) and tumor necrosis factor-á[11]. PAP therapy has been linked with physiological benefits in OS including improved arterial blood gases (reduced PaCO2 and increased PaO2)[12].

Currently, there is no formal guidance for the use of PAP therapy in patients with COPD and SRBD. In the absence of well-designed RCTs, our understanding is limited to large observational studies and extrapolations of evidence from related conditions such as OSA, COPD with chronic hypercapnia and OHS. We have presented a decision-tree of a proposed phenotypebased management algorithm of SRBD in COPD (Figure-2)

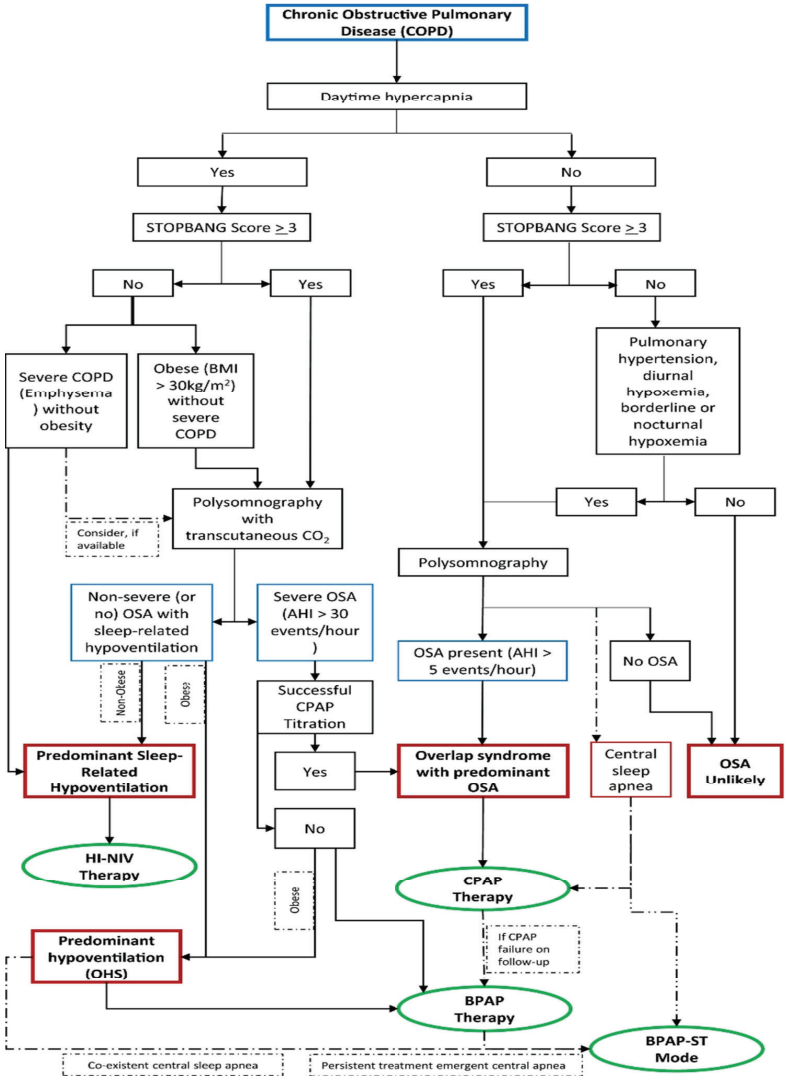

Fig.-2: *phenotype-guided approach toward the diagnosis and positive airway pressure therapy of sleeprelated breathing disorders with Chronic Obstructive Pulmonary Disease.*

OTHER THERAPIES FOR OVERLAP SYNDROME

Lifestyle Modifications

Structured exercise program and pulmonary rehabilitation are shown to be beneficial in both OSA and COPD. Structured exercise programs aim to improve the skeletal muscle wasting in patients with COPD. Likewise, structured exercise program in OSA patients have shown improvement in AHI, daytime sleepiness, and overall sleep quality[13].

Supplemental Oxygen Therapy

Studies have shown that supplemental oxygen therapy for more than 18 hours a day including during sleep can help to improve daytime and nocturnal hypoxemia and reduce the risk of mortality in these patients.

Bronchodilators and Corticosteroids

Treatment of the underlying obstructive lung disease is helpful in preventing or ameliorating nocturnal oxygen desaturation in those with COPD.

Bi-level PAP

The effects of bi-level PAP on overlap syndrome have not been specifically evaluated. However, one study that found benefit from NIV in hypercapnic COPD may have included overlap-syndrome patients[14]. Whether longterm NIV would improve outcomes in the overlap syndrome, compared to CPAP, perhaps in addition to supplemental oxygen, is unknown.

Conclusions

Keeping in mind the increased risk of cardiovascular morbidity and mortality with OS, it is important for clinicians to screen COPD patients with OSA and vice versa. Patients with a high index of suspicion should be clinically assessed and advised effective treatment options for the same. A phenotype-based approach of selecting PAP therapy which is tailored to correct the pathophysiology of SRBD demonstrates potential to improve clinical outcomes. To strengthen the evidence base, additional research is needed in the form of well-designed clinical trials which use the phenotypic approach to the management of OS and SRBD in COPD.

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INSTRUCTION TO AUTHORS ABOUT UNIFORM MANUSCRIPT WRITING

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