Bronchoscopic Evaluation in Clinically and Radiologically Suspected Lung Carcinoma

Sukanta Kodali[1], Sumanta Jha[2], Subhankar Chakraborty[3], Jaydip Deb[4], Amiya Dwari[5], Abhijit Mandal[6]

[1]Department of Pulmonary Medicine, Nilratan Sircar Medical College and Hospital, Kolkata, West Bengal, India.
[2]Department of Pulmonary Medicine, Nilratan Sircar Medical College and Hospital, Kolkata, West Bengal, India.
[3]Department of Pulmonary Medicine, Nilratan Sircar Medical College and Hospital, Kolkata, West Bengal, India.
[4]Department of Pulmonary Medicine, Nilratan Sircar Medical College and Hospital, Kolkata, West Bengal, India.
[5]Department of Pulmonary Medicine, Nilratan Sircar Medical College and Hospital, Kolkata, West Bengal, India.
[6]Department of Pulmonary Medicine, Nilratan Sircar Medical College and Hospital, Kolkata, West Bengal, India.

ABSTRACT

BACKGROUND

Lung cancer is generally diagnosed during late stage of the disease; so, early diagnosis of lung cancer is very important to reduce lung cancer death rate. Flexible fibreoptic bronchoscopy (FOB) is an important diagnostic technique performed in patients with suspected malignant lung lesion as it provides sufficient cytologic and histologic specimens in the form of bronchial washing, bronchial brushing and bronchial forceps biopsy.

METHODS

The present descriptive study analysed cytology of bronchial washing, bronchial brushing and histology of bronchial biopsy in 100 patients with suspected lung cancer. Patients in whom clinical and radiological findings suggested lung carcinoma, were included in the study. Patients with coagulopathy, refractory hypoxemia, cardiac instability, poor ability to cooperate with the procedure were excluded from this study. Age, gender, smoking habits, clinical and radiological findings, various histological types of malignancies, and yield of various bronchoscopic diagnostic techniques in the diagnosis of lung cancer were evaluated.

RESULTS

Of the 100 cases, 86 (86%) were males and 14 (14%) were females with male to female ratio of 6.14:1. The mean age in this study group was 58 years. Overall diagnostic yield by means of all techniques during bronchoscopy was 90% (90/100 patients). Squamous cell carcinoma was the most common primary bronchogenic tumour 36.67% (33/90 patients) followed by Adenocarcinoma 25.56% (23/90 patients), small cell carcinoma 24.44% (22/90 patients), Undifferentiated Non-Small Cell Carcinoma (NSCLC) 12.22% (11/90 patients), poorly differentiated carcinoma 1 patient. No evidence of malignancy was found in 10 patients by all techniques during bronchoscopy.

CONCLUSIONS

Lung cancer is a common malignancy with male preponderance. Bronchial washing and brushing cytology in combination with bronchial biopsy has a very high diagnostic yield. Therefore, all these techniques may be used concurrently to diagnose lung malignancy.

KEY WORDS

Fibreoptic Bronchoscopy, Non-Small Cell Carcinoma, Bronchoalveolar Lavage

Corresponding Author:
Dr. Sukanta Kodali,
Andul Chowdhury Para,
P.O. Andul-Mouri,
District-Howrah-711302,
West Bengal, India.
E-mail: sukantakodali@gmail.com

DOI: 10.14260/jemds/2020/360

Financial or Other Competing Interests: None.

How to Cite This Article:
Kodali S, Jha S, Chakraborty S, et al. Bronchoscopic evaluation in clinically and radiologically suspected lung carcinoma. J. Evolution Med. Dent. Sci. 2020;9(21): 1641-1645, DOI: 10.14260/jemds/2020/360

Submission 16-02-2020 ,
Peer Review 04-05-2020,
Acceptance 11-05-2020,
Published 25-05-2020.

BACKGROUND

Lung cancer is the most frequently diagnosed cancer and also the leading cause of all cancer associated deaths in the world.[1] Previously bronchogenic carcinoma was considered to be infrequent in India, but in the recent past a trend of increase in its incidence has been noticed.[2] In India, lung cancer is the fifth most common cancer.[2,3] Squamous cell type is the most common cell type in smokers and adenocarcinoma in non-smokers.[4]

Flexible fibreoptic bronchoscopy was developed in the late 1960s by S. Ikeda and has become the mainstay investigation in the evaluation of patients suspected of lung cancer.[5] It is employed mainly as a diagnostic tool providing tissue to determine the histological type of tumour. The flexibility of the bronchoscope allows the operator to inspect the majority of fourth order and often up to sixth order bronchi.[6] The main sampling techniques performed at flexible fibreoptic bronchoscopy include endobronchial forceps biopsy for central tumours and transbronchial forceps biopsy for more peripheral tumours.[7,8] Bronchial washing and bronchial brushing specimens can also be obtained for cytopathological examination.[9] The diagnostic yield of bronchial biopsy specimens varies from 70 to 90 per cent depending on the site and type of the tumour, number of specimens examined, and experience of the pathologist and the bronchoscopist. Central lesions, with visible tumours and multiple samples give a better diagnostic yield.[2]

An attempt was made to evaluate clinically and radiologically suspected lung carcinoma patients by various bronchoscopic techniques. Age, gender, smoking habits, clinical and radiological manifestations, various histological types of malignancy and the yield of various bronchoscopic techniques in the diagnosis of this disease were evaluated.

METHODS

It was a descriptive study conducted in the Department of Pulmonary Medicine of a tertiary care hospital. The samples for cytological and histological examination were collected from the patients in whom clinical and radiological findings suggested lung carcinoma. A total of 100 cases were included in the study. Flexible fibreoptic bronchoscopy was performed under local anaesthesia along with sedation with intravenous midazolam wherever required. Bronchial washing was obtained by aspiration of any secretion and instillation, followed by immediate aspiration of two aliquots of 20 ml of sterile isotonic 0.9% saline solution. Samples were centrifuged and prepared into air dried smear. Bronchial brushing was obtained from the surface of endobronchial lesions by the use of a stiff-bristle sheathed disposable brush. Brushing material was smeared directly on to at least three clean glass slides. Bronchial biopsies were performed with alligator forceps with serrated jaws. The specimens were immediately fixed in 10% buffered formalin.

Inclusion Criteria

The patients were included in the study were all the patients, admitted in Department of Pulmonary Medicine of our hospital in whom clinical and radiological findings suggested lung carcinoma.

Exclusion Criteria

Patients with coagulopathy which cannot be corrected, platelets <50,000 per microliter, refractory hypoxemia, recent myocardial infarction or unstable angina, major cardiac arrhythmia, hemodynamic instability, and poor ability to cooperate with the procedure were excluded from this study.

RESULTS

Of the 100 cases, 86% (86/100 patients) were males and 14% (14/100 patients) were females with male to female ratio of 6.14:1. The mean age in this study group was 58 years with a range of 25-82 years (table I). The prevalence of smoking was 79% (79/100 patients) in the study population. 89.53% (77/86 patients) male patients and 14.29% (2/14 patients) female patients were smoker. Most frequent observed symptoms were cough (65%), shortness of breath (35%), chest pain (32%), haemoptysis (27%), and hoarseness of voice (5%). The most common observed general physical sign was clubbing (18%). Other signs such as lymphadenopathy and superior vena cava syndrome were seen in 15% and 10%, respectively. Radiological abnormalities documented in study were mass lesion 86%, hilar opacity 47%, collapse (segmental/lobar) 29%, and pleural effusion 34%.

All clinically and radiologically suspected patients of lung malignancy underwent fibreoptic bronchoscopy in our bronchoscopy suit. During bronchoscopic procedure, abnormalities were noted as exophytic endobronchial, submucosal, peribronchial lesions. Exophytic endobronchial lesions were seen in 65 cases (65%), submucosal lesions in 29 cases (29%) and peribronchial lesions in 06 cases (06%). Bronchial washing was positive for malignant cells in 61.54% (40/65 patients) in exophytic endobronchial lesions, 51.72% (15/29 patients) in submucosal lesions, 33.33% (2/6 patients) in peribronchial lesions. Bronchial brushing had positive diagnostic yield of 80% (52/65 patients) in exophytic endobronchial lesions, 58.62% (17/29 patients) in submucosal lesions, 50% (3/6 patients) in peribronchial lesions. Bronchial biopsy had positive diagnostic yield of 100% (65/65 patients) in exophytic endobronchial lesions, 68.97% (20/29 patients) in submucosal lesions, 66.67% (4/6 patients) in peribronchial lesions. Bronchial biopsy was most sensitive (89%) followed by bronchial brushing (72%) and bronchial washing (57%) (table II).

In one case, bronchial brushing and biopsy were negative but bronchial washing was positive for malignancy. Overall diagnostic yield by means of all techniques during bronchoscopy was 90% (90/100 patients). Table III showed evaluation of the role of bronchoscopic techniques in diagnosis of lung cancer. Squamous cell carcinoma was the predominant histopathological pattern 28/65 patients (43.08%) in exophytic endobronchial lesions. Small cell carcinoma and Adenocarcinoma were the predominant histopathological pattern 9/21 patients (42.86%) and 8/21

patients (38.10%) respectively in submucosal lesions. Squamous cell carcinoma was the predominant histopathological pattern 2/4 patients (50%) in peribronchial lesions (Table IV).

Overall, Squamous cell carcinoma was the most common primary bronchogenic tumour 36.67% (33/90 patients) followed by Adenocarcinoma 25.56% (23/90 patients), small cell carcinoma 24.44% (22/90 patients), Undifferentiated Non-Small cell carcinoma 12.22% (11/90 patients), poorly differentiated carcinoma 1 patient (table V). No evidence of malignancy found in 10 patients by all techniques during bronchoscopy.

Age Groups (years)	Male	Female	Total	Percentage
<40	1	3	4	4
40-49	10	3	13	13
50-59	26	3	29	29
60-69	36	5	41	41
70-79	11	0	11	11
≥80	2	0	2	2
Total	**86**	**14**	**100**	**100**

Table I. Age and Sex Distribution

Technique	Endobronchial Exophytic Growth			Submucosal Lesions			Peribronchial Lesions			Overall yield (%)
	Attempted	Positive	Yield (%)	Attempted	Positive	Yield (%)	Attempted	Positive	Yield (%)	
Bronchial washing	65	40	61.54	29	15	51.72	6	2	33.33	57
Bronchial brushing	65	52	80	29	17	58.62	6	3	50	72
Bronchial biopsies	65	65	100	29	20	68.97	6	4	66.67	89

Table II. Yield from Various Bronchoscopic Techniques

Bronchial Washing, Brushing and Biopsy Positivity	Total No. of Cases. (n=100)	%
Negative by all three techniques	10	10
Positive by all three techniques	90	90
Positive by biopsy but negative by washing and brushing	17	17
Positive by brushing but negative by washing and biopsy	0	0
Positive by washing but negative by brushing and biopsy	1	1
Biopsy and brushing positive but washing negative	15	15
Biopsy and washing positive but brushing negative	18	18
Washing and brushing positive but biopsy negative	0	0

Table III. Evaluation of the Role of Bronchoscopic Techniques in Diagnosis of Lung Cancer

Histological Types	Endobronchial Exophytic Growth (Positive Yield =65 Cases)	Submucosal Lesions (Positive Yield =21 Cases)	Peribronchial Lesions (Positive Yield =4 Cases)	Total
Squamous cell carcinoma	28	3	2	33
Adenocarcinoma	14	8	1	23
Undifferentiated NSCLC	9	1	1	11
Small cell carcinoma	13	9	0	22
Poorly differentiated carcinoma	1	0	0	1
No evidence of malignancy	0	8	2	10

Table IV. Distribution of Lung Cancer Cell Types among Different Bronchoscopically Visible Lesions

Histological Types	Male	Female	Total (n=90)	%
Squamous cell carcinoma	33	0	33	33.67
Adenocarcinoma	12	11	23	25.56
Undifferentiated NSCLC	10	1	11	12.22
Small cell carcinoma	21	1	22	24.44
Poorly differentiated carcinoma	1	0	1	1.11

Table V. Histopathological Diagnosis by Means of All Techniques during Bronchoscopy

DISCUSSION

In current study majority of the patients diagnosed to have bronchogenic carcinoma were in their sixth and seventh decades of life (50-70 years). The mean age in study group was 58 years. These observations are consistent with many Indian studies done in the past in which the mean age was between fifty and seventy years.[2,3] The disease is known to be more common in males than in females. In current study, 86 (86%) were males and 14 (14%) were females with male to female ratio of 6.14:1. In another study of 638 patients diagnosed to have lung cancers, males and females were in a ratio of 6.7:1.[10] Other authors have also reported similar ratio in the previous studies.[2]

Tobacco smoking along with rising levels of environmental pollution has been implicated in causation of lung cancer. In the present study, 79% of the patients were smokers, once again suggesting a close link between this habit and the development of the disease. 89.53% (77/86 patients) male patients and 14.29% (2/14 patients) female patients were smoker in our study. In a study by Gupta et al, 80% of men and 33% of women among the patients were ever-smokers as compared to 60% of men and 20% of women among controls.[11] In the present study, smoking has been the predominant contributory factor both in males and females. Due to the same reason, squamous cell carcinoma was the commonest malignancy (36.67%) detected in present study.

Most frequent observed symptoms were cough (65%), shortness of breath (35%), chest pain (32%), haemoptysis (27%), and hoarseness of voice (5%). The most common observed general physical sign was clubbing (18%). Other signs such as lymphadenopathy and superior vena cava syndrome were seen in 15% and 10%, respectively. Shital Patil et al reported similar types of observations.[12] Radiological abnormalities documented in study were mass lesion 86%, hilar opacity 47%, collapse (segmental/lobar) 29%, and pleural effusion 34%. Sharma CP et al reported mass with or without collapse is the commonest radiological finding in lung cancer.[13] All clinically and radiologically suspected patients of lung malignancy underwent fibreoptic bronchoscopy in our Bronchoscopy suit.

During bronchoscopic procedure, abnormalities were noted as exophytic endobronchial, submucosal, peribronchial lesions. Exophytic endobronchial lesions predominant bronchoscopic findings were cauliflower, polypoidal-like or nodular or multinodular endobronchial growth. Submucosal lesions predominant bronchoscopic findings were erythema, vascular flares and enhanced rugal pattern, loss of normal bronchial markings, or thickening of mucosa and narrowing of bronchus. Peribronchial lesions predominant bronchoscopic findings are narrowing of airway due to extrinsic compression of airways by tumour or lymphadenopathy, or bulge seen in the lumen. Exophytic endobronchial lesions were seen in 65 cases (65%), submucosal lesions in 29 cases (29%) and peribronchial lesions in 06 cases (06%).

Bronchial washing was positive for malignant cells in 61.54% (40/65 patients) in exophytic endobronchial lesions, 51.72% (15/29 patients) in submucosal lesions, 33.33% (2/6 patients) in peribronchial lesions. However, the sensitivity of

BAL (bronchoalveolar lavage) in various other studies from literature varies widely from 21% to 78%.[14,15] This wide range of sensitivity may be due to difference in case selection. The adequacy of BAL samples depends on several crucial factors such as the degree of differentiation of malignant growth, preservation of the morphology of cytological material obtained and technical skill of the pulmonologist. Rennard SI suggested that yield can be improved by taking multiple samples.

Bronchial brushing had positive diagnostic yield of 80% (52/65 patients) in exophytic endobronchial lesions, 58.62% (17/29 patients) in submucosal lesions, 50% (3/6 patients) in peribronchial lesions. Chopra et al have reported the sensitivity of bronchial brushing to be as high as 86.3% in their study.[16] Bronchial biopsy had positive diagnostic yield of 100% (65/65 patients) in exophytic endobronchial lesions, 68.97% (20/29 patients) in submucosal lesions, 66.67% (4/6 patients) in peribronchial lesions. Bhat N evaluated 902 bronchial biopsy specimens in suspected cases of lung cancer and found that 760 (84.25%) cases were diagnosed by bronchial biopsy to be suffering from lung cancer, of which 647 were males and 113 were females.[17] Bronchial biopsy was most sensitive (89%) followed by bronchial brushing (72%) and bronchial washing (57%).

Overall diagnostic yield by means of all techniques during bronchoscopy was 90% (90/100 patients) in our study. Rivera MP, Mehta AC et al produced Data from 4507 patients revealed that central endobronchial biopsies provide the highest sensitivity (74%), followed by brushing (61%) and washing (47%). The combination provides a diagnosis in 88% of cases.[18] Bronchial biopsy was most sensitive (89%) followed by bronchial brushing (72%) and bronchial washing (57%). In one case, brushing and biopsy were negative but bronchial washing was positive for malignancy. This is possible when sometimes the biopsy is taken from the necrotic part of the tumour.

Squamous cell carcinoma was the predominant histopathological pattern 28/65 patients (43.08%) in exophytic endobronchial lesions. Small cell carcinoma and Adenocarcinoma were the predominant histopathological pattern 9/21 patients (42.86%) and 8/21 patients (38.10%) respectively in submucosal lesions. Squamous cell carcinoma was the predominant histopathological pattern 2/4 patients (50%) in peribronchial lesions.

Overall, Squamous cell carcinoma was the most common primary bronchogenic tumour 36.67% (33/90 patients) followed by Adenocarcinoma 25.56% (23/90 patients), small cell carcinoma 24.44% (22/90 patients), Undifferentiated Non-Small cell carcinoma 12.22% (11/90 patients), poorly differentiated carcinoma 1 patient. No evidence of malignancy found in 10 patients by all techniques during bronchoscopy. Most of the studies in India suggest a higher prevalence of Squamous cell carcinoma. Gupta et al, detected 42.3% squamous cell carcinoma and 19.9% adenocarcinoma in their study.[19] Similarly, Thippanna et al, in their study done in 1998 found 67.5% patients of squamous cell carcinoma in contrast to 18.75% adenocarcinoma patients.[20] Kashyap et al, also found 58.3% squamous cell and 10.8% adenocarcinoma patients in their study group.[10] The yield of diagnosis was highest with bronchoscopic biopsies and in maximum number of cases, specific histological diagnosis was made by biopsies alone. The number of biopsies taken has been shown to affect the positive yield rate; one study reporting that 5 biopsies were needed to achieve a greater than 90% probability of obtaining at least one positive sample in cases of carcinoma.[21] but it is best to combine all the diagnostic modalities like biopsies, brushing and lavage in any patient.

One of the limitations of our study was use of only bronchial biopsy for the validation of cytological techniques and the absence of other confirmatory tests like surgical biopsy, transbronchial needle aspiration, transthoracic needle aspiration, mediastinoscopy, biopsies of extrapulmonary lesions and autopsy. Other limitation was the inability to further sub-typing of poorly differentiated non-small cell carcinomas in the absence of immunohistochemistry.

CONCLUSIONS

The present study emphasizes the fact that lung cancer is common among male smokers with squamous cell carcinoma as the most common histological type. Bronchial washing and brushing cytology in combination with bronchial biopsy has a very high diagnostic yield. Therefore, all these techniques may be used concurrently to diagnose lung malignancy.

REFERENCES

[1] Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55 (2):74-108.
[2] Behera D, Balamugesh T. Lung cancer in India. Indian J Chest Dis Allied Sci 2004;46 (4):269-81.
[3] Agarwal A, Ghotekar LH, Garbyal RS, et al. Evaluation of pulmonary malignancies in Kathmandu valley and role of bronchoscopic techniques in diagnosis of such cases. J Indian Academy Clin Med 2003;4 (2):127-33.
[4] Kumar V, Gupta KB, Aggarwal R. Yield of different bronchoscopic techniques in diagnosis of lung cancer. International Journal of Research in Medical Sciences 2017;5 (9):4098-103.
[5] Ohata M. History and progress of bronchology in Japan. Japan Society for Brochology 1998;20:539-46.
[6] Barle´si F, Doddoli C, Greillier L, et al. Bronchoscopy in the diagnosis of lung cancer: an evaluation of current practice. Rev Mal Respir 2006;23 (Suppl 2):17-26.
[7] Zavala DC. Diagnostic fiberoptic bronchoscopy: techniques and results of biopsy in 600 patients. Chest 1975;68 (1):12-9.
[8] Schreiber G, McCrory DC. Performance characteristics of different modalities for diagnosis of suspected lung cancer: summary of published evidence. Chest 2003;123 (Suppl 1):S115-28.
[9] Rennard SI. Bronchoalveolar lavage in the diagnosis of cancer. Lung 1990; (Suppl 168):1035-40.
[10] Kashyap S, Mohapatra PR, Negi RS. Pattern of primary lung cancer among bidi smokers in North-Western Himalayan region of India. Lung Cancer 2003;41 (Suppl 2):S111.

[11] Gupta D, Boffetta P, Gaborieau V, et al. Risk factors of lung cancer in Chandigarh, India. Indian J Med Res 2001;113:142-50.
[12] Patil S, Rujuta A. Bronchoscopic characterization of lesions: significant impact on lung cancer diagnosis with use of Transbronchial Needle Aspiration (TBNA) in comparison to conventional diagnostic techniques (CDTs). Clinical Cancer Investigation Journal 2017;6 (6):239-46.
[13] Sharma CP, Behera D, Aggarwal AN, et al. Radiographic patterns in lung cancer. Indian J Chest Dis Allied Sci 2002;44 (1):25-30.
[14] Garg S, Handa U, Mohan H, et al. Comparative analysis of various cyto-histological techniques in diagnosis of lung diseases. Diagn Cytopathol 2007;35 (1):26-31.
[15] Truong LD, Underwood RD, Greenberg SD, et al. Diagnosis and typing of lung carcinomas by cytopathologic methods. A review of 108 cases. Acta Cytol 1985;29 (3):379-84.
[16] Chopra SK, Genovesi MG, Simmons DH, et al. Fiberoptic bronchoscopy in the diagnosis of lung cancer comparison of pre-and post-bronchoscopy sputa, washing, brushing and biopsies. Acta Cytol 1977;21(4):524-7.
[17] Bhat N, Nazeir MJ, Bashir H, et al. Correlation of bronchial biopsy with bronchoalveolar lavage in lung malignancies. Int J Res Med Sci 2016;4 (2):428-35.
[18] Rivera MP, Mehta AC, American College of Chest Physicians. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132 (Suppl 3):131S-48S.
[19] Gupta RC, Purohit SD, Sharma MP, et al. Primary bronchogenic carcinoma: clinical profile of 279 cases from mid-west Rajasthan. Indian J Chest Dis Allied Sci 1998;40 (2):109-16.
[20] Thippanna G, Venu K, Gopalkrishnaiah V, et al. A profile of lung cancer patients in Hyderabad. J Indian Med Assoc 1999;97 (9):357-9.
[21] Gellert AR, Rudd RM, Sinha G, et al. Fibreoptic bronchoscopy: effect of multiple bronchial biopsies on diagnostic yield in bronchial carcinoma. Thorax 1982;37 (9):684-7.

International Journal of Research in Medical Sciences
Chakraborty S et al. Int J Res Med Sci. 2020 Feb;8(2):484-491
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20200222

Original Research Article

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

Subhankar Chakraborty, Swapnendu Misra, Sumanta Jha, Sukanta Kodali, Abhijit Mandal*

Department of Pulmonary Medicine, Nilratan Sircar Medical College and Hospital, Kolkata, West Bengal, India

Received: 24 July 2019
Revised: 05 December 2019
Accepted: 27 December 2019

***Correspondence:**
Dr. Abhijit Mandal,
E-mail: swarajabdi@yahoo.co.in

ABSTRACT

Background: Patients with COPD often have exacerbations which frequently require hospitalization, resulting in higher mortality rates and costs than patients managed at OPD. Some easily available blood parameters in both stable COPD and AECOPD patients are measured that can be done in every patient even in poor resource settings. Finally, Results were analysed statistically to find out if there is any presence of significant difference of biochemical profile in stable COPD patients and AECOPD patients with or without any prognostic significance.
Methods: In institution based observational case control study, authors measured 1. FBS and PPBS 2. Serum Urea and Creatinine 3. Serum Electrolytes- Na+, K+, Cl- 4. LFT 5. Uric acid in both stable COPD(n=50) and AECOPD (n=50) patients. Finally, Results were analysed statistically to find out if there is any presence of significant difference of biochemical profile in stable COPD patients and AECOPD patients.
Results: AECOPD patients had statistically significant higher urea, uric acid levels and higher fasting hyperglycemia than stable COPD patients. Hypernatremia, hyponatremia and hyperkalemia, hypokalemia - all were significantly higher in AECOPD group. Low level of serum bilirubin and higher level of AST and ALP were common in AECOPD patients. AECOPD patients with high urea value (>50 mg/dl) (but not high creatinine) was associated with poor patient outcome in respect to ICU transfer, death and prolonged hospital stay. Low bilirubin, high ALP and AST level in AECOPD patients was associated with higher ICU transfer and mortality but only high ALP level was associated with prolonged hospital stay. High uric acid level (>6 mg/dl) was a major determinant of ICU transfer, mortality and prolonged hospital stay.
Conclusions: Predicting exacerbation by these parameters early in the course of disease can decrease morbidity and mortality as well as health care cost to great extent. By measuring the changes in it can also be predicted early who will need ICU support in future and who can be treated at ward.

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

INTRODUCTION

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

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

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

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

METHODS

This study was carried out at the Chest Department, NRS Medical College and Hospitals, during the period from October 2014 to September 2015 (One Year) with 50 AECOPD patients (cases) from indoor and 50 stable COPD patients from OPD (controls). AECOPD patients were diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, supported by spirometric evidence of airflow obstruction [FEV1/FVC <0.70] when clinically stable, with clinical criteria of exacerbation including increased dyspnea, increased sputum volume, or sputum purulence. Criteria for exclusion were as follows:1) Bronchial Asthma / Lung Abscess/ Lung Cancer. 2) Subjects who were recently started on Antibiotic / Antioxidant Therapy. 3) Known case of Pulmonary Koch's. 4) Ischaemic Heart Disease. 5) Previously diagnosed Diabetic and hypertensive patients. 6) Patients not giving informed consent for participating in the study.

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

Relevant History and thorough clinical examination of those patients were done. Diagnosis of COPD and severity of airway obstruction was confirmed by Spirometry with bronchodilator reversibility testing (as per GOLD guideline 2014 and 2015). Chest X ray was done. Pulse Oxymeter was then used to determine SpO2 at rest. Then 5 ml blood was drawn in a clot vial and sent for estimation of Blood for FBS, PPBS, Serum Urea, Creatinine, LFT, Uric acid, Serum Electrolytes - Sodium, Potassium and Chloride.

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

Statistical analysis

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

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

RESULTS

Demographic data

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

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

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

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

Table 2: Correlation between LFT

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

Correlation of different biochemical parameters in AECOPD and stable COPD patients

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

Stratified data correlation

Urea

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

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

Creatinine

Data wise 15 AECOPD patients (30%) were having higher creatinine level (>1.5 mg/dl), but only 4 stable COPD patients (8%) having higher creatinine level than that, which is also statistically significant (p value 0.005).

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

Sodium

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

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

Potassium

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

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

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

Chloride

Hypochloremia (<96 meq/L) was found in 12 patients (24%) in each group, whereas Hyperchloremia (>108 meq/L) was found in 7 AECOPD patients (14%) and in 5 stable COPD (10%) patients. Values were statistically not significant (p value >0.5).

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

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

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

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

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

Liver Function Test (LFT)

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

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

Uric acid

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

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

Blood sugar level

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

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

Different patient outcome and correlation with blood parameters

Correlation of Blood sugar level with patient outcome

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

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

Correlation of serum electrolyte and outcome in AECOPD

Among 9 AECOPD patient shifted to ICU, 4 patient (44.4%) had hyponatremia and 2 patient (22.2%) had hypernatremia, which was statistically significant (p value 0.022). Among them 2 patients had hyperkalemia and 2 patients had hypokalemia (22.2% each) which was also statistically significant (p value 0.046) Among the 3 patient died, all had hyponatremia (100%) and 2 patient had hypokalemia (66.6%), both of which are statistically significant (p value 0.017 and 0.025 respectively).

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

Correlation of LFT and AECOPD patient outcome

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

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

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

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

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

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

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

Table 8: Serum electrolytes and patient outcome.

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

Table 9: Serum LFT and patient outcome.

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

Table 10: Uric acid level and patient outcome.

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

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

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

Correlation of Uric acid level and AECOPD patient outcome

Among the 9 AECOPD patient shifted to ICU and the 3-patient died, all had uric acid level >6mg/dl, which are statistically significant (p value 0.00 and 0.022). Mean uric acid level in ICU transferred and general non-ICU patient was 7.9 and 4.7 mg/dl respectively (p value <0.001). Those patients who died had mean uric acid level 8.3 mg/dl (p value 0.006). Highest uric acid level observed in this group was 9.1 mg/dl (Table 11).

Serum Urea and Creatinine level and AECOPD patient outcome

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

Different biochemical parameters and correlation with duration of hospital stay.

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

DISCUSSION

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

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

AECOPD patients had lower bilirubin level than stable COPD group. Higher circulating bilirubin levels are associated with less airflow obstruction, slower longitudinal lung function decline, and less incident chronic obstructive pulmonary disease (COPD). Increased serum bilirubin in patients with moderate-to-severe COPD is associated with decreased risk of acute exacerbations of COPD (AECOPD).[12]

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

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

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

CONCLUSION

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

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Arora N, Daga MK, Mahajan R, Prakash SK, Gupta N. Chronic Obstructive Airway Disease in a Hospital Based Study. Indian J Chest Dis Allied Sci. 2001;43:157-62.
2. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. Jama. 1995 Dec 20;274(23):1852-7.
3. Louhelainen N, Myllärniemi M, Rahman I, Kinnula VL. Airway biomarkers of the oxidant burden in asthma and chronic obstructive pulmonary disease:

current and future perspectives. Inter J Chronic Obstructive Pulmonary Dis. 2008 Dec;3(4):585-603.
4. Koutsokera A, Kostikas K, Nicod LP, Fitting JW. Pulmonary biomarkers in COPD exacerbations: a systematic review. Respiratory Res. 2013 Dec;14(1):111.
5. Shoki AH, Mayer-Hamblett N, Wilcox PG, Sin DD, Quon BS. Systematic review of blood biomarkers in cystic fibrosis pulmonary exacerbations. Chest. 2013 Nov 1;144(5):1659-70.
6. Agusti A, Sin DD. Biomarkers in COPD. Clinics Chest Med. 2014 Mar 1;35(1):131-41.
7. Kamat Sudhakar R. Chronic Obstructive Pulmonary Disease. Lung Biology in health and disease An Indian pusputre. 1991;51:399-422.
8. Sethi S, Muscarella K, Evans N, Klingman KL, Grant BJ, Murphy TF. Airway inflammation and etiology of acute exacerbations of chronic bronchitis. Chest. 2000 Dec 1;118(6):1557-65.
9. Das P, Bandyopadhyay M, Baral K, Paul R, Banerjee AK. Dyselectrolytemia in chronic obstructive pulmonary diseases with acute exacerbation. Nigerian J Physiol Sci. 2010;25(1):25-7.
10. Farber MO, Bright TP, Strawbridge RA, Robertson GL, Manfredi F. Impaired water handling in chronic obstructive lung disease. J Lab Clini Med. 1975 Jan 1;85(1):41-9.
11. Farber MO, Kiblawi SS, Strawbridge RA, Robertson GL, Weinberger MH, Manfredi F. Studies on plasma vasopressin and the renin-angiotensin-aldosterone system in chronic obstructive lung disease. J Lab Clini Med. 1977 Aug;90(2):373-80.
12. Brown KE, Sin DD, Voelker H, Connett JE, Kunisaki KM. Association Between Serum bilirubin And Risk Of COPD Exacerbations. InB42. COPD: BIOMARKERS. American Thoracic Society. 2016 May:A3503-A3503.
13. Braghiroli A, Sacco C, Erbetta M, Ruga V, Donner CF. Overnight urinary uric acid: creatinine ratio for detection of sleep hypoxemia. Am Rev Respir Dis. 1993 Jul;148(1):173-8.
14. Lewis JG, Gardner JE. The relation of serum uric acid to haemoglobin level in patients with cardiac and respiratory disease. J Clini Pathol. 1960 Nov 1;13(6):502-5.
15. Saito H, Nishimura M, Shibuya E, Makita H, Tsujino I, Miyamoto K, et al. Tissue hypoxia in sleep apnea syndrome assessed by uric acid and adenosine. Chest. 2002 Nov 1;122(5):1686-94.
16. Lopez IH. Serum uric acid levels among patients with chronic obstructive pulmonary disease. Chest 2003;124(4_MeetingAbstracts):168S-a.

Cite this article as: Chakraborty S, Misra S, Jha S, Kodali S, Mandal A. Comparative study of some routinely measured Serum biochemical parameters between Acute Exacerbation of Chronic obstructive pulmonary disease and stable Chronic obstructive pulmonary disease patients in a tertiary care hospital of Kolkata: an attempt to make simple prognostic indicators. Int J Res Med Sci 2020;8:484-91.

A STUDY OF BACTERIAL ISOLATES AND THEIR SENSITIVITY PATTERN TO ANTIBIOTICS IN EMPYEMA THORACIS CASES IN A TERTIARY CARE HOSPITAL

Amiya Kumar Dwari[1], Sumanta Jha[2], Somnath Sarkar[3], Swapnendu Misra[4], Subhankar Chakraborty[5], Abhijit Mandal[6]

[1]Associate Professor, Department of Respiratory Medicine, NRS Medical College, Kolkata, West Bengal, India.
[2]Assistant Professor, Department of Respiratory Medicine, NRS Medical College, Kolkata, West Bengal, India.
[3]Medical Officer, Swasthya Bhawan, Kolkata, West Bengal, India.
[4]Assistant Professor, Department of Respiratory Medicine, NRS Medical College, Kolkata, West Bengal, India.
[5]Medical Officer (Specialist), Department of Respiratory Medicine, NRS Medical College, Kolkata, West Bengal, India.
[6]Professor, Department of Respiratory Medicine, NRS Medical College, Kolkata, West Bengal, India.

ABSTRACT

BACKGROUND

Empyema thoracis refers to accumulation of pus in the pleural space. The pathogenic organisms isolated in cases of empyema depend on prior antibiotic use and route of infection i.e. whether infection arises as a complication of pneumonia or following oesophageal surgery. It also depends on the age of the patient and presence of co-morbid illness.

MATERIALS AND METHODS

It is a descriptive study. It was designed to investigate the bacterial isolates of thoracic empyema and to find out the antibiogram pattern of the isolated organisms in a tertiary care hospital over one-year period. In this study, bacteriological spectrum was analysed in 50 empyema cases. Samples of pleural fluid were sent for bacterial culture (Aerobic) and for Gram's stain as well as for cytologic studies and mycobacterial and fungal smears and cultures, also if clinically indicated Cartridge Based Nucleic Acid Amplification test (CBNAAT). Patients with tubercular empyema were excluded.

RESULTS

24 cases were culture positive. Among the 24 culture positive cases, Streptococcus pneumoniae was the commonest bacterium isolated followed by Staphylococcus aureus. A strong inverse correlation was found between prior antibiotic use with chance of culture positivity. In present study Gram-positive organisms were found to be most sensitive to Vancomycin, Linezolid and some are sensitive to Clindamycin, Ciprofloxacin, Levofloxacin and Co-amoxyclav. Gram negative organisms were mostly sensitive to Ceftriaxone, Cefoperazone, Cefepime, Piperacillin-Tazobactam, Meropenem and Colistin. All the strains of Pseudomonas aeruginosa were sensitive to Amikacin. Resistance to Co-amoxyclav was noted in many strains of the Gram negative organisms except Klebsiella.

CONCLUSION

Gram positive organisms were the commonest organisms isolated in our study. This study also supports the view that prior antibiotic use reduces the chances of detecting the micro-organism through culture and determination of sensitivity.

KEY WORDS

Empyema, Pneumonia, Bacteria, Culture.

HOW TO CITE THIS ARTICLE: Dwari AK, Jha S, Sarkar S, et al. A study of bacterial isolates and their sensitivity pattern to antibiotics in empyema thoracis cases in a tertiary care hospital. J. Evolution Med. Dent. Sci. 2018;7(38):4978-4981, DOI: 10.14260/jemds/2018/934

BACKGROUND

Empyema thoracis is the collection of pus in the pleural space. Empyema commonly results from pneumonia, blood-borne infection, thoracic surgery, trauma, abdominal infection or neoplasm.[1] Pneumonia causes more than half the cases of empyema, post-surgical infection accounts for additional 20 percent.[2] Richard W Light[2] defined the term empyema as those pleural effusions with thick, purulent appearing fluid.

'Financial or Other Competing Interest': None.
Submission 07-08-2018, Peer Review 01-09-2018,
Acceptance 07-09-2018, Published 17-09-2018.
Corresponding Author:
Dr. Sumanta Jha,
Assistant Professor,
Department of Respiratory Medicine,
NRS Medical College, Kolkata,
West Bengal, India.
E-mail: sumantajha@gmail.com
DOI: 10.14260/jemds/2018/934

The pathogenic organisms isolated in cases of empyema depends on- (i) Prior antibiotic use; (ii) Whether the infection arises as a complication of community-acquired or aspiration pneumonia or as a result of some other predisposing factor such as oesophageal surgery; and (iii) The age of the patient and presence of co-morbid illness.[3] At present, Streptococcus pneumoniae and Staphylococcus aureus account for approximately 70% of aerobic Gram-positive cultures in cases of empyema. Presently, aerobic organisms are isolated slightly more frequently than anaerobic organisms. Klebsiella, Pseudomonas and Haemophilus species are the three most commonly isolated aerobic Gram-negative organisms. Bacteroides and Peptostreptococcus species are the two most commonly isolated anaerobic organisms.[4,5] Nowadays empyema thoracis is most often associated with aspiration pneumonia with mixed bacterial flora containing aerobic and anaerobic bacteria. The usual organism isolated in empyema thoracis complicating previous surgery is Staphylococcus aureus.[6]

There are approximately one million patients hospitalised in the United States each year with pneumonia. Of those hospitalised, 20 to 40% have a parapneumonic effusion. The mortality is higher in patients with pneumonia who have a pleural effusion. In one study, the mortality risk was 6.5 times higher if the effusions were bilateral, whereas the mortality risk was 3.7 times higher if the effusion was unilateral. Although, some of the increased mortality is due to comorbid conditions, some of it is due to mismanagement of the pleural effusion. In assessing whether patients with community-acquired pneumonia require hospitalisation, the presence of a pleural effusion is given the same weight as a PaO_2 level of less than 60 mmHg.

Symptoms of parapneumonic effusion and empyema may be acute or chronic. Anaerobic pulmonary infections frequently have an associated pleural effusion and are characterised by a more chronic course. Weight loss and anaemia are common with anaerobic infections. In patients with pneumonia, the clinical picture such as the degree of leukocytosis or the incidence of chest pain is very similar whether or not they have a parapneumonic effusion. Similarly, if the patient has a parapneumonic effusion the clinical picture is similar whether or not the effusion is complicated.

- The possibility of a parapneumonic effusion should be considered during the initial evaluation of every patient with a bacterial pneumonia.
- At this evaluation, it is important to determine whether a complicated parapneumonic effusion is present, because a delay in instituting proper pleural drainage in such patients substantially increases morbidity.
- The possibility of a parapneumonic effusion should also be suspected in patients who do not respond to antimicrobial therapy.
- Radiologically presence of pleural effusion is diagnosed with the help of chest x-ray PA view, lateral view, lateral decubitus view, thoracic ultrasonography, computed tomography etc. We quantify pleural effusion by measuring the distance between the inside of the chest wall and the bottom of the lung on either the decubitus radiograph or the CT scan of the chest. This distance is also measured with ultrasound.

MATERIALS AND METHODS

It is a descriptive study. The pleural fluid was examined grossly for colour, turbidity and odour. Aliquots were sent for determination of the pleural fluid differential and total WBC counts, glucose, protein, ADA and LDH levels. Samples of pleural fluid were also sent for bacterial culture (Aerobic) and for Gram's stain as well as for cytologic studies and mycobacterial and fungal smears and cultures, also if clinically indicated Cartridge Based Nucleic Acid Amplification test (CBNAAT). Patients with tubercular empyema were excluded.

Pleural fluid samples from fifty suspected cases of empyema were analysed. After collection and assessing the pleural sample it was cultured on blood agar, chocolate agar or MacConkey's agar plates.

These inoculated plates were then incubated for a period of 24 hours, after which they were examined for evidence of bacterial growth. In case of bacterial growth on the medium, the bacteria were further identified using standard tests.

The following Tests were Performed according to Standard Methods

Gram's staining, Hanging drop test, Catalase test, Oxidase test, Indole test, Methyl red test, Citrate utilisation test, Urease test, Hydrogen sulfide production test, Sugar fermentation test, Nitrate reduction test, Coagulase test (for Staphylococci), Bile solubility test (For Streptococcus pneumoniae), Bacitracin test (for β-haemolytic Streptococci) and optochin sensitivity test (for Pneumococci).

Antibiotic sensitivity test of the isolates were performed on Mueller-Hinton agar plates by the disc diffusion method of Kirby-Bauer. After the plates were dried, broth suspension of the organisms was made and adjusted to McFarland's opacity factor 0.5. A lawn culture was made over the surface of the media using a sterile swab, then appropriate antibiotics discs were placed and incubated at 37° C for 24 hours after which readings were taken. The zone of inhibition was measured and reported. Any resistance colony found within the inhibiting zone gave an indication as to the presence of resistance mutants. Sensitivity was performed using control strains of Klebsiella pneumoniae ATCC 700603, Staphylococcus aureus ATCC 25923, E. coli ATCC 25922 and Pseudomonas ATCC 27853.

The concentrations of the antibiotics employed in the antibiotic disc were as per CLSI guidelines.[7] Antibiogram was read, that is zones of inhibition were measured and sensitivities to various antibiotics were determined using standard guidelines for each antibiotic regarding the zone of inhibition and sensitivity.

Statistical Analysis

The data collected were analysed statistically using IBM SPSS Statistics software version 20. Chi-square test was used as the test of significance. A p-value of < 0.05 was considered significant.

RESULTS

In culture of pleural fluid of all the 50 patients with empyema twenty six (52%) were culture negative, eight (16%) showed growth of Streptococcus pneumoniae, seven (14%) were positive for Staphylococcus aureus, one (2%) for Escherichia coli, two (4%) for Haemophilus influenzae, three (6%) for Klebsiella sp. and the rest three (6%) for Pseudomonas aeruginosa.

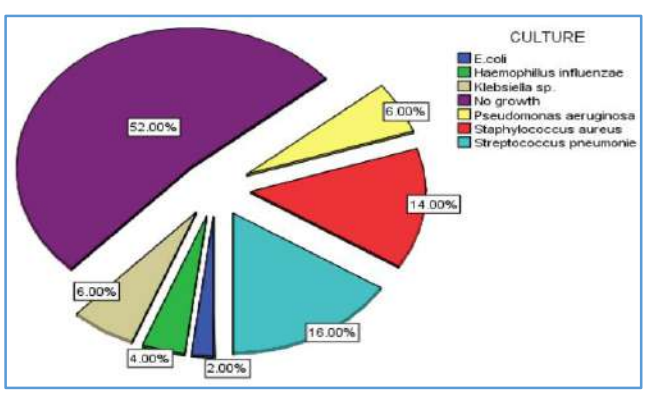

Figure 1. Bacterial Isolates in Empyema Thoracis Cases

Among the total twenty-four culture positive samples eight (33.33%) were positive for Streptococcus pneumoniae, seven (29.17%) for Staphylococcus aureus, one (4.16%) for

Escherichia coli, two (8.33%) for Haemophilus influenzae, three (12.50%) for Klebsiella sp. and three (12.50%) for Pseudomonas aeruginosa.

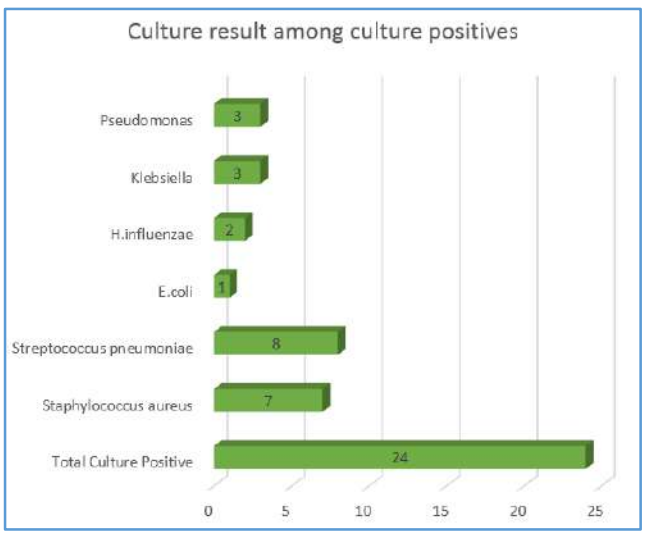

Figure 2. Bacterial Strains in Culture Positive Samples

Staphylococcus aureus was the commonest organism isolated in age group of 20 - 39 years and Streptococcus pneumoniae was the commonest in age groups of 40 - 60 years and > 60 years. However, there was no statistically significant relationship between age of the patient and bacterial strains isolated.

Streptococcus pneumoniae was the commonest causative organism of empyema in diabetic patients and patients without any comorbid condition. However, there was no statistically significant relationship between different co-morbid conditions and causative organisms.

Staphylococcus aureus was the commonest organism isolated in patients with empyema caused by iatrogenic factors and Streptococcus pneumoniae in parapneumonic empyema. However, there was no statistically significant correlation found between aetiology and bacterial strains isolated in culture.

No statistically significant correlation was found between prior antibiotic use and bacterial strain isolated in culture of pleural fluid. However, there was a statistically significant inverse correlation between prior antibiotic use and chance of culture positivity of pleural fluid. Among twenty one patients without use of prior antibiotics, nineteen (90%) gave positive result in pleural fluid culture and out of twenty nine patients who used prior antibiotics only five (17%) were culture positive.

Prior Antibiotic Use	Culture		P value -.00
	Positive	Negative	
	No. of Patients	No. of Patients	
No	19	2	
Yes	5	24	

Table 1. Correlation between Prior Antibiotic Use and Culture Positivity

All the Staphylococcus aureus strains isolated were sensitive to Vancomycin (100%) followed by Linezolid (86%) and Clindamycin (43%). Only 14% were sensitive to Ciprofloxacin, Levofloxacin, Amikacin and Co-amoxyclav.

Streptococcus pneumoniae strains were mostly sensitive to Vancomycin (88%) followed by Linezolid (75%), Cefoperazone (75%), Meropenem (75%) and Piperacillin-Tazobactam (75%). They were also sensitive to Co-amoxyclav (63%), Ceftriaxone (63%), Ciprofloxacin (50%), Clindamycin (50%) and Levofloxacin (37%).

Drugs		Staphylococcus aureus		Streptococcus pneumoniae	
		n=7	%	n=8	%
Co-amoxyclav	S	1	14%	5	63%
	R	6	86%	3	37%
Ceftriaxone	S	0	0%	5	63%
	R	7	100%	3	37%
Cefoperazone	S	0	0%	6	75%
	R	7	100%	2	25%
Ciprofloxacin	S	1	14%	4	50%
	R	6	86%	4	50%
Meropenem	S	0	0%	6	75%
	R	7	100%	2	25%
Linezolid	S	6	86%	6	75%
	R	1	14%	2	25%
Piperacillin+ Tazobactam	S	0	0%	6	75%
	R	7	100%	2	25%
Clindamycin	S	3	43%	4	50%
	R	4	57%	4	50%
Amikacin	S	1	14%	1	13%
	R	6	86%	7	87%
Levofloxacin	S	1	14%	3	37%
	R	6	86%	5	63%
Vancomycin	S	7	100%	7	86%
	R	0	0%	1	14%
Gentamicin	S	1	14%	0	0%
	R	6	86%	8	100%

Table 2. Sensitivity result of Staphylococcus aureus and Streptococcus pneumoniae to different Antibiotics

The only Escherichia coli strain isolated was sensitive to Ceftriaxone, Cefoperazone, Ciprofloxacin, Meropenem, Amikacin, Colistin, Levofloxacin and Gentamicin. It was resistant to Netilmicin and Piperacillin-Tazobactam.

Among the two strains of Haemophilus influenzae the two (100%) were sensitive to Ceftriaxone, Cefoperazone, Ciprofloxacin, Piperacillin-Tazobactam and Levofloxacin. One (50%) was sensitive to Netilmicin, Meropenem, Amikacin, Colistin and Doxycycline. Both (100%) were resistant to Co-amoxyclav.

Among the three strains of Klebsiella sp. All three (100%) were sensitive to Ceftriaxone, Meropenem and Levofloxacin. Two (67%) were sensitive to Co-amoxyclav, Ciprofloxacin, Netilmicin, Colistin and Gentamicin. One (33%) was sensitive to Cefoperazone, Piperacillin-Tazobactam and Amikacin.

Out of the three Pseudomonas aeruginosa strains all three (100%) were sensitive to Meropenem, Colistin, Amikacin and Cefepime. Two (67%) were sensitive to Ciprofloxacin, Ceftazidime, Piperacillin-Tazobactam, Levofloxacin and Gentamicin. All three (100%) were resistant to Co-amoxyclav, Netilmicin and Doxycycline.

		E. coli		H. influenzae		Klebsiella sp		Pseudomonas	
		n=1	%	n=2	%	n=3	%	n=3	%
Co-amoxyclav	S	0	0%	0	0%	2	67%	0	0%
	R	1	100%	2	100%	1	33%	3	100%
Ceftriaxone	S	1	100%	2	100%	3	100%	0	0%
	R	0	0%	0	0%	0	0%	0	0%
Ceftazidime	S	0	0%	0	0%	0	0%	2	67%
	R	1	100%	0	0%	0	0%	1	33%
Cefoperazone	S	1	100%	2	100%	1	33%	0	0%
	R	0	0%	0	0%	2	67%	1	33%
Ciprofloxacin	S	1	100%	2	100%	2	67%	2	67%
	R	0	0%	0	0%	1	33%	1	33%
Netilmicin	S	0	0%	1	50%	2	67%	0	0%
	R	1	100%	1	50%	1	33%	3	100%
Meropenem	S	1	100%	1	50%	3	100%	3	100%
	R	0	0%	1	50%	0	0%	0	0%
Piperacillin + Tazobactam	S	0	0%	2	100%	1	33%	2	67%
	R	1	100%	0	0%	2	67%	1	33%
Amikacin	S	1	100%	1	50%	1	33%	3	100%
	R	0	0%	1	50%	2	67%	0	0%
Colistin	S	1	100%	1	50%	2	67%	3	100%
	R	0	0%	0	0%	0	0%	0	0%
Levofloxacin	S	1	100%	2	100%	3	100%	2	67%
	R	0	0%	0	0%	0	0%	1	33%
Cefepime	S	0	0%	0	0%	0	0%	3	100%
	R	1	100%	0	0%	0	0%	0	0%
Gentamicin	S	1	100%	0	0%	2	67%	2	67%
	R	0	0%	0	0%	1	33%	1	33%
Doxycycline	S	0	0%	1	50%	0	0%	0	0%
	R	1	100%	1	50%	1	33%	3	100%
S-Sensitive, R-Resistant									

Table 3. Sensitivity result of E. coli, H. influenzae, Klebsiella sp. and Pseudomonas aeruginosa to different Antibiotics

DISCUSSION

In the present study bacteriological spectrum was analysed in 50 empyema cases, of which 24 were culture positive. It was observed that empyema is higher in males (68%) than in females (32%) with the ratio of 2: 1 and the peak was in the age group of 40 to 60 years. In a study conducted by Alfageme et al[8] showed average age of patient with empyema was 54, which is similar to our present study.

Among the 24 culture positive cases Streptococcus pneumoniae was the commonest bacteria isolated in 8 cases followed by Staphylococcus aureus isolated in 7 cases, Klebsiella sp. in 3 cases, Pseudomonas aeruginosa in 3 cases, Haemophilus influenzae in 2 cases and Escherichia coli in 1 case. It was also observed that out of 24 cases, all were single bacterial isolates. In this study, the prevalence of Gram positive isolates was 63% as compared to 37% of Gram negative. In an analysis of thirty-seven cases of pleural empyema done by Meyerovitch et al[9] revealed that Streptococcus pneumoniae was the most frequently isolated pathogen (41%) followed by Staphylococcus aureus (14%). Our present study show similar pattern of aetiological agents.

In our present study empyema was caused by iatrogenic factors in 8 (16%) cases, as a consequence of lung abscess in 2 (4%) cases and the rest 40 (80%) cases were parapneumonic.

In this study no statistically significant correlation was found between bacterial strain isolated in culture with age of the patient, co-morbidities, aetiology of empyema and prior antibiotic use. However, a strong inverse correlation was found between prior antibiotic use with chance of culture positivity.

In the present study Gram positive organisms were found to be most sensitive to Vancomycin, Linezolid and some were sensitive to Clindamycin, Ciprofloxacin, Levofloxacin and Co-amoxyclav. Some strains of Streptococcus pneumoniae were well sensitive to Cefoperazone, Ceftriaxone, Piperacillin-Tazobactam and Meropenem.

Gram negative organisms were mostly sensitive to Ceftriaxone, Cefoperazone, Cefepime, Piperacillin-Tazobactam, Meropenem and Colistin. All the strains of Pseudomonas aeruginosa were sensitive to Amikacin. Resistance to Co-amoxyclav was noted in many strains of all the Gram negative organisms except Klebsiella.

CONCLUSION

Gram positive organisms were the commonest organisms isolated in our study. This study also supports the view that prior antibiotic use reduces the chances of detecting the micro-organism through culture and determination of sensitivity.

REFERENCES

[1] Fishman AP, Elias JA, Fishman JA, et al. Fishman's pulmonary diseases and disorders. The McGraw-Hill Companies, Inc., 2008: p. 2144-7.

[2] Light RW. Pleural diseases. Chapter - 12. 5th edn. Philadelphia, PA: Lipincott Williams & Wilkins 2007.

[3] Seaton A, Seaton D, Lt. Leitch GA. Crofton and Douglas's respiratory diseases. Blackwell Science Ltd., 2000: p. 454-5.

[4] Jerng JS, Hsueh PR, Teng LJ, et al. Empyema thoracis and lung abscess caused by viridans streptococci. Am J Respir Crit Care Med 1997;156(5):1508-14.

[5] Tsang KY, Leung WS, Chan VL, et al. Complicated parapneumonic effusion and empyema thoracis: microbiology and predictors of adverse outcomes. Hong Kong Med J 2007;13(3):178-86.

[6] Barlett JG, Gorbach SL, Thadepalli H, et al. Bacteriology of empyema. Lancet 1974;303(7853):338-40.

[7] Clinical and Laboratory Standards Institute (CLSI). Analysis and presentation of cumulative antimicrobial susceptibility test data. 3rd edn. Approved guideline M39-A3. Wayne PA. CLSI, 2009.

[8] Alfageme I, Munoz F, Pena N, et al. Empyema of the thorax in adults. Etiology, microbiologic findings and management. Chest 1993;103(3):839-43.

[9] Brims FJ, Lansley SM, Waterer GW, et al. Empyema thoracis: new insights into an old disease. European Respiratory Review 2010;19(117):220-8.

Oxidants and Antioxidants in COPD Associated with Tobacco Smoke and Biomass Exposure

Sumanta Jha[1], Debojyoti Bhattacharjee[2], Subho Chowdhuri[3], Apratim Mitra[4], Abhradip Das[5], Kheya Mukherjee[6]

[1]Department of Pulmonary Medicine, Nilratan Sircar Medical College & Hospital, Kolkata, West Bengal, India. [2]Department of Biochemistry, Institute of Postgraduate Medical Education and Research and SSKM Hospital, Kolkata, West Bengal, India. [3]Murshidabad Medical College and Hospital, Berhampore, West Bengal, India. [4]Department of Pulmonary Medicine, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India. [5]Department of Pulmonary Medicine, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India. [6]Department of Microbiology, ID and BG Hospital, Kolkata, West Bengal, India.

ABSTRACT

BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of chronic morbidity and mortality. Apart from tobacco smoke, biomass fuel has been implicated as an important etiological factor for development of COPD. Oxidant-antioxidant imbalance is known to play a key role in pathophysiology of COPD. The study was undertaken to evaluate the role of oxidative stress and antioxidant status among COPD cases due to tobacco smoking and biomass exposure.

METHODS

Serum MDA, and erythrocyte SOD and GSH levels, were estimated among 40 COPD cases due to tobacco smoking (Group 1), 20 COPD cases due to biomass exposure (Group 2). 40 age and sex matched healthy controls (Group 0) were also included. Serum MDA, SOD and GSH were measured calorimetrically by TBA method, Marklund & Marklund method and method by Beutler et al respectively.

RESULTS

IBM SPSS Ver. 20 was used for statistical analysis and preparation of tables. Significantly higher levels of MDA were seen among COPD cases due to tobacco smoke (58.08±52 vs 15.3705±6.6; p value <0.01) compared to controls. SOD levels were significantly lower in both case groups compared to controls (1123.3±301.2, 1147.01±200.5 vs 1315.23±209.1; p value<0.01). GSH levels were lower in tobacco smoking group when compared to biomass exposed group (7.98±2.7 vs 9.61±2.1; p value 0.01). Positive correlation was found between FEV1% and SOD in group 1 cases.

CONCLUSIONS

The results support the hypothesis of presence of increased oxidative stress and oxidant-antioxidant imbalance in pathogenesis of COPD. It plays an important role in disease severity which is higher among COPD in tobacco smokers compared to biomass exposed COPD.

KEY WORDS

COPD, Smoking, Biomass, Oxidants, Antioxidants

Corresponding Author:
Dr. Debojyoti Bhattacharjee,
Department of Biochemistry,
Institute of Postgraduate Medical Education and Research and SSKM Hospital, Kolkata, West Bengal, India.
E-mail: debojyoti1979@rediffmail.com

DOI: 10.14260/jemds/2019/747

Financial or Other Competing Interests: None.

How to Cite This Article:
Jha S, Bhattacharjee D, Chowdhuri S, et al. Oxidants and antioxidants in COPD associated with tobacco smoke and biomass exposure. J. Evolution Med. Dent. Sci. 2019;8(46):3449-3453, DOI: 10.14260/jemds/2019/747

Submission 22-08-2019,
Peer Review 02-11-2019,
Acceptance 08-11-2019,
Published 18-11-2019.

BACKGROUND

Aetiology of COPD in India: Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and is associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[1] Exacerbations and co morbidities contribute to the overall severity in individual patients. Much of the increase in incidence of COPD is associated with projected increase in tobacco use and the indoor exposure to smoke from the combustion of solid biomass fuel, for heating and cooking.[2] Significantly ratios for COPD in India for both Male: Female and smoker: non-smoker are not as high as in the Western populations. This is largely attributed to the indoor air pollution from domestic combustion of solid biomass fuels.[3],[4],[5] Commonly used solid biomass fuels for cooking are cow dung cake, wood and coal. Environmental tobacco smoke (ETS) from passive smoking mainly from male smokers in the house is also another important risk factor for COPD in non-smoker women.[3]

Cigarette smoke and inflammation: Oxidative stress has been attributed to play the central role in the pathogenesis of COPD. In addition to causing direct injury to the respiratory tract, oxidative stress triggers and exacerbates chiefly three other mechanisms namely inflammation, apoptosis and protease-antiprotease imbalance.[6],[7] Cigarette smoke contains approximately five thousand toxic compounds, including potent oxidants (Approximately 1014 free radicals per inhalation) such as acrolein, hydrogen peroxide (H_2O_2), hydroxyl (OH**.**) and organic free radicals.[8] Reactive oxygen species (ROS) directly recruit inflammatory cells such as neutrophils, eosinophils, lymphocytes and macrophages resulting in inflammation.[9] ROS cause overexpression of the genes of proinflammatory mediators (e.g. tumour necrosis factor [TNF]-α, interleukin[IL]-1, and interleukin[IL]-8) via transcription factor NF-κb(Nuclear factor kappa B) and AP-1 (Activator protein-1), thus further recruiting inflammatory cells.[10] ROS can also form reactive aldehydes by lipid peroxidation of membrane phospholipids like 4-hydroxy-2-nonenal (4HNE) and MDA (Malondialdehyde) which are capable of inducing caspase (A major promoter of cell apoptosis).[11]

Human biological antioxidants: In normal cell, there is an appropriate pro-oxidant: antioxidant balance. Indigenous compounds and reactions disposing of these species, scavenging them, suppressing their formation or opposing their actions are antioxidants and include compounds such as NADPH (Reduced nicotinamide adenine dinucleotide phosphate), GSH (reduced glutathione), ascorbic acid, vitamin E, superoxide dismutase (SOD), glutathione peroxidase (GPx) etc.[12] SOD and GSH associated enzymes are enzymatic antioxidants which are active at the beginning of reaction through which reactive species are formed, and this avoids accumulation of O_2**.-** and H_2O_2.[13] There are three isomers of SOD, all neutralize superoxide. GSH is one of the primary non-enzymatic antioxidants in lung and exists in epithelial lining fluid, reduces H_2O_2 and lipid peroxides and neutralizes xenobiotic radicals.[14]

Effects of oxidative stress: Oxidative stress causes peroxidation of Polyunsaturated Fatty Acid (PUFA) present in cell membrane phospholipids. This leads to alteration in the structure and permeability of the cell membrane, resulting in loss of ion exchange selectivity, release of contents of organelles, i.e. hydrolytic enzymes of lysosome and formation of cytotoxic products such as MDA.[15]

Measurements of Human Oxi-Antioxidants

Oxidative stress can be measured through indirect quantification of products of lipid peroxidation like MDA, in the alveolar space, in the exhaled breath condensate, in the sputum and the blood.[16] Simultaneous estimation of antioxidant status can be made by measurement of serum levels of antioxidants like SOD, GSH.

METHODS

Place of study and patient selection: A total of 100 subjects including cases and controls had participated in the study. 60 stable COPD cases, none having acute exacerbation at the time of study, diagnosed clinically and confirmed with spirometry attending or admitted in Department of Pulmonary and Chest Medicine,Calcutta National Medical College and Hospital, Kolkata, West Bengal. Sample size was taken based on the convenience of the study. Approval from the institutional ethical committee was obtained for the study. The cases were divided into two groups based on current smoking history and history of exposure to biomass consisting of 40 (Group 1) and 20 (Group 2) cases respectively. Similarly, 40 age and sex matched healthy controls without history of smoking or biomass exposure were selected from persons who accompanied the patients and also from health care workers who participated voluntarily in the study (Group 0). Subjects with dual exposure to tobacco smoke and biomass were excluded from this study. Informed consent was obtained from all the subjects prior to the study.

Subject exclusion criteria and analyte estimation: Patients with pleural disease, malignancy of lung, tuberculosis, human immunodeficiency virus (HIV) infection, diffuse parenchymal lung disease (DPLD), diabetes mellitus, dyslipidemia, hypertension, connective tissue disorders, chronic renal or hepatic diseases were excluded from the study. Chest skiagram PA view, pulmonary function test (PFT) with bronchodilator reversibility were done in all cases and controls. About 6 ml of blood was drawn from a large peripheral vein under aseptic precaution after overnight fasting with a heparinised syringe and was transported immediately to the laboratory, Department of Biochemistry, Calcutta National Medical College and Hospital. The sample was then centrifuged to separate serum and prepare RBC lysate. Serum MDA activity was measured in serum by thiobarbituric acid method.[17] SOD and reduced GSH activities were measured in RBC lysate by methods of Marklund and Marklund[18] and Beutler et al[19] respectively.

Statistical Analysis

Statistical analysis was done with IBM SPSS Ver. 20. Chi-square test was performed to analyze the age and sex distribution pattern among cases and controls. Post-hoc ANOVA with and without Bonferroni correction was performed to estimate the statistical significance between variables like MDA, SOD and GSH among case groups and controls.

RESULTS

Age comparison among case groups and controls: The mean age distribution among COPD in smokers, COPD among biomass exposed and controls, selected for the study were close to each other as much as possible (Table 1) [Chi-square Test: p-value >0.068, degree of freedom=1].

Comparison of MDA, SOD and GSH levels among case groups and controls: The mean ± SD values for MDA, SOD, and GSH among the case groups (1 and 2) and controls (0) were represented in (Table 2). The values of MDA were significantly higher in Group 1 cases when compared to Group 0 (p-value < 0.001). No statistical difference was seen between cases and between Group 2 and Group 0. SOD levels were significantly lower among the case groups when compared to controls (p value <0.05). Higher level of GSH was found in biomass exposed COPD cases than COPD with smoking history (p value < 0.05) (Table 3A, Table 3B).

Correlation between FEV1% and various oxi-antioxidants: In Group 1, FEV1% was positively correlated to SOD value (p value <0.015). SOD and GSH values were also correlated to each other among smokers (Table 4). No similar correlation existed for FEV1%, MDA, SOD and GSH among the group 2 cases and controls.

Groups		Group 1 (n=40)	Group 2 (n=20)	Group 0 (n=40)
Age (in yrs.) Mean ± SD		59.15±8.92	58.6±9.43	55±5.16
Sex	Male	32	4	31
	Female	8	16	9
Smoking History (Pack yrs)		27	Nil	Nil
Biomass Exposure (yrs)		Nil	32	Nil
FEV1 (ml)		845	753.75 1373.875	
FVC (ml)		1611	1373.87	
FEV1/ FVC %		57	55.95 44.483193	
FEV1% of predicted value		44.1	44.48	
GOLD stage of airflow limitation		.	3	

Table 1. Distribution Pattern for Age, Sex, Smoking History, Biomass Exposure and COPD Levels among Cases and Controls

Groups		MDA (nmol/ml)	SOD (units/gm of Hb)	GSH (µmol/gm of Hb)
Smokers (Group 1: n=40)	Mean ±S.D.	58.0892 ± 52.53836	1123.3922 ± 301.24220	7.9755 ± 2.70204
Biomass (Group 2:n=20)	Mean ±S.D.	35.8219 ± 23.73494	1147.0161 ± 200.58413	9.6113 ± 2.09725
Control (Group 0: n=40)	Mean ±S.D.	15.3705 ± 6.67772	1315.2305 ± 209.16684	8.2895 ± 1.08898

Table 2. Mean Serum Levels for MDA, SOD and GSH among Cases and Controls

F-test of ANOVA	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	39760814.19	2	19880407.099	699.36	.000
Within Groups	4349244.795	153	28426.437		
Total	**44110058.99**	**155**			

Table 3A. Comparison Between and within Case Groups and Controls

Multiple Comparisons Post-hoc ANOVA with Bonferroni Correction					
Dependent Variable	**(X) Grouping**	**(Y) Grouping**	**Mean Difference (X-Y)**	**Std. Error**	**Level of Significance (p Value)**
MDA	0 vs	1	- 42.71867*	7.86790	.000
	0 vs	2	- 20.45145	9.63617	.109
	1 vs	2	22.26722	9.63617	.069
SOD	0 vs	1	191.83835*	55.65845	.003
	0 vs	2	168.21445*	68.16740	.046
	1 vs	2	-23.62390	68.16740	1.000
GSH	0 vs	1	.31405	.46227	1.000
	0 vs	2	-1.32180	.56616	.065
	1 vs	2	-1.63585*	.56616	.014

Table 3B. Comparison for MDA, SOD and GSH among Case Groups and Controls

Comparison of different oxidative stress markers in three study groups
The mean difference is significant at the <0.05 level
Control group=0(X), Smokers with COPD=group1(Y), Biomass exposed COPD=group2(Y)
(X-Y): Difference between mean values between cases and controls and those between the two case groups. Abbreviation- vs: Versus

Parameters	r Value	p Value
FEV1%: MDA	-.061	.711
FEV1%: SOD	.383	.015
FEV1%: GSH	.148	.368
MDA: SOD	.023	.886
MDA: GSH	-.181	.263
SOD: GSH	.356	.024

Table 4. Pearson's Correlation Between MDA, SOD, GSH and FEV1% in COPD Cases with History of Smoking Tobacco

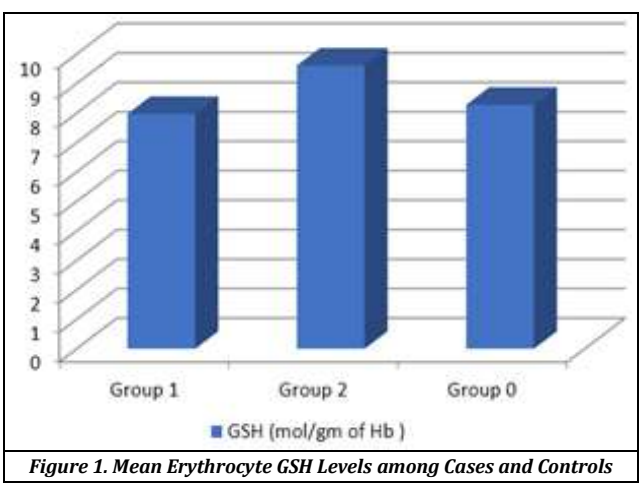

Figure 1. Mean Erythrocyte GSH Levels among Cases and Controls

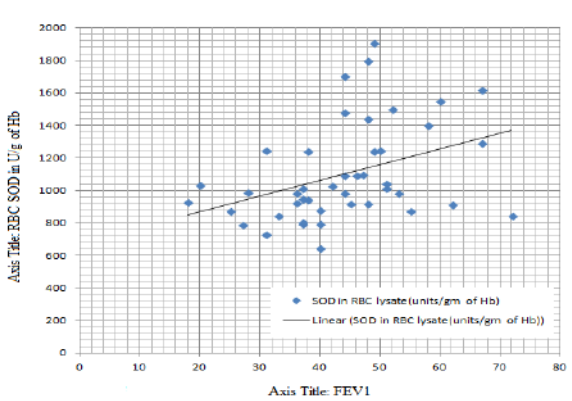

Figure 2. Scatter Graph of Correlation Between SOD and FEV1% in COPD Cases with History of Tobacco Smoking

DISCUSSION

Serum MDA levels alteration among smokers and biomass exposed subjects: It is known that oxidative stress is a major pathogenic component of airway inflammation that is characteristic of COPD.[20] Oxidative radicals cause damage to cellular components including membrane lipids, protein, carbohydrate and DNA.[21] It is well known that both cigarette and biomass exposure causes COPD in which free radicals and ROS increase.[22],[23] In this study, we found that plasma MDA level, an indicator of lipid peroxidation was higher in both smoking and biomass exposed COPD compared to healthy controls. PUFA and Fatty acids are major targets for free radical attack, resulting in lipid peroxidation, that continues as a chain reaction.[24] It had been shown that the levels of MDA, produced due to lipid peroxidation reaction in plasma are correlated inversely with the FEV1 percent in a population study.[25] There are reports indicating increased MDA level in both cigarette smoking and biomass exposure.[25] It is reported that there is significant decrease in antioxidant enzyme activity in females exposed to biomass fuel.

Depleted SOD Stores in COPD

SOD functions as a scavenger of O_2. Radical in the body. The level of SOD is decreased in oxidative stress which plays an important role in pathogenesis of various diseases including COPD.[26] Studies of Raghunath R Rai et al,[26]Nagaraj et al[27] and Ahmad A et al[28] showed decreased level of SOD amongst patients with COPD. This is in accordance to our study results. However, Montano et al[25] have found increased SOD levels in COPD patients compared to healthy controls. These alterations in antioxidant enzymes such as SOD emphasize to redox imbalance in COPD patients. Mechanism involved in variable SOD activity is due to increased production of free radicals in COPD patients resulting in increased SOD biosynthesis as a protective mechanism as well as its increased consumption, leading to depleted intracellular levels.

GSH Level Variability among Cases

Under non-stress condition, most of the intracellular glutathione is stored in reduced form (GSH). During increased oxidative stress by tobacco smoke or biomass, the free sulfhydryl (-SH) groups become oxidized resulting in loss of GSH. The gaseous phase of cigarette smoke irreversibly reacts with GSH to form GSH derivatives which cannot be reduced back, thus depleting the total GSH pool.[29] In our study, GSH among biomass exposed COPD was statistically higher than tobacco smokers with COPD (p value <0.02). Toth and colleagues (1986) stated that RBC glutathione plays a prominent role in detoxification of hydrogen peroxide (H_2O_2). Increased GSH in RBC of COPD patients is presumably due to constant exposure to oxidative stress, resulting in induction of protein synthesis.[30] However the activities of glutathione synthesis and redox system enzymes like glutathione peroxidase (GPx) and glucose-6-phosphate dehydrogenase (G6PD), gamma-glutamyl cysteine synthetase are transiently decreased in alveolar epithelial cells after chronic exposure to cigarette smoke condensate. This is due to action of highly electrophilic free radicals on the active sites of these enzymes, thus there is a time-dependent depletion of intracellular soluble GSH.[31] Studies had also shown a gradual age dependent decrease in serum glutathione levels among smokers.[32]

High Pathogenicity of Tobacco Smoke in Causing COPD

Studies have shown tobacco smoke induced COPD was associated with worse emphysema index in HRCT compared to biomass exposed COPD. This suggests tobacco smoke is more aggressive and leads to more parenchymal destruction than other forms of inhaled toxins.[32] Much in the same way our study explains lower GSH levels in tobacco smoke induced COPD cases compared to biomass exposed COPD cases.

Exposure to Both Tobacco Smoke and Biofuels Cause COPD

These results indicate the role of oxidative stress in causing COPD associated with tobacco smoke and inhalation of toxin for multiple hours per day, during use of solid biomass fuel for cooking food, a trend and a job done mostly by females all across India.[33] Since unlike contents of tobacco smoke the details of various chemicals present in commonly used biofuels in rural India are yet not analyzed their individual mechanism as oxidants in pathogenesis of COPD requires further investigation.

CONCLUSIONS

Our study confirmed the presence of an oxidant-antioxidant imbalance in COPD subjects supporting the concept of systemic oxidative stress in this condition.

ACKNOWLEDGEMENT

The authors wish to convey their gratitude Dr. Subir Kumar Dey, Former Professor and Head of the Department, Dept. of Pulmonary Medicine, Calcutta National College, Kolkata, West Bengal.

REFERENCES

[1] Global strategy for diagnosis, management, and prevention of COPD. Global initiative for chronic obstructive lung disease (GOLD). [Cited 2014 January]. http://www.goldcopd.org.
[2] COPD predicted to be third leading cause of death in 2030. Geneva: Global alliance against chronic respiratory disease, WHO statistics 2008. [Cited 2008 May 20]. http://www.who.int/gard/news_events/World_Health_Statistics_2008/en/
[3] Jindal SK, Aggarwal AN, Chaudhry K, et al. A multicentric study on epidemiology of chronic obstructive pulmonary disease and its relationship with tobacco smoking and environmental tobacco smoke exposure. Indian J Chest Dis Allied Sci 2006;48(1):23-9.

[4] Jindal SK, Aggarwal AN, Gupta D. A review of population studies from India to estimate national burden of chronic obstructive pulmonary disease and its association with smoking. Indian J Chest Dis Allied Sci 2001;43(3):139-47.
[5] Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet 2009;374(9691):733-43.
[6] MacNee W. Pathogenesis of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005;2(4):258-66.
[7] MacNee W, Rahman I. Is oxidative stress central to the pathogenesis of chronic obstructive pulmonary disease? Trends Mol Med 2001;7(2):55-62.
[8] Rajendrasozhan S, Yang SR, Edirisinghe I, et al. Deacetylases and NF-kappa B in redox regulation of cigarette smoke induced lung inflammation: epigenetics of pathogenesis of COPD. Antioxid Redox Signal 2008;10(4):799-811.
[9] Sadeghi-Hashjin G, Folkerts G, Henricks PA, et al. Peroxynitrite induces airway hyperresponsiveness in guinea pigs in vitro and in vivo. Am J Respir Crit Care Med 1996;153(5):1697-701.
[10] Rahman I, Gilmour PS, Jimenez LA, et al. Oxidative stress and TNF-alpha induce histone acetylation and NF-κb/AP-1 activation in alveolar epithelial cells: potential mechanism in gene transcription in lung inflammation. Mol Cell Biochem 2002;234-235(1-2):239-48.
[11] Ji C, Amarnath V, Pietenpol JA, et al. 4-hydroxynonenal induces apoptosis via caspase-3 activation and cytochrome C release. Chem Res Toxicol 2001;14(8):1090-96.
[12] Murray RK. Red & White blood cells. In: Murray RK, Granner DK, Mayes PA, et al. eds. Harper's Illustrated Biochemistry. 26th edn. India: McGraw-Hill Companies Inc., 2003;52:609-13.
[13] Lakari E, Paakko P, Kinnula VL. Manganese superoxide dismutase, but not CuZn superoxide dismutase, is highly expressed in the granulomas of pulmonary sarcoidosis and extrinsic allergic alveolitis. Am J Respir Crit Care Med 1998;158(2):589-96.
[14] Smith LJ, Houston M, Anderson J. Increased levels of glutathione in bronchoalveolar lavage fluid from patients with asthma. Am Rev Respir Dis 1993;147(6 Pt 1):1461-4.
[15] Cavalcante A, De Bruin PF. The role of oxidative stress in COPD: current concepts and perspectives. J Bras Pneumol 2009;35(12):1227-37.
[16] Owen CA. Proteinases and oxidants as targets in the treatment of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005;2(4):373-85.
[17] Devasagayam TPA, Boloor KK, Ramasarma T. Methods for estimating lipid peroxidation: an analysis of merits and demerits. Indian Journal of Biochemistry & Biophysics 2003;40(5):300-8.
[18] Marklund S, Marklund G. Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase. European Journal of Biochemistry 1974;47(3):469-74.
[19] Beutler E, Duron O, Kelly BM. Improved method for the determination of blood glutathione. J Lab Clin Med 1963;61:882-8.
[20] Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease. Oxidative Stress Study Group. Am J Respir Crit Care Med 1997;156(2 Pt 1):341-57.
[21] Halliwell B. Oxidant and human disease: some new concepts. FASEB J 1987;1(5):358-64.
[22] American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152(5 Pt 2):S77-121.
[23] Smith KR, Aggarwal AL, Dave RM. Air pollution and rural biomass fuels in developing countries: a pilot village study in India and implications for research and policy. Atmospheric Environment 1983;17(11):2343-62.
[24] Ceylan E, Kocygit A, Gencer M, et al. Increased DNA damage in patients with chronic obstructive pulmonary disease who had once smoked or been exposed to biomass. Respiratory Medicine 2006;100(7):1270-6.
[25] Montano M, Cisneros J, Ramirez-Venegas A, et al. Malondialdehyde & superoxide dismutase correlate with FEV (1) in patients with COPD associated with wood smoke exposure and tobacco smoking. Inhal Toxicol 2010;22(10):868-74.
[26] Rai RR, Phadke MS. Plasma oxidant-antioxidant status in different respiratory disorders. Indian J Clin Biochem 2006;21(2):161-4.
[27] Nagaraj, Chandrakanth KH, Anand P, et al. Oxidative stress and antioxidant status in chronic obstructive pulmonary disease patients. IJPBS 2011;1(4):447-56.
[28] Ahmad A, Shameem M, Husain Q. Altered oxidant-antioxidant levels in the disease prognosis of chronic obstructive pulmonary disease. International Journal of Tuberculosis & Lung Diseases 2013;17(8):1104-9.
[29] Van der Toorn M, Smit-de Vries MP, Slebos DJ, et al. Cigarette smoke irreversibly modifies glutathione in airway epithelial cells. Am J Physiol Lung Cell Mol Physiol 2007;293(5):L1156-62.
[30] McCord JM, Fridovich I. Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein). J Biol Chem 1969;244(22):6049-55.
[31] Rahman I, MacNee W. Oxidant/antioxidant imbalance in smokers and chronic obstructive pulmonary disease. Thorax 1996;51(4):348-50.
[32] Bizoń A, Milnerowicz H. Effect of tobacco smoking on glutathione concentration in the blood. Przegl Lek 2012;69(10):809-11.
[33] Brashier B, Kajale S, Tambe S, et al. High resolution CT scan (HRCT) thorax, differences between biomass smoke exposure induced COPD (BM COPD) and tobacco-smoking COPD (TS COPD). Eur Respir J 2012;40:P268.

Original Article

DOI: 10.7860/JCDR/2018/35651.11666

Public Health Section

CBNAAT Co-Testing of Sputum and BAL Fluid with Sputum Microscopy: May it Halt the March of Tuberculosis !

AMIYA KUMAR DWARI[1], SUMANTA JHA[2], DIBAKAR HALDAR[3], BISANKA BISWAS[4], SANJAY KUMAR SAHA[5], PARTHA PRATIM ROY[6], ABHIJIT MANDAL[7], BAISAKHI MAJI[8]

ABSTRACT

Introduction: Growing concern for Tuberculosis (TB) epidemic forces World Health Organization (WHO) and government of India (GOI) to incorporate newer rapid and highly specific diagnostic test like Cartridge Based Nucleic Acid Amplification Test (CBNAAT).

Aim: To find the usefulness of CBNAAT in increasing Acid Fast Bacilli (AFB) positive patient pool over and above the yield of traditional sputum microscopy.

Materials and Methods: The cross-sectional survey was conducted in the Department of Respiratory Medicine, Nilratan Sircar Medical College and Hospital (NRSMCH), Kolkata, India. The study involved 94 smear negative TB suspects referred from other health facilities as well as diagnosed by the department itself. After collecting baseline information like age, sex, previous history of TB and its treatment by interview and scrutinizing records using predesigned questionnaire, the patients were put on sputum CBNAAT and Broncho-Alveolar Lavage (BAL)-CBNAAT testing. Data were analysed by estimating mean, Standard Deviation (SD), proportion and using independent t-test, chi-square test.

Results: Overall, average age of participants was 44.7±15.3 (mean±SD) years. Male-female ratio was 1:2.8. Altogether 44.7% patients were detected sputum positive out of which 34.0% were detected only by sputum CBNAAT and another 10.7% detected when BAL-CBNAAT testing was used among the negatives yielded from sputum CBNAAT only. These differences were statistically significant.

Conclusion: Utility of CBNAAT over and above traditional diagnostic methods was reaffirmed. With added advantage of detecting MDR cases simple, sensitive, speedy and automated CBNAAT seems new mile stone in 'Stop TB' strategy and needs utilised to its highest potentiality through monitoring and supervision.

Keywords: Drug resistant tuberculosis, Lavage, Nucleic acid amplification, Sputum microscopy

INTRODUCTION

In May, 2012 India declared TB a notifiable disease [1]. TB can present with clinical features and some radiologic findings indistinguishable from those of Community-Acquired Pneumonia (CAP) [2]. Revised National Tuberculosis Control Programme (RNTCP) guidelines seemingly motivate physicians waiting 02 weeks before initiating diagnostic investigations for presumptive tuberculosis [3]. During this interval, clinicians usually prescribed courses of antibiotics for lower respiratory tract infection before pulmonary TB is correctly diagnosed [4]. It fosters development of antimicrobial resistance apart from Adverse Drug Reactions (ADRs), financial burden and emotional turbulence to patients and spreading of TB in the mean time. Initial sputum negatives were further put on antibiotic treatment for 10-14 days and provided with repeat sputum smear for AFB if symptoms persist. Finally, with radiological findings the patient is categorised as sputum negative TB [3]. Thus, the patients have got the scope for spreading disease for almost 3 weeks or more whatever may be the intensity of transmission.

Being simple, rapid yielding, Sputum Microscopy (SM) has been the main diagnostic tool for nearly a century, followed by sputum culture, the 'gold standard'. However, both tools have limitations like sensitivity (as low as 50%) of SM and 2-6 weeks duration to obtain results of culture [5]. Though cheap (costs USD 0.50) and highly specific, the low sensitivity of SM is further reduced in patients with extra-pulmonary TB, children and HIV/TB co-infected patients [6]. The smear negative TB also spreads the disease and only tool for diagnosing has been chest X-ray with low specificity [7].

Accurate and prompt diagnosis of all cases is required for control of TB and can only be achieved through affordable newer diagnostic tools. It may help reduce the direct costs of diagnostic burden on patients and their families and also help national TB control programs to start early treatment. For this purpose SM shouldn't be relied upon as a primary diagnostic tool (being so in resource limited settings) because of its high yield of false negatives [6]. The CBNAAT is one of these newer methods that simultaneously identifies Mycobacterium tuberculosis and detects rifampicin resistance as a surrogate of MDR, directly from clinical specimens. Since December 2010, WHO has recommended the CBNAAT as a bonafide test due to its high-quality performance as compared to SM, especially in cases of smear-negative cases [8]. It has high sensitivity and specificity and results can be obtained much quicker but at the expense of high cost (USD 25-30) [6]. Although SM exhibits low sensitivity on fiberoptic bronchoscopy samples with 5-35% on Bronchial Aspirates (BA) and 10-30% on BAL, CBNAAT of BAL has been established as a good diagnostic tool for the purpose of bacteriological confirmation of TB suspects who were otherwise sputum negative or could not produce adequate sputum for SM [7].

Studies have already established its utility in Indian perspective with more than 90% sensitivity and 90-100% specificity [9,10]. Indian guidelines on TB care are envisaged in RNTCP 'National strategic plan for TB control 2012-2017' [11]. RNTCP is currently using Xpert MTB/RIF to diagnose Pulmonary TB, Paediatric TB, Extrapulmonary TB and Rifampicin resistance and MDRTB in high risk populations like HIV positives as recommended by WHO under 2013 policy recommendations [12-14]. The present study aim to find the effectiveness of CBNAAT test in detecting the AFB positivity among the smear negative TB patients.

MATERIALS AND METHODS

A cross-sectional survey was carried out from October, 2016 to March, 2017 in the Department of Respiratory Medicine situated at Nilratan Sircar Medical College and Hospital (NRSMCH), Kolkata. The hospital has CBNAAT facility and acts as a referral unit for providing the opportunity of this test, specially to all the smear negative TB cases referred to as well as those who were self-reporting to the Department of Respiratory Medicine.

94 radiologically suspected sputum negative TB cases either referred from other health facilities or diagnosed in the Department of Respiratory Medicine, NRSMCH, Kolkata, were included in the present study. After obtaining informed consent, the patients were interviewed using a predesigned questionnaire for collecting baseline information like age, sex, history of TB and its treatment etc. Relevant records were also scrutinised. Then, each of them were subjected to sputum CBNAAT.

Those who were found still AFB negative were further put on BAL-CBNAAT testing. Finally, the patients were categorised either into CBNAAT positive or CBNAAT negative TB and the referred patients were sent back to their original health facilities and those diagnosed at Department of Respiratory Medicine, NRMCH were put on TB treatment as per the RNTCP guidelines. The study was conducted after obtaining the approval of Institutional Ethics Committee.

Collected data were compiled in Microsoft (MS) excel sheet and analysed using statistical package for Social Science (SPSS) version-22. Continuous variables were described by mean, SD and the categorical ones were by proportion. Continuous data were tested for normality distribution by Shapiro-Wilk's test. Tables and charts were used for displaying data. Interrelationship among the variables was determined by inferential statistical test like chi-square ($\chi 2$) test, Fisher's-exact test, Odds Ratio (OR) with its 95% Confidence Interval (CI). A p-value less than 0.05 was considered statistically significant at 95% confidence limit.

RESULTS

Data collected from 94 sputum negative patients were analysed. Continuous data were found to follow normal distribution as reflected by normality test.

Half of the patients belonged to 41-60 years age group followed by 32.9% in 21-40 years group. The females were significantly higher in 21-40 years group compared to >60 years group containing no women participants [Table/Fig-1].

Age category (year)	Gender			$\chi 2$	p-value at df 1
	Male No. (%)	Female No. (%)	Total No. (%)		
Up to 20	5 (83.3)	1 (16.7)	6 (100.0)	@	0.375
21-40	16 (51.6)	15 (48.4)	31 (100.0)	7.63	0.005
41-60	38 (80.9)	9 (19.1)	47 (100.0)	2.27	0.131
>60	10 (100.0)	-	10 (100.0)	*	*
Total	69 (73.4)	25 (26.6)	94 (100.0)	---	----

[Table/Fig-1]: Distribution of participants as per age category and gender (N=94). *Reference group, df: Degree of freedom; @ Fisher-exact test (two tailed)

Overall, average age was estimated to be 44.7±15.3 (mean±SD) with a range of 15-87 years. The corresponding values across the gender were 47.3±16.0, 17-60 years versus 44.7±15.3 and 15-87 years in males and females, respectively. As per independent t-test the female participants were significantly younger than their counterpart (t=2.821 at df 92 with p-value of 0.006). Eight (8.5%) patients had previous history of TB.

Either sputum CBNAAT or BAL-CBNAAT examination over and above the SM was found to be significantly more effective in regard to clinical benefit for guiding in the management of TB patients [Table/Fig-2]. Both the newer tools together provided a total 42 positive cases (32 in sputum- CBNAAT + 10 in BAL-CBNAAT) out of 94 patients revealed to be negative in SM. It was a statistically significant yield over and above SM {$\chi 2$=54.1 at df 1 with p-value of 0.000; OR=0.00 (0.00-0.07)}. However, the effectiveness of BAL-CBNAAT providing a yield of 10 positive cases out of 62 patients found negative in sputum-CBNAAT was also shown to be statistically significant {$\chi 2$=10.88 at df 1 with p-value of 0.0009; OR=0.00 (0.00-0.47)} .

Laboratory method	Results			$\chi 2$, df, p	OR (95% CI)
	Positive No. (%)	Negative No. (%)	Total No. (%)		
Sputum microscopy	0	94 (100)	94 (100)	*	1
Sputum CBNAAT	32 (34.0)	62(66.0)	94(100.0)	38.56,1,0.000	0.00 (0.00-0.11)
BAL-CBNAAT	10(16.1)	52(83.9)	62(100.0)	16.20,1,0.000	0.00 (0.00-0.3)

[Table/Fig-2]: Distribution of participants as per results of sputum CBNAAT and BAL-CBNAAT.

Attributes		AFB Negative	AFB Positive	Total	$\chi 2$, df	p-value
Sputum CBNAAT						
Sex	Female	19	6	25	1.530,1	0.216
	Male	43	26	69		
Total		62	32	94	----------	----------
BAL-CBNAAT						
Sex	Female	21	2	23	1.494,1	0.222
	Male	31	8	39		
Total		52	10	62	---------	----------

[Table/Fig-3]: Distribution of patients as per gender and CBNAAT results (N=94).

Test results of sputum CBNAAT and BAL-CBNAAT were found not to differ significantly across the gender [Table/Fig-3]. Even, both the yields together failed to reveal any significant difference across the gender {χ^2=2.22 at df 1 with p-value of 0.137; OR=0.48 (0.16-1.39)}.

DISCUSSION

TB control guidelines developed by Centres for Disease Control and Prevention (CDC), United States, recommends CBNAAT for at least one respiratory specimen of patients having clinical features suggestive of pulmonary TB and for whom diagnostic endeavour is going on but yet to confirm [15]. Similarly, Korean guidelines for management and control of TB adopted strategy for Nucleic Acid Amplification (NAA) testing in combination with SM for AFB and culture at least once for the pulmonary TB suspects [16].

CBNAAT should not be thought as a substitute for culture and SM. However, it can act as an adjuvant of traditional tests and clinical data for confirming TB. It cannot be used for monitoring the therapeutic response as it can produce false-positive results in presence of non-viable TB bacteria; though identification of M. tuberculosis out of Non-Tubercular Mycobacterium (NTM) is possible by it [17]. Thus, CBNAAT is helpful diagnostic armamentarium towards AFB smear-positive patients for rapidly detection of pulmonary TB and getting it differentiated from NTM [18]. In the present study 34% yield was obtained out of CBNAAT test.

However, a study conducted by Avashia S et al., reported 47.2% gain in respect of sputum positivity among smear negative TB cases [7]. The results of the present study have concurrence with this where 34.0% yield for sputum CBNAAT, 10.7% for BAL-CBNAAT and together it was 44.7%. This 10.7% increase in the yield arising out of BAL-CBNAAT over and above the yield of sputum CBNAAT was also revealed to be statistically significant. Here, the yield of 10.7% sputum positive patients would be taken as a major gain from the epidemiological point of view so far as the transmission of TB concerns.

A Cochrane systematic review done in 2013 showed high accuracy of CBNAAT compared to culture. It showed about 88% sensitivity and 98% specificity for pulmonary TB in adults. Among smear-negative TB patients, Xpert had a sensitivity of 67% [19]. Ioannidis

P et al., reported that GeneXpert MTB/RIF assay has positive predictive values for pulmonary and extra-pulmonary samples 93.5% and 50%, whereas negative predictive values for those are 91.7% and 100%, respectively. In case of microscopically negative specimens, the figures are 79% and 95.6% [20].

From their research conducted in 2012, Moure R et al., concluded that out of 108 smear-negative extrapulmonary samples 58.3% were positive with the Xpert MTB/RIF assay (GX) for Mycobacterium tuberculosis [21]. Vadwai V et al., carried out a similar study in 2011 and observed the sensitivity of the Xpert assay as 64% for smear-negative TB cases [22].

In a study on 132 patients in a single South-Korean centre Lee HY et al., reported sensitivity and specificity values for Xpert MTB/RIF assay and smear microscopy in the level of 81.6% and 100.0% versus 13.2% and 98.8% respectively compared to the culture [23]. In their South-African single-centre study involving 154 suspected TB patients, Theron et al., analysed the BAL samples in which sensitivity and specificity values compared to the culture were 92.6% and 96.0% for the Xpert MTB/RIF assay, and 57.7% and 99.3% for SM, respectively [24]. Palud PL et al., observed 80.0% and 98.6% sensitivity and specificity for the Xpert MTB/RIF assay as compared to culture [25].

LIMITATION

The participants were less in number restricting the external validity of the study. Radiologically suspected smear negative TB patients were considered for present study and the sensitivity as well as specificity of the CBNAAT tool could not have been estimated in this setting by comparing its effectiveness with that of the 'gold standard' i.e., culture.

CONCLUSION

Present study reaffirmed the usefulness of the CBNAAT over and above the traditional smear microscopy for a significantly higher yield. It leads to early detection and treatment of TB for stopping the transmission of the disease in the community. BAL-CBNAAT shows additional advantage of confirmatory diagnosis of the disease even if sputum CBNAAT is negative. Simplicity, sensitivity, speed and automation of CBNAAT makes this technique a very attractive tool for diagnosis of Mycobacterium tuberculosis from smear negative cases of TB suspects. With the added advantage of detection of multi-drug resistant cases, it seems to be another mile stone in 'Stop TB' strategy and needs to be utilised to its highest potential level through monitoring and supportive supervision at every level of RNTCP. Grass-root level workers, program implementers and managers require necessary re-orientation and motivation for integrated actions for maximum achievement.

REFERENCES

[1] "TB India 2016 Revised National TB Control Programme Annual Status Report", New Delhi, 2016 www.tbcindia.nic.in (http://www.tbcindia.nic.in/).
[2] Woodring JH, Vandiviere HM, Fried AM, Dillon ML, Williams TD, Melvin IG. Update: the radiographic features of pulmonary tuberculosis. AJR Am J Roentgenol. 1986;146:497-506.
[3] Govt. of India (2010), TB India 2010, RNTCP Status report, Central TB Division, Ministry of Health and Family Welfare, New Delhi.
[4] Grossman RF, Hsueh PR, Gillespie SH, Blasi F. Community-acquired pneumonia and tuberculosis: differential diagnosis and the use of fluoroquinolones. Int J Infect Dis. 2014;18:14-21.
[5] World Health Organization. Global tuberculosis report 2014. Geneva: WHO; [1] 2014. Available from: http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1
[6] Sagili K, Shringarpure K, Nilgiriwala K, Muniyandi K. Cost-effectiveness of GeneXpert, LED FM and chest X-ray for diagnosis of pulmonary tuberculosis: a systematic review and meta-analysis. PROSPERO 2016:CRD42016043333 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp? ID=CRD42016043333
[7] Avashia S, Choubey S, Mishra S, kharate A. To study the usefulness of CBNAAT (cartridge based nuclear acid amplification test) in BAL (bronchoalveolar lavage) samples in the diagnosis of smear-negative/non sputum producing patients with suspected tuberculosis. J Evolution Med Dent Sci. 2016;5(1):55-59.
[8] World Health Organization: WHO report 2010: global tuberculosis control. Geneva, Switzerland: WHO; 2010.
[9] Sharma SK, Kohli M, Yadav RN, Chaubey J, Bhasin D, Sreenivas V, et al. Evaluating the diagnostic accuracy of Xpert MTB/RIF assay in pulmonary tuberculosis. PLoS One. 2015;10(10):e0141011.
[10] Agrawal M, Bajaj A, Bhatia V, Dutt S. Comparative study of GeneXpert with ZN stain and culture in samples of suspected pulmonary tuberculosis. Journal of Clinical and Diagnostic Research. 2016;10(5):9-12.
[11] Chaudhuri AD. Recent changes in technical and operational guidelines for tuberculosis control programme in India-2016: A paradigm shift in tuberculosis control. J Assoc Chest Physicians. 2017;5:1-9. Available at: http://www.jacpjournal.org on Thursday, October 5, 2017, IP: 101.63.4.154.
[12] Tuberculosis. WHO Global Tuberculosis Report 2014. http://www.who.int/tb/publications/factsheet_global.pdf
[13] Automated Real-Time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF Assay for the Diagnosis of Pulmonary and Extrapulmonary TB in Adults and Children: Policy Update. Geneva: World Health Organization; Issued date 2013.
[14] Guidance document for use of Catridge Based-Nucleic Acid Amplification Test (CB-NAAT) under Revised National TB Control Programme (RNTCP) issued central TB division, directorate general of health services September 2013.
[15] Greco S, Girardi E, Navarra A, Saltini C. Current evidence on diagnostic accuracy of commercially based nucleic acid amplification tests for the diagnosis of pulmonary tuberculosis. Thorax. 2006;61:783-90.
[16] Joint Committee for the Revision of Korean Guidelines for Tuberculosis, Korea Centers for Disease Control and Prevention. Korean guidelines for tuberculosis. 2nd ed. Seoul and Cheongwon: Joint Committee for the Revision of Korean Guidelines for Tuberculosis, Korea Centers for Disease Control and Prevention; 2014.
[17] Centers for Disease Control and Prevention (CDC). Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. MMWR Morb Mortal Wkly Rep. 2009;58:7-10.
[18] Kwon YS, Koh WJ. Diagnosis of pulmonary tuberculosis and nontuberculous mycobacterial lung disease in Korea. Tuberc Respir Dis. 2014;77:1-5.
[19] Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M, et al. Cochrane Library 2013 http://doi.wiley.com/10.1002/14651858.CD009593.pub2
[20] Ioannidis P, Papaventsis D, Karabela S, Nikolaou S, Panagi M, Raftopoulou E, et al. Cepheid GeneXpert MTB/RIF assay for mycobacterium tuberculosis detection and rifampin resistance identification in patients with substantial clinical indications of tuberculosis and smear-negative microscopy results. Journal of Clinical Microbiology. 2011;49(8):3068-70.
[21] Moure R, Martín R, Alcaide F. Effectiveness of an integrated real-time PCR method for detection of the mycobacterium tuberculosis complex in smear-negative extrapulmonary samples in an area of low tuberculosis prevalence. J Clin Microbiol. 2012;50(2):513-15.
[22] Vadwai V, Boehme C, Nabeta P, Shetty A, Alland D, Rodrigues C. Xpert MTB/RIF, a New Pillar in diagnosis of extrapulmonary tuberculosis? J Clin Microbiol. 2011;49(7):2540-45.
[23] Lee HY, Seong MW, Park SS, Hwang SS, Lee J, Park YS, et al. Diagnostic accuracy of Xpert MTB/RIF on bronchoscopy specimens in patients with suspected pulmonary tuberculosis. Int J Tuberc Lung Dis. 2013;17(7):917-21.
[24] Theron G, Peter J, Meldau R, Khalfey H, Gina P, Matinyena B, et al. Accuracy and impact of Xpert MTB/RIF for the diagnosis of smear negative or sputum-scarce tuberculosis using bronchoalveolar lavage fluid. Thorax. 2013;68(11):1043-51.
[25] Palud PL, Cattoir V, Malbruny B, Magnier R, Campbell K, Oulkhouir Y, et al. Retrospective observational study of diagnostic accuracy of the Xpert® MTB/RIF assay on fiberoptic bronchoscopy sampling for early diagnosis of smear-negative or sputum-scarce patients with suspected tuberculosis. BMC Pulmonary Medicine. 2014;14:137.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Respiratory Medicine, NRS Medical College, Kolkata, West Bengal, India.
2. Assistant Professor, Department of Respiratory Medicine, NRS Medical College, Kolkata, West Bengal, India.
3. Associate Professor, Department of Community Medicine, Bankura Sammilani Medicak College, Bankura, West Bengal, India.
4. Post Graduate Trainee, Department of Community Medicine, Bankura Sammilani Medicak College, Bankura, West Bengal, India.
5. Assistant Professor, Department of Community Medicine, Bankura Sammilani Medicak College, Bankura, West Bengal, India.
6. Professor, Department of Respiratory Medicine, NRS Medical College, Kolkata, West Bengal, India.
7. Professor, Department of Respiratory Medicine, NRS Medical College, Kolkata, West Bengal, India.
8. Demonstrator, Department of Community Medicine, Bankura Sammilani Medicak College, Bankura, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Dibakar Haldar,
Associate Professor, Department of Community Medicine, Anandapally, Sitko Road, Duttapara, Baruipur, Kolkata-700144, West Bengal, India.
E-mail: dibahaldar@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jan 25, 2018**
Date of Peer Review: **Mar 27, 2018**
Date of Acceptance: **Apr 10, 2018**
Date of Publishing: **Jun 01, 2018**

Sleep and Vigilance
https://doi.org/10.1007/s41782-025-00304-y

ORIGINAL ARTICLE

Oxygen Desaturation Index in Patients of OSA: Correlation with Sleepiness and Hypertension

Sumanta Jha[1] · Shibdas Chakrabarti[1] · Tanmaya Talukdar[1] · Rohit Kumar[1] · Rajnish Kaushik[1] · Nitesh Gupta[1] · Pranav Ish[1]

Received: 12 November 2024 / Revised: 21 February 2025 / Accepted: 1 March 2025

Abstract

Introduction Excessive Daytime Sleepiness (EDS) is commonly associated with underlying Obstructive Sleep Apnea (OSA). Several studies concluded a high hypoxic burden in OSA patients with EDS. Intermittent hypoxia in OSA patients leads to oxidative stress, systemic, and vascular inflammation with endothelial dysfunction, and sympathetic activation, contributing to multiorgan comorbidities.

Materials and methods This prospective observational study was done in a tertiary care hospital with a facility of level 1 polysomnography with CPAP titration. A total of 120 adult patients with typical OSA symptoms were included. Patients were classified into mild (ESS ≤ 8), moderate (9–14), and severe (15–24) groups in terms of severity of sleepiness based on Epworth Sleepiness Scale(ESS) score. Demographic and anthropometric data, vitals, and comorbidities were recorded. Arterial blood gas (ABG) analysis, spirometry, thyroid function test, lipid profile, and HbA_1C were done in each patient. A 3% Oxygen Desaturation Index (ODI), an indicator of hypoxic burden, was compared with the Apnea Hypopnea Index (AHI) in predicting the severity of sleepiness in OSA patients.

Results The current study showed ODI (r 0.340, p 0.0002) has a stronger correlation with ESS score than AHI (r 0.218, p 0.017). The ESS score also showed a positive correlation with desaturation below 90% (r 0.236, $p = 0.010$) and a weak negative correlation with SpO_2 nadir ($r -0.184$, p 0.045). A strong positive correlation between AHI and ODI (r 0.903 $p < 0.0001$) was found. A significant association of AHI (p 0.033), ODI (p 0.001), and desaturation below 90% (p 0.03) with ESS score was also found. The current study concluded a significant positive correlation of prevalent hypertension with both ODI (r 0.311, p 0.001) and AHI (r 0.330, p 0.0002).

Conclusion This study concluded stronger correlation of ODI with ESS score than AHI and significant positive correlation of prevalent hypertension with both ODI and AHI. Good concordance between ODI and AHI suggests a promising role of modern fingertip pulse oximetry in predicting OSA in patients with high pretest probability of severe OSA.

Keywords OSA · EDS · ESS score · AHI · ODI · Hypertension

✉ Pranav Ish
pranavish2512@gmail.com

Sumanta Jha
sumantajha@gmail.com

Shibdas Chakrabarti
shibdas1@yahoo.co.in

Tanmaya Talukdar
8talukdar@gmail.com

Rohit Kumar
dr.rohitkumar@mail.com

Rajnish Kaushik
drrajnishkaushik@gmail.com

Nitesh Gupta
niteshgupta2107@gmail.com

[1] Department of Pulmonary Medicine, Critical Care and Sleep Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

Published online: 18 March 2025

1 Introduction

Obstructive Sleep Apnea (OSA) is the most common Sleep-Related Breathing Disorder (SRBD). OSA is a heterogeneous and complex disease associated with Excessive Daytime Sleepiness (EDS), impaired cognitive performance, reduced quality of life, metabolic dysfunction, cardiovascular morbidity, and mortality. However, up to 25–50% of OSA patients do not report subjective sleepiness [1]. Fragmentation of sleep due to multiple arousals at the termination of hypopneas or apneas, disrupted rapid eye movement (REM) and slow wave sleep [2, 3], repeated hypoxia-induced cell loss in the wake promoting neural networks, and hypoxia- and hypercapnia-induced orexin neuron activity inhibition often led to EDS in OSA patients. Several studies concluded a high hypoxic burden in OSA patients with EDS, as reflected by lower oxygen saturation indices in polysomnograms. Although AHI is considered the gold standard for diagnosing and assessing the severity of OSA, it does not contain information about the duration of respiratory events and the degree of related oxygen desaturation. The 3% Oxygen Desaturation Index (ODI) is defined by the number of events per hour in which oxygen saturation decreases by 3% or more from baseline. As oxygen desaturation is not a prerequisite for apnea and hypopnea, AHI and ODI values will be different, especially where arousal forms part of the definition of respiratory events. So, the hypoxic burden and physiological stress levels can be very different in patients with similar AHI. Although AHI is gold standard in assessing severity of OSA, it does not always reflect the magnitude of hypoxic burden, rather ODI is a more accurate predictor of magnitude of hypoxia. Several studies have shown no significant correlation between AHI and sleepiness [4, 5]. Oxygen saturation indices like Oxygen desaturation index (ODI), SpO_2 nadir, average SpO_2, the sum of all desaturations, desaturations below 90%, total arousal index, and respiratory arousal index have recently attracted interest as a more accurate predictor of OSA severity. In a retrospective analysis of polysomnographic data of 321 patients by Dastan Temirbekov et al. [6], a stronger correlation was found between ODI and ESS, higher than between AHI and ESS ($r = 0.504$ and $r = 0.435$, respectively) and a positive correlation was found between AHI and ODI ($p < 0.05$). A study by Siraj Omar Wali et al. [7] concluded that desaturation Index, respiratory arousal index, and SpO_2 nadir were independent predictors of OSA severity.

Intermittent hypoxia in OSA leads to oxidative stress, systemic, and vascular inflammation with endothelial dysfunction, and sympathetic activation, contributing to multiorgan comorbidities, Several population-based studies [8–11], but not all found an association between OSA and hypertension independent of potential confounders. The European Sleep Apnea Project study revealed that the 4% oxygen desaturation index (ODI) was superior to AHI in predicting hypertension [12].

The current study was undertaken to analyze whether ODI has a stronger correlation with subjective sleepiness and hypertension than AHI in OSA patients.

2 Materials and Methods

This study was performed in the Department of Pulmonary, Critical Care & Sleep Medicine of a tertiary hospital with a facility of level 1 PSG with CPAP titration. It was a prospective, observational study over 18 months with sample size of 120. Ethical clearance was taken from the appropriate authority. Adult patients attending the outpatient department/admitted in the ward with typical OSA symptoms were included in this study; patients with mandibular advancement devices and those already on PAP therapy before diagnosis of OSA were excluded. Patients on sedatives, anxiolytics, antidepressants, anticonvulsants, antipsychotics, and systemic steroids which can interfere with sleep architecture were excluded.

Written informed consent was taken from each eligible patient. Demographic and anthropometric data and vitals were recorded. Patients were classified into mild (ESS ≤ 8), moderate (9–14), and severe (15–24) groups in terms of severity of sleepiness based on ESS score. Risk stratification for OSA was done using the Berlin Score and STOP-BANG questionnaire. Details of comorbidities were recorded along with ongoing treatment. Single blood pressure measurements in a sitting position at our center (possibility of "white coat" effect) were not used to diagnose hypertension; instead, self-reported hypertensive patients already on medication were considered hypertensive in this study. Incidence of any accident because of sleepiness was recorded. Baseline arterial blood gas analysis, spirometry, lipid profile, thyroid function test, Fasting blood sugar (FBS), postprandial blood sugar (PPBS), and glycosylated hemoglobin (HbA_1C) were performed in each patient. Each patient had undergone Level 1 overnight Polysomnography (PSG) with CPAP titration in our sleep lab. PSGs of total sleep time (TST) of at least 240 min and who went into REM sleep were considered for analysis. Patients with AHI < 5 were excluded from this study. Along with AHI, ODI, SpO_2 nadir, average SpO_2, desaturation below 90%, and total and respiratory arousal indexes were recorded for analysis. ODI was compared with AHI in predicting the severity of sleepiness (based on ESS score) in OSA patients. Whether ODI has a stronger correlation with hypertension in OSA patients compared to AHI had been analyzed.

2.1 Statistical Analysis

The categorical variables are presented in numbers and percentages (%). On the other hand, the quantitative data are presented as the means ± SD and median with interquartile range. The data normality was checked by using the Shapiro–Wilk test. Non-parametric tests were used where the data were not normal. The association of the variables that were quantitative and not normally distributed in nature was analyzed using Mann–Whitney test (for two groups) and Kruskal–Wallis test (for more than two groups), and variables that were quantitative and normally distributed in nature were analyzed using an independent t test (for two groups) and ANOVA (for more than two groups). The association of the qualitative variables was analyzed using the Chi-Square test. Fisher's exact test was used if any cell had an expected value of less than 5. Receiver operating characteristic curve was used to assess cut off point, sensitivity, specificity, positive predictive value, and negative predictive value of ODI for predicting AHI ≥ 30. The Spearman rank correlation coefficient was used to correlate the ESS with ODI and AHI and between ODI and AHI. Bland–Altman plot was used to compare ODI and AHI. Point biserial correlation was used to assess the correlation of hypertension with ODI and AHI. Z statistics were used to compare the correlation of hypertension with ODI and AHI. The data entry was done in the Microsoft Excel spreadsheet, and the final analysis was done using the Statistical Package for Social Sciences (SPSS) software from IBM manufacturer, Chicago, USA, version 25.0. For statistical significance, a p value of less than 0.05 was considered statistically significant.

3 Result and Analysis

Out of 120 patients included in this study, 75% of patients were male, 25% were female. 93.33% of patients were in the 31 to 70 years age group. The mean age was 51.47 ± 11.17 years. 7.5%, 33.33%, and 58.33% cases were normal, overweight, and obese, respectively, as per WHO classification, with a mean BMI of 31.75 ± 5.98 kg/m^2. Mean height, weight, neck, hip, and waist circumference were 164.32 ± 8.35 cm, 85.73 ± 16.90 kg, 16.67 ± 1.17 inches, 41.17 ± 3.00 inches, and 39.25 ± 3.48 inches, respectively (Table 1). Subjective sleepiness was assessed by ESS score, and patients were classified into mild (ESS score ≤ 8), moderate (ESS score 9–14), and severe (ESS score 15–24) groups; the mean ESS score was 12.12 ± 6.02. Mild, moderate, and severe sleepiness was reported by 37(30.83%), 42(35.00%), and 41(34.17%) patients, respectively (Table 2). 92.50% of patients reported snoring, followed by tiredness/fatigue (82.50%) and observed apnea (52.50%). The current study found no statistically significant differences in demographic and anthropometric characteristics between

Table 1 Anthropometric parameters distribution in patients

Anthropometric parameters	Frequency	Percentage (%)
Body mass index (kg/m^2)		
< 18.5 kg/m^2 {Underweight}	1	0.83
18.5 to 24.99 kg/m^2 {Normal BMI}	9	7.50
25 to 29.99 kg/m^2 {Overweight}	40	33.33
≥ 30 kg/m^2 {Obese}	70	58.33
Mean ± SD	31.75 ± 5.98	
Median (25th–75th percentile)	31.15 (27.675–34.925)	
Height (cm)		
Mean ± SD	164.32 ± 8.35	
Median (25th–75th percentile)	165 (158–170)	
Weight (kg)		
Mean ± SD	85.73 ± 16.90	
Median (25th–75th percentile)	86 (73.25–95)	
Neck circumference (inches)		
Mean ± SD	16.67 ± 1.17	
Median (25th–75th percentile)	17 (16–17.37)	
Hip circumference (inches)		
Mean ± SD	41.17 ± 3.00	
Median (25th–75th percentile)	42 (40–43)	
Waist circumference (inches)		
Mean ± SD	39.25 ± 3.48	
Median (25th–75th percentile)	40 (37.25–42)	

Table 2 Classification of patients based on the severity of sleepiness (ESS grading)

Severity of sleepiness (ESS grading)	Frequency	Percentage (%)
Mild (ESS score ≤ 8)	37	30.83
Moderate (ESS score 9–14)	42	35.00
Severe (ESS score 15–24)	41	34.17
Total	120	100.00

the groups. The groups did not significantly differ in mean values of hematological parameters, lipid profile, thyroid function, glycemic parameters, or CRP. Blood sugar was inadequately controlled ($HbA_1C \geq 7\%$) in 11 patients out of 32 diabetic patients (34.38%). 14 patients had raised TSH levels, among them physician-diagnosed hypothyroidism was present in 12 patients. 68 patients had normal spirometry, possible restriction was observed in 40 patients, and obstructive pattern was observed in 12 patients. Mean FEV1, FVC, and FEV1/FVC were 2.2 ± 0.63 l, 2.79 ± 0.71 l, and 78.4 ± 8.85%, respectively. No significant differences were observed concerning ABG parameters between the groups. The mean Berlin score was 5.9 ± 1.93 with a median of 6(4–8). 2.5%, 29.17%, and 68.33% of patients had a low, intermediate, and high risk of OSA by STOP-BANG questionnaire. The mean score was 5.05 ± 1.26 with a median score of 5(4–6). Statistically significant positive association of STOP-BANG score with AHI ($p < 0.0003$), ODI ($p < 0.0005$), desaturation below 90% (p 0.01), and a negative association with SpO_2 nadir (p 0.009) was found (Table 3).

Hypertension was found to be the commonest comorbidity (57.50%), followed by diabetes (26.66%), dyslipidemia (13.33%), hypothyroidism (10.00%), ischemic heart disease (6.67%), and congestive cardiac failure (2.5%). Prevalent hypertension was more common in moderate to severely sleepy patients than in mild sleepy patients. Diabetes was also common in moderate to severe sleepy patients. The mean ESS score was significantly higher in patients with hypertension (12.66 ± 5.19) than in normotensive patients (11.39 ± 6.96) ($p < 0.05$). Mean systolic BP was 130.52 ± 8.38 mm Hg (range 112–148) and mean diastolic BP was 81.78 ± 5.9 (range 64–102) in all patients. No

Table 3 Association of polysomnography parameters with STOP-BANG grading

Polysomnography parameters	Low risk (0–2) ($n = 3$)	Intermediate risk (3–4) ($n = 35$)	High risk (5–8) ($n = 82$)	Total	p value
AHI					
Mild OSA{5–14}	1 (33.33%)	7 (20%)	5 (6.10%)	13 (10.83%)	< .0001*
Moderate OSA{15–29}	2 (66.67%)	13 (37.14%)	12 (14.63%)	27 (22.50%)	
Severe OSA{≥ 30}	0 (0%)	15 (42.86%)	65 (79.27%)	80 (66.67%)	
Mean ± SD	17.27 ± 8.5	34.54 ± 25.03	54.45 ± 29.38	47.72 ± 29.56	0.0003**
Median (25th–75th percentile)	17.2 (13–21.5)	23.2 (16.4–51.4)	57.35 (31.625–72.3)	43.3 (20.25–65.2)	
ODI					
Mean ± SD	10.63 ± 6.35	31.7 ± 29.72	52.98 ± 34.07	45.71 ± 34.18	0.0005**
Median (25th–75th percentile)	14.1 (8.7–14.3)	23 (10–41.8)	49.3 (26.05–74.025)	38.35 (15.85–68.2)	
SpO_2 nadir(%)					
Mean ± SD	92 ± 3.61	83.14 ± 10.38	78.33 ± 10.15	80.08 ± 10.47	0.009¶
Median (25th–75th percentile)	93 (90.5–94)	87 (77.5–90.5)	80 (71–86)	83.5 (72–88.25)	
Average SpO_2(%)					
Mean ± SD	97.33 ± 2.08	95.26 ± 2.83	94.16 ± 3.52	94.56 ± 3.35	0.093¶
Median (25th–75th percentile)	98(96.5–98.5)	96(94.5–97)	95(93–97)	96(93–97)	
Desaturation below 90%(minutes)					
Mean ± SD	0.13 ± 0.23	13.18 ± 35.24	20.27 ± 31.84	17.7 ± 32.61	0.01**
Median (25th–75th percentile)	0 (0–0.2)	0.4 (0–5.65)	3.85 (0.325–31.925)	2.85 (0.075–19.2)	
Total arousal index					
Mean ± SD	26 ± 17.32	22.07 ± 13.63	26.56 ± 17.97	25.24 ± 16.8	0.524**
Median (25th–75th percentile)	22.2 (16.55–33.55)	19.6 (10.15–29.45)	23.9 (13.725–35.95)	22.65 (12.75–32.8)	
Respiratory arousal index					
Mean ± SD	6.1 ± 4.26	8.99 ± 9.55	14.29 ± 14.62	12.54 ± 13.37	0.083**
Median (25th–75th percentile)	5.8 (3.9–8.15)	5.5 (2.95–10.1)	9.5 (4.6–19.9)	8.05 (3.875–18.15)	

*Fisher's exact test, ¶ANOVA, **Kruskal–Wallis test

significant difference in systolic and diastolic blood pressure with severity of sleepiness was observed (Table 4). Mean systolic and diastolic blood pressure was higher in severe OSA patients (Table 5). Mean AHI and ODI values were significantly higher in hypertensive patients when compared with patients without hypertension (56.05 ± 29.18/hr vs. 36.43 ± 26.35/hr and 54.81 ± 33/hr vs. 33.39 ± 31.61/hr respectively). Among 69 hypertensive patients, mild, moderate, and severe OSA was diagnosed in 3, 11, and 55 patients, respectively. 24 patients were on single antihypertensive medication, 34 were on antihypertensives from two different classes, and 11 were on antihypertensives from three different classes. CCB was the most commonly used antihypertensive, followed by ACEI/ARB. Most diabetic patients were on Biguanides followed by sulfonylurea, gliptins, and insulin.

Mild OSA, moderate OSA, and severe OSA were present in 13 (10.83%), 27 (22.5%), and 80 (66.67%) patients, respectively; mean AHI was 47.72 ± 29.56/hr, and the median AHI was 43.3/hr (20.25–65.2). The mean ODI value was 45.71 ± 34.2/hr with a median of 38.4 (15.85–68.2).

A statistically significant but weak correlation was found between ESS and AHI (r 0.218, p 0.017) and ESS and ODI (r 0.340, p 0.0002); however, correlation with ODI was stronger than AHI (Fig. 1). Apart from AHI and ODI, the ESS score has a weak positive correlation with desaturation below 90% (r 0.236, $p = 0.010$) and a weak negative correlation with SpO_2 nadir (r −0.184, $p = 0.045$). A statistically significant strong positive correlation (r 0.903, $p < 0.0001$) was found between AHI and ODI (Fig. 2). Bland–Altman plot shows good agreement between AHI and ODI as most of the values are aligned close to the mean of the difference line and within the limits of agreement (Fig. 3). Six COPD patients and three patients with congestive cardiac failure at higher risk of desaturation were included in the current study, all had baseline oxygen saturation > 90% at room air. Analysis excluding these patients also showed similar correlation of ESS score with AHI (r 0.216, p 0.023), ODI (r 0.343, p 0.0001), SpO_2 nadir (r −0.239 p 0.011), average SpO_2 (r −0.196 p 0.039), and desaturation below 90% (r 0.292 p 0.002) ($n = 111$). No significant correlation of ESS score with AHI and ODI was observed in this cohort ($n = 9$).

Statistically significant association of ESS score with AHI (p 0.033), ODI (p 0.001), and desaturation below 90% (p 0.03) was found. Median AHI values in mild, moderate, and severe sleepy groups were 31.00/hr, 44.35/hr, and 59.30/hr, respectively; ODI values were 21.9/hr, 39.15/hr, and 56.30/hr, respectively; and desaturation below 90% was 1min, 2.25 min, and 6.50 min, respectively (Table 6, Fig. 4).

The current study showed a significant positive correlation of prevalent hypertension with both ODI (r 0.311, p 0.001) and AHI (r 0.330, p 0.0002) (Table 7).

When patients were categorized into sleepy (ESS score ≥ 10) and non-sleepy (ESS score < 10) groups, 40 (33.33%) patients were non-sleepy and 80 patients (66.67%) were sleepy. Statistically significant differences ($p < 0.05$) in BMI were found between the groups. Significant associations of AHI (p 0.024) and ODI (p 0.003) were found with ESS score. No association of ESS score was found with SpO_2 nadir, average SpO_2, desaturation below 90%, and total and respiratory arousal index. While analyzing only in sleepy patients ($n = 80$), ESS score showed weak positive correlation with ODI (r 0.249, p 0.026) only, not with AHI (r 0.088, p 0.435).

Median AHI values were 35.25/hr and 53.60/hr in non-sleepy and sleepy OSA patients, respectively, and median ODI values were 23.9/hr and 46.65/hr, respectively (Table 8, Fig. 5). Prevalent hypertension was more common in sleepy

Table 4 Distribution of blood pressure with severity of sleepiness

Blood pressure (mm Hg)	All patients ($n = 120$)	Sleepy patients ($n = 80$)		Non-sleepy patients ($n = 40$)	
		Without hypertension ($n = 27$)	With hypertension ($n = 53$)	Without hypertension ($n = 24$)	With hypertension ($n = 16$)
Systolic blood pressure (mean ± SD)	130.52 ± 8.38	125.59 ± 8.01	133.68 ± 7.32	126.63 ± 7.02	133.31 ± 8.18
Diastolic blood pressure (mean ± SD)	81.78 ± 5.9	80.07 ± 5.48	83.30 ± 5.92	78.92 ± 4.79	83.88 ± 6.04

Table 5 Distribution of blood pressure related with grading of AHI and ODI

Blood pressure (mm Hg)	Mild OSA ($n = 13$)	Moderate OSA ($n = 27$)	Severe OSA ($n = 80$)	ODI < 15/hr ($n = 30$)	ODI 15–30/hr ($n = 19$)	ODI > 30/hr ($n = 71$)
Systolic blood pressure (mean ± SD)	128.77 ± 8.80	129.74 ± 7.46	131.01 ± 8.61	127.67 ± 8.49	129.53 ± 6.05	131.9 ± 8.60
Diastolic blood pressure (mean ± SD)	81.38 ± 7.80	79.89 ± 5.53	82.48 ± 5.60	80.30 ± 6.46	78.89 ± 6.74	83.17 ± 5.01

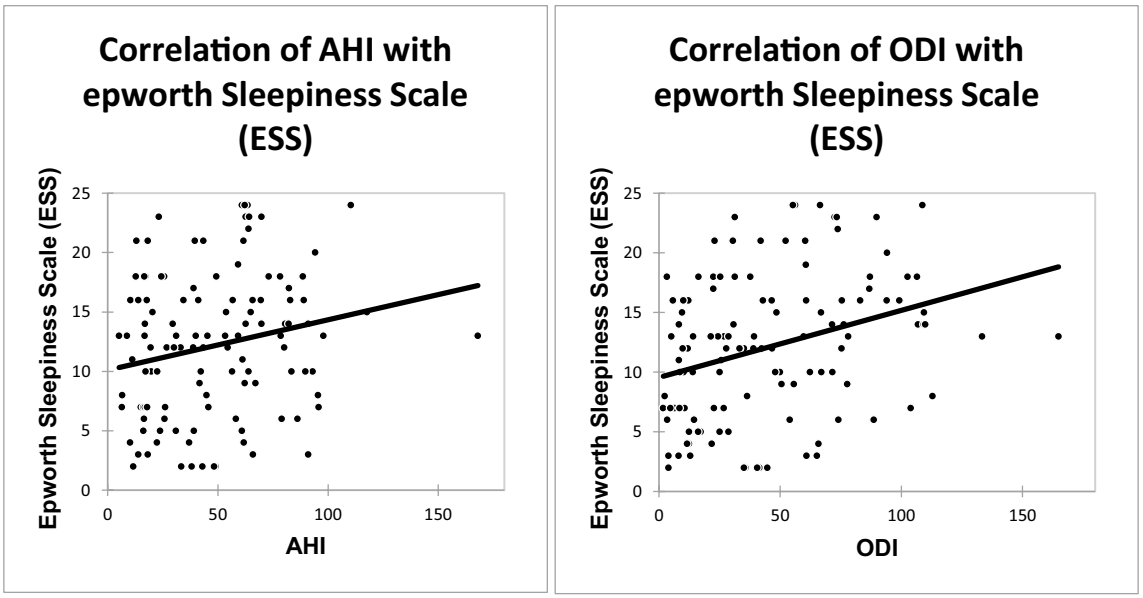

Fig. 1 Correlation of AHI and ODI with Epworth Sleepiness Scale (ESS)

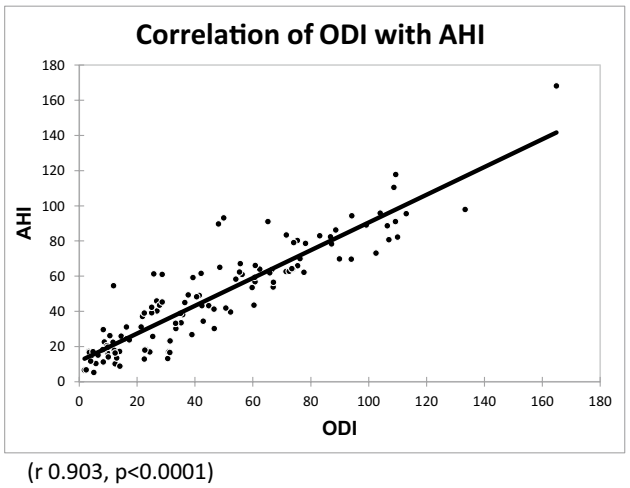

Fig. 2 Correlation of ODI with AHI

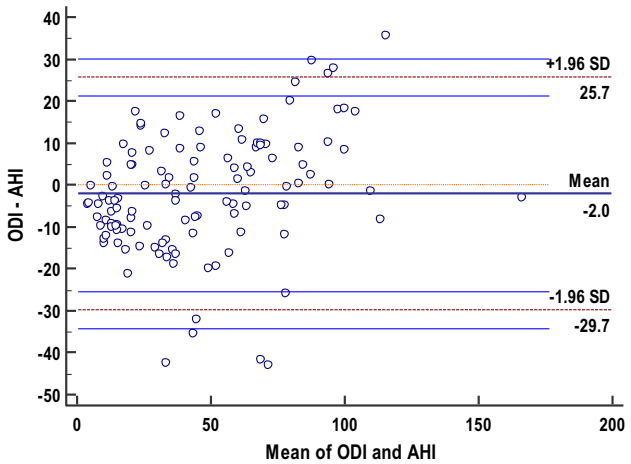

Fig. 3 Bland–Altman plot comparing ODI and AHI. The x-axis represents the mean of AHI and ODI and the Y-axis represents the difference of AHI and ODI (AHI-ODI)

patients compared to non-sleepy patients. Diabetes was also common in sleepy patients.

Receiver operating characteristic curve showed ODI value > 31.4/hr can predict severe OSA (AHI ≥ 30) with a sensitivity of 83.5%, specificity of 97.6%, PPV of 98.5%, and NPV of 75.5% (diagnostic accuracy 88.33%) (Table 9**,** Fig. 6).

4 Discussion

In the current study, the male-to-female ratio was 3:1, reflecting the difference in prevalence of OSA among males and females reflected in previous studies, patients had a mean BMI of 31.75 ± 5.98 kg/m^2, which suggests an association between obesity and OSA severity consistent with previous studies. More than 90% of patients with moderate to severe OSA were overweight, and more than 60% were obese. The Sleep Heart Health Study [13] and

Table 6 Association of polysomnography parameters with ESS grading

Polysomnography parameters	Mild ($n=37$) (ESS score ≤ 8)	Moderate ($n=42$) (ESS score 9–14)	Severe ($n=41$) (ESS score ≥ 15)	Total	p value
AHI					
Mean ± SD	37.84 ± 26.4	51.65 ± 31.78	52.6 ± 28.38	47.72 ± 29.56	0.033**
Median (25th–75th percentile)	31 (16.5–49)	44.35 (29.75–69.2)	59.3 (24.4–69.6)	43.3 (20.25–65.2)	
ODI					
Mean ± SD	31.01 ± 29.28	48.57 ± 36.58	56.07 ± 31.84	45.71 ± 34.18	0.001**
Median (25th–75th percentile)	21.9 (9.8–41.5)	39.15 (24.575–70.4)	56.3 (30.6–83.1)	38.35 (15.85–68.2)	
SpO_2 nadir (%)					
Mean ± SD	82.68 ± 9.57	80.4 ± 10.05	77.39 ± 11.24	80.08 ± 10.47	0.08¶
Median (25th–75th percentile)	85 (77–90)	84 (71.25–89)	76 (70–87)	83.5 (72–88.25)	
Average SpO_2 (%)					
Mean ± SD	95.27 ± 2.71	94.48 ± 3.95	94 ± 3.17	94.56 ± 3.35	0.245¶
Median (25th–75th percentile)	96 (95–97)	96 (93–97)	95 (92–96)	96 (93–97)	
Desaturation below 90%(minutes)					
Mean ± SD	13.85 ± 35.58	15.81 ± 33.9	23.1 ± 28.25	17.7 ± 32.61	0.03**
Median (25th–75th percentile)	1 (0–6)	2.25 (0–15.525)	6.5 (0.6–39.4)	2.85 (0.075–19.2)	
Total arousal index					
Mean ± SD	23.29 ± 11.73	23.79 ± 19.27	28.48 ± 17.85	25.24 ± 16.8	0.193**
Median (25th–75th percentile)	22.2 (13.9–30)	18.45 (10.525–28.7)	29 (14.2–36.7)	22.65 (12.75–32.8)	
Respiratory arousal index					
Mean ± SD	10.22 ± 8.64	12.48 ± 15.93	14.7 ± 13.95	12.54 ± 13.37	0.54**
Median (25th–75th percentile)	6.8 (4.9–12.9)	6.1 (3.95–14.5)	10.6 (2.9–22.2)	8.05 (3.875–18.15)	

*Fisher's exact test, ¶ANOVA, **Kruskal–Wallis test

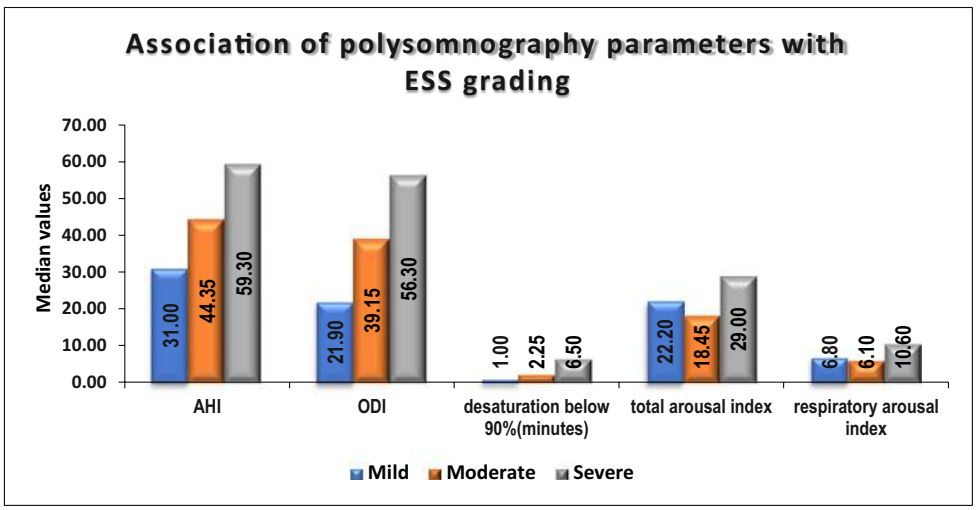

Fig. 4 Association of polysomnography parameters with ESS grading

a study by Deng et al. [14]. also reported obesity as a risk factor for OSA. 33.33% of our patients were non-sleepy (ESS score < 10), which is consistent with the result of a comparative study by R D Chervin [1]. Sleepy patients had a significantly higher BMI when compared with non-sleepy patients (mean 32.55 ± 5.93 kg/m^2 vs. 30.16 ± 5.83 kg/m^2, p 0.039).

This study showed a significant association of STOP-BANG score with AHI ($p < 0.0003$), ODI ($p < 0.0005$), desaturation below 90% (p 0.01), and significant negative association with SpO2 nadir (p 0.009), consistent with the study by Luo Jinmei et al. [15].

A statistically significant but weak correlation was found between ESS and AHI (r 0.218, p 0.017) and ESS and ODI

Table 7 Correlation of ODI and AHI with hypertension

Variables	Hypertension
ODI	
Correlation coefficient	0.311
P value	0.001
AHI	
Correlation coefficient	0.330
P value	0.0002
Comparison of r using *z* statistics	0.871

Point biserial correlation

(*r* 0.340, *p* 0.0002); however, correlation with ODI was stronger than AHI, consistent with the study by Dastan Temirbekov [6] and Seyda Akbal et al. [16]. This signifies a pivotal role of hypoxic burden with sleepiness in OSA patients. The ESS score has also a weak positive correlation with desaturation below 90% (r 0.236, $p = 0.010$) and a weak negative correlation with SpO_2 nadir ($r - 0.184$, $p = 0.045$). Similar results were observed in the study by Wali et al. [7]. No significant correlation of average SpO_2, total, and respiratory arousal index with the severity of sleepiness was found, contrary to a study by Seyda Akbal et al. [16]. Several studies showed that the arousal index does not have a significantly higher correlation with subjective or objective sleepiness than AHI [17]. A study by Katharina Bahr et al. [18]. showed a lack of correlation between the arousal index and ESS. Although arousal index can be an indicator of disrupted sleep, it does not indicate hypoxic burden in OSA patients.

The current study showed a significant positive association of ESS score with AHI, both in mild, moderate, and severe sleepy groups ($p < 0.03$) and sleepy and non-sleepy groups ($p < 0.02$). This finding is consistent with the study by Juen-Haur Hwang [19] and Dastan Temirbekov [6]. A significant positive association of ESS score with ODI, both in mild, moderate, and severe sleepy groups ($p < 0.001$) and sleepy and non-sleepy groups ($p < 0.003$) was found. Similar results were reported by Juen-Haur Hwan et al. [19]. and Dastan Temirbekov et al. [6]. in their studies. The current study also demonstrated a significant association of desaturation below 90% with ESS score in mild, moderate, and severe sleepy groups ($p < 0.03$), consistent with a study by Seyda Akbal et al. [16].

A strong correlation between AHI and ODI (r 0.903, $p < 0.0001$) was found in this study, consistent with the study by Dastan Temirbekov [6]. Receiver operating characteristic curve showed ODI value > 31.4/hr can predict severe OSA (AHI ≥ 30) with a sensitivity of 83.5%, specificity of 97.6%, PPV of 98.5%, and NPV of 75.5%. (Diagnostic accuracy 88.33%). Although PSG is the gold standard for diagnosing

Table 8 Association of polysomnography parameters with non-sleepy and sleepy

Polysomnography parameters	Non-sleepy ($n = 40$)	Sleepy ($n = 80$)	Total	*p* value
AHI				
Mean ± SD	39.27 ± 26.05	51.94 ± 30.44	47.72 ± 29.56	0.024[§]
Median (25th–75th percentile)	35.25 (16.875–58.875)	53.6 (25.375–69.825)	43.3 (20.25–65.2)	
ODI				
Mean ± SD	33.28 ± 29.45	51.93 ± 34.85	45.71 ± 34.18	0.003[§]
Median (25th–75th percentile)	23.9 (10.4–51.55)	46.65 (24.925–74.2)	38.35 (15.85–68.2)	
SpO_2 nadir (%)				
Mean ± SD	82.25 ± 9.61	78.99 ± 10.77	80.08 ± 10.47	0.108[‡]
Median (25th–75th percentile)	85 (76–90)	80.5 (71–88)	83.5 (72–88.25)	
Average SpO_2 (%)				
Mean ± SD	95.2 ± 2.64	94.24 ± 3.63	94.56 ± 3.35	0.101[‡]
Median (25th–75th percentile)	96 (95–97)	95 (93–97)	96 (93–97)	
Desaturation below 90% (minutes)				
Mean ± SD	13.76 ± 34.28	19.66 ± 31.77	17.7 ± 32.61	0.125[§]
Median (25th–75th percentile)	1 (0–9.525)	3.45 (0.175–31.4)	2.85 (0.075–19.2)	
Total arousal index				
Mean ± SD	22.57 ± 11.6	26.58 ± 18.79	25.24 ± 16.8	0.485[§]
Median (25th–75th percentile)	20.35 (13.8–29.925)	23.95 (11.6–36.7)	22.65 (12.75–32.8)	
Respiratory arousal index				
Mean ± SD	10.04 ± 8.38	13.79 ± 15.16	12.54 ± 13.37	0.751[§]
Median (25th–75th percentile)	6.8 (5.125–12.525)	8.3 (3.225–20.525)	8.05 (3.875–18.15)	

[‡]Independent t test, [§]Mann–Whitney test, *Fisher's exact test

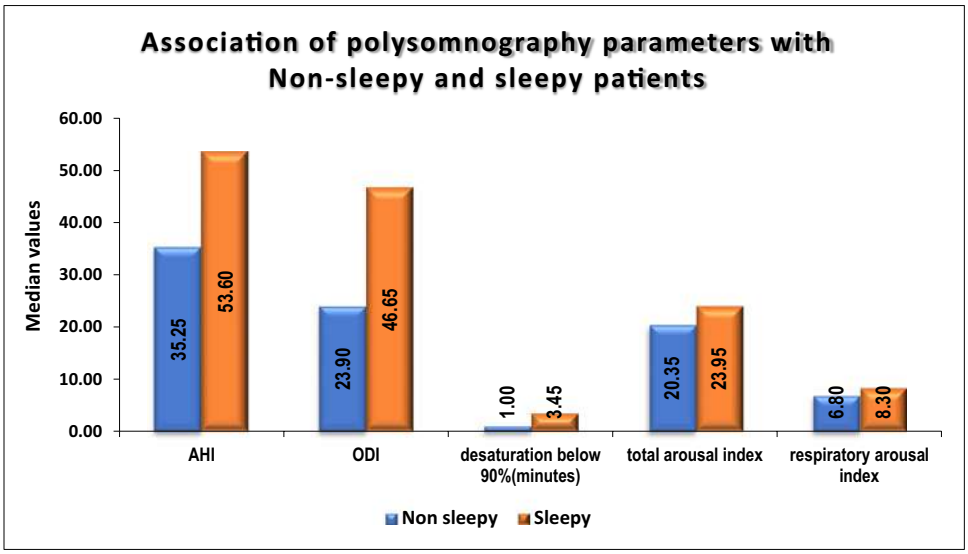

Fig. 5 Association of polysomnography parameters with non-sleepy and sleepy patients

Table 9 Receiver operating characteristic curve of ODI for predicting AHI ≥ 30

Variables	Values
Area under the ROC curve (AUC)	0.966
Standard error	0.0133
95% Confidence interval	0.940 to 0.992
P value	< 0.0001
Cut off	> 31.4
Sensitivity (95% CI)	83.54% (73.5–90.9%)
Specificity (95% CI)	97.56% (87.1–99.9%)
PPV (95% CI)	98.5% (92.0–100.0%)
NPV (95% CI)	75.5% (61.7–86.2%)
Diagnostic accuracy	88.33%

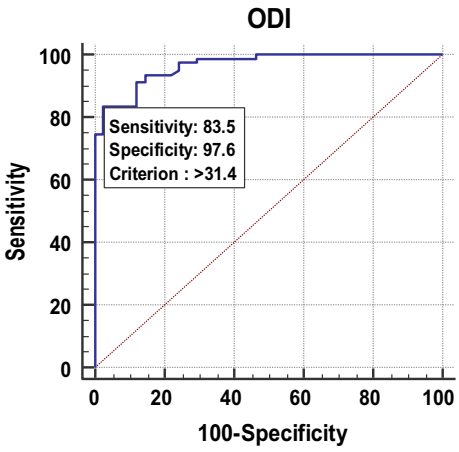

Fig. 6 Receiver operating characteristic curve of ODI for predicting AHI ≥ 30

OSA, financial implications, and limited availability of slots restrict its use, and the level III Portable Monitoring device for HSAT recommended by AASM is also not widely available. Good concordance between AHI and ODI suggests less expensive high-resolution finger pulse oximetry by a modern pulse oximeter can be used to screen (rule in) for OSA in subjects with a high pretest probability of severe OSA, especially in a resource-limited setting consistent with study by Lalee Varghese et al. [20]

The current study also showed a significant positive correlation of prevalent hypertension with both ODI (*r* 0.311, *p* 0.001) and AHI (*r* 0.330, *p* 0.0002), consistent with the study by Ruzena Tkacova et al. [12]. Patients with hypertension had a higher ESS score compared to normotensive patients ($p < 0.05$), similar to the finding of a study by Meng-Shi Tao et al. [21]. However, the relationship between OSA and hypertension is complicated by several confounding covariates like age, sex, BMI, smoking habit, alcohol intake, diabetes, dyslipidemia, etc. No causal relationship between hypertension and OSA can be concluded from this study, so this needs further large-scale study to evaluate the same.

5 Limitations

The sample size was small. As it was an observational study, the causal relationship between hypertension and OSA cannot be concluded from this study. Baseline low oxygen saturation (> 90% but < 95%) during this study in a few patients may have had an impact on desaturation below 90% and average SpO2 during sleep. We considered 3% ODI in our study, which predicts a comparatively lower hypoxic burden when compared to 4% ODI. Most of the studies showed

an association of 4% or more ODI with cardiovascular morbidities.

6 Conclusion

The current study concluded that the correlation of ODI is stronger than AHI with subjective sleepiness, reflecting the possible pivotal role of the hypoxic burden behind EDS. Our study also showed good concordance between ODI and AHI along with 88.33% diagnostic accuracy of ODI > 31.4/hr to predict severe OSA (AHI ≥ 30/hr), which suggests a promising role of modern fingertip pulse oximetry to screen (rule in) for severe OSA, especially in a resource-limited setting.

Prevalent hypertension in OSA patients has a significant but weak correlation with AHI and ODI without any significant difference between the two.

Author Contributions All authors were involved in the literature search, planning, conduct, writing the original draft of the manuscript, literature search, and editing of the study; Nitesh Gupta is the corresponding author and guarantor for all. All the authors have agreed with the submitted manuscript.

Funding The current study is not funded by any source.

Declarations

Conflict of Interests The authors declare that they have no conflicts of interest regarding the current study.

Ethical Clearance Ethical clearance was taken from the Institutional Ethics Committee, VMMC, and Safdarjung Hospital, New Delhi.

Patient Consent for Publication Written informed consent has been obtained from all patients for the publication of the data.

References

1. Chervin RD. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. Chest. 2000;118:372–9.
2. Mediano O, Barcelo A, de la Pena M, et al. Daytime sleepiness and polysomnographic variables in sleep apnoea patients. Eur Respir J. 2007;30(1):110–3.
3. Bixler EO, Vgontzas AN, Lin HM, et al. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. J Clin Endocrinol Metab. 2005;90(8):4510–5.
4. Kingshott R, Douglas N. The effect of in-laboratory polysomnography on sleep and objective daytime sleepiness. Sleep. 2000;23(8):1–5.
5. Deegan PC, McNicholas WT. Predictive value of clinical features for the obstructive sleep apnea syndrome. Eur Respir J. 1996;9(1):117–24.
6. Temirbekov D, Güneş S, Yazıcı ZM, et al. The ignored parameter in the diagnosis of obstructive sleep apnea syndrome: the oxygen desaturation index. Turk Arch Otorhinolaryngol. 2018;56:1–6.
7. Wali SO, Abaalkhail B, AlQassas I, et al. The correlation between oxygen saturation indices and the standard obstructive sleep apnea severity. Ann Thorac Med. 2020;15:70–5.
8. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. JAMA. 2000;283:1829–36.
9. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ. 2000;320:479–82.
10. Young T, Peppard P, Palta M, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. Arch Intern Med. 1997;157:1746–52.
11. Worsnop CJ, Naughton MT, Barter CE, et al. The prevalence of obstructive sleep apnea in hypertensives. Am J Respir Crit Care Med. 1998;157:111–5.
12. Tkacova R, McNicholas WT, Javorsky M, et al. Nocturnal intermittent hypoxia predicts prevalent hypertension in the European sleep apnoea database cohort study. Eur Respir J. 2014;44:931–41.
13. Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the sleep heart health study. Arch Intern Med. 2002;162:893–900.
14. Deng X, Gu W, Li Y, et al. Age-group-specific associations between the severity of obstructive sleep apnea and relevant risk factors in male and female patients. PLoS One. 2014;9: e107380.
15. Jinmei L, Rong H, Zhong Xu, et al. Value of STOP-Bang questionnaire in screening patients with obstructive sleep apnea hypopnea syndrome in sleep disordered breathing clinic. Chin Med J. 2014;127(10):1843–8.
16. Akbal S, Karakurt SE, Orhan Z, et al. Correlation of Epworth sleepiness scale with polysomnography parameters in obstructive sleep apnea patients, Cyprus. J Med Sci. 2021;6(2):146–50.
17. Berry RB. Fundamentals of sleep medicine, ISBN: 9781437703269, 1st edition.
18. Bahr K, Geisler V, Huppertz T, et al. Intensity of respiratory cortical arousals is a distinct pathophysiologic feature and is associated with disease severity in obstructive sleep apnea patients. Brain Sci. 2021;11(3):282.
19. Hsieh PS, Hwang SW, Hwang SR, et al. Association between various breathing indexes during sleep and the Epworth Sleepiness Scale score in adults. Medicine (Baltimore). 2022;101(48): e32017.
20. Varghese L, Rebekah G, Priya NP, Oliver A, Kurien R. Oxygen desaturation index as alternative parameter in screening patients with severe obstructive sleep apnea. Sleep Sci. 2022;15(Spec 1):224–8.
21. Tao M, Dong X, Tu J, et al. Symptoms and comorbidity burden in hypertensive patients with obstructive sleep apnea. Front Endocrinol (Lausanne). 2024;15:1361466.