ISSN 1562 - 5044

http://chabjournal.org
Indexed & Member: Cross Ref.

Chest & Heart Journal

Volume 43 Number 02 July 2019

A Journal
and
Official Organ
of the Chest &
Heart Association
of Bangladesh

Chest & Heart Journal

Volume 43, Number 02, Page 59-113 **July 2019**

CONTENTS

Chest & Heart Journal

chabjournal.org

Publication of The Chest & Heart Association of Bangladesh

Dedicated to Scientific & Professional Development of Pulmonologist & Cardiologist

ISSN: 1562-5044

ONLINE

http://chabjournal.org.
http://www.chabjournal/writer/register

PUBLISHED BY:

Editor in Chief
on behalf of the Chest and Heart
Association of Bangladesh

INDEX

Member: Cross Ref.
Indexed in: Cross Ref.

PRINTED BY:

Asian Colour Printing
130 DIT Extension Road
Fakirerpool, Dhaka-1000, Bangladesh
Phone: 49357726, 58313186
E-mail: asianclr@gmail.com

This publication is a dedication of The Chest & Heart Association of Bangladesh towards knowledge & professional development of Pulmonologist and Cardiologist practice in Bangladesh & the whole world. It is published biannually and accepts original article, review article and case reports. We try to accommodate any content which may help in promotion of knowledge, quality of patient care and research potential amongst concerned personnel. While every effort is always made by the Editorial Board to avoid inaccurate or misleading information appearing in the Journal, information within the individual articles are the responsibility of its author(s). The Chest and Heart Journal, its Editorial Board accept no liability whatsoever for the consequences of any such inaccurate and misleading information, opinion or statement.

CORRESPONDENCE

The Editor in Chief, The Chest and Heart Journal.
Association Secretariat, Administrative Block, National Institute of Diseases of the Chest & Hospital.
Mohakhali, Dhaka-1212, Phone/Fax: +88-02-55067145
E-mail: chestheart@gmail.com Website: www.chestheart.org

THE CHEST & HEART ASSOCIATION OF BANGLADESH

EXECUTIVE COMMITTEE

President	:	Professor Mirza Mohammad Hiron
Vice-President	:	Professor Biswas Akhtar Hossain Professor Bashir Ahmed Dr. Md. Rafiqul Islam
Secretary General	:	Dr. Md. Abu Raihan
Treasurer	:	Professor Krishna Chandra Ganguly
Joint Secretary	:	Dr. Golam Sarwar L.H. Bhuiyan
Organizing Secretary	:	Dr. Md. Mofizur Rahman Mia
Office Secretary	:	Dr. S.M. Abdur Razzaque
Members	:	Professor Md. Rashidul Hassan Professor Md. Abdur Rouf Professor Md. Shahedur Rahman Khan Professor S.M. Mostafa Zaman Dr. Md. Khairul Anam Dr. Barkat Ullah Dr. Md. Zahirul Islam Shakil Dr. Nihar Ranjan Saha Dr. Mahmud Masum Attar Dr. Abdullah Al Mujahid Dr. Md. Serazul Islam

Chest Heart Journal
Vol. 43, No. 2, July 2019

EDITORIAL

Latent Tuberculosis: A Concealed Global Burden

[Chest Heart J. 2019; 43(2) : 59-63]
DOI: http://dx.doi.org/10.33316/chab.j.v43i2.

Introduction

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by

Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB[1]. As there is no "gold standard" test for LTBI, the global burden is not known with certainty; however, up to one third of the world's population is estimated to be infected with *M. tuberculosis*[2–4], and the vast majority have no signs or symptoms of TB disease and are not infectious, although they are at risk for active TB disease and for becoming infectious. Several studies have shown that, on average, 5–10% of those infected will develop active TB disease over the course of their lives, usually within the first 5 years after initial infection[5]. The risk for active TB disease after infection depends on several factors, the most important being immunological status[1].

Prevention of active TB disease by treatment of LTBI is a critical component of the WHO End TB Strategy *(6)*. The efficacy of currently available treatments ranges from 60% to 90% *(1)*. The potential benefit of treatment should, however, be carefully balanced against the risk for drug-related adverse events. Management of LTBI involves a comprehensive package of interventions: identifying and testing those individuals who should be tested, delivering effective, safe treatment in such a way that the majority of those starting a treatment regimen will complete it with no or minimal risk of adverse events, and monitoring and evaluation of the process.

Identification of populations for testing and treatment of latent tuberculosis infection

Generally, persons at risk for developing TB disease fall into 2 broad categories:

- Those who have an increased likelihood of exposure to persons with TB disease
- Those with clinical conditions or other factors associated with an increased risk of progression from LTBI to TB disease

Also at risk are those with certain conditions and other factors associated with progression from LTBI to TB disease. These conditions and factors include the following:

- HIV infection
- Injection drug use
- Radiographic evidence of prior healed TB
- Low body weight (10% below ideal)
- Other medical conditions, such as: silicosis, diabetes mellitus, chronic renal failure or on hemodialysis, gastrectomy, jejunoileal bypass, solid organ transplant, head and neck cancer, conditions that require prolonged use of corticosteroids or other immunosuppressive agents such as TNFá antagonists
- Recent TST converters (that is, persons with baseline testing results who have an increase of 10 mm or more in the size of the TST reaction within a 2-year period).
- Infants and children under the age of 5 years who have a positive TB test result

Of note, the risk of progression is greatest in the first 1 or 2 years after infection.

Diagnosis of Latent TB Infection

The diagnosis of LTBI is based on information gathered from the medical history, TST or IGRA result, chest radiograph, physical examination, and in certain circumstances, sputum examinations. The presence of TB disease must be excluded before treatment for LTBI is initiated because failure to

Submission on: 25 May, 2019 **Accepted for Publication:** 10 June, 2019
Available at http.//www.chabjournal.org

do so may result in inadequate treatment and development of drug resistance (see Table 1).

No symptoms or physical findings suggestive of TB disease. TST or IGRA result usually positive. Chest radiograph is typically normal. If done, respiratory specimens are smear and culture negative. Cannot spread TB bacteria to others. Should consider treatment for LTBI to prevent TB disease. Symptoms may include one or more of the following: fever, cough, chest pain, weight loss, night sweats, hemoptysis, fatigue, and decreased appetite. TST or IGRA result usually positive. Chest radiograph is usually abnormal. However, may be normal in persons with advanced immunosuppression or extrapulmonary disease. Respiratory specimens are usually smear or culture positive. However, may be negative in persons with extrapulmonary disease or minimal or early pulmonary disease. May spread TB bacteria to others. Needs treatment for TB disease.

Tests for TB Infection

A. Tuberculin Skin Test (TST)

The TST is used to determine if a person is infected with *M. tuberculosis*. If a person is infected, a delayed-type hypersensitivity reaction is detectable 2 to 8 weeks after infection. The skin test is administered intradermally using the Mantoux technique by injecting 0.1ml of 5 TU purified protein derivative (PPD) solution. The reading and interpretation of TST reactions should be conducted within 48 to 72 hours of administration.

B. Interferon–Gamma Release Assays (IGRAs)

IGRAs are used to determine if a person is infected with *M. tuberculosis* by measuring the immune response to TB proteins in whole blood. Specimens are mixed with peptides that simulate antigens derived from *M. tuberculosis* and controls. In a person infected with *M. tuberculosis*, the white blood cells recognize the simulated antigens and release interferon-gamma (IFN-γ); results are based on the amount of IFN- ã released.

As noted earlier, there are 2 U.S. Food and Drug Administration (FDA) approved IGRAs commercially available:

- QuantiFERON® -TB Gold-in-Tube test (QFT-GIT)
- T-SPOT® *TB* test

Table-I

Differentiating Between Latent TB Infection and TB Disease

LTBI	TB Disease
No symptoms or physical findings suggestive of TB disease.	Symptoms may include one or more of the following: fever, cough, chest pain, weight loss, night sweats, hemoptysis, fatigue, and decreased appetite.
TST or IGRA result usually positive.	TST or IGRA result usually positive.
Chest radiograph is typically normal.	Chest radiograph is usually abnormal. However, may be normal in persons with advanced immunosuppression or extrapulmonary disease.
If done, respiratory specimens are smear and culture negative.	Respiratory specimens are usually smear or culture positive. However, may be negative in persons with extrapulmonary disease or minimal or early pulmonary disease.
Cannot spread TB bacteria to others.	May spread TB bacteria to others.
Should consider treatment for LTBI to prevent TB disease.	Needs treatment for TB disease.

Advantages of IGRAs include the following: Requires a single patient visit to conduct the test.

- Does not cause booster phenomenon.
- Laboratory test not affected by health care worker perception or bias.
- Results can be available within 24 hours.
- Unaffected by BCG and most environmental mycobacteria.

Limitations of IGRAs include the following:

- Blood sample must be processed within 8-30 hours after collection.
- Limited data exist on use in groups such as children younger than 5 years of age, persons recently exposed to TB, immunocompromised persons, and those who will be tested repeatedly (serial testing).

Selecting a Test to Detect TB Infection

- IGRAs are the preferred method of testing for:
  - o Groups of people who have poor rates of return for TST reading and interpretation (e.g., homeless persons)
  - o Persons who have received BCG vaccination
- TST is the preferred method for testing for: Children under the age of 5 years
- Either TST or IGRA may be used without preference for other groups that are tested for LTBI.

Special Considerations in Testing for TB Infection

BCG Vaccine

In many parts of the world where TB is common like Bangladesh, BCG vaccine is used to protect infants and young children from serious, life-threatening disease, specifically miliary TB and TB meningitis. The World Health Organization (WHO) recommends that BCG vaccine be administered during infancy in TB endemic countries. BCG vaccination is not generally recommended in the United States. The effect of BCG vaccine on TST results often causes confusion. TST reactivity caused by BCG vaccine generally wanes with the passage of time, but periodic skin testing may prolong (boost) reactivity in vaccinated persons. A person with a history of BCG vaccination can be tested and treated for LTBI if they react to the TST. TST reactions should be interpreted based on risk stratification regardless of BCG vaccination history.

IGRAs use *M. tuberculosis* specific antigens that do not cross react with BCG, and therefore, do not cause false positive reactions in BCG recipients.

HIV Infection

The risk of progression from LTBI to TB disease is 7% to 10% each year for those with both LTBI and untreated HIV infection. Those with LTBI who are not HIV-infected have a 10% risk over their lifetime. Thus the risk of progression to TB disease is 10 times greater for those who are HIV infected. This risk is reduced with antiretroviral therapy for HIV, but is still higher than that in HIV-negative persons with LTBI.

HIV-infected persons should be tested for LTBI as soon as their HIV status becomes known. A negative TST or IGRA result does not exclude LTBI as they may have a compromised ability to react to tests for TB infection.

After the initiation of antiretroviral therapy (ART), repeat testing for LTBI is recommended for HIV-infected persons previously known to have negative TST or IGRA results. This is because the immune response may be restored by ART.

Other Diagnostic Considerations

Chest Radiograph

A chest radiograph should be ordered as part of a medical evaluation for a person who has a positive TST or IGRA result. A chest radiograph is also indicated in the absence of a positive test result for TB infection when a person is a close contact of an infectious TB patient and treatment for LTBI will be started (e.g., "window prophylaxis" in a young child or immunocompromised person).

Children less than 5 years of age should have both posterior-anterior and lateral views; all others should have at least posterior-anterior views.

Persons with nodular or fibrotic lesions consistent with old TB are high-priority candidates for treatment of LTBI after TB disease is excluded. Persons with fully calcified, discrete granulomas do not have an increased risk for progression to TB disease.

Sputum Examination for AFB Smear and Culture

Sputum examination is indicated for persons with positive test results for TB infection and either an abnormal chest radiograph or the presence of respiratory symptoms (even when the chest radiograph is normal).

Physical Examination and Medical History

Physical examination and medical history, which includes obtaining information about previous positive tests for TB infection, previous treatment for LTBI or TB disease, and a risk assessment for liver disease, are indicated for an individual with positive TB test results. Written documentation of a previously positive TST or IGRA result is required; a patient's verbal history is not sufficient.

Treatment options for LTBI

Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence. *(Strong recommendation, high-quality evidence. Existing* recommendation)

Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence. *(Strong recommendation, low-quality evidence. New recommendation)*

Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence.

(Conditional recommendation, moderate-quality evidence. New recommendation)

The following options are recommended for treatment of LTBI in countries with a low TB incidence as alternatives to 6 months of isoniazid monotherapy: 9 months of isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months of isoniazid plus rifampicin, or 3–4 months of rifampicin alone.

(Strong recommendation, moderate–high-quality evidence. Existing recommendation)

In settings with high TB incidence and transmission, adults and adolescents living with HIV who have an unknown or a positive TST and are unlikely to have active TB disease should receive at least 36 months of isoniazid preventive therapy (IPT), regardless of whether they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy.

Table-II

Recommended dosages of drugs for the treatment of LTBI

Drug regimen	Dose per kg body weight	Maximum dose
Isoniazid alone, daily for 6 or 9 months	Adults, 5 mg Children, 10 mg (range, 7-15 mg)	300 mg
Daily rifamoicin alone for 3-4 months	Adults, 10mg Children, 15 mg (range, 10-20 mg)	600 mg
Daily isoniazid plus rifampicin for 3-4 months	Isoniazid: Adults, 5 mg Children, 10 mg (range, 7-15 mg) Rifampicin Adults, 10 mg Children, 15 mg (range, 10-20 mg)	Isoniazid, 300 mg Rifampicin, 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Individuals aged ≥ 12 years; Isoniazid: 15 mg Individuals aged 2-11 years; isoniazid: 25 mg Rifapentine; 10.0-14,0 kg = 300 mg 14.1-25.0 kg = 450 mg 25.1-32.0 kg = 600 mg 32.1-50.0 kg =750 mg >50 kg = 900mg	Isoniazid, 900 mg Rifapentine, 900 mg

(Conditional recommendation, low quality evidence. Existing recommendation).

Prof. Dr. Md. Abdur Rouf
Professer
Dept. of Respiratory Medicine
NIDCH, Dhaka
E-mail: *drrouf@gmail.com*
Mobile: +8801711487002

References

1. Kasambira TS, Shah M, Adrian PV, Holshouser M, Madhi SA, Chaisson RE, et al. QuantiFERON–TB Gold In–Tube for the detection of Mycobacterium tuberculosis infection in children with household tuberculosis contact. Int J Tuberc Lung Dis. 2011;15(5):628–34.
2. Kenyon TA, Creek T, Laserson K, Makhoa M, Chimidza N, Mwasekaga M, et al. Risk factors for transmission of Mycobacterium tuberculosis from HIV–infected tuberculosis patients, Botswana. Int J Tuberc Lung Dis. 2002;6(10):843–50.
3. Klausner JD, Ryder RW, Baende E, Lelo U, Williame JC, Ngamboli K, et al. Mycobacterium tuberculosis in household contacts of human immunodeficiency virus type 1–seropositive patients with active pulmonary tuberculosis in Kinshasa, Zaire. J Infect Dis. 1993;168(1):106–11.
4. Bokhari SY, Ahmad A, Shaikh MY, Ahmad I. A study of tuberculosis contacts. J Pak Med Assoc. 1987;37(2):48–52.
5. Biraro IA, Kimuda S, Egesa M, Cose S, Webb EL, Joloba M, et al. The Use of Interferon Gamma Inducible Protein 10 as a Potential Biomarker in the Diagnosis of Latent Tuberculosis Infection in Uganda. PLoS One. 2016;11(1):e0146098.
6. Rutherford ME, Nataprawira M, Yulita I, Apriani L, Maharani W, van Crevel R, et al. QuantiFERON(R)–TB Gold In–Tube assay vs. tuberculin skin test in Indonesian children living with a tuberculosis case. Int J Tuberc Lung Dis. 2012;16(4):496–502.

Chest Heart Journal
Vol. 43, No. 2, July 2019

ORIGINAL ARTICLE

Relation of Patient Characteristics (BMI, FEV_1) with Bacterial Colonization Pattern of Sputum In Patients Suffering from Acute Exacerbation of Chronic Obstructive Pulmonary Diseases

Kamruzzaman Md. Zahir,[1] A.K.M. Mostafa Hussain,[2] Md. Sayedul Islam,[3] Md. Ali Hossain,[4] Md. Muhammed Arshad Ul Azim,[5] Tanwir Iqbal Ahmed,[6] S.M Lutfor Rahman[7]

Abstract

Background: *In patient with exacerbation of COPD positive sputum microbiology is associated with FEV_1, active tobacco smoking, prior exacerbations, presence of bronchiectasis, prior use of systemic corticosteroid, and/or antibiotics, sputum purulence.*

Methods: *It is a case control prospective study. This study was carried out in the indoor and outdoor of National Institute of diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period September 2010 to August 2011 on 65 patients having the diagnosis of acute exacerbation of COPD.*

Result: *It was observed according to BMI, the mean pseudomonous was found 21.50±1.76 kg/m^2, candida 23.57±1.51 kg/m^2, klebsiella 21.43±1.97 kg/m^2, E. Coli 22.13±1.65 kg/m^2, streptococcus 22.50±3.54 kg/m^2, S. aureus was 20.75±0.35 kg/m^2, no growth was 23.65±2.06 kg/m^2.*

In this present series according to FEV_1 it was observed that the mean FEV_1 was 50.9±8.8 (%) in patients having pseudomonous, 48.4±7.8 (%) in klebsiella, 50.0±7.1 (%) in streptococcus, 42.0±5.7 (%) in H. Influenjae and 60.5±9.8 (%) in no growth. The positive sputum culture pseudomonous, klebsiella, streptococcus and H.influenjae are associated with low FEV_1.

Conclusions: *This study was undertaken to identify the patients of COPD who are more prone to have respiratory tract infection and thus acute exacerbation and also the ability to clinically identify patients likely or unlikely to yield bacterial sputum isolates. Pseudomonous, klebsiella, streptococcus and H.influenjae are associated with underweight and low FEV_1 patients. FEV_1 (<52%) and BMI (<20 kg/m^2) significantly influence to develop sputum culture positivity.*

[Chest Heart J. 2019; 43(2) : 65-70]
DOI: http://dx.doi.org/10.33316/chab.j.v43i2.2019602

Introduction:

COPD Is Highly Prevalent, underdiagnosed, undertreated and underperceived disease. It affects millions of individuals, limits the functional capacity of many, and has become an important cause of death worldwide.

1. Assistant Professor, Respiratory Medicine, Sher-E-Bangla Medical College, Barishal.
2. Professor cum Director NIDCH
3. Associate Professor, NIDCH
4. Professor of respiratory medicine,NIDCH
5. Assistant Professor, Department of nephrology, Shahid Sheikh Abu Naser Specialized hospital, Khulna
6. Registrar, NIDCH, 7.Associate Professor, NIDCH.

Correspondence to: Dr. Kamruzzaman Md. Zahir, Assistant Professor, Respiratory Medicine, Sher-E-Bangla Medical College, Barishal. Mobile: 01718-426134, E-mail: imam_md2004@yahoo.com

Submission on: 25 May, 2019 **Accepted for Publication:** 10 June, 2019
Available at http.//www.chabjournal.org

COPD diagnosis is strongly suspected in the presence of more than a 10 pack year smoking history in combination with a complaint of chronic cough with sputum production, shortness of breath, and infection which takes longer to resolve than usual.By 2020 it will represent the third most important cause of death world wide.[1] The anticipated rise in mortality and morbidity from COPD will be greatest in Asia and African countries as a result of their increasing tobacco consumption.

Exacerbations of COPD are important contributors to the severity of the patient's disease, by accelerating lung function decline, precipitating poor health status, increasing health care cost and negatively affecting survival.

In patient with exacerbation of COPD positive sputum microbiology is associated with FEV1, active tobacco smoking , prior exacerbations, presence of bronchiectasis, prior use of systemic corticosreroides, and/or antibiotics, sputum purulence. A prediction model based on the variables of purulent sputum, FEV1, and BMI predicted sputum culture result with about 90% accuracy.[2]

Rationale:

COPD burden is increasing in developing countries like Bangladesh. Acute exacerbation of COPD compels patient to admit into hospital. There are several factors causing acute exacerbation of COPD including respiratory tract infection.So if sputum bacterial colonization correlates patients characteristics like BMI FEV1, sputum purulence, age gender; it will help to institute antibiotic early without the delay of sputum microbiological report, thereby facilitating the orientation of antibiotic treatment and reducing the high number of failures recorded with empiric treatment as well as will reduce hospital admission.

Materials and Method:

It is a case control prospective study.This study was carried out in the indoor and outdoor of National Institute of diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period September 2010 to August 2011 on 65 patients having the diagnosis of acute exacerbation of COPD. Inclusion criteria was, age >40 years,diagnosed case of COPD, Worsening symptoms like breathlessness, increased respiratory rate, fever, purulence of sputum. Exclusion criteria was, age <40 years COPD with allergic component, Bronchiectasis, antibiotic treatment within last month.

Observations and Results:

Table-I

Age distribution of the study patients (n=65)

Age (in year)	Number of patients	Percentage
40-50	20	30.8
51-60	17	26.2
61-70	18	27.7
71-80	7	10.8
>80	3	4.6
Mean ± SD	59.58	±12.31
Range (min-max)	(40	-85)

The above table shows the age distribution of the study patients. Most of the patients was found 20(30.8%) in age group of 40-50 years. The mean age was found 59.58±12.31 years with range from 40 to 85 years. Other results are depicted in the table.

Table-II

Sex distribution of the study patients (n=65)

Sex	Number of patients	Percentage
Male	55	84.6
Female	10	15.4

The above table shows the sex distribution of the study patients. Male was found 55(84.6%) and female was 10(15.4%). Male to female ratio was 5.5:1.

Table-III

Distribution of the study patients according sputum (n=65)

Sputum	Number of patients	Percentage
Yellow/purulent	36	55.4
Muco-purulent	12	18.5
Mucoid	17	26.2

The above table shows the sputum colour of the study patients. According to sputum, yellow/ purulent was found 36(55.4%), Muco-purelent was 12(18.5%) and Mucoid was 17(26.2%).

Table-IV

Distribution of the study patients according to smoking (n=65)

Smoking	Number of patients	Percentage
Smoker	50	76.9%
Non smoker	10	15.4%
Ex smoker	5	7.7%

The above table shows the smoking pattern of the study patients. Maximum patients were smoker, which was 50(76.9%), 10(15.4%) non smoker and 5(7.7%) ex smoker.

Table-V

Distribution of the study patients according to use of antibiotics and steroid (n=65)

Use of antibiotics and steroid	Number of patients	Percentage
Occasional	23	35.4%
$^1/_2$ per yrs	20	30.8%
$^1/_3$ per yrs	4	6.2%
$^2/_3$ per yrs	13	20.0%
$^3/_4$ per yrs	5	7.7%

The above table shows the use of antibiotics and steroid of the study patients. More than one third (35.4%) of the patients received antibiotics and steroid occasionally and 20(30.8%) received 1/2 per year and other results are depicted in the table.

Table-VI

Distribution of the study patients according to BMI(n=65)

BMI (kg/m^2)	Number of patients	Percentage
Under weight	1	1.5%
Normal weight	55	84.6%
Over weight	9	13.8%
Obesity	0	0.0%
Mean±SD	22.29±2.03	
Range (min-max)	(18-26)	

Under weight: <18.5 kg/m^2
Normal weight: 18.5-24.9 kg/m^2
Over weight: 25-29.9 kg/m^2
Obesity: ≥30 kg/m^2

The above table shows the distribution body mass index(BMI) of the study patient. Most 55(84.6%) of the patients had normal body weight (18.5-24.9 kg/m^2) followed by 9(13.8%) over weight, 1(1.5%) under weight and obesity was not found. The mean BMI was 22.29±2.03 kg/m^2 with range from 18 to 26 kg/m^2.

Table-VII

Distribution of the study patients according to FEV_1 (%) (n=65)

FEV_1 (%) of predicted	Number of patients	Percentage
≤40	5	7.7
41-50	24	36.9
51-60	18	27.7
61-70	16	24.6
>70	2	3.1
Mean±SD	53.74	±10.84
Range (min-max)	(22	-74)

The above table shows the FEV_1 of the study patients. Maximum FEV_1 was found 24(36.9%) in 41-50 %. The mean FEV_1 was found 53.74±10.84 % with range from 22 to 74 %.

Table-VIII

Distribution of the study patients according to Sputum culture (n=65)

Sputum culture	Number of patients	Percentage
Pseudomonous	23	35.4
No growth	15	23.1
Candida	7	10.8
Klebsiella	7	10.8
E. Coli	4	6.2
Streptococcus	2	3.1
S.aureus	2	3.1
Acinetobactor/Psudomonous	1	1.5
Haemophilusinfluenjae	1	1.5
H.influenjae	1	1.5
Pseudomonous, Klebsiela	1	1.5
Streptococcus pneumoni	1	1.5

The above table shows the sputum culture of the study patients. Pseudomonous was found 23(35.4%) followed by no growth was 15(23.1%), candida was 7(10.8%), klebsiella was 7(10.8%), 4(6.2%) was E. coli, 2(3.1%) was streptococcus, 2(3.1%) was s. aureus and acinetobactor/psudomonous, haemophilus influenjae, H. influnjae, pseudomonous klebsiela & stereptococcus pneumoni was 1(1.5%).

Table-IX

Mean distribution of BMI according to sputum culture of the study patients (n=65).

Sputum culture		BMI (kg/m^2)			
	n	Mean	±SD	(Min	-max)
Pseudomonous	23	21.50	±1.76	(19	-26)
Candida	7	23.57	±1.51	(22	-26)
Klebsiella	7	21.43	±1.97	(18	-24)
E. Coli	4	22.13	±1.65	(20.5	-24)
Streptococcus	2	22.50	±3.54	(20	-25)
S.aureus	2	20.75	±0.35	(20.5	-21)
Acinetobactor/Psudomonous	1	24	.	(24	-24)
Haemophilusinfluenjae	1	19	.	(19	-19)
H.influenjae	1	22.3	.	(22.3	-22.3)
Pseudomonous,Klebsiela	1	21.5	.	(21.5	-21.5)
Streptococcus pneumoni	1	22.8	.	(22.8	-22.8)
No growth	15	23.65	±2.06	(18.5	-26)

The above table shows the mean distribution of BMI according to sputum culture of the study patients. According to BMI, the mean pseudomonous was found 21.50±1.76 kg/m^2, candida 23.57±1.51 kg/m^2, klebsiella 21.43±1.97 kg/m^2, E. Coli 22.13±1.65 kg/m^2, streptococcus 22.50±3.54 kg/m^2, S. aureus was 20.75±0.35 kg/m^2, no growth was 23.65±2.06kg/m^2.

Table-X

Mean distribution of FEV_1 (%) according to sputum culture of the study patients (n=65).

Sputum culture		FEV_1 (%)			
	n	Mean	±SD	(Min	-Max)
Pseudomonous	23	50.91	±8.75	(22	-70)
Candida	7	59.0	±15.95	(24	-70)
Klebsiella	7	48.43	±7.76	(40	-62)
E. Coli	4	52.25	±10.37	(45	-67)
Streptococcu	2	50.0	±7.07	(45	-55)
S.aureus	2	66.0	±11.31	(58	-74)
Acinetobactor/Psudomonous	1	45	.	(45	-45)
Haemophilusinfluenjae	1	38	.	(38	-38)
H.influenjae	1	46	.	(46	-46)
Pseudomonous,Klebsiela	1	45	.	(45	-45)
Streptococcus pneumoni	1	47	.	(47	-47)
No growth	15	60.53	±9.78	(40	-74)

The above table shows the mean distribution of FEV_1 according to sputum culture of the study patients. According to FEV_1, the mean pseudomonous was found 50.91±8.75 (%), candida 59.0±15.95 (%), klebsiella 48.43±7.76 (%), E. Coli 52.25±10.37 (%), streptococcus 50.0±7.07 (%), S. aureus was 66.0±11.31 (%), no growth was 60.53±9.78(%).

Discussion:

This cross sectional study was carried out with an aim to identify the patients of COPD who are more prone to have respiratory tract infection and thus acute exacerbation and also the ability to clinically identify patients likely or unlikely to yield bacterial sputum isolates. In addition to reduce unnecessary tests and to forecast the infective exacerbations in some patient of COPD. A total number of 65 consecutive patients having acute exacerbation of COPD who came in the national institute of diseases of the Chest and Hospital(NIDCH) Mohakhali, Dhaka, during the period of September 2010 to August 2011 were included in this study.The present study findings were discussed and compared with previously published relevant studies.

In this present study it was observed that more than one third (35.4%) of the patients was in 6th decade and the mean age was 59.58±12.31 years with range from 40 to 85 years. Almost similar age range observed by Tsimogianni et al. (2009) where they found age ranged between 44-91 years.[2] Similar almost consistent mean age observed by Patel et al. (2002) where they found age mean age 65.9±7.84 years.[3]

Regarding the sex incidence male was predominant, which was 84.6% and male to female ratio was 5.5:1, which indicates that male was predominant in this current study. Similarly, Tsimogianni et al. (2009) and Diamantea et al. (2007) showed male female ratio were 2.8:1 and 8:1 respectively, which is closely resembled with the current study.[2,4]

According to sputum, yellow/purulent was found in 55.4%, Muco-purelent in 18.5% and Mucoid in 26.2%. Maximum patients were smoker, which was more than three fourth 76.9%, had previous history of smoking 7.7% and rest 15.4% was never smoke, which is comparable with Tsimogianni et al. (2009),[2] where they found 55.3% were currently smoker, 44.7% had previous history of smoking and never smoker was not found.

Nearly a half (47.7%) of the patients were under weight (<18.5 kg/m^2), 38.5% were normal, 13.8% over weight and obesity was not found. The mean BMI was 20.8±3.43 kg/m^2 with range from 16.5 to 26 kg/m^2. (Tsimogianni et al. 2009) found mean BMI was 28±1 kg/m^2 with range from 17-54 kg/m^2, which is higher with the current study, this may be due to higher body surface area in their study patients.[2]

36.9% patients FEV_1 was found in 41-50%, more than one fourth(27.7%) patient belonged to 51- 60%, almost one fourth (24.6%) belonged to 61- 70%, 7.7% patients FEV1 was d"40% and 3.1% patient had more than 70%. The mean FEV_1 was found 53.74±10.84% with range from 22 to 74 %. Similarly, (Tsimogianni et al. 2009) have showed that mean FEV_1 (%) were 47±2% with Range from 15-87%, which support the current study.[2]

In this study sputum culture was observed and found that Pseudomonous was found 35.4%, candida in 10.8%, klebsiella in 10.8%, 6.2% was E. coli, 3.1% was streptococcus, 3.1% was s. aureus and acinetobactor/psudomonous, haemophilus influenjae, H. influnjae, pseudomonous klebsiela & stereptococcus pneumoni was 1.5% and no growth in 23.1%. (Bari et al. 2010) observed 30 patients with stable COPD, out of which 3(20.0%) patients showed positive sputum culture for bacteria, Pseudomonas 3, Klebsiellia 1, Streptococcus pneumoniae 1, Haemophilus influenza 1 and majority were Gram-negative organism.[5]

Clinical markers of COPD severity determined during an exacerbation of the disease can predict the isolation of bacteria from the sputum (Tsimogianni et al. 2009).[2] The authors showed that the presence of pus in the sputum, a post-bronchodilator FEV_1, lower than 35% predicted and a BMI lower than 22kg/m^2, were all associated with the isolation of bacteria in the sputum. The isolation of bacteria from the sputum of patients with an exacerbation of COPD can be predicted by the presence of pus in the sputum, low FEV_1 and BMI with an approximate accuracy of 90% found by (Tsimogianni et al. 2009).

According to BMI, the mean pseudomonous was found 21.50±1.76 kg/m^2, candida 23.57±1.51 kg/m^2, klebsiella 21.43±1.97 kg/m^2, E. Coli 22.13±1.65 kg/m^2, streptococcus 22.50±3.54 kg/m^2, S. aureus was 20.75±0.35 kg/m^2, no growth was 23.65±2.06kg/m^2.Tsimogianni et al. (2009) mentioned that patients with an exacerbation of COPD, pseudomonous, klebsiella, streptococcus and H.influenjae are associated with underweight patients.[2] Similar, findings also obtained by (Valk et al. 2004), (Rossi et al. 2007), (Lode et al. 2007) and (Niederman et al 2001), thus support the current study.[6,7,8]

Bacterial colonization in COPD is an important factor in disease progression mentioned by (Wilkinson et al. 2003).In this present series according to FEV_1 it was observed that the mean FEV_1 was 50.9±8.8 (%) in patients having pseudomonous, 48.4±7.8 (%) in klebsiella,50.0±7.1 (%) in streptococcus, 42.0±5.7 (%) in H. Influenjae and 60.5±9.8 (%) in no growth. The positive sputum culture pseudomonous, klebsiella, streptococcus and H.influenjae are associated with low FEV_1. In patients having an exacerbation of COPD (Tsimogianni et al. 2009) reported that positive suptum microbiology associated with FEV_1, active tobacco smoking, prior exacerbations, presence of bronchiectasis, prior use of systemic corticosteroids and/or antibiotics, sputum purulence. Patients with the greatest degree of functional impairment, as measured by their FEV_1, presented a higher probability of having an isolation of *P aeruginosa or H influnenzae* in significant concentration in sputum during an exacerbation observed by Miravitlles et al. (2010). The diagnostic yield of sputum in patients with an FEV_1 >50% was low, with a predominance of non-PPMs. Low FEV_1 and active tobacco smoking are data that should be considered when establishing an empire antibiotic treatment for exacerbated COPD (Miravitlles et al. 2010).[9] In another study, (Eller et al. 1998) have shown there is a correlation

between deterioration of lung function and the bacteria isolated from patients with infective exacerbations of COPD.[10] In acute infective exacerbations, Enterobacteriaceae and Pseudomonas spp are the predominant bacteria in patients with an FEV_1< or=35% of the predicted value. Allegra et al. (2005) evaluated whether functional impairment (FEV_1) orientates as to the infectious etiology of exacerbations and found Gram negative and P. aeruginosa/Enterobacteriaceae were isolated more frequently in the sputum when FEV_1 was <35%.[11] (Monso et al. 2003), (Patel et al. 2002) and (Zalacain et al. 1999) concluded in their respective studies that severe impairment of lung function, smoking and poor compliance with therapy are risk factors for bacterial infection in COPD, and p. aerugnosa should be suspected in patients who have been treated with antibiotics and in those not vaccinated against influenza. Thus the current study strongly consistent with the above mentioned studies.[12,3,13]

In this current study it was observed that sputum purulence, FEV_1 (<52%) and BMI (<20kg/m^2) significantly influence to develop sputum culture positivity independently. Tsimogianni et al. (2009) showed a positive sputum culture was three-fold for BMI ≤22 kg/m (OR=12.1; 95% CI: 2.9-50.5; p=0.001), and one-fold for FEV_1<35% (OR=3.9; 95% CI: 1.3-11.5; p=0.014) which is comparable with the current study.[2]

Conclusions:

This study was undertaken to clinically identify patients of COPD with exacerbation likely or unlikely to yield bacterial sputum isolates. Pseudomonous, klebsiella, streptococcus and H.influenjae are associated with underweight (low BMI) and low FEV_1 patients. FEV_1 (<52%) and BMI (<20kg/m^2) significantly influence to develop sputum culture positivity.

References:

1. Rodrigues-Roisin R, Anzeut A, Borbeau J et al. 2009, 'Global Strategy For the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease', (updated 2009).
2. Tsimogianni AM, Papiris SA, Kanavaki S et al. 'Predictors of positive sputum culture in exacerbations of chronic obstructive pulmonary disease', Respirology, 2009;14: 1114-1120.
3. Patel IS, Seemungal TA, Wilks M et al. 'Relationship between bacterial colonisation and the frequency, character and severity of COPD exacerbations', Thorax. 2002; 57: 753-4.
4. Diamantea FP, Nakou A, Drakopanagiotakis F et al. 'COPD exacerbation: correlation between sputum culture results with indices of systemic inflammation, respiratory function and factors related to exacerbation outcome', American College of Chest Physicians. 2007; 132(4): 479.
5. Bari MR, Hiron MM, Zaman SM et al. 'Mircobes responsible for acute exacerbation of COPD', Mymensingh Med J. 2010; 19(4): 576-85.
6. Van Der Valk P, Monninkhof E, Van der Palen J et al. 'Clinical Predictors of bacterial involvement in exacerbations of chronic obstructive pulmonary disease', Clin, Infect, Dis.2004; 39(7): 960-6.

   Voelkel NF, Tuder R. 'COPD: exacerbation', Chest, 2000;117(5): suppl 2, 376S-379S.
7. Lode H, Allwelt M, Balk S et al. 'A prediction model for bacterial etiology in acute exacerbation of COPD, Infection. 2007; 35: 143-9.
8. Niederman MS, Mndell LA, Anzueto A et al. 'Guidelines for the management of adults with Community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy and prevention', Am J Respir. Crit. Care Med. 2001; 163 (1): 1730-54.
9. Miravitlles M, Espinosa C, Fernandez-Laso E. 'Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Study group of bacterial infection in COPD', Chest. 1999; 116(1): 40-6.
10. Eller J, Ede A, Schaberg T et al. 'Infective exacerbations of chronic bronchitis: relation between bacteriologic etiology and lung function', Chest. 1998; 113(6):1542-8.
11. Allegra L, Blasi F, Diano PL et al. 'Sputum color as a marker of acute bacterial exacerbations of chronic obstructive pulmonary disease'. Respiratory Medicine. 2005; 99(6): 742-747.
12. Monso E, Garcia-Aymerich J, Soler N et al. 'Bacterial infection in exacerbated COPD with cahnges in sputum characteristics,' Epidemiol. Infect. 2003; 131(1): 799-804.
13. Zalacain R, Sobradillo V, Amilibia J et al. 1999, 'Predisposing factors to bacterial colonization in chronic obstructive colonization in chronic obstructive.

Chest Heart Journal
Vol. 43, No. 2, July 2019

ORIGINAL ARTICLE

Prevalence of Secretor and Non-Secretor Status Among the Random Blood Donor

Kamrun Nahar[1], Jolly Biswas[2], Subrina yesmin Binni[3], SMA Zulker Nine[4], Sk. Golam Raihan[5], Snehasish Nag[6]

Abstract:

The present study was carried out in the department of Transfusion medicine, BSMMU, Dhaka, during the period July 2008 to June 2009 to find out prevalence of secretor and non secretor among the random blood donor. For this work 100 apparently healthy donor of age between 18-60yrs of either sex were taken. Secretor status of the saliva was detected by haemagglutination inhibition (HAI) method. Among all respondents 21.0% (n=21) were 19-25 years, 54.0% (n=54) within 25 to 35 years, 25% (n=25) were 35-46 years. Mean (±SD) age of the donors was 30.95 (±6.71) years and all donors were within 19 to 46 years age range. Approximately 49% (n=49) of the respondents are B, 35.0% (n=35) are A, 10.0% (n=10) are O and 6.0% (n=6) are AB blood groups. Out of all respondents of secretor status 39.2% (n=20) are A blood group, 41.2% (n=21) are B blood group, 5.9% (n=3) are AB blood group and 13.7% (n=7) are O blood group. In respondents with non secretor status 30.6% (n=15) are A blood group, 57.0% (n=28) are B blood group, 6.1% (n=3) are AB blood group and 6.1% (n=3) are O blood group (P>0.05). Among the respondents male was 85.0% (n=85) and female was 15.0% (n=15) of total study population. Among the male respondents 52.9% (n=45) are secretor and 47.1% (n=40) are non secretor and in female respondents 40.0% (n=6) are secretor and 60.% (n=9) are non secretor (p>0.05). Out of all respondents 51.0% (n=51) had secretor status and 49.0% (n=49) had non secretor status. There is no association of any type of blood group or sex differentiation among the secretor and non secretor status of the blood donor.

[Chest Heart J. 2019; 43(2) : 71-77]
DOI: http://dx.doi.org/10.33316/chab.j.v43i2.2019604

Introduction

In 1900, Karl Landsteiner, the Austrian physiologist discovered the existence of three blood groups in human beings which he designated as A, B and O. In 1902 fourth blood group AB was established by Von Decastlello and Sturle. Then the entire population was classified into group A, B,O and AB by the presence or absence of A and B antigens on red blood cell membrane.[1]

In human, over 400 red cell antigens have been identified[2] but the recognized blood group systems by the ISBT are 26 in number.[3] ABO system is the most important blood group system as far as the

1. Assistant Professor, Department of Transfusion Medicine, Bangladesh Medical College and Hospital, Dhanmondi, Dhaka, Bangladesh.
2. Professor Department of Transfusion Medicine, BSMMU, Dhaka, Bangladesh
3. Assistant Professor, Shahid Ziaur Rahman Medical college, Bogura, Bangladesh.
4. Specialist, Apollo Hospitals Dhaka, Bangladesh.
5. Medical Officer, Department of Transfusion Medicine, Bangladesh Medical college and Hospital, Dhanmondi, Dhaka, Bangladesh.
6. Registrar, Respiratory Medicine, NIDCH, Mohakhali, Dhaka

Correspondence to: Dr. Kamrun Nahar, Department of Transfusion Medicine, Bangladesh Medical college and Hospital, Dhanmondi, Dhaka, Bangladesh. Email: kamrunznp@gmail.com

Correspondence to:
Submission on: 10 May, 2019 **Accepted for Publication:** 22 June, 2019
Available at http.//www.chabjournal.org

transfusion is concerned. ABO system is under the control of ABO and Hh genes. The person who inherits at least one H gene produces N-acetyl galactosaminyl transferase, which converts H substance into A antigen. On the other way, person having B genes produces D-galactosyl transferase, and converts H substance into B antigen. O gene is amorph and no enzymes produced and thus H substance remains as H antigen on the red cell of O individual.[4]

The ABO determinants are oligosaccharides, which remain bound to cell membrane lipid as glycolipid and to proteins as glycolproteins[4]. These group specific oligosaccharides are not only confined to the red cells but also have a wide distribution. They also present on other tissue cells and in the body fluids, if the person is secretor. ABH substances are secreted in a water soluble form as glycoprotein by mucous glands, glands in the upper respiratory tract, gastrointestinal and the uterine. Prostatic gland and the lactating mammary glands of secretors also produce ABH substances.[1]

ABH blood group antigens are expressed by the attachment of the specific monosaccharide to precursor substances. There are four types of precursor substances. The human genome encodes two different ±1-2 fucosyl transferases corresponding to the products of H (FUT-1) and the secretor loci (FUT-2). The ± 1-2 fucosyl transferases (FUT-1) utilizes type 2,3,4 precursorsubstances and expresses h antigen on red cell. The (FUT-2) ± 1-2 fucosyl transferase utilizes type 1 precursor to express ABH antigen in secretor and plasma but can also use type 2 structures.[5]

The term secretor is applied to those persons who secret H with or without A or B group specific substances into secretory fluids like saliva and mucous of the digestive and respiratory tract etc. While those individuals who do not secret ABH group specific substances in body fluid are known as non secretors. A person who is an ABH secretor will secret group specific substances according to their ABO blood group: for example- group O individual will secret H soluble antigen and group A individual will secret A and H antigens.[6]

It is established that the secretor status is controlled by a pair of allelic genes- Se and Se. Those individual who are homozygous (Se Se) or heterozygous (Se Se) are secretors and those who are homozygous for se se are non secretors. It is not only the Se gene but also the interaction of Hh gene is necessary for an individual to be a secretor. So, for a person of A phenotype, to be secretor, must posses at least one A gene. One Se gene and one H gene. If a person is Bombay phenotype but posses Se gene will secret no ABH substances in the secretion due to lacking of H gene.[4]

ABH group specific substances are detected in the following secretion- Saliva, Tear, urine, Bile, Milk, Amniotic fluid, Seminal fluid. One of the richest and readily available sources is Saliva. So, Saliva is used in laboratory to detect the secretor status of an individual.

It can be quite useful to determine ABH secretor status as in certain doubtful cases of ABO grouping in conventional method, can be actually detected specially the subgroup of ABO system.[4]

The secretor or non secretor status also provides some degree of generalized information regarding disease condition. A Copenhagen study found the lifetime prevalence of peptic ulcer in ABH non secretor was 15%. Non Secretors are less resistant to infection by H. Pylori than secretors.[7]

A study among the women with acute uncomplicated pyelonephritis revealed that non secretor has a risk of recurrent urinary tract infection. Among 106 woman with acute uncomplicated pyelonephritis 41% (44 out of 106) were non secretors which was greater than the 22.6% (217 out of 960) of non secretors among control group (P<.001).[8]

Secretor status (secretor and non-secretor)

The term secretor is applied to those persons who secret H with or without A or B group specific substances into secretory fluids like saliva and mucous of the digestive and respiratory tract etc. While those individuals who do not secret ABH group specific substances in secretory body fluid are known as non-secretors. A person who is an ABH secretor will secret group specific substances according to their ABO blood group; for example, a group O individual will secret H soluble antigen and a group A individual will secret A and H soluble antigens etc.

It is established that the secretor status is controlled by a pair of allelic genes, Se and se. Thus individuals who are homozygous (SeSe) or heterozygous (Sese) are secretors and those who are homozygous for sese are non-secretors. It is not only the Se (FUT2) gene but also the interaction of Hh (FUT1) gene is necessary for an individual to be a secretor. Thus, for a person of A phenotype, to be a secretor, must possesses at least

one A gene, one Se gene and one H gene. If a person is Bombay phenotype but possesses Se gene will secret no ABH substances in the secretion due to lacking of H gene.[9]

Frequency of Secretor and non-secretor status

Approximately 80% of the random US population has inherited the Se gene and are secretors.[10] In Negroes 40% are non-secretors.[11] There was no study on secretor and non-secretor status, so far, in Bangladesh.

Objectives

General objective:

To find out the prevalence rate of secretor and non secretor status among the random blood donors

Specific objectives:

1. To find out the demographic status of the respondents
2. To find out the frequency of ABO blood group among different secretor status

Methodology

Type of study:

It was a cross sectional study

Study period:

This study was conducted during the period from July 2008 to June 2009 for duration one year

Study place:

This study was conducted at the Department of Transfusion Medicine, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka

Study population:

All voluntary blood donors who were attended in the Department of Transfusion Medicine, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka during the study period were considered as study population

Sample size:

Total 100 respondents were enrolled as study sample

Sampling method:

Systematic sampling

Variables:

- Age
- Sex
- ABO blood group
- Rh typing
- Height
- Weight
- Secretor status

Ethical consideration:

Prior to commencement of this study, the research protocol was approved. The aims and objectives of the study along with its procedure, risks and benefits of this study were explained to the respondents in easily understandable local language and then written informed consent from the patients or their parents were obtained. It was assured that all information and records would be kept confidential and the procedure would be helpful for both physicians and patients in making decision for management.

Data collection tool

Data were collected by semi-structured questionnaire by the investigator

Data analysis:

All the data were checked and edited after collection. Then the data were entered into computer and analyzed with the help of SPSS-14 (SPSS incorporation, Chicago, IL, USA) (Statistical package for social sciences) win version 14 software programmed. An analysis plan has developed keeping in view with the objectives of the study.

After processing of all available information, statistical analysis was done. For all statistical tests p less than 0.05 will be considered as statistically significant. Continues variable was presented as mean ± SD and numerical variable was presented as frequency and percentage. Chi square test was done to measure the level of significance.

Results and observation

Table-I

Distribution of the respondents by age (n=100)

Age (in year)	Frequency	Percent
19-<25	21	21.0
25-35	54	54.0
>35-46	25	25.0
Total	100	100.0
Mean ± SD (Range)	30.95 ± 6.71	(19-46)

Table shows the age distribution of the respondents. Among all respondents 21.0% were up to 25 years age, 54.0% within 25 to 35 years and 25.0% above 35 years. Mean (±SD) age of the donors was 30.95 (± 6.71) years and all donors were within 19 to 46 years age range.

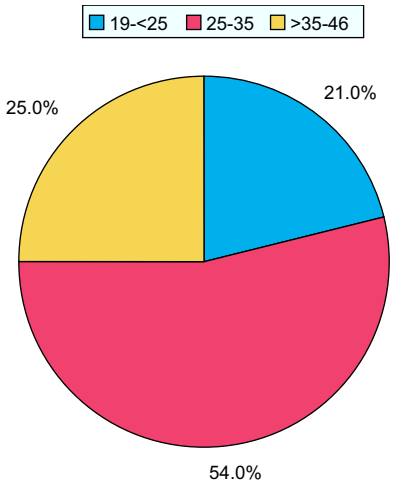


Fig.-1: *Pie diagram of the respondents by age*

Table-II

Distribution of the respondents by sex (n=100)

Sex	Frequency	Percent
Male	85	85.0
Female	15	15.0
Total	100	100.0

Sex distribution of the respondents revealed male was 85.0% and female was 15.0% of total study population.

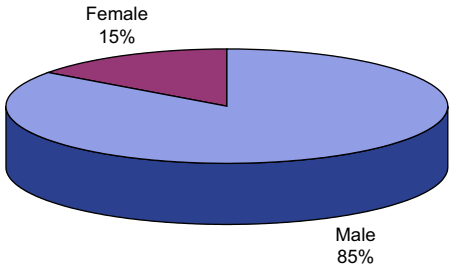


Fig.-2: *Pie diagram of the respondents by sex*

Table-III

Distribution of the respondents by blood group (n=100)

Blood group	Frequency	Percent
A	35	35.0
B	49	49.0
AB	6	6.0
O	10	10.0
Total	100	100.0

Table shows the blood group distribution of the respondents. Approximately half of the respondents had B, 35.0% had A, 10.0% had O and 6.0% had AB blood group.

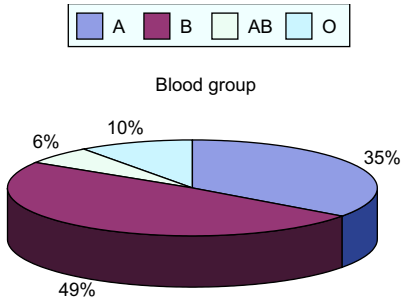


Fig.-3: *Pie diagram of the respondents by blood group*

Table-IV

Distribution of the respondents by secretor status

Secretor status	Frequency	Percent
Secretor	51	51.0
Non secretor	49	49.0
Total	100	100.0

Out of all respondents 51.0% had secretor status and 49.0% had non-secretor status

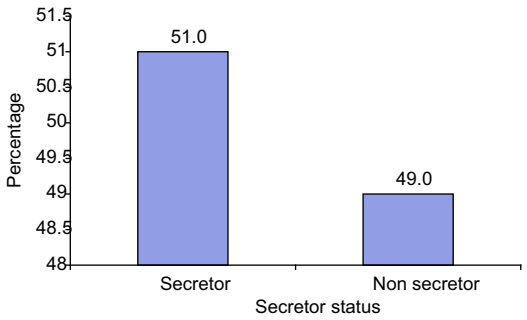


Fig.-4: *Bar diagram Secretor and non-secretor status of respondents*

Table-V

Distribution of the respondents by ABO blood grouping and secretor status

ABO Blood grouping	Secretor status		p value*
	Secretor	Non secretor	
A	20 (39.2)#	15 (30.6)	
B	21 (41.2)	28 (57.1)	
AB	3 (5.9)	3 (6.1)	0.351
O	7 (13.7)	3 (6.1)	
Total	51 (100.0)	49 (100.0)	

Figure within parenthesis denoted corresponding column percentage

* Chi square test was done to measure the level of significance

Out of all respondents of secretor status 39.2% had A, 41.2% had B, 5.9% had AB and 13.7% had O blood group. In respondents with non secretor status 30.6% had A, 57.0% had B, 6.1% had AB and 6.1% had O blood group. No statistically significant difference was observed between secretor and non secretor status in term of ABO blood grouping (p>0.05).

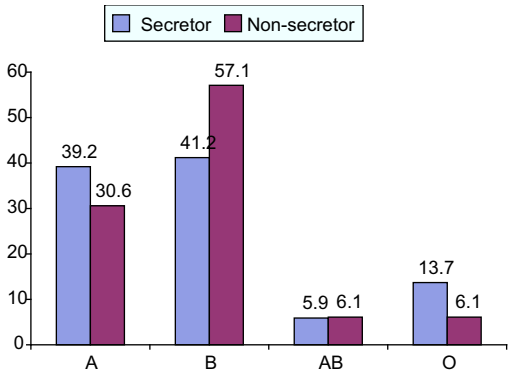


Fig.5: *Bar diagram of the respondents by ABO blood grouping and secretor status*

Table-VI

Distribution of the respondents by sex and secretor status

Sex	Secretor status		p value*
	Secretor	Non secretor	
Male	45 (52.9)#	40 (47.1)	
Female	6 (40.0)	9 (60.0)	0.355
Total	51 (51.0)	49 (49.0)	

Out of all male respondents 52.9% had secretor status and 47.1% had non secretor status and in female respondents 40.0% had secretor and 60.0% had non secretor status.

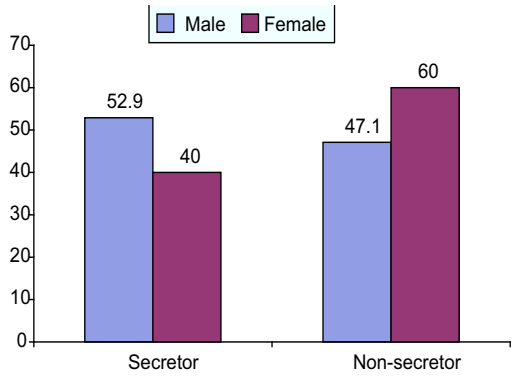


Fig.-6: *Bar diagram of the respondents by sex and secretor status*

Discussion:

A person can be either a secretor or a non-secretor. This is completely independent of whether their blood type is A, B, AB or O. In a simplified sense, a secretor is defined as a person who secretes their blood type antigens into body fluids and secretions like the saliva in mouth, the mucus in digestive tract and respiratory cavities, etc. A non-secretor on the other hand puts little to none of their blood type into these same fluids.

All respondents of the present study were within 19 to 46 years age range and mean (±SD) age of them was 30.95 (± 6.71) years. Maximum 54.0% respondents were within 25 to 35 years age group.

Sex distribution of the patient revealed male and female ratio 5.67:1 in present series.

In the present study out of all male respondents 52.9% (n=45) had secretor status and 47.1% (n=40) had non secretor status and in female respondents 40.0% (n=6) had secretor and 60.0% (n=9) had non secretor status.

Ronchetti et al[12] series 21.4% (n=42) male had non secretor and 78.6% (n=154) had secretor and in female controls 19.9% (n=33) had non secretor and 80.1% (n=133) had secretor status.

In the present study approximately half (n=49) of the patients had B, 35.0% (n=35) had A, 10.0% (n=10) had O and 6.0% (n=6) had AB blood group.

Out of all respondents of secretor status 39.2% (n=20) had A, 41.2% (n=21) had B, 5.9% (n=3) had AB and 13.7% (n=7) had O blood group. In respondents with non secretor status 30.6% (n=15) had A, 57.1% (n=28) had B, 6.1% (n=3) had AB and 6.1% (n=3) had O blood group (p>0.05).

In the present study among all blood donor 51.0% (n=51) had secretor status and 49.0% (n=49) had non-secretor status.

In Dodge series[13] of 531 salivas from school children in Belfast showed a non-secretor frequency of only 26.55% (n=41). Nerell[14] has collected together the figures of 12 investigated populations as far flung as Egypt and Canada with frequencies of non-secretors ranging from 11.1% to 25.4%. Pradhan et al[15] found 28.17% non-secretors among medical students at Kanpur. An investigation has been carried out by Nerell[16] on the frequency of secretors and non-secretors respectively in a

central Swedish population. Out of 2093 individuals tested, 1631 (78%) to be secretors and 462 (22%) non-secretors

All of these studies showed considerably lower frequency of non secretor status, but in the present study 49.0% (n=49) of non secretor status, it may be due to small sample size.

In a study by Chaim et al[17], the relative percentages of healthy subjects carrying oral candida were higher in O group. There were a higher number of non-secretors (48.9%) with oral and vaginal candida infection compared to their proportion (26.6%) in healthy population.

In Macafee[18] series, 387 out of 616 (62.83%) diabetic patients were secretor and 229 out of 616 (37.17%) non secretor, on the other side in control group 306 out of 475 (64.4%) and 169 out of 475 (35.58%) were Secretor and Non-secretor respectively.

It was observed that in Kulkarni and Venkatesh [11] series out of the 64 patients, 15 were secretors and 49 were non-secretors. However 43 subjects were secretors and 13 non-secretors among the 56 controls.

Our results suggest that secretor status was more frequent in normal blood donor in our country and it is comparable with a previously done Bangladeshi study by Akhter.[19] The frequency of ABH secretor and non secretor was 25 out of 42 (60.0%) and 17 out of 42 (40.0%) respectively.

Conclusion:

It can be concluded in the present study that secretor status of ABH blood group is dominant in normal blood donor of our country and comparable with many other studies conducted in different parts of the world.

In this study sample size was small and it is a single centered study. This study can be done with large sample and the detection of secretor status was conducted by conventional haemagglutination inhibition method not by highly sensitive ELISA method

Recommendations

1. A longitudinal study with large sample size should be conducted
2. Multicentred study should be conducted
3. ELISA method should be used instead of HAI method

References

1. Boorman KE, Dodd BE, Lincoln PJ. Blood group serology. 6th edn., Churchill Livingstone, UK. 1988; P.48-49, 82,120.
2. Brozovic B, Brozovic M. Manual of clinical blood transfusion. Churchill Livingstone, UK, 1987, p. 2
3. Greer JP, Rodgers GM, Foerster J, Paraskevas F, Lukens JN, Glader B (eds) 1999, Wintrobe's clinical hematology, 11th ed, Lippincott Williams and Wilkins, Philadelphia, USA p. 793
4. Mollison PL, Engelfriet CP, Contreras M. Blood transfusion in clinical Medicine. 10th edn. Blackwell Science, UK, 1997, p. 69-133.
5. Mollison P.L, Engelfriet CP, Contreras M. Blood transfusion in clinical Medicine. 11th edn. Blackwell Science, UK, 1997, p. 144-145.
6. Rahman M. Laboratory techniques on transfusion medicines, 2001; (11): P- 246.
7. D'Adamo PJ, Kelly GS, Metabolic and Immunologic Consequences of ABH Secretor and Lewis Subtype Status. Altern Med Rev 2001;6(4):390-405
8. Ishitoya S, Yamamoto S, Mistumori K, Ogawa O, Terai A. Non-secretor status is associated with female acute uncomplicated pyenolnephritis, BJU, International, June 2002; vol- 89. P. 851.
9. Mollison PL, Engelfriet CP, Contreras M. Blood transfusion in clinical Medicine. 10th edn. Blackwell Science, UK, 1997, p. 69-133.
10. Wilkinson SL. Secretor and soluble ABH antigens: The Lewis, I, P, and Globoside Blood Group Systems. In: Sally V. Rudmann (ed) Textbook of blood banking and transfusion medicine. 2nd edn. Chapter 4 Elsevier Health Sciences, 2005 p.86
11. Race RR, Sanger R. Blood groups in man, 6th edn. Blackwell Scientific Publications, Oxford 1975, p. 311-40

12. Ronchetti F, Villa MP, Ronchetti R, Bonci E, Latini L, Pascone R et al. ABO/Secretor genetic complex and susceptibility to asthma in childhood. Eur Respir J 2001; 17: 1236–1238.

13. Dodge JA. ABO blood groups and infantile hypertrophic pyloric stenosis. British Medical Journal, 1967;4:781-782.

14. Nerell G. Secretors of ABH antigen in a central Swedish population. Annals of Human Genetics 1964;27:119-123.

15. Pradhan S, Pradhan AC, Singh KN, Sarnuel KC, Singh B. Some observations on the secretion of blood group substances in the saliva in health. Indian Journal of Medical Sciences 1970;24:586.

16. Nerell G. Secretors of ABH antigen in a central Swedish population. Ann. Hum. Genet., Lond. 1963;27:119-23.

17. Chaim W, Foxman B, Sobel JD. Association of recurrent vaginal candidates and secretory ABO and Lewis phenotype. J Infect Dis 1997; 176: 828–830.

18. Macafee AL. Blood groups and diabetes mellitus. J. Clin. Path. 1964;17:39-41

19. Akhter S. Association or Non-association of secretor status with transfusion dependant thalassaemic patients. Bangladesh 2006

Chest Heart Journal
Vol. 43, No. 2, July 2019

ORIGINAL ARTICLE

Role of Acetazolamide for the Correction of Metabolic Alkalosis in Post-NIV COPD Patients

Md. Sanwar Nawaz Khan[1] , Md. Abdur Rouf[2], K.M. Monjurul Alam[3], Romal Chowdhury[4], Titop Kumar Bala[5],Syed Nesar Ahmed[6], Mofazzal Haider Siddique[6], Arjuman Sharmin[7], Bipul Kanti Biswas[8], Mahmud Rahim[8], Salah Uddin Anach[6]

Abstract:

Background: *COPD is a leading cause of morbidity and mortality. Acute hypercapnic respiratory failure in acute exacerbation of COPD (AECOPD) patients can be effectively treated by non invasive ventilation (NIV). But NIV may be less successful if it induce metabolic alkalosis (MA).*

Objective: *This study aims to assess the role of acetazolamide (ACET) for the correction of metabolic alkalosis (MA) in post-NIV COPD patients.*

Methods: *This quasi experimental study was conducted in Respiratory Medicine department of National Institute of the Diseases of The Chest & Hospital (NIDCH), Mohakhali, Dhaka from april, 2017 to march, 2019 in fifty two AECOPD patients with hypercapnic respiratory failure who developed MA following NIV. Twenty six patients were treated with acetazolamide 500mg orally daily for two consecutive days (Day 0 and 1) and compared with twenty six patients without acetazolamide. Both groups were non invasively ventilated in a bilevel positive airway pressure (BiPAP). The following parameters were measured: arterial pH, PO2, PCO2, HCO3-, serum electrolytes (Na+, K+, Cl-) and urinary pH. Results were expressed as mean ± SD. A value of $p < 0.05$ was considered statistically significant for all tests.*

Results: *In this study, maximum patients were male and within age group of 60 - 69 years. Analysis within acetazolamide group showed significant reduction of arterial pH (7.41 ± 0.03 vs. 7.49 ± 0.02, p value < .001), PCO2 (55.95 ± 3.12 vs. 61.93 ± 4.87, p value < 0.001), HCO3- (35.76 ± 2.90 vs. 46.79 ± 3.48 , p value < 0.001). Moreover, acetazolamide group showed significant increase of PO2 (62.83 ± 7.64 vs. 54.19 ± 5.71, p value < 0.001) and urine pH (6.64 ± 0.33 vs. 5.87 ± 0.38, p value <0.001). Analysis between groups showed significant difference between change of arterial pH, PCO2, HCO3-, PO2 and urine pH. No adverse events were observed in both acetazolamide group and without acetazolamide group.*

Conclusions: *Acetazolamide has a role for the correction of metabolic alkalosis in post-NIV COPD patients.*

[Chest Heart J. 2019; 43(2) : 78-83]
DOI: http://dx.doi.org/10.33316/chab.j.v43i2.2019605

Introduction:

Acute exacerbations of chronic obstructive pulmonary disease are critical events in the natural history of the disease and are associated with accelerated loss of lung function and poor quality of life[1].

1. RMO, National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh.
2. Professor, Respiratiry Medicine, NIDCH, Mohakhali, Dhaka, Bangladesh.
3. Assistant Professor, Respiratory Medicine, Shaheed Ziaur Rahman Medical College, Bogra, Bangladesh.
4. Medical Officer, NIDCH, Mohakhali, Dhaka, Bangladesh.
5. Registrar, NIDCH, Mohakhali, Dhaka, Bangladesh.
6. MD Phase B Resident, NIDCH, Mohakhali, Dhaka, Bangladesh.
7. Assistant Professor, Enam Medical College and Hospital, Savar, Dhaka.
8. Associate Professor, NIDCH, Mohakhali, Dhaka, Bangladesh.

Correspondence to: Dr. Md. Sanwar Nawaz Khan, RMO, MU-IX, National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh. Cell: 01712217618, e-mail: sanwarnawaz@gmail.com

Correspondence to:
Submission on: 22 May, 2019 **Accepted for Publication:** 8 June, 2019
Available at http.//www.chabjournal.org

Non-invasive ventilation (NIV) has been shown to be an effective treatment for acute hypercapnic respiratory failure (AHRF) during COPD hospitalization. The addition of NIV to standard medical treatment for AHRF decreases the need for endotracheal intubation, reduces rate of complications, mortality and the duration of hospitalization[2,3,4].

If a chronically elevated PCO2 is rapidly lowered in patients undergoing mechanical ventilation, the plasma bicarbonate concentration may remain elevated for a period of time. Reduction of the PCO2 with a persistently elevated bicarbonate concentration results in a form of metabolic alkalosis that is called "posthypercapnic" metabolic alkalosis[5]. Metabolic alkalosis causes hypoventilation and reduce improvement of respiratory failure[6].

Acetazolamide (ACET) is a carbonic anhydrase inhibitor has been used to increase renal bicarbonate loss in metabolic alkalosis after proper fluid loading and potassium supplementation[7,8]. Correction of metabolic alkalosis also causes improvement of ventilation and helps in reduction of PaCO2[8].

Methods:

This was a quasi experimental study. Patients with AECOPD who develop metabolic alkalosis after getting NIV (BiPAP) treatment in the inpatient department of Respiratory Medicine of National Institute of diseases of the Chest and Hospital (NIDCH) during the study period from April 2017 to March 2019, were the study population and those fulfilling the inclusion and exclusion criteria were enrolled as study sample by non random purposive sampling. All patients of AECOPD with hypercapnic respiratory failure (PaCO2 e" 45 mmHg, PaO2 <60 mmHg) who develop metabolic alkalosis (pH e"7.45 and $HCO3^-$ e"30 mmol/L) following NIV treatment were included whereas patints having concomitant respiratory and neuromuscular diseases, renal failure, serum potassium levels <3.0 mEq/L, known hypersensitivity to acetazolamide or recent administration of bicarbonates were excluded.

Study Procedure:

Acute exacerbation of COPD (AECOPD) with acute hypercapnic respiratory failure patients were treated in ICU or RCU with NIV (BiPAP). Among them who developed metabolic alkalosis (pH > 7.45) as diagnosed by arterial blood gas analysis (ABG), were enrolled. Enrolled subjects were properly explained the study and written informed consent was obtained from all participants. All included subjects were concomitantly treated following international guidelines for COPD exacerbation, with systemic corticosteroids and empirical antibiotic therapy and for related comorbidities. After enrollment, 26 patients were treated with acetazolamide and 26 patients were not treated with acetazolamide. At the day of enrollment (day 0), acetazolamide 500 mg was given orally once a day at morning and continue for two consecutive days. The following laboratory parameters were measured at enrollment (day 0) and after 24 (day 1) and 48 hours (day 2): Arterial pH, partial pressure of O2 (PaO2), partial pressure of CO2 (PaCO2), Urine pH, Serum potassium, chloride, sodium and bicarbonates ($HCO3^-$). Enrolled 26 patients with acetazolamide were compared with 26 patients control group (without acetazolamide) on the basis of laboratory parameters.

Results:

Table-I

Demographic profile of the patients in two groups (n-52)

	With Acetazolamide	Without Acetazolamide	p value
Age (years)			
50 - 59	8 (30.8)	5 (19.2)	
60 - 69	10 (38.5)	12 (46.2)	
≥70	8 (30.8)	9 (34.6)	
Mean±SD	63.34 ± 7.81	64.19 ± 7.08	0.684
Gender			
Male	25 (96.2)	25 (96.2)	1.000
Female	1 (3.8)	1 (3.8)	

Unpaired t test and Chi-Square test was done to measure the level of significance

Table-II

Smoking status of the patients in two groups (n-52)

	With Acetazolamide	Without Acetazolamide	p value
Smoker	16 (61.5)	15 (57.7)	0.958
Ex-smoker	9 (34.6)	10 (38.5)	
Biomass	1 (3.8)	1 (3.8)	

Chi-Square test was done to measure the level of significance

Table-III

Co-morbidities of the patients in two groups (n-52)

	With Acetazolamide	Without Acetazolamide	p value
Diabetes mellitus	7 (26.9)	11 (42.3)	0.382
Hypertension	12 (46.2)	15 (57.7)	0.405
IHD	10 (38.5)	12 (46.2)	0.575

Chi-Square test was done to measure the level of significance

Table-IV

Comparison of arterial pH at enrollment, after 24 hours and after 48 hours between two groups (n-52)

Arterial pH	With Acetazolamide	Without Acetazolamide	p value
At enrollment	7.49 ± 0.02	7.47 ± 0.02	0.382
After 24 hours	7.44 ± 0.03	7.49 ± 0.02	0.405
After 48 hours	7.41 ± 0.03	7.50 ± 0.03	0.575
% change after 48 hrs from enrollment	-1.10 ± 0.37	0.41 ± 0.43	<0.001
p-value (at enrollment vs after 48 hours	<0.001	<0.001	

Unpaired t test was done between groups and paired t test was done within groups (between at enrollment and after 48 hours) to measure the level of significance

Table-V

Comparison of urine pH at enrollment, after 24 hours and after 48 hours between two groups (n-52)

Urine pH	With Acetazolamide	Without Acetazolamide	p value
At enrollment	5.87 ± 0.38	5.77 ± 0.33	0.300
After 24 hours	6.35 ± 0.40	5.78 ± 0.36	<0.001
After 48 hours	6.64 ± 0.33	5.84 ± 0.33	<0.001
% change after 48 hrs from enrollment	13.66 ± 4.77	1.28 ± 3.91	<0.001
p-value (at enrollment vs after 48 hours	<0.001	0.116	

Unpaired t test was done between groups and paired t test was done within groups (between at enrollment and after 48 hours) to measure the level of significance.

Table-VI

Comparison of PO2 at enrollment, after 24 hours and after 48 hours between two groups (n-52)

PO_2	With Acetazolamide	Without Acetazolamide	p value
At enrollment	54.19 ± 5.71	54.00 ± 4.86	0.896
After 24 hours	59.31 ± 6.96	58.04 ± 5.73	0.476
After 48 hours	62.83 ± 7.64	60.08 ± 6.11	0.168
% change after 48 hrs from enrollment	16.29 ± 8.44	11.40 ± 8.03	0.043
p-value (at enrollment vs after 48 hours	<0.001	<0.001	

Unpaired t test was done between groups and paired t test was done within groups (between at enrollment and after 48 hours) to measure the level of significance

Table-VII

Comparison of PCO_2 at enrollment, after 24 hours and after 48 hours between two groups (n-52)

PCO_2	With Acetazolamide	Without Acetazolamide	p value
At enrollment	61.93 ± 4.87	60.09 ± 4.46	0.163
After 24 hours	58.57 ± 3.46	57.49 ± 3.84	0.293
After 48 hours	55.95 ± 3.12	57.58 ± 3.12	0.074
% change after 48 hrs from enrollment	-8.99 ± 6.46	-3.84 ± 6.56	0.008
p-value (at enrollment vs after 48 hours	<0.001	0.005	

Unpaired t test was done between groups and paired t test was done within groups (between at enrollment and after 48 hours) to measure the level of significance

Table-VIII

Comparison of serum electrolytes at enrollment, after 24 hours and after 48 hours between two groups (n-52)

	With Acetazolamide	Without Acetazolamide	p value
HCO_3^-			
At enrollment	46.79 ± 3.48	42.23 ± 2.79	<0.001
After 24 hours	39.85 ± 4.24	44.52 ± 2.75	<0.001
After 48 hours	35.76 ± 2.90	45.69 ± 3.86	<0.001
% change after 48 hrs from enrollment	-23.93 ± 5.08	8.34 ± 8.08	<0.001
p-value (at enrollment vs after 48 hours)	<0.001	<0.001	
K^+			
At enrollment	4.06 ± 0.38	3.90 ± 0.31	0.117
After 24 hours	3.69 ± 0.35	3.75 ± 0.30	0.530
After 48 hours	3.09 ± 1.16	3.78 ± 0.24	0.004
% change after 48 hrs from enrollment	-14.47 ± 7.21	-2.77 ± 5.93	<0.001
p-value (at enrollment vs after 48 hours)	<0.001	0.012	
Na^+			
At enrollment	138.65 ± 3.11	137.04 ± 3.12	0.067
After 24 hours	137.54 ± 2.55	136.81 ± 2.28	0.281
After 48 hours	136.78 ± 2.26	136.42 ± 1.75	0.533
% change after 48 hrs from enrollment	-1.51 ± 1.79	-0.42 ± 1.88	0.043
p-value (at enrollment vs after 48 hours)	0.001	0.232	
Cl^-			
At enrollment	96.31 ± 2.98	96.85 ± 3.09	0.525
After 24 hours	95.23 ± 2.79	96.46 ± 2.20	0.083
After 48 hours	94.86 ± 2.63	96.73 ± 1.59	0.004
% change after 48 hrs from enrollment	-1.56 ± 1.22	-0.18 ± 2.87	0.038
p-value (at enrollment vs after 48 hours)	<0.001	0.847	

Unpaired t test was done between groups and paired t test was done within groups (between at enrollment and after 48 hours) to measure the level of significance

Discussion:

In this study, maximum patients were within age group of 60 – 69 years. Mean age of the patients was 63.34 ± 7.81 years and 64.19 ± 7.08 years in acetazolamide and without acetazolamide groups respectively. In this study most of the patients were male. Out of 26 patients in each group 25 were male and 1 was female with male : female ratio of 25: 1.

More than half of the COPD patients were current smoker in both groups in this study.

Most common co-morbidity was hypertension in both groups followed by IHD and diabetes mellitus. There were no significant differences between groups in co-morbidities in this study.

Serum pH level decreased significantly in COPD patients treated with acetazolamide whereas serum pH level increased in COPD patients treated without acetazolamide. In this study serum pH significantly decreased from 7.49 ± 0.02 to 7.41 ± 0.03 (p value < .001). In the study of Fontana et al.[9] serum pH significantly decreased from 7.46 ± 0.06 to 7.41 ± 0.06 (p value = 0.004).

In this present study, urine pH level increased significantly in COPD patients treated with acetazolamide. Change of urine pH level was significantly higher in COPD patients treated with acetazolamide than that of without acetazolamide.

In this current study, urine pH increased from 5.87 ± 0.38 to 6.64 ±0.33 (p value <0.001). Fontana et al[9] found urine pH significantly increased from 5.80 ± 0.82 to 6.94 ± 0.77 (p value = 0.006).

PCO_2 level decreased significantly in both groups. But change of PCO_2 level was significantly higher in COPD patients treated with acetazolamide than that of without acetazolamide. In this study PCO2 decreased from 61.93 ± 4.87 mmHg to 55.95 ± 3.12 mmHg (p value < 0.001). Similarly in the study of Fontana et al[9] PaCO2 decreased from 63.9 ± 9.8 mmHg to 54.9 ± 8.3 mmHg (p value = 0.01).

PO_2 level increased significantly in both groups. But change of PO_2 level was significantly higher in COPD patients treated with acetazolamide than that of without acetazolamide. With acetazolamide group PO2 increased from 54.19 ± 5.71 to 62.83 ± 7.64 (p value <0.001) and without acetazolamide group PO2 increased from 54.00 ± 4.86 to 60.08 ± 6.11 (p value <0.001).

HCO_3^- level significantly decreased in COPD patients treated with acetazolamide whereas serum HCO_3^- level significantly increase in COPD patients treated without acetazolamide. Serum HCO_3^- level decreased from 46.79 ± 3.48 to 35.76 ± 2.90 (p value < 0.001). Fontana et al[9] also found serum HCO_3^- level decreased from 43.5 ± 5.9 to 36.1 ± 5.4 (p value = 0.005).

K^+, Na^+ and Cl^- level decreased significantly in COPD patients treated with acetazolamide. K^+ also significantly decreased in COPD patients treated without acetazolamide.

Conclusion:

Acetazolamide can significantly reduce arterial pH in AECOPD patients with metabolic alkalosis following NIV. It also helps to reduce PCO2 and improve PO2. So, it can be concluded that Acetazolamide has an important role for the correction of metabolic alkalosis in post-NIV COPD patients.

References:

1. Rabe, K.F., Hurd, S., Anzueto, A., Barnes, P.J., Buist, S.A., et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2007;176:532-55.
2. Nava, S., Grassi, M., Fanfulla, F., Domenighetti, G., Carlucci, A., et al. Non-invasive ventilation in elderly patients with acute hypercapnic respiratory failure: a randomised controlled trial. *Age and ageing.* 2011;40(4), 444-450.
3. Ambrosino, N. and Vagheggini, G. Non-invasive ventilation in exacerbations of COPD. *International journal of chronic obstructive pulmonary disease.* 2007;2(4):471.
4. Evans, T.W., Albert, R.K., Angus, D.C., Bion J.F., Chiche J., et al. International Consensus Conference in Intensive Care Medicine: non-invasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med.* 2001;163:283–91.

5. Schwartz, W.B., Hays, R.M., Polak, A. and Haynie, G.D. Effects of chronic hypercapnia on electrolyte and acid-base equilibrium. II. Recovery, with special reference to the influence of chloride intake. *The Journal of clinical investigation.* 1961;40(7):1238-1249.

6. Berthelsen, P. Cardiovascular performance and oxyhemoglobin dissociation after acetazolamide in metabolic alkalosis. *Intensive care medicine* 1982;8(6):269-274.

7. Heming, N., Faisy, C. and Urien, S. Population pharmacodynamic model of bicarbonate response to acetazolamide in mechanically ventilated chronic obstructive pulmonary disease patients. *Critical Care*. 2011;15(5):213.

8. Faisy, C., Mokline, A., Sanchez, O., Tadié, J.M. and Fagon, J.Y. Effectiveness of acetazolamide for reversal of metabolic alkalosis in weaning COPD patients from mechanical ventilation. *Intensive care medicine*. 2010;36(5):859-863.

9. Fontana, V., Santinelli, S., Internullo, M., Marinelli, P., Sardo, L., et al. Effect of acetazolamide on post-NIV metabolic alkalosis in acute exacerbated COPD patients. *Eur Rev Med Pharmacol Sci*. 2016;20(1):37-43.

Chest Heart Journal
Vol. 43, No. 2, July 2019

ORIGINAL ARTICLE

Association between Platelet Indices and the Severity of Acute Exacerbation of COPD

Mahmuda Begum[1], Snehashis Nag[2], Md. Sayedul Islam[3], Sanjoy Kumar Kar[4], Subrata Kumar Gain[4]

Abstract

Background: *Chronic obstructive pulmonary disease (COPD) is the most commonly encountered respiratory problem in hospital setting which leads to disability and even death. Recent studies have shown that the platelet indices are associated with several cardiovascular diseases including COPD. There is little data on COPD and its relation with platelet indices and more limited data is observed regarding the relationship between platelet indices and the severity acute exacerbation of COPD.*

Objective: *To find out the association between platelet indices and severity of acute exacerbation of COPD*

Methods*: This cross-sectional observational study was conducted at the National Institute of Diseases of the Chest and Hospital (NIDCH) for July 2018 to June 2019. The study adhered with the declaration of Helsinki and all ethical measures were taken properly throughout the study. All adult patients with COPD admitted during the study period were approached and included into the study. Before final selection, informed consent was taken from all participants. All patients were subjected to detailed history taking, physical examination and relevant examination especially a complete blood count. Total 100 patients were interviewed with a preformed and pretested questionnaire. Following completion of the data collection, all data were inputted into the statistical software. Final analysis was done with the help of SPSS 20.*

Results: *Among the 100 study participants, mean age was 61.94±10.30 years (age range: 42 to 85 years). Male-female ratio was 2.70:1 (73% vs 27%). About 37% had moderate severity, 28% had very severe disease, 25% had severe disease and 10% had mild severity of COPD during admission. Platelet count was similar across the severity of the patients ($p>0.05$) but PLR, MPV, PDW and Plateletcrit increased significantly with increasing severity of COPD ($p<0.05$ all). According to the clinical assessment, 48% patients had acute respiratory failure non-life-threatening condition, 28% had no respiratory failure and 24% of them presented with life-threatening acute respiratory failure. Further analysis suggests that PLR, MPV, and PDW increased significantly with increasing severity of exacerbations ($p<0.05$ all). But TPC, PLR and Plateletcrit are not significantly related with severity of COPD exacerbation.*

Conclusion: *Platelet indices (MPV, PDW, Pct, PLR) change with severity of exacerbation of COPD patients and with severity of COPD (worsening of FEV_1) and can assess the severity of these conditions.*

[Chest Heart J. 2019; 43(2) : 84-92]
DOI: http://dx.doi.org/10.33316/chab.j.v43i2.2019606

Introduction:

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually

1. Junior Consultant, Medicine, National Institute of Neurosciences, Hospital, Shere Bangla Nagar, Agargoan, Dhaka-1207.
2. Registrar, Respiratory Medicine, NIDCH, Mohakhali, Dhaka-1212.
3. Associate Professor, Respiratory Medicine, NIDCH, Mohakhali, Dhaka-1212.
4. Registrar, Respiratory Medicine, NIDCH, Mohakhali, Dhaka

Correspondence to: Dr. Md. Sayedul Islam, Associate Professor of Respiratory Medicine, NIDCH, Mohakhali, Dhaka-1212, Mob: 01552-390582, E-mail: drsayedul@gmail.com

Submission on: 1 July, 2019 **Accepted for Publication:** 5 July, 2019
Available at http.//www.chabjournal.org

caused by significant exposure to noxious particles or gases. The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. These changes do not always occur together, but evolve at different rates over time. Chronic inflammation causes structural changes, narrowing of the small airways and destruction of the lung parenchyma that leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil. In turn, these changes diminish the ability of the airways to remain open during expiration. A loss of small airways may also contribute to airflow limitation and mucociliary dysfunction is a characteristic feature of the disease. Airflow limitation is usually measured by spirometry as this is the most widely available and reproducible test of lung function[1].

COPD is currently the fourth leading cause of death in the world (Lozano, Naghavi, Foremen[2] but is projected to be the 3rd leading cause of death by 2020. COPD represents important public health challenge. Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and increasing age of the population[3].

COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy[4]. These are complx events usually associated with increased airway inflammation,increased mucus production and marked gas trapping. These changes contribute to increased dyspnea that is the main sympom of an exacerbation. Other symptoms include increased sputum purulence and volume, together with increased cough and wheeze.

Exacerbations of COPD are important events in the management of COPD because they negatively impact health status, rates of hospitalization and readmission and disease progression. Hospitalizaion for an exacerbation is associated with poor prognosis and increased risk of death.

Inspite of such alarming outtcomes, very less data are available regarding the precipitating factors and predictors of prognosis in patient with acute exacerbation of COPD especially from developing countries[5] .

COPD is identified mainly post bronchodilator forced expiratory volume in 1st second (FEV1) / forced vital capacity ratio less than 0.7; severity determined by FEV1 alone combined with a history of exposure to risk factors. (GOLD 2019). In mild and moderate group there is considerable evidence of under diagnosis. Due to heterogenic presentation and lack of available diagnostic tests, acute exacerbation of COPD (AECOPD), are often diagnosed based on clinical gestalt, which is subjective and variable within and across physicans.

Therefore there is clearly a need for a biomarker or simple diagnostic tool that can aid with the diagnosis, risk stratification and assessment of therapeutic iterventions. It an provide an insight in the pathophysiological mechanism in exacerbation of COPD[6].

According to several studies, platelet and their indices may be used as inflammatory markers for cardiovascular, inflammatory and thromboembolic diseases[7]. The parameters related to platelet size reflect platelet activity and termed as platelet indices. These include the mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT)[8]. Previous studies have shown that high MPV, PDW and PCT are associated with increased inflammatory state in the body, as well as with the severity and acute exacerbation of COPD. Platelet interact with the leukocytes and secrete a number of mediators that are involved in immune modulation. Therefore, novel platelet indices reflecting platelet activity may provide information on the inflammatory status on certain diseases. The lymphocyte count in peripheral blood has been shown to inversely correlate with inflammation. The platelet –to-lymphocyte ratio (PLR) is an index to calculated through dividing platelet count by lymphocyte count in the peripheral blood[9]. It was on this background that the present study was conducted, which was aimed to investigate the association between platelet parameters including the MPV, PDW, PCT, PLR with the severity of acute exacerbation of COPD.

Objectives of the Study

General Objective:

- To find out any association between platelet indices and severity of acute exacerbation of COPD.

Specific Objectives:

- To find out relationship between Platelet Distribution Width (PDW) and acute exacerbation of COPD.
- To find out relationship between Mean Platelet Volume (MPV) and acute exacerbation of COPD.
- To find out relationship between plateletcrit and acute exacerbation of COPD.
- To find out any relationship between Platelet-Lymphocyte Ratio and acute exacerbation of COPD

Materials and methods

Study design: Cross sectional observational study

Study place: Respiratory Medicine Department of NIDCH

Study period: July 2018 – June 2019

Study population: COPD Patients admitted in NIDCH.

Inclusion criteria: Patients admitted with acute exacerbation of COPD.

Exclusion criteria:

Age less than 40 years, COPD patients with following diseases: Ischaemic heart disease, ACO, Active PTB/ Pneumonia, Cardiac failure, Renal Disease, Thromboembolic disorder, Carcinoma, Inflammatory bowel disease, Hepatic failure, Patient with antiplatelet medication, Recent blood transfusion, Unwilling to take part in study.

Study Procedure:

- Data were collected by following procedure:
- Before starting the study, the study was ethically permitted by ERB of NIDCH.
- Total 145 adult patients with shortness of breath who were admitted in NIDCH within study period were approached, after few days when they were stable to perform spirometry, spirometry with reversibility were done. 45 patients were excluded as asthma and ACO. Data of 100 patients was included in this study.
- After admission the patients were clinically assessed by duty doctor and then by researcher. Following that, chest x-ray, ABG and other relevant investigations were sent.
- After describing the purpose and objective of the study, written Informed consent was obtained from the patients.
- Data were collected by face to face interview by using a semi-structured questionnaire containing socio-demographic parameters and clinical presentations of COPD. Risk factor profiles and data on respiratory system findings were noted properly.
- All patients were subjected to perform blood test especially for CBC following admission. Blood samples were obtained before medication. Samples were collected in EDTA-containing and anticoagulant-free tubes.
- After immediate centrifugation for 10 minutes, at 4 °C, plasma and serum samples were separated in Eppendorf tubes and frozen immediately at -80 °C until analysis. Complete blood count parameters [including platelet (PLT) ($\times 10^5$/¼L), MPV (fL), PDW (fL), platelet lymphocyte cell ratio (P-LCR) (%), plateletcrit (PCT) (%)] were obtained with automatic hematology analyzer (Siemens-Sysmex, Germany).
- Few days after admission Spirometry was performed and COPD patients were diagnosed based on the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD), they were classified into four groups on basis of airflow limitation severity, according to the guideline based on post bronchodilator forced expiratory volume in one second (FEV1).
- Patients with acute exacerbation of COPD sub-divided into 3 classes: a) No respiratory failure; b) Acute respiratory failure non-life threatening, c) Life threatening acute respiratory failure.
- All collected data were noted into case record form.
- Data were verified and summarized.

Tabulation, Graphical presentation and analysis were done by SPSS (version 25.0.0.0) and Epi (version 7.1.5.0) info software.

Data processing and analysis:

After collection of all required data were checked, verified for consistency and then tabulated into the computer using the Microsoft excel 2016 software. SPSS (Statistical Package for Social Sciences) for Windows 20.0 package program was used for

statistical evaluations. Statistical significance was set as 95% confidence level at 5% acceptable error level. Descriptive statistics were obtained, and data were tested for normality using the Kolmogorov-Smirnov test for Gaussian distribution. Patients' characteristics were reported as percentages in case of categorical variables whereas continuous variables were expressed with mean ± standard deviation. The relationship between the categorical variables of the groups was examined by chi-square test. For comparison of parameters with normal distribution, parametric tests and comparison of parameters with abnormal distribution, non-parametric tests were used. Relationships between variables were assessed with Pearson's or Spearman's correlation coefficient. A p value <0.05 was considered as statistically significant.

Observation & Results

Total 100 patients of COPD who were admitted with acute exacerbations were included in the study. The

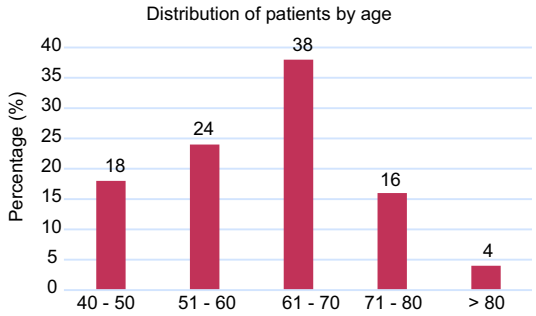


Fig.-1: *Distribution of patients by age (n=100)*

mean age was 61.94±10.30 years, ranging from 42 to 85 years. Majority of the patients were aged between 61 – 70 years (38%). figure I.

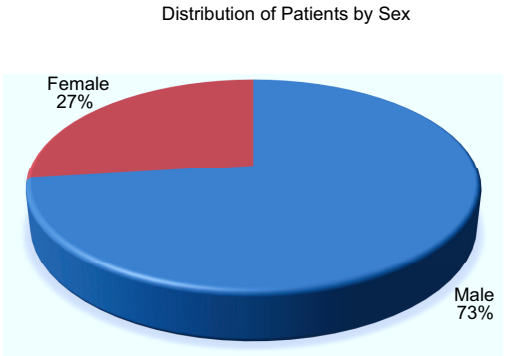


Fig.-2: *Distribution of patients by sex (n=100)*

Most of the patients were male (73%) and rest was females (27%). Male-female ratio was 2.70:1. (Figure 2)

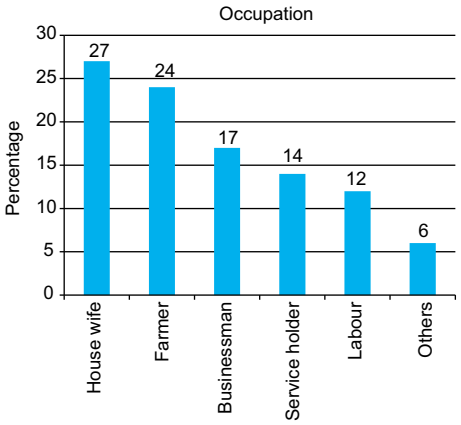


Fig.-3: *Distribution of patients by their occupation (n=100)*

Among all patients, 27% were housewives, 24% were famers, 17% were businessman, 14% were service holders, 12% were day labourer and 6% were doing other jobs. (Figure 3)

Table-I

Risk factors of study population (n=100)

Risk factors	Percent (%)
Smoking	68
Number of cigarettes smoked (pack year)	28.42±8.35*
Passive smoking	11
Biomass fuel use	17
Exposure to dust fumes at work place	21
Alcohol intake	4

* Mean±SD

Among all COPD patients, 68% percent patients were active smokers and 11% were passive smokers. Seventeen percent were using biomass fuel and 21% were exposed to work space dust/ fumes. Only 4% patients were alcohol users.

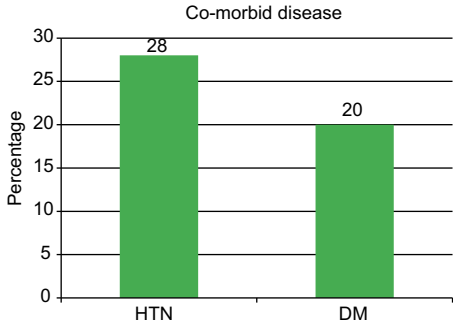


Fig.-4: *Distribution of patients according to presence of co-morbid disease (n=100)*

Among all twenty eight percent had HTN and twenty percent had DM. (Figure 4)

Table-II

Symptoms leading to hospitalization (n=100)

Symptoms	Percent (%)
Increased shortness of breath	84
Increased cough with sputum production	49
Cough with purulent sputum production	42
Fever	32
Bilateral leg swelling	32
Weakness and fatigue	83
Disorientation	48

The most common symptom leading to hospitalization in these patients was increasing shortness of breath (84%) followed in by weakness and fatigue (83%). Besides, 49% patients had increased cough with sputum production, 48% had disorientation, 42% cough with purulent sputum, 32% had fever, and 32% had bilateral leg swelling.

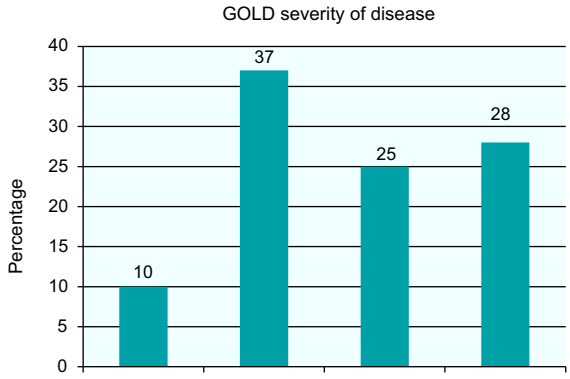


Fig.-5: *Distribution of patients according to their disease severity (n=100)*

Table-III

Previous history of exacerbations and hospitalization (n=100)

Variable	Percent (%)
Past history of Exacerbations	
None	23
One	26
Two	25
Three	15
Four	11
Past history of Hospitalization	
One	32
Two	8
Three	5

Majority 26% patients had one previous episodes of exacerbation and 32% patients had at least one previous history of hospitalization.

Severity was calculated using GOLD criteria. Among all 37% had moderate severity, 28% had very severe disease, 25% had severe disease and 10% had mild severity.

Total platelet count were increasing across severity groups ($p>0.05$). But lymphocyte count decreased with increasing severity ($p<0.05$). PLR, MPV, PDW and Plateletcrit increased significantly with increasing severity of CPD ($p<0.05$ all).

Among all 48% patients had acute respiratory failure non-life-threatening state, 28% had no respiratory failure and 24% of the patients had life threatening acute respiratory failure..

Table-IV

Platelet indices of patients in relation to severity of disease according to GOLD criteria (n=100)

Parameters	Severity of disease				P value
	Mild N = 10 Mean±SD	Moderate N = 37 Mean±SD	Severe N = 25 Mean±SD	Very Severe N = 28 Mean±SD	
Lymphocyte (/ml)	2552±1067	1920±1428	1862±1105	1340±564	0.027
Total platelet count (/ml)	244000±47628	240729±77392	2716000±77308	280321±77592	0.144
PLR	111±43.90	159.32±62.34	203.28±122.66	226.24±72.82	<0.001
MPV, fl	7.77±0.30	7.95±0.55	9.06±0.36	9.88±0.79	<0.001
PDW	13.34±0.50	14.30±1.36	15.81±0.99	17.47±1.41	<0.001
Plateletcrit, %	0.18±0.02	0.25±0.14	0.26±0.06	0.29±0.04	0.002

P value determined by ANOVA; PLR: Platelet lymphocyte ratio; MPV: mean platelet volume, PDW: Platelet distribution width

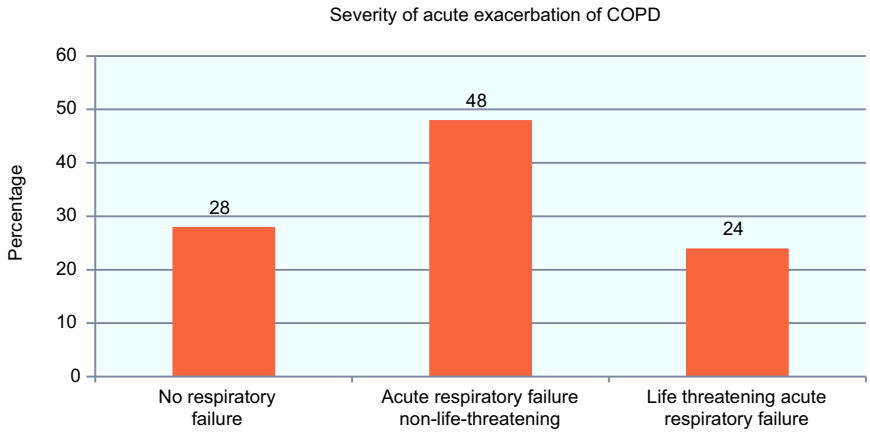


Fig.-6: *Distribution of patients according to clinical severity of acute exacerbation of COPD (n=100)*

Table-V

Platelet indices of patients in relation to severity of acute exacerbations of COPD (n=100)

Parameters	Severity of acute exacerbations			P value
	No respiratory failure N = 28 Mean±SD	Acute respiratory failure non-life-threatening N = 48 Mean±SD	Life threatening acute respiratory failure N = 24 Mean±SD	
Total platelet count (/ml)	250607±71536	257958±80719	274458±72582	0.520
PLR	169.34±97.37	177.80±83.61	214.39±88.96	0.255
MPV, fl	8.52±0.85	8.48±0.95	9.57±0.92	<0.001
PDW	14.93±1.86	15.28±1.74	16.47±1.92	0.008
Plateletcrit, %	0.23±0.06	0.25±0.11	0.28±0.09	0.263

P value determined by ANOVA; PLR: Platelet lymphocyte ratio; MPV: mean platelet volume, PDW: Platelet distribution width

PLR, MPV, and PDW increased significantly with increasing severity of exacerbations ($p<0.05$ all). TPC, PLR and Plateletcrit also increased with severity but was not significant.

Discussion:

A number of previous studies have shown that high MPV, PDW, and PCT are associated with increased inflammatory state in the body, as well as with the severity and acute exacerbation of COPD[10]. This study evaluated the platelet indices of COPD patients admitted with acute exacerbation and tested the association of platelet indices with COPD severity.

One hundred patients with acute exacerbation of COPD were included in this study. Mean age of the patients were 61.94±10.30 years ranging from 42 to 85 years. Approximately 2/3rd of the patients were aged above 60 years (58%). COPD is a disease of the old age. A study conducted by Alam and colleagues in both urban and rural settings of Bangladesh found a higher prevalence of COPD among older individuals[11]. In their study COPD prevalence was 27.5% among patients aged 60 – 69 years, 13.6% among patients aged 50 – 59 years and 5.2% among patients aged 40 – 49 years. A similar pattern was noted in among COPD patients in this study- 38% were aged 61 – 70 years, 24% were aged 51 – 60 years and 18% were aged 40 – 50 years.

Male patients were 2.70 times higher than the female patients constituting 73% of the study

population. Kabir et al noted that COPD prevalence is high among male patients(Kabir, Hasan and Rahman, 2016). This was also noted by Hossain and Karim who found 76.9% male and 23.1% female COPD patients in their study[12]. This can be explained by the fact that significantly more male are smokers in the Bangladesh than female (Demeo and Silverman, 2004). Worldwide a higher prevalence of COPD among male was also noted. Ntritsos et al. conducted a systematic review and meta-analysis to determined sex specific prevalence of COPD worldwide and found a summary prevalence of 9.23% in men and 6.16% in women[13].

In this study 58% patients came from rural area and 42% came from urban area. This is comparable with the findings of Alam et al who found a higher prevalence of COPD among rural participants.

The present study found that 40% patients had primary education and 20% were illiterate creating a bulk of lower educated individuals. On the other hand, 36% of the study population were manual workers (24% patients were farmers and 12% patients were labourers). COPD in these groups can be linked to the findings of Khandker et al. They found that 50% of the people with primary education were smokers and 66.75 of the manual workers were smokers in their study[14]. While in this study 68% patients were active smokers and 11% were passive smokers. A large of proportion of housewives was also noted with a history of exposure to biomass fuel.

Among all 45 were from middle class family and 39% were from lower class family. Only 16% were from upper class family. This may be due to improved hygienic practice in this higher class of people. Grigsby et al found that COPD prevalence is lower with higher monthly household income supporting picture of this study[15].

HTN was found in 28% patients and DM in 20% patients. Hypertension is one of the five most prevalent comorbidities among COPD patients which is responsible of hospitalization of these patients (Pavord *et al.*, 2016). DM is also an important co-morbidity found among hospitalized COPD patients .

The present study found that 77% patients had past history of one or more exacerbations and 45% patients had at least one past history of hospitalization. Bahadori and Fitzgerald ran a systematic study on the factors associate with recurrent exacerbations and admissions in the COPD patients[16] and found that three predictive factors: previous hospital admission, dyspnea and oral corticosteroids were all found to be significant risk factors of read- missions and variables including using long term oxygen therapy, having low health status or poor health related quality of life and not having routine physical activity were all associated with an increased risk of both admission and readmission to hospital. In the present study 84% patients were readmitted due to increasing shortness of breath, and 31% patients were using oral corticosteroid. Poor adherence to medication can be another cause for frequent readmissions.

Among 100 patients, 37% had moderate severity, 28% had very severe disease, 25% had severe disease and 10% had mild severity according to GOLD criteria. Among hematological parameters hemoglobin decreased significantly with increasing GOLD severity of COPD ($p<0.05$). WBC count and total platelet count was similar across severity groups ($p>0.05$). But lymphocyte count decreased with increasing severity ($p<0.05$). PLR, MPV, PDW and Plateletcrit increased significantly with increasing GOLD severity of CPD ($p<0.05$ all). Severe COPD was associated with significantly low hemoglobin, higher total platelet count, higher PLR, higher MPV, higher PDW and higher plateletcrit in comparison to patients with mild COPD ($p<0.05$). This is consistent with the findings of a similar study conducted by Kalemci et al. (2018). They found an increase in PDW, MPV, PCT, PLR and RDW values with an increase in the severity of COPD. They also noted that patients in the severe COPD group had higher, PDW, MPV, PCT, and PLR values but had lower hemoglobin levels and lymphocyte count compared with the mild COPD group. On the other hand, among all platelet indices only PDW and MPV showed significant change with increasing clinical severity. This indicates a disjunction between platelet indices and clinical severity while a significant association between GOLD severity and platelet indices were noted.

An increase in PDW as the severity of COPD increased could be related to an elevation in the

thrombosis load and/ or increased inflammation that occurs as the disease becomes more severe. PDW was shown to increase in various pulmonary diseases other than COPD such as obstructive sleep apnea syndrome, pulmonary tuberculosis, pulmonary embolism and pulmonary hypertension.[17]

Increased MPV is a marker of platelet activation. The MPV acts as an acute phase reactant in inflammatory conditions depending on the severity of systemic inflammation. It has been shown to increase in low grade inflammations but to decrease due to intensive degradation of platelets in inflammatory regions in severe inflammatory conditions. In a study by Zhang et al the MPV was higher in patients with COPD compared with controls, and even higher in patients during acute exacerbations compared with those in the convalescence period. On the other hand, some other studies suggested that the MPV decreases in patients with inflammatory disorders including COPD[17] which is consistent with the findings of this study.

Low lymphocyte count is related with increased inflammation. Combined with the platelet count, the PLR reflects the inflammatory status in the body more accurately. Karadeniz et al found that the PLR was higher in patients with COPD during acute exacerbation compared with stable ones and healthy controls, and they concluded that the PLR might be a useful and easily accessible tool for evaluating the ongoing inflammation during the stable period and the disease severity during acute exacerbations in patients with COPD.[10] Results of this study were in line with those findings in terms of high PLR values in patients with more severe COPD.

1. No comparison was done among the findings in patients with different modalities of treatment prior hospitalization.

Patients with multiple diseases was not considered into the study.

Limitation

Conclusion

Platelet indices particularly MPV is associated with the severity of the COPD exacerbation. It is observed that the more severe the exacerbation the higher the value of MPV, Pct, PDW and PLR. Value of these indices also rise with the severity of airflow limitation in COPD (FEV_1).

References:

1. GOLD 2009. 'GOLD 2019 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Inititiative For Chronic Obstructive Lung Disease, 1–139.
2. Lozano, R. Naghavi, M. Foreman, K. et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systemic analysis of Global Burden of Disease Study 2010', Lancet. 2012;380(9859): 2095-128.
3. Mathers, CD & Loncar, D. Projections of global mortality and bren of disease from 2002 to 2030',PLos Med. 2006;3(11): e442.
4. Wedzicha, JA. & Seemngal, TA. COPD exacerbations: defining their cause and prevention', Lancet. 2007;370(9589) 786-96.
5. Mohan, A. Premananda, R. Reddy, L.N., Rao, M.H., Sharma, S.K.Kamity, R. & Bollineni, S. Clinical presentation and predictors of outcome in patients with severe acute exacerbation of chronic obstructive pulmonary disease requiring admission in intensive care unit, BMC Pulmonary Medicine. 2006;6(1): 7.
6. Cazzola, M. MacNee, W. Martinez, F.J. Rabe, K.F. Franciosi, L.G., Barnes, P. J. Brusasco, V. Burge, P.S. Calverley, P.M.A. Celli, B.R. & Jones, P.W. Outcomes of COPD pharmacological trial: from lung function to biomarkers',European Respiratory Journal. 2008;31(2):416-469.
7. Briggs, C, Mellors, I, Roderick, A, Ward, A, O'Malley, C, Barker, J, De La Salle, B, McTaggart, P, Hyde, K & MacHin, SJ. Quality counts: New parameters in blood cell counting, International Journal of Laboratory Hematology. 2009;31(3):277–297.
8. Mahdavi-Zafarghandi, R, Shakiba, B, Keramati, MR & Tavakkoli, M. Platelet volume indices in patients with varicocele, Clinical and Experimental Reproductive Medicine. 2014;41(2):92–95.

9. Kumar, P, Law, S & Sriram, KB. Evaluation of platelet lymphocyte ratio and 90-day mortality in patients with acute exacerbation of chronic obstructive pulmonary disease', Journal of Thoracic Disease. 2017;9(6): 1509–1516.

10. Bahadori, K & FitzGerald, JM. Risk factors of hospitalization and readmission of patients with COPD exacerbation - Systematic review, International Journal of COPD. 2007;2(3): 241–251.

11. Alam, DS, Chowdhury, MA, Siddiquee, AT, Ahmed, S & Clemens, JD. 'Prevalence and determinants of chronic obstructive pulmonary disease (COPD) in Bangladesh', COPD: Journal of Chronic Obstructive Pulmonary Disease. 2015;12(6): 658–667.

12. Hossain, AM & Islam, K. Prevalence and risk factors of Chronic Obstructive Pulmonary disesae (COPD) in Dhaka City Bangladesh', Chest. The American College of Chest Physicians. 2009;136(4): 90S-b–91S.

13. 13. Ntritsos, G, Franek, J, Belbasis, L, Christou, MA, Markozannes, G, Altman, P, Fogel, R, Sayre, T, Ntzani, EE & Evangelou, E. Gender-specific estimates of COPD prevalence: a systematic review and meta-analysis', International Journal of Chronic Obstructive Pulmonary Disease. 2018;13: 1507–1514.

14. Khandker, NN, Biswas, T, Khan, ANS, Hasib, E & Rawal, LB. Socio-demographic characteristics and tobacco use among the adults in urban slums of Dhaka, Bangladesh, Tobacco Induced Diseases. Tobacco Induced Diseases. 2017;15(1):1–8.

15. Grigsby, M, Siddharthan, T, Chowdhury, MAH, Siddiquee, A, Rubinstein, A, Sobrino, E, Miranda, JJ, Bernabe-Ortiz, A, Alam, D & Checkley, W. Socioeconomic status and COPD among low-and middle-income countries', International Journal of COPD. 2016;11(1):2497–2507.

16. Karadeniz, G, Aktoçu, S, Erer, OF, Kir, SB, Doruk, S, Demir, M & Sonat, K. Predictive value of platelet-to-lymphocyte ratio in exacerbation of chronic obstructive pulmonary disease, Biomarkers in Medicine. 2016;10(7):701–710.

17. Zhang, S, Cui, YL, Diao, MY, Chen, DC & Lin, ZF. Use of platelet indices for determining illness severity and predicting prognosis in critically ill patients. Chinese Medical Journal. 2015;128(15):2012–2018.

Chest Heart Journal
Vol. 43, No. 2, July 2019

REVIEW ARTICLE

Use of Beta Blocker in COPD Patient: A Dilemma to Prescribe

Mohammad Ashiqur Rahman[1], Md. Abdur Rouf[2], Nazifa Tasnim[3]

Abstract:

Cardiovascular disease, which is common in patients with chronic obstructive pulmonary disease (COPD), has a profound effect on morbidity and mortality. Despite the clear evidence of beta blockers effectiveness, there is a general reluctance of physicians to use them in patients with COPD due to a perceived contraindication and fear of inducing adverse reactions and bronchspasm. But it is seen that Beta blockers are well tolerated in patients with cardiac disease and concomitant COPD. The cumulative evidence from trials and meta-analysis indicates that cardioselective Beta blockers should not be withheld in patients with reactive airway disease or COPD. Patients with COPD have a high incidence of cardiac events necessitating careful consideration of prophylactic treatment. The benefits of beta blockade in this group appear to outweigh any potential risk of side effects according to the available evidence. In this article, we will discuss the effect of Beta blockers in patients with COPD with and without cardiac indication and review the result of these two groups.

Keywords: COPD, Beta blocker, Heart failure, MI.

[Chest Heart J. 2019; 43(2) : 93-95]
DOI: http://dx.doi.org/10.33316/chab.j.v43i2.2019607

Introduction:

Beta-blockers have an established position in the management of coronary artery disease and heart failure. COPD management strategies also state that the benefits of selective beta-1 blocker treatment in heart failure clearly outweigh any potential risk associated with treatment even in patients with severe COPD [1]. Despite this guidance there is a reluctance of physicians to prescribe even cardioselective beta-blockers in COPD, even in the presence of known cardiac disease, because of persistent concerns regarding potential bronchoconstriction, especially in more severe patients.

Cardiovascular comorbidity, including coronary artery disease and heart failure, commonly coexists in chronic obstructive pulmonary disease (COPD) due to the effects of smoking, systemic inflammation, hypoxaemia and other shared risks. COPD may also be associated with impaired diastolic filling due to lung hyperinflation, which may be compounded by the negative lusitropic effects of hypoxaemia and left ventricular hypertrophy. The use of beta-blockers in COPD has been proposed because of their known cardioprotective effects as well as reducing heart rate and improving systolic function.

1. Registrar, Department of Respiratory Medicine, National Institute of Diseases of the Chest & Hospital, Mohakhali, Dhaka.
2. Professor, Department of Respiratory Medicine, National Institute of Diseases of the Chest & Hospital, Mohakhali, Dhaka.
3. Medical Officer, Upazila health complex, Sonaimuri, Noakhali, Chittagong.

Correspondence to: Dr. Mohammad Ashiqur Rahman, MBBS, MRCP (UK), Registrar, Department of Respiratory Medicine, National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka. Email:ashique49@yahoo.com

Submission on: 19 May, 2019 **Accepted for Publication:** 15 June, 2019
Available at http.//www.chabjournal.org

Effect of Beta blockers:

Beta-blockers have positive effects on morbidity and mortality in patients with heart failure and in those who have had a myocardial infarction. Most retrospective observational studies have suggested that such positive effects also occur in patients with COPD who have cardiovascular disease. [2] Along with their potential cardiac effects, beta-blockers have noncardiac targets with potential beneficial effects in patients with COPD, such as reducing systemic inflammation, the number of goblet cells, and mucus release. Thus, beta-blockers may have beneficial effects in patients with COPD who do not have clear cardiac indications.

Potential cardiac targets for beta-blockers in COPD

- Improved left ventricular systolic and diastolic function
- Reduced left ventricular dilatation
- Protection against myocardial ischaemia
- Reduced left ventricular mass
- Reduced heart rate
- Anti-arrhythmic effects
- Inhibition of myocyte apoptosis
- Protection against hypoxic sympathetic drive
- Protection against adverse effects of beta-agonists

Potential non-cardiac targets for beta-blockers in COPD

- Inhibition of endothelin-1 release
- Reduction in circulating pro-inflammatory cytokines
- Inhibition of neutrophil chemotaxis and respiratory burst
- Reduction in goblet cell number and mucus release

Box: *Cardiac and non-cardiac effect of Beta Blocker*

Now question is what will be the outcome if beta blocker is given to the patient of COPD with cardiac indication in comparison to patients without cardiac indication.

Study Result:

In this article here is given two different study discussion where beta blocker was given to one group patient of COPD with cardiac indication and another group was beta blocker to the COPD patients without any cardiac indication.

In a meta-analysis of 15 retrospective studies involving patients of COPD with cardiac indication, those who received beta-blockers had a 28% lower frequency of death and a 38% lower frequency of exacerbation than those who did not receive a beta-blocker. [3] These studies indicate positive role of beta blocker in COPD with cardiac disease patient.

The second group of study was the BLOCK COPD (Beta-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease) trial, where moderate or severe COPD patients were chosen who did not have an established indication for beta-blocker use. Patients with COPD were randomly assigned to receive a beta-blocker (extended-release metoprolol, dose 25–100 mg daily, depending on heart rate and blood pressure) or placebo, with a primary outcome of the first exacerbation of COPD.

During average follow-up of nearly 1 year, no significant difference was observed between groups in overall exacerbation rates. However, metoprolol recipients were significantly more likely to be hospitalized for COPD exacerbations (0.45 vs. 0.28 exacerbations per person-year). At routine follow-up visits, metoprolol recipients reported more dyspnea than did placebo recipients, but no differences in FEV_1 were noted. On the basis of these data, current COPD management strategies indicate that beta-blockers should be prescribed in patients with COPD who have cardiovascular indications, even in those with severe COPD.[4]

Prescribing Information:

Initiating treatment with beta-blockers is not simple as it requires dose titration over a period of weeks along with monitoring of heart rate, blood pressure and perhaps spirometry, all of which take time, incurring extra healthcare costs. Moreover beta-blockers may be less well tolerated in older patients with coexisting comorbidities such as diabetes, peripheral vascular disease and renal impairment, who are more prone to postural hypotension.

- Beta-1 selective antagonists including metoprolol, bisoprolol and nebivolol exhibit dose related beta-2 receptor blockade.

- Bisoprolol has a licensed indication for use in heart failure and coronary artery disease and has a beta-1:2 receptor selectivity ratio of 14:1, which is higher than either atenolol (5:1) or metoprolol (2:1) [5]
- Nebivolol has been shown to exhibit greater *in vitro* beta-1/2 receptor selectivity than bisoprolol in human myocardium [6] and also suppresses endothelial nitric oxide [7].
- Carvedilol is a nonselective beta-antagonist that is more likely to cause bronchoconstriction than beta-1 selective antagonists.
- Slowly titrate the dose of beta-blockers at 1–2 weekly intervals up to the usual maintenance dose.
- Monitor supine and erect blood pressure, heart rate and spirometry during dose titration.
- Concomitant long-acting muscarinic antagonists may obviate potential bronchoconstriction.
- Symptomatic bradycardia may occur if beta-blockers are used with other rate-limiting drugs such as calcium blockers (*e.g.* verapamil and diltiazem), ivabradine or anti-arrhythmic agents (*e.g.* digoxin, amiodarone and flecainide)
- Symptomatic hypotension may occur when beta-blockers are used with other vasodilatory drugs (*e.g.* angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers and alpha receptor blockers)

Conclusions:

There are compelling reasons to use cardioselective beta-blockers in patients with COPD who have coexistent heart failure or are post-myocardial infarction. Current evidence would suggest that there remains a reticence to prescribe beta-blockers in such patients because of a fear of adverse events, particularly worsened lung function. Cardioselective â-blockers remain appropriate for COPD patients who have valid cardiovascular indications for their use, but this study suggests that COPD patients without such indications should avoid these drugs.

Key messages:

- The main indications for beta-blockers in patients with COPD are post-myocardial infarction and heart failure with reduced ejection fraction
- Meta-analyses of retrospective studies with beta-blockers in COPD have shown pooled estimates for reductions in mortality of 28% and exacerbations of 38%.
- Initiating treatment with beta-blockers requires careful dose titration and monitoring. Slowly titrate the dose of beta-blockers at 1–2 weekly intervals up to the usual maintenance dose.
- Beta-1 selective antagonists such as bisoprolol, nebivolol and metoprolol are preferred to the nonselective carvedilol as they are less likely to produce bronchoconstriction in COPD. Among them nebivolol has the highest selectivity to the beta 1 receptor.
- Long-acting muscarinic antagonists, which are commonly used in COPD, protect against the potential for bronchoconstriction due to dose related beta-2 receptor antagonism.

References:

1. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013; 187: 347–365
2. Hawkins NM, Petrie MC, Jhund PS, et al. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail. 2009; 11: 130–139.
3. Etminan M, Jafari S, Carleton B, et al. Beta-blocker use and COPD mortality: a systematic review and meta-analysis. BMC Pulm Med. 2012; 12: 48.
4. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). JAMA. 2000;283:1295-1302.
5. Baker JG. The selectivity of beta-adrenoceptor antagonists at the human beta1, beta2 and beta3 adrenoceptors. Br J Pharmacol 2005; 144: 317–322.
6. Bundkirchen A, Brixius K, Bölck B, et al. Beta 1-adrenoceptor selectivity of nebivolol and bisoprolol. A comparison of [3H]CGP 12.177 and [125I]iodocyanopindolol binding studies. Eur J Pharmacol. 2003; 460: 19–26.
7. Kamp O, Metra M, Bugatti S, et al. Nebivolol: haemodynamic effects and clinical significance of combined beta-blockade and nitric oxide release. Drugs. 2010; 70: 41–56.

Chest Heart Journal
Vol. 43, No. 2, July 2019

REVIEW ARTICLE

Measurement of Fractional Exhaled Nitric Oxide (FENO), A Complementary Tool

Pulak Kumar Dey[1], Sanjoy Kumar Kar[2], Subrata Kumar Gain[2]

Abstract:

Measurement of fractional nitric oxide (NO) concentration in exhaled breath (FENO) is a quantitative, noninvasive, simple,

and safe method of measuring airway inflammation that provides a complementary tool to other ways of assessing airways disease, including asthma. Common reasons for measuring FENO are to assessing the etiology of respiratory symptoms, to help identify the eosinophilic asthma phenotype, to assess response or failure to respond to anti-inflammatory agents, notably inhaled corticosteroids (ICS). ATS recommend that FENO 50 parts per billion (35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely (strong recommendation, moderate quality of evidence). ATS also recommend that FENO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously with reference to the clinical context. It may be used to asses airway inflammation in asthma patient. In asymptomatic individuals, including patients with well-controlled asthma, low FENO suggests that ICS dose could be reduced or even that ICS treatment may be withdrawn altogether. FENO also predict response to omalizumab. Other conditions FENO may be useful are COPD, Pulmonary hypertension and cystic fibrosis. Conclusion and future directions :Advances in technology and standardization have made FENO measurements simple, permitting their use as a biomarker in the assessment of inflammatory airways diseases. Countries like Bangladesh where parasite infestation as well as eosinophilia is high which may interfere with FENO. Research is needed in this aspect.

Key words: FENO, eosinophilic asthma, ATS, ICS

[Chest Heart J. 2019; 43(2) : 96-101]
DOI: http://dx.doi.org/10.33316/chab.j.v43i2.2019608

Introduction:

Measurement of fractional nitric oxide (NO) concentration in exhaled breath (FENO) is a quantitative, noninvasive, simple,

and safe method of measuring airway inflammation that provides a complementary tool to other ways of assessing airways disease, including asthma. NO is present in the exhaled breath of all humans.[1] It plays key roles in all aspects of lung biology and has been implicated in the pathophysiology of lung diseases, including asthma.[2] The functions of NO in the lung/airways reflect its key roles as a vasodilator, bronchodilator, neurotransmitter, and inflammatory mediator. Patients with eosinophilic asthma have high levels of NO in their exhaled breath and high levels of inducible nitric oxide synthase (NOS2) enzyme expression in the epithelial cells of their airways, suggesting a role for NO in asthma pathogenesis.[3] The use of chemiluminescence analyzers allowed for the

1. Assistant Professor, Respiratory Medicine, NIDCH
2. Registrar, Respiratory Medicine, NIDCH

Correspondence to: Dr.Pulak Kumar Dey, Assistant Professor, Respiratory Medicine, NIDCH.
Mobile: 01712-993758

Submission on: 7 May, 2019 **Accepted for Publication:** 2 June, 2019
Available at http.//www.chabjournal.org

detection of NO in exhaled breath in the early 1990s.[2] Patients with asthma were found to have high FENO in their exhaled breath[4-7] that decreased in response to treatment with corticosteroids.[8] Advantages for FENO include the noninvasive nature of the test, ease of repeat measurements, and the relatively easy use in patients with severe airflow obstruction where other techniques are difficult to perform.[9] By providing information about airway inflammation,[10,11] FENO adds a new dimension to the traditional clinical tools (history, physical exam, and lung function tests).

Why should a FENO test be obtained?

Common reasons for measuring FENO.

- To assessing the etiology of respiratory symptoms.
- To help identify the eosinophilic asthma phenotype'
- To assess response or failure to respond to anti-inflammatory agents, notably inhaled corticosteroids (ICS)
- To establish a baseline FENO during clinical stability for subsequent monitoring of chronic persistent asthma
- To guide changes in doses of anti-inflammatory medications: step-down dosing, step-up dosing, or discontinuation of anti-inflammatory medications.
- To assist in the evaluation of adherence to anti-inflammatory medications
- To assess whether airway inflammation is contributing to poor asthma control particularly in the presence of other contributors (e.g., rhinosinusitis, anxiety, gastro-esophageal reflux, obesity, or continued allergen exposure).

Can FENO be used to diagnose asthma?

Asthma is a clinical diagnosis and there is no single diagnostic test for the disease. Pathology of asthma is often but not always due to eosinophilic airway inflammation. The two are not synonymous. This is extremely important in the interpretation of FENO measurements. In cases of asthma not due to airway eosinophilia, FENO may be low. Similarly, the value of exhaled FENO as a predictor of steroid responsiveness is high even in the absence of induced sputum eosinophils.[12]

FENO is associated with eosinophilic airway inflammation.

There are several inflammatory phenotypes in asthma most commonly described as eosinophilic, neutrophilic, mixed, and paucigranulocytic.[13] Determination of the subtype may help a physician decide which therapies to select or stop.[14]

FENO predicts likelihood of corticosteroid responsiveness.

Treatment response in asthma is heterogeneous.[15-17] Not all patients respond to corticosteroids and an important reason to use FENO is to help decide who might benefit from steroid treatment, and who should try other medications (e.g., leukotriene modifiers). FENO may also be used to determine patients in whom steroid therapy may be safely withdrawn. FENO has been shown to predict the likelihood of steroid responsiveness more consistently than spirometry, bronchodilator response, peak flow variation, or AHR to methacholine.[18-20]

FENO can support a diagnosis of asthma. The diagnosis of asthma is well defined, and the background pathology is often but not always due to eosinophilic airway inflammation. Early studies in populations comprising mainly patients with eosinophilic asthma explored the performance characteristics of FENO as a diagnostic test. The predictive values for FENO (usually at cut points of 25 ppb) were shown to be sufficiently robust for it to be used in this context.[10, 21, 22] Further, the predictive values for FENO are higher than for conventional measurements such as peak flows and spirometry,[10] and similar to those associated with bronchial challenge tests.[22]

FENO may predict AHR.

Irrespective of the specific underlying inflammatory signal which FENO represents, measurements appear to reflect the dynamic interrelationships between the response to allergen or other triggers and evolving eosinophilic airway inflammation/AHR.[2,23]

Normal values versus relevant cut points for FENO.

In a clinical study, Shaw and colleagues reported that the optimum cut point for a clinically significant FENO (corresponding to a sputum eosinophil count of > 2%) was 26 ppb . Similarly,

studies designed to determine the optimum cut point to diagnose asthma using FENO have usually pointed to a diagnostic cut point ranging from 20 to 25 ppb.[10,24–26]. However, in patients with stable, well-controlled asthma, FENO values range from 22 to 44 ppb.[27] Clearly, there is considerable overlap between mean FENO levels in healthy and populations with stable asthma.

Confounding factors that may affect FENO.

FENO values can be affected by several factors, including measurement technique, exhalation flow rate, nasal NO contamination, the NO analyzer used,[28] age, height, smoking, and antiinflammatory medications.

ATS recommend that FENO 50ppb (35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely (strong recommendation, moderate quality of evidence). ATS also recommend that FENO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously with reference to the clinical context (strong recommendation, low quality of evidence).

Low FENO (<25 ppb [20 ppb in children): implies noneosinophilic or non-aiway inlammation

Low FENO can help diagnosis of GERD, smoking related or anxiety related cough, brochiectasis.

Monitoring airway inflammation in asthma

Serial measurements obtained when patients' asthma is both stable and unstable allows each patient to act as his/her own control when assessing subsequent measurements and as a result "personal best" can be used.[29-34] The same cut points used in detecting airway inflammation apply when monitoring patients with asthma. In asymptomatic individuals, including patients with well-controlled asthma, low FENO suggests that ICS dose could be reduced or even that ICS treatment may be withdrawn altogether. In a study of children with stable asthma, withdrawal of ICS did not result in symptom relapse when FENO remained consistently low (optimum cut point 22 ppb) when measured 2 to 4 weeks after treatment withdrawal .

Minimally important differences, and prognostic significance of FENO .

In one study, FENO levels were 50% higher during acute asthma compared with when stability was restored.[35] Data obtained from steroid withdrawal studies show that the mean increase in FENO associated with the advent of loss of control ranges from 16 ppb to 25 ppb,[36] the latter representing a 60% increase from baseline. However, the range of the increase in FENO between stability and loss of control is high (up to 141 ppb) . Michils and colleagues have reported that the transition from good control to poorly controlled asthma is likely to be associated with a rise in FENO of 40% or greater.[37] An acute rise (over 12–24 h) in FENO may occur after infection or exposure to an allergen to which the patient is sensitized. The magnitude of the rise may be as high as 150 ppb. FENO also predict response to omalizumab.

How should a FENO measurement be interpreted and reported?

1. ATS/ERS guidelines should be followed for the measurement of FENO. . Breath should be taken upto TLC over 2-3 second through mouth piece and nasal NO contamination should be avoided. Exhalation should be performed at a flow rate of 50 ml/second.
2. Reason for the test should be determined and the type of subject being tested: does the patient have asthma-like symptoms or an already established diagnosis of asthma?
3. Interpretation of FENO measurement: clinically relevant cut points.
4. Minimum reporting requirements for FENO. When reporting FENO results, a minimum information set should be included.

This should include but not be limited to: date, time of the day, age, sex, ethnicity, height, smoking status, reason for the test, and prior diagnosis (if known), and whether or not the patient was using inhaled or oral corticosteroids at the time of testing.

The format of the reporting should include the device used to make the measurement, the number of measurements made, and the flow rate (currently approved FDA devices use 50 ml/s flow rate).

Other situations in which FENO may be useful COPD.

The exact role of exhaled nitric oxide

measurements in patients with established COPD remains to be defined. In a significant

number of patients, an overlap comprising features of both asthma and COPD is found . The airway inflammatory cell infiltrate may be mixed, including eosinophilic inflammation. Studies show that, at least in the short term, the response to corticosteroids is likely to be greater in patients with COPD who also have sputum eosinophilia.[38,39] or elevated FENO.[40] This raises the possibility that FENO measurements might be used in predicting steroid responsiveness in COPD.

Pulmonary hypertension. NO is one of the important pathophysiological mediators of pulmonary hypertension. Interestingly, patients with pulmonary hypertension have low levels of FENO.[41-42] Although this is a far more complex issue than the simple lack of a vasodilator,[43] giving NO therapeutically seems to work well.[44] Therapies that target the NO pathway have revolutionized the treatment of this disease, including the widely used phosphodiesterase type 5 (PDE5) inhibitors, which prevent the breakdown of the NO effector molecule 39,59-cyclic guanosine monophosphase (cGMP), thus prolonging NO effects on tissues (122).

Cystic fibrosis and nasal NO measurements.

Continuous and high production of NO takes place in the human nose and paranasal sinuses , and this NO is readily measurable by noninvasive techniques . It has been shown that the nasal NO levels are altered in several respiratory disorders—including primary ciliary dyskinesia (PCD) , cystic fibrosis (CF) , and allergic rhinitis,[45,46] and this has led to the proposal that nasal NO may be clinically useful in diagnosis and monitoring of these diseases.

Conclusions and Future Directions

Advances in technology and standardization have made FENO measurements simple, permitting their use as a biomarker in the

assessment of inflammatory airways diseases. Countries like Bangladesh where parasite infestation as well as eosinophilia is high which may interfere with FENO. Research is needed in this aspect.

References

1. Nathan C, Xie QW. Nitric oxide synthases: roles, tolls, and controls. Cell. 1994;78: 915–918.
2. Dweik RA, Comhair SA, Gaston B, Thunnissen FB, Farver C, Thomassen MJ, Kavuru M, Hammel J, Abu-Soud HM, Erzurum SC. NO chemical events in the human airway during the immediate and late antigen-induced asthmatic response. Proc Natl Acad Sci USA. 2001;98:2622–2627.
3. Guo FH, Comhair SA, Zheng S, Dweik RA, Eissa NT, Thomassen MJ, Calhoun W, Erzurum SC. Molecular mechanisms of increased nitric oxide (NO) in asthma: evidence for transcriptional and posttranslational regulation of NO synthesis. J Immunol. 2000;164:5970–5980.
4. Gustafsson LE, Leone AM, Persson MG, Wiklund NP, Moncada S. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. Biochem Biophys Res Commun 1991;181: 852–857.
5. Alving K, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in exhaled air of asthmatics. Eur Respir J. 1993;6: 1368–1370.
6. Kharitonov SA, Yates D, Robbins RA, Logan-Sinclair R, Shinebourne EA, Barnes PJ. Increased nitric oxide in exhaled air of asthmatic patients. Lancet. 1994;343:133–135.
7. Gaston B, Drazen J, Chee CBE, Wohl MEB, Stamler JS. Expired nitric oxide concentrations are elevated in patients with reactive airways disease. Endothelium. 1993;1:87–92.
8. Silkoff PE, McClean P, Spino M, Erlich L, Slutsky AS, Zamel N. Dose– response relationship and reproducibility of the fall in exhaled nitric oxide after inhaled beclomethasone dipropionate therapy in asthma patients. Chest. 2001;119:1322–1328.
9. Ozkan M, Dweik RA. Nitric oxide and airway reactivity. Clin Pulm Med. 2001;8:199–206.
10. Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, Taylor DR.

Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. Am J Respir Crit Care Med. 2004;169:473–478.

11. Khalili B, Boggs PB, Shi R, Bahna SL. Discrepancy between clinical asthma control assessment tools and fractional exhaled nitric oxide. Ann Allergy Asthma Immunol. 2008;101:124–129.
12. Cowan DC, Cowan JO, Palmay R, Williamson A, Taylor DR. Effects of steroid therapy on inflammatory cell subtypes in asthma. Thorax. 2010;65:384–390.
13. Wenzel SE. Phenotypes in asthma: useful guides for therapy, distinct biological processes, or both? Am J Respir Crit Care Med. 2004;170: 579–580.
14. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. 2006;8:23.
15. Dweik RA, Sorkness RL, Wenzel S, Hammel J, Curran-Everett D, Comhair SA, Bleecker E, Busse W et al. Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma. Am J Respir Crit Care Med. 2010;181:1033–1041.
16. Szefler SJ, Martin RJ. Lessons learned from variation in response totherapy in clinical trials. J Allergy Clin Immunol. 2010;125: 285-294.
17. Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti- Sheehan G, Herbison GP, Taylor DR. Exhaled nitric oxide: a predictor of steroid response. Am J Respir Crit Care Med. 2005;172:453–459.
18. Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, Craig TJ, Dolovich M, Drazen JM, Fagan JK, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol. 2002;109:410–418.
19. Knuffman JE, Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Martinez FD et al. Phenotypic predictors of long-term response to inhaled corticosteroid and leukotriene modifier therapies in pediatric asthma. J Allergy Clin Immunol. 2009; 123:411–416.
20. Deykin A, Massaro AF, Drazen JM, Israel E. Exhaled nitric oxide as a diagnostic test for asthma: online versus offline techniques and effect of flow rate. Am J Respir Crit CareMed. 2002;165:1597–1601.
21. Berkman N, Avital A, Breuer R, Bardach E, Springer C, Godfrey S. Exhaled nitric oxide in the diagnosis of asthma: comparison with bronchial provocation tests. Thorax. 2005;60:383–388.
22. Ihre E, Gustafsson LE, Kumlin M, Gyllfors P, Dahlen B. Early rise in exhaled no and mast cell activation in repeated low dose allergen challenge. Eur Respir J. 2006;1:1.
23. Arora R, Thornblade CE, Dauby PA, Flanagan JW, Bush AC, Hagan LL. Exhaled nitric oxide levels in military recruits with new onset asthma. Allergy Asthma Proc. 2006;27: 493–498.
24. Deykin A, Massaro AF, Coulston E, Drazen JM, Israel E. Exhaled nitric oxide following repeated spirometry or repeated plethysmography in healthy individuals. Am J Respir Crit Care Med. 2000;161: 1237–1240.
25. Dupont LJ, Demedts MG, Verleden GM. Prospective evaluation of the validity of exhaled nitric oxide for the diagnosis of asthma. Chest. 2003;123:751–756.
26. Olin AC, Rosengren A, Thelle DS, Lissner L, Bake B, Toren K. Height, age, and atopy are associated with fraction of exhaled nitric oxide in a large adult general population sample. Chest. 2006;130: 1319–1325.
27. Borrill Z, Clough D, Truman N, Morris J, Langley S, Singh D. A comparison of exhaled nitric oxide measurements performed using three different analysers. Respir Med. 2006;100:1392–1396.
28. Kharitonov SA, Gonio F, Kelly C, Meah S, Barnes PJ. Reproducibility of exhaled nitric

oxide measurements in healthy and asthmatic adults and children. Eur Respir J. 2003;21: 433–438.

29. Buchvald F, Baraldi E, Carraro S, Gaston B, De Jongste J, Pijnenburg MW et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol. 2005; 115:1130–1136.

30. Olivieri M, Talamini G, Corradi M, Perbellini L, Mutti A, Tantucci C, Malerba M. Reference values for exhaled nitric oxide (reveno) study. Respir Res. 2006;7:94.

31. Travers J, Marsh S, Aldington S, Williams M, Shirtcliffe P, Pritchard A et al. Reference ranges for exhaled nitric oxide derived from a random community survey of adults. Am J Respir Crit Care Med. 2007;176:238–242.

32. Dressel H, de la Motte D, Reichert J, Ochmann U, Petru R, Angerer P et al. Exhaled nitric oxide: independent effects of atopy, smoking, respiratory tract infection, gender and height. Respir Med. 2008;102:962–969.

33. Smith AD, Cowan JO, Taylor DR. Exhaled nitric oxide levels in asthma: personal best versus reference values. J Allergy Clin Immunol. 2009;124:714–718.

34. Massaro AF, Gaston B, Kita D, Fanta C, Stamler JS, Drazen JM. Expired nitric oxide levels during treatment of acute asthma. Am J Respir Crit Care Med. 1995;152:800–803.

35. Beck-Ripp J, Griese M, Arenz S, Koring C, Pasqualoni B, Bufler P. Changes of exhaled nitric oxide during steroid treatment of childhood asthma. Eur Respir J. 2002; 19:1015–1019.

36. Michils A, Baldassarre S, Van Muylem A. Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. Eur Respir J. 2008;31:539–546.

37. Pizzichini E, Pizzichini MM, Gibson P, Parameswaran K, Gleich GJ, Berman L et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. Am J Respir Crit Care Med 1998;158:1511–1517.

38. Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomized controlled trial. Lancet 2000;356:1480–1485.

39. Zietkowski Z, Kucharewicz I, Bodzenta-Lukaszyk A. The influence of inhaled corticosteroids on exhaled nitric oxide in stable chronic obstructive pulmonary disease. Respir Med. 2005;99:816–824.

40. Dweik R. Pulmonary hypertension and the search for the selective pulmonary vasodilator. Lancet. 2002;360:886.

41. Kaneko FT, Arroliga AC, Dweik RA, Comhair SA, Laskowski D, Oppedisano R et al. Biochemical reaction products of nitric oxide as quantitative markers of primary pulmonary hypertension. Am J Respir Crit Care Med. 1998;158:917–923.

42. Dweik RA. The lung in the balance: arginine, methylated arginines, and nitric oxide. Am J Physiol Lung Cell Mol Physiol. 2007;292: 15–17.

43. Ozkan M, Dweik RA, Laskowski D, Arroliga AC, Erzurum SC. High levels of nitric oxide in individuals with pulmonary hypertension receiving epoprostenol therapy. Lung. 2001;179:233–243.

44. Arnal JF, Didier A, Rami J, M'Rini C, Charlet JP, Serrano E, Besombes JP. Nasal nitric oxide is increased in allergic rhinitis. Clin Exp Allergy. 1997;27:358–362.

45. Kharitonov SA, Rajakulasingam K, O'Connor B, Durham SR, Barnes PJ. Nasal nitric oxide is increased in patients with asthma and allergic rhinitis and may be modulated by nasal glucocorticoids. J Allergy Clin Immunol. 1997;99:58–64.

46. Hanania et al. Am J Respir Crit Care Med. 2013;17.804-11

Chest Heart Journal
Vol. 43, No. 2, July 2019

CASE REPORT

Gastrointestinal Stromal Tumour of the Lower end of Esophagus involving gastroesophageal Junction, a case report.

Mohammad Zakir Hossain Bhuiyan[1], Syed Aminul Haque[2],Md. Noor Hossain Bhuiyan[3], Mofizur Rahman Mia[4], Kazi Saiful Islam[4], Nazmul Islam[5], Abdur Rahim[5], Mobarok Hossain[5], Zahidul Islam[5], Mashukur Rahman Chishty[6], Shafia Alam[7]

Abstract

Gastrointestinal Stromal Tumours (GIST) are rare mesenchymal tumours of the Alimentary tract which represent 0.1 – 3% of all GIT malignancies. Lesions are frequently located in the stomach (60%) and only 1-2% in the esophagus. They are believed to result from mutation of protooncogenes c Kit or Platelet derived growth factor receptor alpha polypeptide which increases Tyrosine Kinase receptor activity, leading to uncontrolled proliferation of stem cells that differentiate into cells of Cajal. They can occur at any age but predominantly in middle aged people & in the elderly. We are going to present a case of 30 years old male patient, admitted in our hospital with dysphagia, anorexia, regurgitation. Diagnostic studies suggested a GIST involving lower end of esophagus and cardioesophageal junction of the stomach.

[Chest Heart J. 2019; 43(2) : 102-108]
DOI: http://dx.doi.org/10.33316/chab.j.v43i2.2019609

Introduction:

Gastrointestinal stromal tumors (GIST) are the mesenchymal tumors of the digestive tract, with an incidencxe of 1-3% of malignancies with this location.[1] The most frequent location is the stomach (60 -70%), followed by the small intestine (20-25%), and colon (5%) and esophagus (about 1%).[2,3] It usually occurs in patients aged 50-60 years. The size ranges from small tumours less than 1 cm, typically discovered incidentally during investigations of other diseases, up to large tumors of 35 cm (mean diameter 5 cm), with various and nonspecific symptomatology.[4-6] Regardless of size, GIST have in common histological and immunohistochemical characterstics: positive tyrosine-kinase receptor (KIT, CD117) and containing a single mutation in the KIT gene (80-85%) or platelet derived growth factor alpha PDGFRA gene (5-7%).[7] Although the majority of GIST occurs by KIT or PDGFRA activating mutations, a small subset is associated with other mutations- wild type, their production mechanism involving other intracellular signaling pathways.[8] Surgery is the main treatment, complemented by

1. Assistant Professor of Thoracic Surgery, Chittagong Medical College & Hospital, Chattogram, Bangladesh.
2. Associate Professor, Department of Thoracic Surgery, Chittagong medical College and Hospital.
3. Associate Professor, Department of Surgery, Chittagong medical College and Hospital.
4. Associate Professor, Department of Thoracic Surgery, National Institute of Diseases of the Chest and Hospital, Mohakhali, Dhaka.
5. Assistant Professor, Department of Thoracic Surgery, National Institute of Diseases of the Chest and Hospital, Mohakhali, Dhaka.
6. MS (Thoracic Surgery) Thesis Student, Department of Thoracic Surgery, National Institute of Diseases of the Chest and Hospital, Mohakhali, Dhaka.
7. Assistant Registrar, Department of Thoracic Surgery, Chittagong Medical College and Hospital, Chattogram.

Address of Correspondence: Dr. Mohammad Zakir Hossain Bhuiyan, Assistant Professor of Thoracic Surgery, Chittagong Medical College & Hospital, Chattogram, Bangladesh, Cell phone number +88017 12152051, Email: drzakirdmc@yahoo.com

Submission on: 13 May, 2019 **Accepted for Publication:** 3 June, 2019
Available at http.//www.chabjournal.org

targeted therapy with tyrosin-kinase inhibitors like imatinib mesylate, in adjuvant or neoadjuvant therapy, when biopsy specimen is accessible.[9]

In our report we will present a case of giant esophageal GIST, significant due to clinical and laboratory investigations, to perioperative anesthetic-surgical issue and to the surgical treatment. The histopathological and immuno-histochemical tests that indicated for the diagnosis, and complementary treatment and follow-up program initiated for this patient are also presented.

Case report:

Mr. Shakil, 30 years old male patient from Rowjan, Chittagong has got admitted into our Hospital with dysphagia, anorexia, regurgitation. Gradually he became intolerant to solid & liquid food and he had been losing body weight day by day. He had no significant family history of sufferings from such type of disease. He had no history of corrosive ingestion but he had history of Endoscopy of UGIT 4 years back with completely normal findings. He is non smoker, no betel nut history. No history of alcohol or drug abuse.

On general physical examination he was found mildly dehydrated and mildly anemic. Systemic examinations were normal in all the systems.

Regarding investigations:

Endoscopy of Upper GIT – Gastric Submucosal lesion.

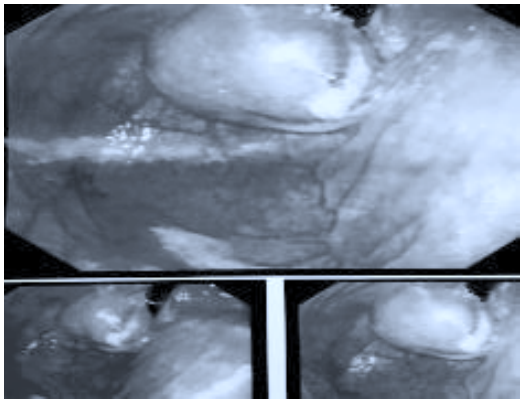


Fig.-1: *Endoscpic View of GIST*

Barium Esophagogram: Dye passed beyond the lesion. USG of whole abdomen - Oval shaped well demarcated hypoechoic soft tissue mass at cardiac end of stomach.

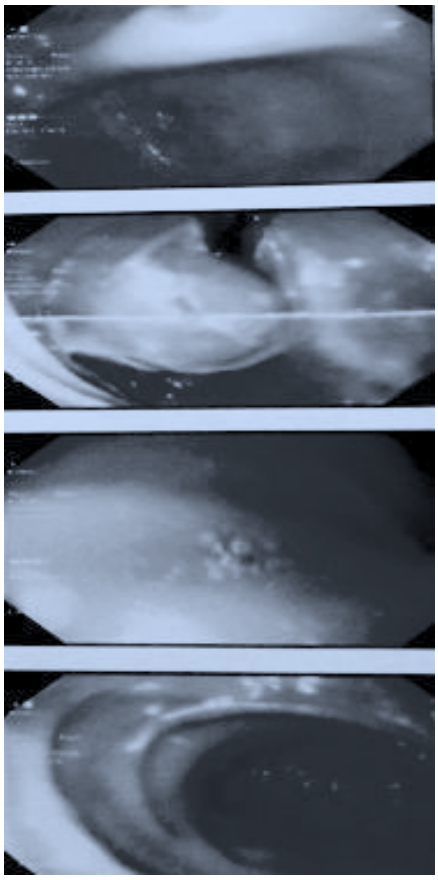


Fig.-2: *Endoscpic View of GIST*

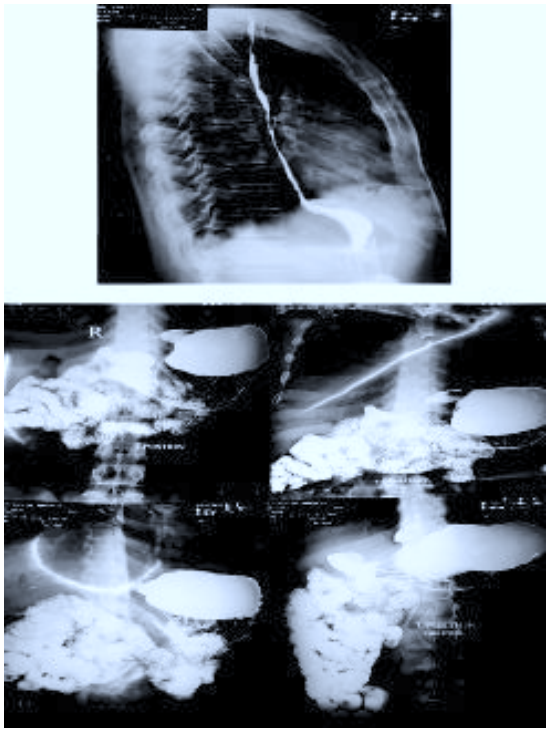


Fig.-3: *Barium esophagogram*

FNAC from GE submucosal lesion- No malignancy

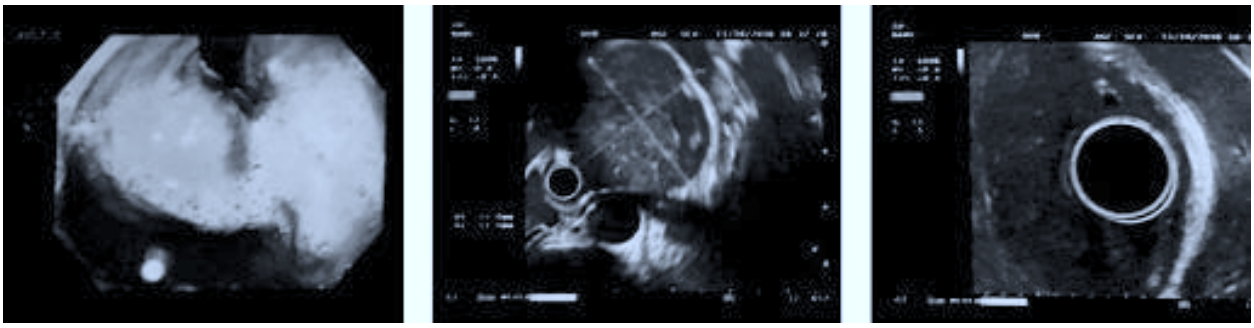


Fig.-4: *Endoscopic Ultrasonic view of GIST*

was seen, Possibility of GIST could not be ruled out. CECT Abdomen- Large hypodense poorly enhancing lesion seen at the GE junction, may be GIST. EUS – Large GIST involving GE junction.

Endosonogram – Submucosal Lesion of Stomach (GIST?).

Our clinical diagnosis was GIST at the lower end of esophagus involving Gastroesophageal junction. We formed a multidisciplinary team composed of general and thoracic surgeons, anaesthesiologists, pathologists, radiologists and oncologists.

Our Planning was Thoracotomy and access to the peritoneal cavity via phrenotomy through left sided thoracoabdominal route under GA with OLV. Anaesthesia was marked by the existance of high risk of potentially fatal accidents such as complete obstruction of the airways, cardiovascular collapse- these complications can occur in transition to the supine position, during induction of the general anaesthesia, placement of the endobronchial tubes, during positioning of the patient into right lateral decubitus position, manipulation and extraction of the tumour, and extubation. In literature, incidence of these complications in the perioperative period is between 7-20%.[10]

During surgery, the team assured jugular central venous catheter, non invasive blood pressure monitoring, selective right bronchus intubation, positive pressure ventilation, muscle relaxant along with thoracotomy. Intraoperatively the mechanical one lung ventilation was difficult but it was meticulously maintained by our anaesthesiologists' team.

Sugery was performed by left thoracoabdominal approach. After opening the thorax, phrenotomy was done and we have found a firm to almost solid globular mass in the lower end of esophagus extending up to the fundus of the stomach measuring about 10 cm x 8 cm. Macroscopically the appearance of the tumor was encapsulated

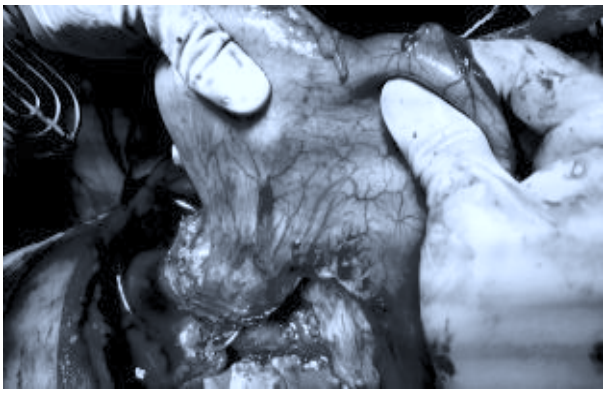


Fig.-5: *GIST after Thoracotomy*

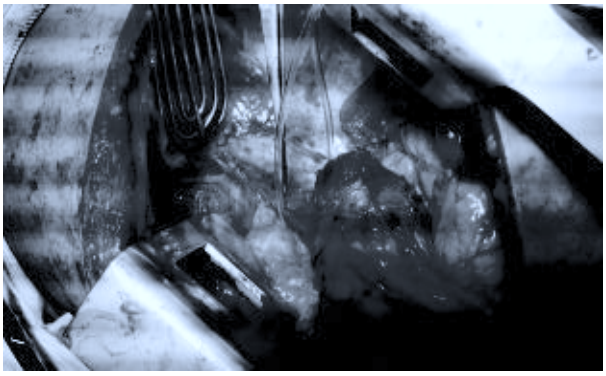


Fig.-6: GIST after Thoracotomy

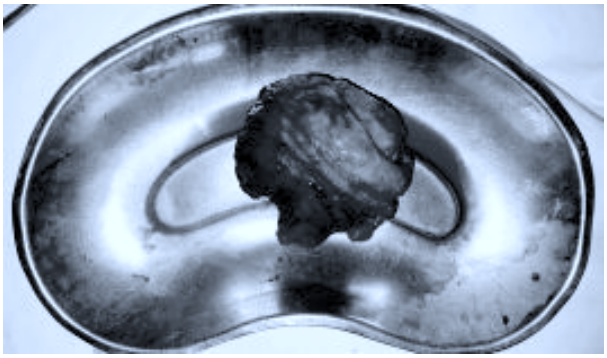


Fig.-7: *Resected GIST*

tumor of a heterogenous consistency, with the alternating areas of necrosis amd fibrous srictures. We have done esophagogastrectomy followed by esophagogastrostomy using circular stapler in the left thoracic cavity. A feeding jejunostomy was also done. After proper hemostasis diaphragm was repaired and wound was closed in layers keeping one abdominal drain and one ICT in situ.

Immediate post operative period was uneventful. Liquid diet like plain water, ORS were started from 3rd POD onward through Feeding jejunostomy Tube. On 7th POD, test meal was given orally, no anastomotic leakage was found and ICT was removed after having contrast CXR. Progressive oral food intake was started and patient didn't have any complications. Patient was discharged on 10th POD with some special advices. He was advised for not taking any solid food, bolus of food, fiber containing food and should take frequent low volume less residual food.

Resected specimen was sent for histopathological examination which revealed GIST and CD117 was positive on immunohistochemistry.

In the 1st post operative month a barium esophagogram was done which revealed passage of dye without any filling defect. There were no signs of local recurrence or metastasis at CT scans made at 6th post operative month.

About one month later, feeding jejunostomy tube was removed and he was referred to the professor of radiation oncology. Now Patient is on imatinib and is running a reasonable good food habit and his general condition is better than previous status.

Patient was advised for regular follow up with CT scans at 3 months in 1st year, at 6 months for 3 years, and annually in the next five years. Clinical and imagery follow up is very important especially in the first month from the beginning of treatment.

The appearance of local recurrence or distant metastases means imatinibmesylate resistance and treatment will be modulated according to clinical guidelines. Genetic tests are necessary and we are supporters of systematic mutational analysis in each case. It can identify the genetic profile that might offer any resistance to imatinibmesylate and orientation to the second line treatment with sunitinib maleate.

Discussion:

GIST is a kind of KIT positive mesenchymal tumors, which usually harbours activating mutations in KIT or platelet derived growth factors receptor or tyrosine kinase genes. The biologic behaviors of GISTs are diverse, varying from a small, harmless tumour nodule to a metastasizing and life threatening sarcoma.[11] Several risk criteria have been proposed for estimating the risk of tumor progression for localized GISTs.[12]

GISTs are rare accounting for 0.1-3% of all GI neoplasm.[1] The biological potential of stomach or small intestinal GIST is related to their size and mitotic activity which may also be true for the esophageal GIST as well. Esophageal GISTs commonly present with dysphagia but bleeding, perforation, back pain, anorexia, regurgitation, weight loss have been reported.[13,14] Initial testing and cytology created a diagnostic dilemma because immunohistochemistry was not advised and diagnostic reports were inconclusive.

The current case represents an extremely peculiar example of subdiaphragmatic abdominal GIST, which presented as mass lesion involving lower end of esophagus and GE junction. And posed diagnostic pitfalls with potential therapeutic consequences. Although GIST is well known in the gastrointestinal tract, thoracic region is an uncommon anatomical location for it. GIST can simulate the other tumors in the thorax. So

identification of GIST involving the thoracic area sometimes might be very challenging, especially in small biopsy samples.

GIST tumor biology allows the development to giant sizes without altering the general condition, which is a clinical characteristic of these tumors. Heterogenous appearance with solid and necrotic areas, encapsulated tumors that also compress the surrounding digestive organs are radiological characteristics which guide the clinician to the suspicion of GIST. The development from interstitial cells of Cajal does not involve the digestive mucosa and often endoscopic mucosal biopsy is negative. Lack of lymphatic dissemination of GIST is another characteristic that can be detected by imaging as absence of lymph nodes. On one hand it makes unnecessary local and regional lymph node dissection and on the other hand it allows resections with organ preservation. The clinical and imaging data may allow the suspicion of GIST and adjustment of diagnostic algorithm according to current guidelines. Being in front of a sarcoma biopsy is to be avoided, although trucut biopsy is acceptable regarding dissemination risk in the opinion of many authors. This would allow a biopsy specimen necessary to start targeted neoadjuvant treatment with tumor down staging and organ spare resections with function preservation.

Surgery is the only curative treatment far available in this type of neoplasia.[9] Surgery of this type of tumor is delicate, performed in the extracapsular plan, in order to obtain R0 resection, avoiding trauma of tumor capsule which would place the tumour in the metastatic setting. This goal can be achieved especially for tumors up to 10 cm diameter, while for larger sizes, the esophagectomy seems to be the correct oncological intervention.[15] After obtaining the biopsy specimen diagnosis is confirmed by IHC staining using a panel of monoclonal antibodies Characterstics are CD117 and DOG1. Stratification of tumour aggressiveness using the scale AFIP (Armed Forces institute of Pathology) is most often used by large volume centyers, taking into account different malignant behavior of GIST, relying on a number of parameters such as tumor size, number of mitosis, tumor site, adding tumor capsule rupture , multiorgan involvement or incomplete resection.[16] Mutational analysis comes to finalize the diagnosis, stating mutant gene which gives a better targeted treatment, tumors with exon 9 mutated KIT gene being recognized as more aggressive than the exon 11ones and known that some GISTs are resistant to standard treatment with tyrosine kinase inhibitors.[17]

Comparing mutational analysis costs with two or three months of ineffective treatment with tyrosine kinase inhibitors it is justified the use of this genetic methods for the benefit of the patient and the healthcare system. It is absolutely necessary to address each case to a multidisciplinary team that includes different specialties working with this type of pathology.[18] This can ensure correct diagnosis and therapy of these patients, according to actual clinical guidelines, applying effective and specific treatment and consistent reporting of each case.

Ethical consideration:

Informed written consent was taken from the patient for presentation and publication of the case report with accompanying images.

Conclusion:

Esophageal GISTs presenting with dysphagia is rare. Imatinib is the 1st line of drug though treatment failure has been reported where sunitinib is used. Future trials with combined or sequential use of tyrosine kinase inhibitors with other medications and personalized therapy after tumour molecular subtyping are promising in the management of GISTs. In this article we presented the issue of diagnosis and surgical treatment of a giant GIST of GE junction. We insist that such a case should be treated in a multidisciplinary team assessing the immediate anaesthetic and surgical risk and also the risk of recurrence by complete pathological and genetic evaluation, in conjunction with adjuvant or even neoadjuvant specific therapy.

Abbreviations:

GIST- Gastrointestinal Stromal Tumour; UGIT- Upper Gastro intestinal tract; USG- Ultrasonography; FNAC- Fine needle aspiration for cytology; CECT- Contrast enhanced computed tomography; EUS- Endoscopic ultrasound, POD- Post operative day; ICT- Intercostal tube; CXR- Chest X ray. OLV- one lung ventilation; GA- General Anaesthesia.; GE- Gastroesophageal; AFIP- Armed Forces institute of Pathology

References:

1. Norman S. Williams, P. Ronan O'Connell, Andrew W. McCaskie, Bailey & Love's Short Practice of Surgery, 27th edn. 2009;2:1140.
2. Miettinen M, Sarlomo-Rikala M, Lasota J: Gastrointestinal stromal tumours. Ann Chir Gynaecol. 1998;87: 278-281.
3. Miettinen M, Lasota J: Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med. 2006;130: 1466-1478.
4. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Tunio GM, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y; Gain-of-Function mutation of c-Kit in human gastrointestinal tumours. *Science*. 1998;279:577-580
5. KindblomLG, remotti HE,Aldenborg F, Meis Kindblom JM,: Gastrointestinal Pacemaker cell Tumour (GIPACT). Gastrointestinal stromal tumours show phenotypic characterstics of the intestinal cells of Cajal. Am J Patho. 1998;153:1259-1269
6. Demetri GD, Benjamin RS, Blanke CD, Blay JY, Casali P, Choi H, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST) update of the NCCN clinical practice guidelines. J NatlComprCancNetw. 2007;5 (Suppl 2): S1-29. 182.
7. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J ClinOncol. 2003;21:4342-9.
8. Miettinen M, Wang ZF, Sarlomo-Rikala M, Osuch C, Rutkowski P, Lasota J. Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. Am J SurgPathol. 2011; 35:1712-21.
9. The ESMO / European Sarcoma Network Working GroupGastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology 23 (Supplement 7): vii49–vii55, 2012 doi:10.1093/annonc/mds252.
10. Béchard P, et al: Perioperative cardio respiratory complications in adults with mediastinal mass: incidence and risk factors Anesthesiology. 2004; 100: 826-34
11. Miettinen. M and Lasota J. Gastrintestinal stromal tumors. Gastrenterol Clin North Am. 2013: 42: 399-415
12. Miettinen. M and Lasota J. Gastrintestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006: 23:70-83
13. Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. Am J Surg Pathol. 2000;24:211–222.
14. Chang WC, Tzao C, Shen DH, Cheng CY, Yu CP, Hsu HH. Gastrointestinal stromal tumor (GIST) of the esophagus detected by positron emission tomography/computed tomography. Dig Dis Sci. 2005;50:1315–1318.
15. Jiang P, Jiao Z, Han B, Zhang X, Sun X, Su J, Wang C and Gao B. Clinical characteristics and surgical treatment of oesophageal-gastrointes- Esophageal GIST 343 Am J Cancer Res. 2015;5(1):333-343.

16. Joensuu H, Vehtari A, Riihimaki J, Nishida T, Steigen SE, Brabec P, Plank L, Nilsson B, Cirilli C, Bordoni A, Magnusson MK, Linke Z, Sufliarsky J, Federico M, Jonasson JG, DeiTos AP, Rutkowski P: Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol. 2012;13: 265–274.

17. Christopher L. Corless et al. Pathologic and Molecular Features Correlate With Long-Term Outcome After Adjuvant Therapy of Resected Primary GI Stromal Tumor: The ACOSOG JCO.2013.53.5971

18. Badulescu A., Badulescu F., Cosntantinoiu S., Popescu C., Schenker M. – Gastrointestinal stromal tumors (GIST) – a new diagnostic and therapeutic paradigm. – Chirugia (Bucur). 2006; 101 (1):87-89.

Chest Heart Journal
Vol. 43, No. 2, July 2019

CASE REPORT

A Very Rare Malignant lesion in the Right Heart almost Occluding Whole of Right Atrium and Part of Right ventricle – Case report

S.M.A Zulker Nine[1], Md. Zulfiqur Haider[2], Md. Sohail Ahmed[3], Niaz Ahmed[4], MdSaiful Islam khan[5], Mohammad Delwar Hossain[6], TaheraMehar[7], Md. Kamrul Hasan[8], Kamrun Nahar[9], Dr Arup Khan[10]

Abstract:

Primary cardiac tumors are rare, with an incidence of 0.056% according to autopsy reports. The most common type is myxoma, while other types, including sarcoma, lipoma, papillary fibroelastoma, rhabdomyoma, fibroma, hemangioma, teratoma, lymphoma and mesothelioma also occur. Primary cardiac tumors usually cause embolization, pericardial effusion and arrhythmia, leading to heart failure. Only 10% of primary cardiac tumors are malignant, approximately 95% of which are sarcomas, while the remaining 5% are cardiac lymphomas and mesotheliomas. This report documents the case of a 44-year-old male with primary cardiac lymphoma.The definitive diagnosis is dependent on Histopathology and Immunohistochemistry. Timely treatment with chemotherapy can be effective.

The goals of this article are to show the difficulties of diagnosing and treating this disease, the role of cardiac surgery in its treatment and to raise awareness of this disease.

Key words: *Heart neoplasm, non Hodgkin lymphoma, primary cardiac lymphoma*

[Chest Heart J. 2019; 43(2) : 109-113]
DOI: http://dx.doi.org/10.33316/chab.j.v43i2.20196010

Introduction:

Primary cardiac lymphoma (PCL) is a rare type of nonHodgkin's lymphoma (NHL) that solely involves the heart, the pericardium, or both and accounts for less than 0.01% of all cardiac tumors.[1–3] The clinical presentation of PCL varies depending on the location, size, and degree of invasion[4]. The rising incidence of PCL is thought to be due to advances in diagnostic radiologic technology, greater exposure to environmental toxins, and a larger number of immunocompromised individuals.[5] Here, we present a case of primary cardiac lymphoma.

1. Specialist, Department of Cardiovascular and Thoracic Surgery, Apollo Hospitals Dhaka.
2. Consultant, Department of Cardiovascular and Thoracic Surgery, Apollo Hospitals Dhaka.
3. Consultant, Department of Cardiovascular and Thoracic Surgery, Apollo Hospitals Dhaka.
4. Consultant, Department of Cardiothoracic Anesthesia, Apollo Hospitals Dhaka.
5. Specialist, Department of Cardiothoracic Anesthesia, Apollo Hospitals Dhaka.
6. Senior registrar, Cardiaothoracic& Vascular Surgery, Apollo Hospitals Dhaka.
7. Registrar, Cardiaothoracic& Vascular Surgery, Apollo Hospitals Dhaka.
8. Registrar, Cardiaothoracic& Vascular Surgery, Apollo Hospitals Dhaka.
9. Assistant Professor, Department of transfusion Medicine, Bangladesh Medical college & Hospital, Dhanmondi, Dhaka, Bangladesh.
10. Senior Medical Officer, Cardiothoracic & Vascular Surgery, Apollo Hospitals Dhaka

Correspondence to: Dr. S.M.A Zulker Nine, Specialist, Department of Cardiovascular and Thoracic Surgery, Apollo Hospitals Dhaka. Email: smazulkernine@gmail.com

Submission on: 15 May, 2019 **Accepted for Publication:** 1 June, 2019
Available at http.//www.chabjournal.org

Cardiac tumors are among the least investigated tumor types in oncology. Primary cardiac tumors are rare with an incidence of 0.056% according to autopsy reports.[6] Approximately 90% of primary cardiac tumors are benign, the most common type of which is myxoma, while other types, including lipoma, papillary fibroelastoma, rhabdomyoma, fibroma, hemangioma, teratoma, sarcoma, lymphoma and pericardial mesothelioma also occur. The remaining 10% of primary cardiac tumors are malignant, 95% of which are sarcomas and 5% of which are cardiac lymphomas and mesotheliomas.[7] Primary cardiac lymphoma (PCL) is defined as non Hodgkin lymphoma (NHL) involving only the heart and/or pericardium (strict criteria), or as NHL presenting with cardiac manifestations, particularly when the bulk of the tumor is found in the heart (loose criteria).[8] It is estimated that PCLs account for 1.3% of primary cardiac tumors and 0.5% of all extranodal NHLs.[9] During 1949-2009, only 197 cases of PCL were reported in the literature. By contrast, secondary cardiac involvement of lymphomas is more common, with an incidence of 9-24% in disseminated and terminal-stage NHL cases.[10]

Primary cardiac lymphoma (PCL) constitutes 5-6% of primary cardiac malignant neoplasms.[11,12] Because of its rapid progress, late diagnosis due to its non-specific symptoms and variable patient responses to treatment, the prognosis for patients with PCL remains poor. Complete remissions have been reported, although the longest period of survival has not exceeded 144 weeks.[13] Approximately 80% of patients live less than 12 months after diagnosis.[14]

Case Report:

A 44-year-old Bangladeshi male patient presented with exertional dyspnea for several months. The patient denied any history of systemic disease and physical examination showed no remarkable abnormalities. Laboratory examination showed creatinine levels of creatinine (1.3 mg/dl; normal range, 0.7 1.5 mg/dl for male and 0.5 1.2 mg/dl for female), lactate dehydrogenase (LDH 603 U/l; normal range, 95 213 U/l), aspartate aminotransferase (83U/l; normal range, 5 35 U/l) and alanine aminotransferase (33 U/l; normal range, 0 40 U/l). Chest X-ray (CXR) showed cardiomegaly with mild left pleural effusion. Electrocardiography (ECG) showed sinus bradycardia. Transthoracic echocardiography (TTE) revealed a left ventricular ejection fraction (LVEF) of 65%, and alarge right atrial myxoma with tricuspid regurgitation. CAGwas done which revealed: Single vessel disease (SVD) recommended for CABG with Excision of RA myxoma. After establishment of cardiopulmonary bypass right atrium opened. A huge myxoma like mass was found in RA with broad base over the IAS near triangle of Koch and commissure between septal leaflet and anterior leaflet of tricuspid valve.Surgical resection was performed. RV cavity and pulmonary valve was checked for any residual tumor fragment. Thorough wash given in RV cavity with saline. Patency of tricuspid valve was checked. Good leaflet coaptation present. RSVG was anastomosed to the LAD.

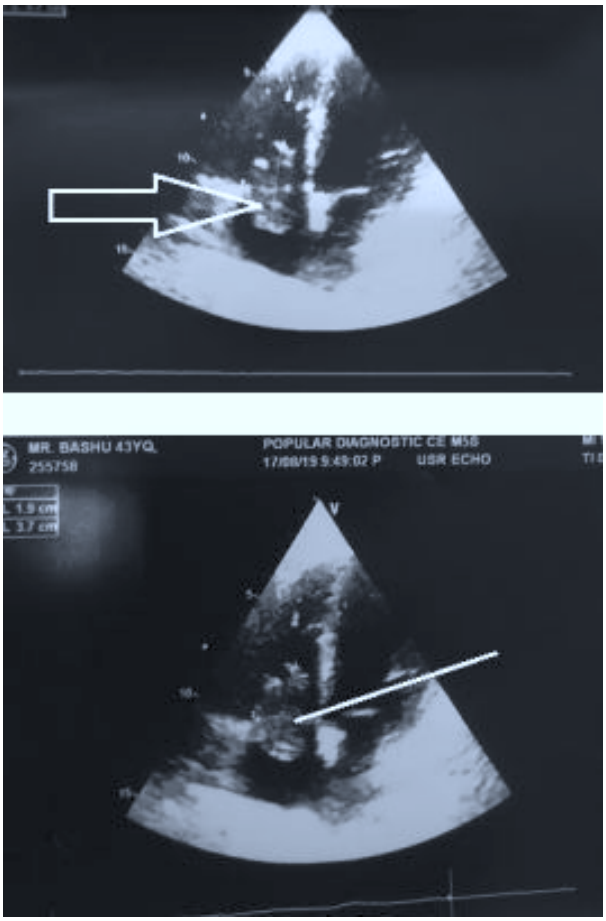
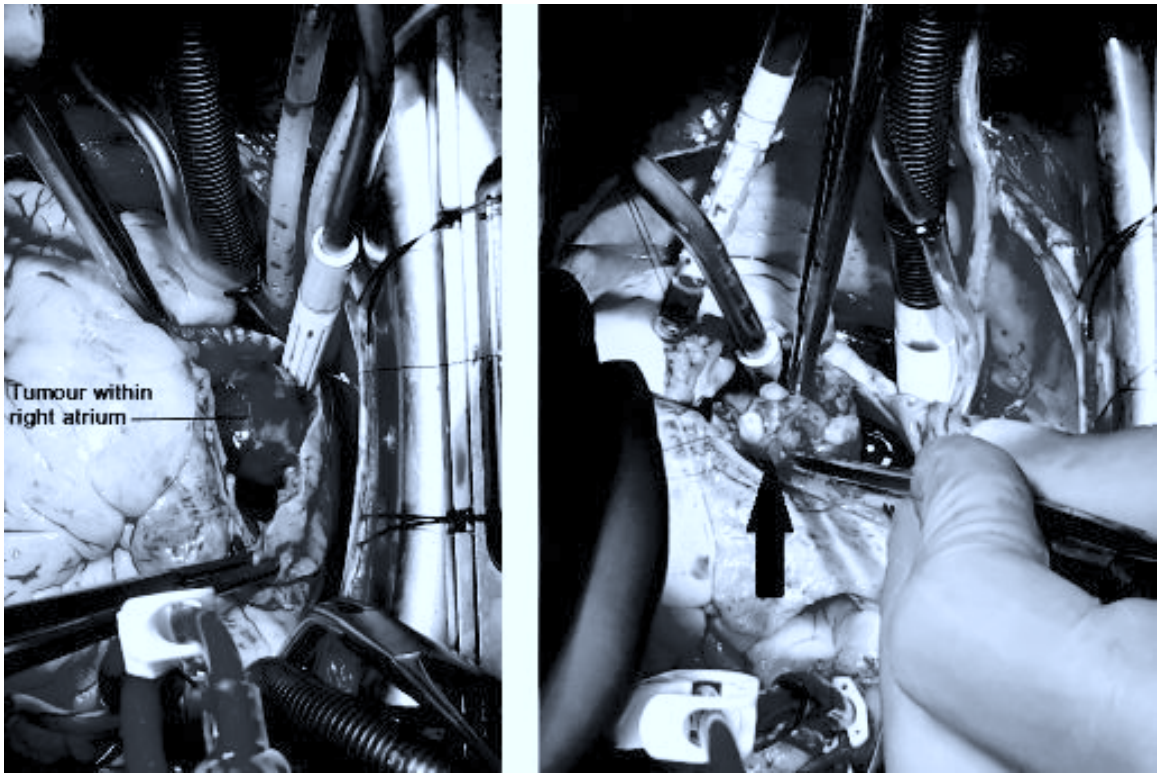


Fig.-1*: Transthoracic echocardiography showing a echogenic mass (3.7 x 1.9) cm within the right atrium (white arrow and line) extending into right ventricle.*



(a) (b)

Fig.-2(a &b): *RA-tomy showing an irregular mass with variegated appearance arising from right atrium (Black line & arrow).*

Histologic sections revealed anintermediate/diffuse proliferation of atypical large lymphocytes. Frequent atypical mitosis and prominent starry sky pattern are evident. Immunohistochemical studies revealed that the malignant cells stained positively with antibodies directed against CD20, BCL2, C-Myc, MUM1.Histomorphological and IHC features are compatible with diffuse large B-Cell Non-Germinal Centre type.The final diagnosis was primary cardiac lymphoma, diffuse large B-cell type. The patient was referred to hematologist for further management.

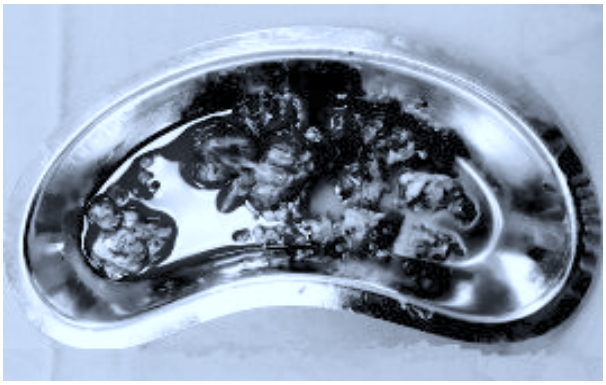


Fig.-3: *Resected cardiac tumor.*

Discussion:

The major clinical features of PCL include dyspnea, heart failure, precordial pain, life-threatening arrhythmia due to tumor invasion of the conduction system or irritation of myocardium, pleural effusion, pericardial effusion and shock due to cardiac tamponade or obstruction of blood flow.[15] Constitutional symptoms, including fever, chills, sweats and weight loss, are also common. In some PCL cases, patients may develop pulmonary or cerebral embolism. The most common ECG abnormalities include atrial arrhythmias and AV block, with up to 61% of patients experiencing complete AV block. Other ECG features are right bundle branch block, inverted T waves, low voltage and life threatening ventricular tachyarrhythmia.[16] CXR usually reveals cardiomegaly or pleural effusion. TTE has a sensitivity of 55 60% for primary cardiac tumors and TEE has a sensitivity of 97 100%. The sensitivity of cardiac magnetic resonance imaging is superior to that of CT (90 92 vs. 71 73%).[17] In 92% of PCL cases reported, the right heart chambers were involved, predominantly the RA.

By contrast, in only 7% of cases, the left heart was involved without right heart invasion. In 25% of PCL cases, the superior vena cava was also affected. Diffuse large B cell lymphoma is the most common sub type of PCL (113 cases reported); the remaining sub types include Burkitt's lymphoma, T cell lymphoma, small lymphocytic lymphoma and plasmablastic lymphoma.[18] At present, no definite guidelines exist for the management of PCL. Early systemic chemotherapy appears to be the only effective therapy. The major regimen is the same as that for other types of NHL, namely cyclophosphamide/hydroxydaunorubicin/oncovin/ prednisone (CHOP) and since 2001, CHOP + rituximab. It is difficult to perform a complete surgical resection of PCL, which provides no survival benefit. Chemotherapy followed by radiotherapy for PCL may enhance survival, although its efficacy remains to be determined[19]. The overall response rate of patients with PCL to chemotherapy is 79% and the complete remission rate is 59%. The median overall survival of patients with PCL is ~12 months. Poor prognosis[19] is associated with extra-cardiac disease, immunocompromised status, LV involvement and, notably, absence of arrhythmia.[20] The pathology of diffuse large B-cell lymphoma also represents the most common cell type of PCL. Primary cardiac tumors are rarely encountered by clinical physicians and PCL is even rarer. Although the development of modern imaging technology has improved the detectability of this disease, invasive tissue biopsy and awareness of clinicians of the disease are required for early pathological diagnosis, which is essential for effective treatment. Despite the poor overall survival of affected patients and limited current knowledge regarding specific treatments, early systemic chemotherapy yields a high response rate and improves the possibility of survival. Lymphoma should be considered by clinicians if cardiac tumors are encountered. Although PCL is associated with poor prognosis and life-threatening complications, timely and appropriate treatment can be beneficial.

Conclusions:

In conclusion, prompt diagnosis and treatment management maximize prolonged survival in PCL. Therefore, the appropriate choice of diagnostic procedure influences the patient's prognosis. Unfortunately, the range of modern diagnostic approaches may be seriously limited in an advanced stage of PCL and when a patient's condition on admission is critical.

References:

1. Burke A, Virmani R. In: Tumors of the Heart andGreat Vessels: Atlas of Tumor Pathology. 3rd series, fasicle 16. Washington, DC: Armed ForcesInstitute of Pathology. 1995:171-177.
2. McAllister HA, Fenoglio JJ. In: Tumors of the CardiovascularSystem: Atlas of Tumor Pathology.2nd series, fasicle 15. Washington, DC: ArmedForces Institute of Pathology. 1978:99-102.
3. Reynen K. Cardiac myxomas. N Engl J Med.1995;333:1610-1617.
4. Ceresoli GL, Ferreri AJ, Eraldo B, Ripa C, PonzoniM, Villa E. Primary cardiac lymphoma in immunocompetentpatients: diagnostic and therapeuticmanagement. Cancer. 1997;80: 1497-1506.
5. Curtsinger CR, Wilson MJ, Yoneda K. Primarycardiac lymphoma. Cancer. 1989;64: 521-525.
6. Cairns P, Butany J, Fulop J, Rakowski H, HassaramS. Cardiac presentation of non-Hodgkin'slymphoma. Arch Pathol Lab Med. 1987;111:80-83.
7. Proctor MS, Tracy GP, Koch LV. Primary cardiacB-cell lymphoma. Am Heart J. 1989;118:180-181.
8. Albat B, Messner-Pellenc P, Thevenet A. Surgicaltreatment for primary lymphoma of the heart simulating prosthetic mitral valve thrombosis.J Thorac Cardiovasc Surg. 1994;108:188-189.
9. Skalidis EI, Parthenkis FI, Zachais EA, DatserisGE, Vardas P. Pulmonary tumor embolism from primary cardiac B-cell lymphoma. Chest. 1999;116:1489-1490.
10. Bestetti RB, Soares FA, Soares EF, Oliveira JS.Primary lymphoma of the right atrium with fatal neoplastic pulmonary embolism. Am Heart J.1992;124:1088-1089.
11. Wargotz ES, Jannotta FS, Nochomovitz LE. Primarycardiac non-Hodgkin's lymphoma. Arch Pathol Lab Med. 1987;111:894-895.

12. Jaffe ES, Harris NL, Stein H, Vardiman JW. eds,World Health Organization Classification of Tumours: Pathology and Genetics of Tumours ofHaematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001.

13. Ito M, Nakagawa A, Tsuzuki T, Yokoi T, YamashitaY, Asai J. Primary cardiac lymphoma: no evidence for an etiologic association with Epstein-Barr virus. Arch Pathol Lab Med. 1996;120:555-559.

14. Nagano M, Uike N, Suzumiya J, et al. Successfultreatment of a patient with cardiac lymphoma who presented with a complete atrioventricular block.Am J Hematol. 1998;59:171-174.

15. Lai R, Medeiros LJ, Dabbagh L, Formenti KS,Copeland RW. Sinusoidal CD30-positive large B-cell lymphoma: a morphologic mimic of anaplasticlarge cell lymphoma. Mod Pathol. 2000; 13:223-228.

16. Kuze T, Nakamura N, Hashimoto Y, Abe M, Wakasa H. Clinicopathological, immunological and genetic studies of CD30_ anaplastic largecell lymphoma of B-cell type; association with Epstein-Barr virus in a Japanese population.J Pathol. 1996;180:236-242.

17. Johri A, Baetz T, Isotalo PA, Nolan RL, Sanfilippo AJ, Ropchan G. Primarycardiac diffuse large B cell lymphoma presenting with superior vena cavasyndrome. Can J Cardiol. 2009;25:e210–2.

18. Zhong L, Yang S, Lei K, Jia Y. Primary cardiac lymphoma: a case report andreview of the literature. Chin-Ger J Clin Oncol. 2013;12: 43–5.

19. Jung YH, Woo IS, Ko YJ, Lee JH, Lim JW, Han CW. A case of primary cardiaclymphoma showing isolated central nervous system relapse. ClinLymphoma Myeloma Leuk. 2014;14:31–3.

20. Chen K-W, Chang J-H, Yeh S-P, Lu C-R. Primary cardiac B-cell lymphomawith atrioventricular block and paroxysmal ventricular tachycardia. JCardiothorac Surg. 2012;7:70.

INSTRUCTION TO AUTHORS ABOUT UNIFORM MANUSCRIPT WRITING

The Chest and Heart Journal is published twice in a year in the months of January and July. The journal publishes original papers, reviews concerned with recent practice and case report of exceptional merits. Papers are accepted for publication with an understanding that they are subject to editorial revision. A covering letter signed by all authors must state that the data have not been published elsewhere in whole or in part and all authors agree their publication in Chest and Heart Journal. All submitted manuscripts are reviewed by the editors and rejected manuscripts will not be returned. Ethical aspects will be considered in the assessment of the paper. Three typed copies of the article and one soft copy in CD or Pen Drive processed all MS Word 6.0 should be submitted to the editor.

Preparation of Manuscripts

Manuscripts should be typed on one side of good quality paper, with margins of at least 25mm and using double space throughout. Each component of the manuscript should begin on a new page in the sequence of title page, abstract, text, references, tables, and legend for illustrations. The title page should include the title of the paper, name of the author(s), name of the departments) to which work should be attributed. The text should be presented in the form of Introduction, Materials and Methods, Results, and Discussion. The text should not exceed 2500 words and a word count should be supplied.

Abstracts/Summary

Provide on a separate page an abstract of not more than 250 words. This abstract should consist of four paragraphs, labeled Background, Methods, Results and Conclusions. They should briefly describe the problem being addressed in the study, how the study was performed, the salient results, and what the authors conclude from the results.

Table

Each table should be typed in on separate sheet. Table should have brief title for each, should be numbered consecutively using Roman numbers and be cited in the consecutive order, internal horizontal and vertical rules should not be used.

Results should be presented in logical sequence in the text, tables or illustration. Do not repeat in the text all data in the tables or illustrations; emphasize or summarize only important observations.

Drug Names

Genetic names should generally be used. When proprietary brands are used in research, include the brand name in parentheses in the Methods section.

Illustrations

Figure should be professionally designed symbols, lettering, and numbering should be clear and large. The back of each figure should include the sequence number and the proper orientation (e.g. “top”). Photographs and photomicrographs should be supplied as glossy black and white prints unmounted. Legend for each illustration should be submitted in separate sheets. All photographs, graphs and diagrams should be referred to as figures numbered consecutively in the text in Roman numerals.

Discussion

Emphasize the new and important aspects of the study and the conclusions that follow from them. The detail data or other material given in the Introduction or the Results section should not be repeated. The implications of the findings and their limitations, including implication for future research should be included in the Discussion section. The observations should be compared and related to other relevant studies, new hypothesis is appreciated, and however they should be clearly labeled as such. Recommendations may be included only when appropriate.

References

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legend by Roman numerals in parenthesis. Use the styles of the example below, which are based on the formats used by the US National Library of Medicine (NLM) in the Index Medicus.

Avoid using abstracts as references. References to paper accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited as "unpublished observations" with written permission from the source. Avoid using a "personal communication" unless it provides essential information not available from a public source. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of a personal communication.

The references must be verified by the authors(s) against the original documents.

1. Articles in Journal

a) List all six authors when six or less;
Connors JP, Roper CL, Ferguson TB. Transbronchial Catheterisation of Pulmonary Abscess. Ann Thorac Surg 1975; 19 : 254-7.

b) When seven or more, list the first three and then add et al;
Karalus NC, Cursons RT, Leng RA, et al. Community acquired pneumonia: aetiology and prognostic Index evaluation. Thorax 1991; 46 : 413-12.

c) No author given;
Cancer in South Africa (editorial). S Afr Med J 1994; 84-15.

d) Organization as author
The Cardiac Society of Australia and New Zealand. Clinical exercise stress training. Safety and performance guideline. Med J Aust 1996; 164 : 282-4.

2. Books and Other Manuscripts

a) Personal author
Tierney LM, -McPhee SJ, Papakadis MA. Current Medical Diagnosis and Treatment. Lange Medical books/Mcgrow Hill 2000.

b) Editor(s), complier(s) as author
Baum GL, Wolinsky E, editor. Text Book of Pulmonary diseases. 5th ed. New York: Little Brown Co. 1994.

c) Organization as author and publisher
World Health Organization, Ethical Criteria for Medical Drug Promotion. Geneva: World Health Organization; 1988.

d) Chapter in a book
Macnee W. Chronic bronchitis and emphysema. Seaton A, Seaton D, editors. Crofton and Douglas's Respiratory Diseases. 5th ed. UK. The Blackwell Science; 2000; p.616-95.

e) Dissertation
Kaplan SJ. Post-hospital home health care: the elderly's access and utilization (dissertation). St. Louis (MO). Washington Univ; 1995.

3. Other published material

a) Newspaper article
Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996, June 21; Sect. A : 3(col. 5).

b) Dictionary and similar references
Student's medical dictionary. 26th ed. Baltimore: Williams & Wilkins; 1995. Apraxia; p.119-20.

4. Unpublished Material

a) In press

Leshner AI. Molecular mechanisms of cocaine addition. N Engl J Med In Press 1997.

5. Electronic Material

a) Journal articles in electronic format

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis Serial online I 1995 Jan-Mar I cited 1996 June 5 I; 1(1): 24 screens I

Available from: URL: http://www.cdc.gov/ncidod/E[D/eid.htm

Nomenclature and Abbreviation

1. Abbreviations and symbols must be standard and SI units should be used thoughtout.
2. Terms such as electrocardiogram, ultrasonogram etc. should when mentioned first, be written in full followed by accepted abbreviations (ECG, USG etc.)

Permissions

A written statement must accompany materials taken from other sources from both author and publisher giving permission to the Journal for reproduction. Obtain permission in writing from at least on a author of papers still in press, unpublished data, and personal communications.

Review and Action

Manuscripts are examined by the editorial staff and are usually sent to reviewers, but we reserve the right of final selection.

Proof

Two marked copies of the proofs may be sent to the principal author, which should be read carefully for error. One corrected copy must be returned to the editor within the next three days. Major alteration in the text can not be accepted.

Editorial Mail

Manuscripts and other communication for the editors should be addressed to

The Editor in Chief
Chest and Heart Journal
Association Secretariat, Administrative Block, National Institute of Diseases of the Chest & Hospital.
Mohakhali, Dhaka-1212, Phone/Fax: 8851668