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Chest Heart Journal
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EDITORIAL

Long COVID or Post COVID-19 Syndrome

Md. Abdur Rouf

[Chest Heart J. 2021; 45(1) : 1-2]
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Most people who develop COVID-19 fully recover, but current evidence suggests approximately 10%-20% of people experience a variety of mid- and long-term effects after they recover from their initial illness. These mid- and long-term effects are collectively known as post COVID-19 condition or "Long COVID."

According to WHO,[1]

"Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time."

Risk factors

According to a King's College London study initially posted on 21 October 2020 risk factors for long COVID may include:[2]

- Age – particularly those aged over 50
- Obesity
- Asthma
- Reporting more than five symptoms (e.g., more than a cough, fatigue, headache, diarrhoea, loss of sense of smell) in the first week of COVID-19 infection; five is the median number reported.
- Gender – Women are less likely to develop severe acute COVID but more likely to develop long COVID than men. Some research suggests this is due primarily to hormonal differences, while other research points to other factors, including chromosomal genetics, sex- dependent differences in immune system behaviour; non-biological factors may also be relevant.

Symptoms

Symptoms after Long COVID are highly variable and wide ranging. The most common symptoms of post COVID-19 condition include:[3]

- extreme tiredness (fatigue)
- shortness of breath
- loss of smell
- muscle aches

However, there are lots of symptoms you can have after a COVID-19 infection, including:

- problems with your memory and concentration ("brain fog")
- chest pain or tightness
- difficulty sleeping (insomnia)
- heart palpitations
- dizziness• pins and needles
- joint pain
- depression and anxiety
- tinnitus, earaches
- feeling sick, diarrhoea, stomach aches, loss of appetite
- a high temperature, cough, headaches, sore throat, changes to sense of smell or taste
- Rashes

Diagnosis

Diagnosis of Long COVID is mostly clinical. There isn't one single test to diagnose long COVID. Routine blood test, CXR, ECG is commonly done. It's a condition that isn't fully understood yet. So diagnosis based on excluding other diseases.For research purpose Xenon MRI is being used to study long COVID, because it provides patients and physicians with explanations for previously unexplained observations. Xenon MRI[4] can measure gas exchange and provide information on how much air is taken up by a patient's bloodstream, which is being researched in long-haul COVID patients.[89][90]Xenon MRI can quantify three components of lung function: ventilation, barrier

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tissue uptake and gas exchange. It helps determine how well air is taken in by the lungs, absorbed into lung tissue, and taken up by the blood.

Management

Unfortunately, there isn't one single treatment or medication to treat long COVID.Everyone's experience is different, so it's important to chat to your GP about the symptoms you are experiencing. They can tell you how to best manage them, and let you know what other support is available.If long COVID is having a big impact on your life, you may be referred to a specialist rehabilitation service, or a specialist who looks after the symptoms you have.Provide integrated, multidisciplinary rehabilitation services, based on local need and resources. Healthcare professionals should have a range of specialist skills, with expertise in managing fatigue and respiratory symptoms (including breathlessness). Additional expertise may be needed depending on the age and symptoms of the person. The core team could include, but not be limited to, the following specialist areas:

- occupational therapy
- physiotherapy
- clinical psychology and psychiatry
- rehabilitation medicine.

Recovering from long COVID

Recovery from long COVID varies. Some symptoms can improve quickly and others last longer.The chances of having long-term symptoms does not seem to be linked to how ill you are when you first get COVID-19.[5]

People who had mild symptoms at first can still have long-term problems.It's important to note that lasting effects aren't unique to COVID-19 – other viral illnesses can also have lasting effects. The study led by Leicester researchers described above suggests that among those who needed hospital treatment for the initial illness, it is common for it to last five months or more, and there are separate reports of it lasting 12 months or more (this includes both people who didn't need hospital treatment initially and those who did.

Conclusion

For reducing the risk of long COVID is to get all the vaccines recommended. The vaccine not only reduces the risk of catching COVID-19, but there is also evidence that for those who do catch it, being vaccinated makes it less likely they will develop long COVID. But it doesn't remove the risk of long COVID entirely, and some research carried out in the United States suggests that among those who catch COVID, the risk may still be significant. So it's a good idea to also try to reduce your risk of exposure to COVID, including wearing face mask in crowded places.

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ORIGINAL ARTICLE

Elevated Red Cell Distribution Width Predicts the Adverse Outcome of Patients Hospitalized with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

S. M. Abdur Razzaque[1], Md. Khairul Anam[2], Bipul Kanti Biswas[3], Jayanta Kumar Saha[4], Mirza Mohammad Idris Ali[3]

Abstract:

Background: *Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in the world. Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) causes repeated hospitalization of patients. The readmission risk of these patients should be assessed by any means specially any laboratory test that would show consistent association. Red Blood Cell Distribution Width (RDW) is an automatically calculated measure of routine hemogram test which is very simple and inexpensive. Increased RDW is associated with prognosis of many medical conditions, but still not well evaluated for the prognosis of AECOPD.*

Objectives: *To evaluate the RDW level for prediction of prognosis in patients hospitalized with AECOPD.*

Methods: *A population-based observational cohort study conducted on patients who were hospitalized due to AECOPD in Shaheed Tajuddin Ahmad Medical College Hospital, Gazipur from January 2017 to December 2018. Clinical and laboratory test reports of all participants were recorded. They were observed to measure the incidence of readmission due to AECOPD, readmission from any other cause and composite end point of readmission or death during 60 days after discharge from hospital.*

Results: *Total 146 patients were included in the study. Overall readmission rate of patients within 60 days of index hospitalization was 28.21%, among them 48.63% readmitted patients were due to AECOPD. Composite end point (readmission or death) were found significant ($p<0.05$) in patients with congestive heart failure, acidosis before discharge and high RDW at admission.*

Conclusion: *High RDW levels in patients with AECOPD admitted in hospital are usually associated with an increased risk for early readmission as well as increased mortality.*

Key words: *Red cell distribution, Chronic obstructive pulmonary disease*

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Introduction:

Chronic obstructive pulmonary disease (COPD) is a chronic inflammation of the respiratory tract and lungs that progressively causes damage to lung tissue and reduces the airflow. The Global Burden of Disease Study estimated that COPD will be the

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third leading cause of death in the world by 2030.[1] Acute exacerbation is a key event of natural history of COPD and Acute exacerbation of Chronic obstructive pulmonary disease (AECOPD) is one of the most common causes of hospitalization worldwide. Many of those patients require readmission in hospital within 60 days of discharge after prior hospitalization for AECOPD.

Red Blood Cell Distribution Width (RDW) is a laboratory parameter that can be evaluated for differential diagnosis of microcytic anemia. Recently, elevated RDW emerged as a negative prognostic factor in variety of medical conditions.[2]

COPD also has a systemic inflammatory effect. The inflammatory process may extend beyond the pulmonary system, resulting in a state of persistent low-grade systemic inflammation which has been implicated in various complications of COPD including cachexia, CVD, and arrhythmias. [3-5] Inflammation has been proposed as a key element in the association of COPD and CVD. It can be concluded that RDW levels, which is considered to be a marker of inflammation, may be elevated in patients with COPD as well as in CVD. Two recent studies have reported that high RDW levels in patients with COPD correlated with right ventricular dysfunction and overall survival. [6]

The RDW level was assessed in patients with stable COPD which showed the association of elevated RDW with severity of stable COPD and risk of mortality. [6-7] But, the RDW level has not been so far evaluated for prediction of prognosis in patients hospitalized with AECOPD. Hence we designed this study to explore whether RDW is useful for prediction of adverse outcomes of patients hospitalized with AECOPD.

Methodology:

We conducted a population-based observational cohort study, using the data of patients who were hospitalized due to AECOPD in Shaheed Tajuddin Ahmad Medical College Hospital, Gazipur from January 2017 to December 2018. The study population included patients 40 years or older with a primary diagnosis of AECOPD. Our study did not include patients who died during an index hospitalization, patients who were discharged on request or with risk bond, and patients transferred to another hospital. All participants were observed to measure the incidence of readmission due to AECOPD, readmission from any other cause and composite end point of readmission or death during 60 days after discharge from hospital. Data like demographics, vital signs at admission, comorbidities and laboratory values were retrieved from the medical records of the patients. Qualitative variables were expressed as numbers and percentage while quantitative variables were expressed as means and standard deviations. Normal distribution of variables was determined by using the Kolmogorov–Smirnov test before comparison of means. An independent samples Student's t test was used to compare normally distributed means. Differences between dichotomous variables were analyzed by the Chi-squared test.

Results:

During the study period total 180 patients were admitted in hospital with primary diagnosis of AECOPD. 11 patients died during hospital stay (6.11%), 4 patients were transferred to other hospital (2.2%) and 19 patients had no available data regarding RDW values (10.56%). Finally 146 patients were included in the study. Overall readmission rate of patients within 60 days of index hospitalization was 28.21%, among them 48.63% readmitted patients were due to AECOPD.

Mean Charlson comorbidity index was found 4.6±2.9 in 60 days readmission and 6.6±36 in 60 days without readmission due to AECOPD. The mean RDW at admission was found 15.9±2.4 in 60 days readmission and 14.7±1.8 in 60 days without readmission due to AECOPD. Majority (85.7%) patients were found hypercapnic at admission in 60 days readmission and 65(49.2%) in 60 days without readmission due to AECOPD. Majority (85.7%) patients were found hypercapnic before discharge in 60 days readmission and 56(42.4%) in 60 days without readmission due to AECOPD. Ten (71.4%) patients were found acidosis at admission in 60 days readmission and 39(29.5%) in 60 days without readmission due to AECOPD. Seven (50.0%) patients were found acidosis before discharge in 60 days readmission and 13(9.8%) in 60 days without readmission due to AECOPD. Which were statistically significant ($p<0.05$) between two group.

Table-I

Baseline characteristics of patients hospitalized for AECOPD and followed by readmission within 60 days due to AECOPD (n=146)

	Total	Readmission due to AECOPD		
	(n=146)	Yes(n=14)	No(=132)	P value
Mean age (years)	69.1±11.8	67.4±12.1	69.6±11.1	0.486
Male	88 (60.2%)	10 (71.4%)	78 (59.1%)	0.370
Current smoker	77 (53.0%)	9 (64.3%)	68 (51.5%)	0.363
Mean charlson comorbidity index	6.4±3.5	4.6±2.9	6.6±3.6	0.046
Hypertension	90 (61.5%)	9 (64.3%)	81 (61.4%)	0.830
Diabetes mellitus	49 (33.7%)	6 (42.9%)	43 (32.6%)	0.310
Congestive heart failure	31 (21.1%)	4 (28.6%)	27 (20.5%)	0.342
History of solid or hematologic malignancy	21 (14.3%)	2 (14.3%)	19 (14.4%)	0.675
Hypotension (MAP <65 mmHg) at admission	10 (7.0%)	2 (14.3%)	8 (6.1%)	0.246
Desaturation (SO_2 <90%) at admission	50 (34.6%)	7 (50.0%)	43 (32.6%)	0.156
Anemia* at admission	54 (36.7%)	5 (35.7%)	49 (37.1%)	0.917
Anemia before discharge	70 (48.0%)	8 (57.1%)	62 (47.0%)	0.469
Leukocytosis at admission (WBC >11 $\times 10^9$/L)	80 (54.8%)	10 (71.4%)	70 (53.0%)	0.188
Mean RDW at admission	15.0±1.9	15.9±2.4	14.7±1.8	0.023
Mean creatinine (mg/dL) at admission	1.16±0.88	1.02±0.38	1.17±0.91	0.543
Mean creatinine (mg/dL) before discharge	1.06±0.76	0.91±0.36	1.08±0.79	0.428
Hypercapnia (pCO_2 >45 mmHg) at admission	77 (52.6%)	12 (85.7%)	65 (49.2%)	0.009
Hypercapnia (pCO_2 >45 mmHg) before discharge	68 (46.3%)	12 (85.7%)	56 (42.4%)	0.002
Acidosis (pH <7.35) at admission	49 (33.5%)	10 (71.4%)	39 (29.5%)	0.003
Acidosis (pH <7.35) before discharge	20 (13.7%)	7 (50.0%)	13 (9.8%)	0.001
Mean length of hospital stay (days)	6.9±5.8	6.4±4.2	7.1±6.5	0.694

* (Hemoglobin <13g/dL male; <12g/dL female)

Table-II

Baseline characteristics of patients hospitalized for AECOPD and followed by readmission within 60 days due to any other causes (n=146)

	Total	Readmission from any other cause		
	(n=146)	Yes(n=37)	No(n=109)	P value
Mean age (years)	69.1±11.8	69.8±12.3	68.9±11.6	0.689
Male	88 (60.2%)	25 (67.6%)	63 (57.8%)	0.294
Current smoker	77 (53.0%)	21 (56.8%)	56 (51.4%)	0.571
Mean charlson comorbidity index	6.4±3.5	6.7±3.4	6.2±3.1	0.410
Hypertension	90 (61.5%)	26 (70.3%)	64 (58.7%)	0.212
Diabetes mellitus	49 (33.7%)	15 (40.5%)	34 (31.2%)	0.298
Congestive heart failure	31 (21.1%)	14 (37.8%)	17 (15.6%)	0.004
History of solid or hematologic malignancy	21 (14.3%)	5 (13.5%)	16 (14.7%)	0.861
Hypotension (MAP <65 mmHg) at admission	10 (7.0%)	4 (10.8%)	6 (5.5%)	0.226
Desaturation (SO_2 <90%) at admission	50 (34.6%)	15 (40.5%)	35 (32.1%)	0.315
Anemia* at admission	54 (36.7%)	15 (40.5%)	39 (35.8%)	0.604
Anemia before discharge	70 (48.0%)	18 (48.6%)	70 (47.7%)	0.921
Leukocytosis at admission (WBC >11 $\times 10^9$/L)	80 (54.8%)	21 (56.8%)	59 (54.1%)	0.781
Mean RDW at admission	15.0±1.9	15.6±2.0	14.8±1.8	0.031
Mean creatinine (mg/dL) at admission	1.16±0.88	1.22±0.82	1.13±0.88	0.585
Mean creatinine (mg/dL) before discharge	1.06±0.76	1.15±0.94	1.02±0.68	0.366
Hypercapnia (pCO_2 >45 mmHg) at admission	77 (52.6%)	24 (64.9%)	53 (48.6%)	0.087
Hypercapnia (pCO_2 >45 mmHg) before discharge	68 (46.3%)	23 (62.2%)	45 (41.3%)	0.028
Acidosis (pH <7.35) at admission	49 (33.5%)	16 (43.2%)	33 (30.3%)	0.149
Acidosis (pH <7.35) before discharge	20 (13.7%)	11 (29.7%)	9 (8.3%)	0.001
Mean length of hospital stay (days)	6.9±5.8	6.7±4.5	7.1±6.8	0.739

* (Hemoglobin <13g/dL male; <12g/dL female)

Table-III

Baseline characteristics of patients hospitalized for AECOPD and followed by 60 days composite end point (n=146)

	Total (n=146)	Composite end point (readmission or death)		
		Yes(n=44)	No(=102)	P value
Mean age (years)	69.1±11.8	69.7±12.2	69.0±11.4	0.739
Male	88 (60.2%)	27 (61.4%)	61 (59.8%)	0.860
Current smoker	77 (53.0%)	21 (47.7%)	56 (54.9%)	0.426
Mean charlson comorbidity index	6.4±3.5	7.1±3.7	5.9±3.0	0.041
Hypertension	90 (61.5%)	27 (61.4%)	63 (61.8%)	0.964
Diabetes mellitus	49 (33.7%)	14 (31.8%)	35 (34.3%)	0.770
Congestive heart failure	31 (21.1%)	15 (34.1%)	16 (15.7%)	0.013
History of solid or hematologic malignancy	21 (14.3%)	6 (13.6%)	15 (14.7%)	0.867
Hypotension (MAP <65 mmHg) at admission	10 (7.0%)	4 (9.1%)	6 (5.9%)	0.351
Desaturation (SO_2 <90%) at admission	50 (34.6%)	14 (31.8%)	36 (35.3%)	0.685
Anemia* at admission	54 (36.7%)	18 (40.9%)	36 (35.3%)	0.519
Anemia before discharge	70 (48.0%)	22 (50.0%)	48 (47.1%)	0.744
Leukocytosis at admission (WBC >11 $\times 10^9$/L)	80 (54.8%)	23 (52.3%)	57 (55.9%)	0.688
Mean RDW at admission	15.0±1.9	15.6±1.8	14.7±1.9	0.009
Mean creatinine (mg/dL) at admission	1.16±0.88	1.22±0.81	1.14±0.87	0.604
Mean creatinine (mg/dL) before discharge	1.06±0.76	1.14±0.94	1.03±0.68	0.428
Hypercapnia (pCO_2 >45 mmHg) at admission	77 (52.6%)	21 (47.7%)	56 (54.9%)	0.426
Hypercapnia (pCO_2 >45 mmHg) before discharge	68 (46.3%)	21 (47.7%)	47 (46.1%)	0.855
Acidosis (pH <7.35) at admission	49 (33.5%)	16 (36.4%)	33 (32.4%)	0.638
Acidosis (pH <7.35) before discharge	20 (13.7%)	12 (27.3%)	8 (7.8%)	0.002
Mean length of hospital stay (days)	6.9±5.8	7.1±5.4	6.9±7.1	0.863

* (Hemoglobin <13g/dL male; <12g/dL female)

Table-IV

Rate ratio[a] of patients with increased RDW values and different characteristics of patients and 60-day adverse events (n=146)

	Readmission due to AECOPD	Readmission from any cause	Composite end point (readmission or death)
Male	0.77	0.82	0.76
Current smoker	0.78	1.40	0.95
Hypertension	1.45	1.23	1.18
Diabetes mellitus	0.84	1.04	0.99
Congestive heart failure	1.55	3.07	2.14
History of solid or hematologic malignancy	0.46	0.41	0.87
Hypotension (MAP <65 mmHg) at admission	0.48	0.52	0.41
Desaturation (SO_2 <90%) at admission	1.05	1.80	1.58
Anemia before discharge	3.01	2.18	3.62
Leukocytosis at admission (WBC >11 $\times 10^9$/L)	1.06	1.11	0.80
Serum creatinine (>1.0 mg/dL) before discharge	0.51	1.99	1.09
Hypercapnia (pCO_2 >45 mmHg) before discharge	1.42	1.77	1.69
Acidosis (pH <7.35) before discharge	0.91	0.68	0.96

[a]Rate ratio for specific risk factor was calculated using the following equation:

Fourteen (37.8%) patients were found congestive heart failure in 60 days readmission and 17(15.6%) in without readmission. The mean RDW at admission was found 15.6±2.0 in 60 days readmission and 14.8±1.8 in without readmission. Twenty three (62.2%) patients were found hypercapnia before discharge in 60 days readmission and 45(41.3%) in without readmission. Eleven (29.7%) patients were found acidosis before discharge in 60 days readmission and 9(8.3%) in without readmission. Which were statistically significant ($p<0.05$) between two group.

Mean charlson comorbidity index were found 7.1±3.7 in 60 days composite end point and 5.9±3.0 in 60 days without composite end point. Fifteen (34.1%) patients were found congestive heart failure in 60 days composite end point and 16(15.7%) in 60 days without composite end point. Mean RDW at admission were found 15.6±1.8 in 60 days composite end point and 14.7±1.9 in 60 days without composite end point. Twelve (27.3%) patients were found acidosis before discharge in 60 days composite end point and 8(7.8%) in 60 days without composite end point. Which were statistically significant ($p<0.05$) between two group.

Rate ratios of patients with increased RDW values and different demographic factors, co-morbidities, vital signs at admission, laboratory test results and 60-day adverse events.

In multivariate analysis, charlson comorbidity index >5 and High RDW at admission were found to be significantly ($p<0.05$) associated with readmission due to AECOPD patients. Congestive heart failure, acidosis before discharge and High RDW at admission were found to be significantly ($p<0.05$) associated with readmission from any cause patients. Congestive heart failure, acidosis before discharge and High RDW at admission were found to be significantly ($p<0.05$) associated with Composite end point patients.

Table-V

Bivariate and multivariate analysis result of correlation between different characteristics of the patients and 60-day adverse events

	Readmission due to AECOPD		Readmission from any cause		Composite end point (readmission or death)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Univariate analysis						
Mean age (years)	0.96 (0.52-1.14	0.069	1.13 (0.83-1.22)	0.189	1.45 (0.76-1.78)	0.441
Male	1.23 (0.42-14.83)	0.875	1.26 (0.53-1.59)	0.943	1.16 (0.80-1.69)	0.342
Current smoker	3.26 (0.51-13.71)	0.212	1.14 (0.47-1.44)	0.631	1.30 (0.88-1.76)	0.156
Charlson comorbidity index >5	0.16 (0.27-0.94)	0.041	1.03 (0.91-2.09)	0.745	1.44 (1.12-2.31)	0.044
Hypertension	2.7 (0.17-9.71)	0.487	2.84 (0.95-3.40)	0.177	1.41 (0.76-2.23)	0.313
Diabetes mellitus	0.89 (0.42-1.81)	0.763	1.20 (0.71-1.74)	0.241	1.19 (0.74-1.87)	0.247
Congestive heart failure	1.04 (0.13-8.03)	0.967	1.76 (1.18-3.10)	0.009	1.98 (1.20-3.19)	0.004
History of solid or hematologic malignancy	0.71 (0.32-1.76)	0.239	0.96 (0.44-1.99)	0.174	1.23 (0.72-2.11)	0.791
Hypotension (MAP <65 mmHg) at admission	1.65 (0.73-2.80)	0.123	1.98 (0.93-3.67)	0.279	1.36 (0.88-2.33)	0.984
Desaturation (SO_2 <90%) at admission	0.99 (0.78-1.83)	0.294	0.84 (0.57-1.63)	0.464	0.91 (0.58-1.48)	0.775
Anemia before discharge	1.06 (0.72-1.94)	0.740	1.33 (0.94-2.18)	0.097	1.73 (0.94-2.49)	0.141
Leukocytosis at admission (WBC >11 $\times 10^9$/L)	1.25 (0.48-2.79)	0.813	1.10 (0.69-1.71)	0.346	1.12 (0.45-1.81)	0.746
High RDW at admission (>14.5%)	1.84 (1.13-3.78)	0.031	1.91 (1.31-2.90)	0.005	1.62 (1.19-2.84)	0.001
Hypercapnia (pCO_2 >45 mmHg) before discharge	3.63 (1.26-10.44)	0.017	1.26 (1.09-2.31)	0.048	1.41 (0.94-2.17)	0.797
Acidosis (pH <7.35) before discharge	3.16 (1.18-8.45)	0.022	2.19 (1.33-4.18)	0.006	1.78 (1.21-3.12)	0.009
High creatinine (>1.4 mg/dL) before discharge	0.65 (0.28-1.60)	0.378	1.80 (1.23-2.70)	0.023	1.46 (1.27-2.83)	0.021
Length of hospital stay (>5 days)	1.01 (0.87-1.74)	0.861	0.74 (0.68-1.41)	0.651	1.13 (0.86-1.41)	0.214
Multivariate analysis						
Charlson comorbidity index >5	3.63 (1.26-10.44)	0.017	-	-	1.09 (0.28-4.82)	0.935
Congestive heart failure	-	-	0.16 (0.02-0.93)	0.043	1.96 (1.87-2.31)	0.041
Acidosis (pH <7.35) before discharge	1.16 (0.48-2.79)	0.740	0.22 (0.14-0.83)	0.001	1.69 (1.06-3.17)	0.033
High RDW at admission (>14.5%)	1.35 (1.25-8.15)	0.021	0.13 (0.08-0.59)	0.045	1.88 (1.19-2.76)	0.009
Hypercapnia (pCO_2 >45 mmHg) before discharge	1.08 (0.43-2.73)	0.864	1.04 (0.13-8.03)	0.967	-	-
High creatinine (>1.0 mg/dL) before discharge	-	-	0.26 (0.04-1.51)	0.132	3.16 (0.84-7.68)	0.083

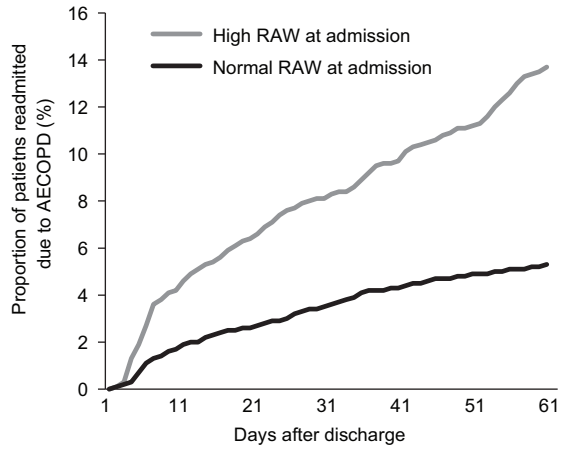

Fig.-1: *Adjusted with high Charlson comorbidity index survival curve for 60-days readmission for AECOPD according to RDW group at admission (p<0.001).*

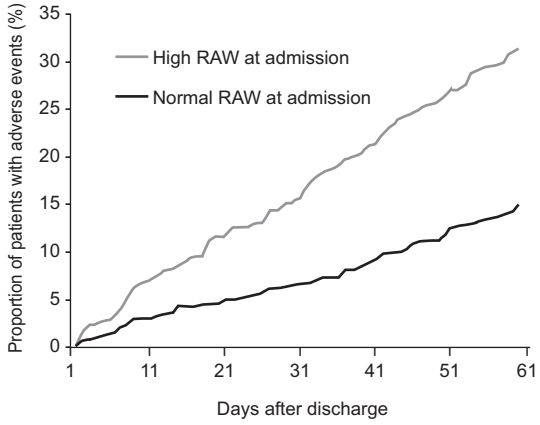

Fig.-2: *Adjusted with CHF and pH survival curve for 60-days adverse outcome (readmission or death) according to RDW group at admission (p<0.001).*

Discussion

During the study period from January 2017 to December 2018 total 180 patients were discharged from Shaheed Tajuddin Ahmad Medical College Hospital with primary diagnosis of AECOPD. Thirty four patients dropout due to died and not complete follow up. Finally 146 patients were included in the study.

In present study observed that the mean charlson comorbidity index was found 4.6±2.9 in 60 days readmission due to AECOPD and 6.6±36 in 60 days without readmission due to AECOPD. The mean RDW at admission was found 15.9±2.4 in 60 days readmission due to AECOPD and 14.7±1.8 in 60 days without readmission due to AECOPD. Majority (85.7%) patients were found hypercapnia at admission in 60 days readmission due to AECOPD and 65(49.2%) in 60 days without readmission due to AECOPD. Majority (85.7%) patients were found hypercapnia before discharge in 60 days readmission due to AECOPD and 56(42.4%) in 60 days without readmission due to AECOPD. Ten (71.4%) patients were found acidosis at admission in 60 days readmission due to AECOPD and 39(29.5%) in 60 days without readmission due to AECOPD. Seven (50.0%) patients were found acidosis before discharge in 60 days readmission due to AECOPD and 13(9.8%) in 60 days without readmission due to AECOPD. Which were statistically significant ($p<0.05$) between two group. Epstein et al.[8] observed that the mean RDW at admission and acidosis at admission were significantly higher in 60 days readmission due to AECOPD than without readmission due to AECOPD. The high rate of readmissions after an index hospitalization due to AECOPD have triggered the development and implementation of US national program that aimed to reduce these events.[9] Although numerous demographic factors and comorbidities were recognized as significant risk factors associated with early readmission, there are no published algorithms that integrate the identified risk factors into a predictive valid model that can be used during index admission [8]. Identifying AECOPD patients subject to early readmission and deployment of interventions during hospitalization are critical challenges for hospitalists.[9] The value of laboratory indexes in risk stratification of patients discharged after AECOPD was addressed only in a few studies. The only laboratory index found to be associated with early readmission is pCO_2.[10] Garcia-Aymerich et al.[11] found a significant correlation between high mean pCO_2 and readmission rate following hospitalization due to AECOPD, while Groenewegen et al.[12] identified pCO_2 as a risk factor associated with higher mortality after hospitalization due to AECOPD.

In this study observed that fourteen (37.8%) patients were found congestive heart failure in 60 days readmission from any cause and 17(15.6%) in 60 days without readmission from any cause. The

mean RDW at admission was found 15.6±2.0 in 60 days readmission from any cause and 14.8±1.8 in 60 days without readmission from any cause. Twenty three (62.2%) patients were found hypercapnia before discharge in 60 days readmission from any cause and 45(41.3%) in 60 days without readmission from any cause. Eleven (29.7%) patients were found acidosis before discharge in 60 days readmission from any cause and 9(8.3%) in 60 days without readmission from any cause. Which were statistically significant ($p<0.05$) between two group. Epstein et al.[8] reported that the male, congestive heart failure, mean RDW at admission, acidosis before discharge and creatinine at admission were significantly higher in 60 days readmission from any cause than without readmission from any cause.

In this study showed that the mean charlson comorbidity index was found 7.1±3.7 in 60 days composite end point and 5.9±3.0 in 60 days without composite end point. Fifteen (34.1%) patients were found congestive heart failure in 60 days composite end point and 16(15.7%) in 60 days without composite end point. Mean RDW at admission were found 15.6±1.8 in 60 days composite end point and 14.7±1.9 in 60 days without composite end point. Twelve (27.3%) patients were found acidosis before discharge in 60 days composite end point and 8(7.8%) in 60 days without composite end point. Which were statistically significant ($p<0.05$) between two group. Epstein et al.[8] reported mean charlson comorbidity index, congestive heart failure, mean RDW at admission, acidosis before discharge and creatinine at admission were significantly higher in 60 days composite end point than without composite end point. Recently it was increasingly investigated as a negative prognostic factor in variety of acute and chronic medical conditions, such as cardiovascular disease, venous thromboembolism, cancer, diabetes, community-acquired pneumonia, liver and kidney failure.[2] In recent years, several studies showed that increased RDW is associated with disease severity and long term mortality in COPD patients.[3,4,13]

In this study revealed that rate ratios of patients with increased RDW values and different demographic factors, co-morbidities, vital signs at admission, laboratory test results and 60-day adverse events. Similar study reported by Epstein et al.[8].

In multivariate analysis, charlson comorbidity index >5 and high RDW at admission were found to be significantly ($p<0.05$) associated with readmission due to AECOPD patients. Congestive heart failure, acidosis before discharge and high RDW at admission were found to be significantly ($p<0.05$) associated with readmission from any cause patients. Congestive heart failure, acidosis before discharge and high RDW at admission were found to be significantly ($p<0.05$) associated with composite end point patients. Epstein et al.[8] study reported RDW may serve as a biological marker for this episodic hypoxia. This theory was recently supported by Ycas et al.[14] who analyzed RDW values of more than two millions subjects and showed that acute hypoxemia could induce increase in RBC size distribution. An emergency room visit in the previous 6 months (1 versus 0) was associated with increased readmission risk with OR 1.90 (95% CI 1.01–3.58) in the study by Bashir et al.[15] and OR 1.25 (95% CI 1.21–1.29) in the study by Hakim et al.[16]. The risk of readmission increased with a greater number of previous emergency room visits (e"4 versus 0) with OR 4.37 (95% CI 1.83–10.46) and OR 2.31 (95% CI 2.23–2.39).[15,17] Previous COPD and non-COPD hospitalizations in the previous year also significantly increased the risk for 30-day readmission by 53% to 56% and 60% to 64%, respectively.[18,19]

In this study observed that high Charlson co-morbidity index survival curve for 60-days readmission for AECOPD according to RDW group at admission ($p<0.001$). Several studies showed correlation between increased RDW and right ventricle dysfunction and pulmonary hypertension.[3] It is possible; therefore, that AECOPD leads to unrecognized acute worsening of cardiac function. Increased RDW was found to be an independent predictor of right ventricle dysfunction and cardiovascular disease in patients with stable COPD.[20] Other mechanisms that may be responsible to increased RDW in patients with poor prognosis after AECOPD include increased oxidative stress, poor nutritional status and high level of inflammatory activity.[21,22] Epstein et al.[8] reported Abnormal RDW was associated with increased risk of readmission due to AECOPD in all Charlson quartiles. They used COX regression model to generate adjusted survival curves for each RDW subgroup, ($p= 0.0038$).

In present study, also observed CHF and pH survival curve for 60-days adverse outcome (readmission or death) according to RDW group at admission ($p<0.001$). Epstein et al.[8] used COX regression model to generate adjusted survival curves for each RDW subgroup, $p<0.0001$.

Limitations

There are several limitations in our study. Many of the patients with AECOPD admitted in hospital could not be included in the study due to lack of all related investigation reports. This was a single centered study with small population. Due to lack of sufficient data we in some instances failed to discriminate the mortality of some patients whether due to respiratory cause or other cause.

Conclusion:

Increased RDW levels in patients with AECOPD admitted in hospital are usually associated with an increased risk for early readmission as well as increased mortality. Raised RDW might be a novel indicator of hypoxemia, associated inflammatory response and oxidative stress in patients with AECOPD. Those patients with increased RDW should be managed with intensive care for improving their clinical outcomes and reassessment of those patients should be done for high-quality discharge decision from the hospital. This simple and inexpensive laboratory investigation may be very much useful for the prognostic information of the patients with AECOPD.

Conflicts Of Interest:

The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Histological Pattern of Bronchial Carcinoma in Tertiary Care Hospital in Bangladesh

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Abstract:

Background: *Lung cancer is the most common malignant neoplasm worldwide. Among all human cancers, carcinoma of the lung has the highest mortality rate and is the leading cause of all cancer deaths. However, histological types may vary with the changes in geographical region, smoking status and other social factors. Among the few published reports, squamous cell carcinoma of lung is more common in male smokers.*

Aim: *This study was aimed to find out the specific histological type of lung cancers patients of Bangladeshi people.*

Methods: *This was a cross-sectional study and was conducted on bronchial carcinoma patients who had been admitted and diagnosed at the department of respiratory medicine, National Institute of the diseases of the Chest & Hospital (NIDCH). Total 120 diagnosed case of bronchial carcinoma were included in the study. The respondents were divided into two groups, smokers and non-smokers.Following informed written consent, 100 smoker and 20 non-smoker patients were interviewed and information was recorded in the questionnaire. The laboratoryinvestigations were collected from patients or attendants. Ethical issues were maintained and the results of histological diagnosis were obtained to complete the data sheet and analyzed by SPSS, Z test, t test, chi-square test.*

Results: *A total of 120 patients were interviewed. Among them, 86.7% were males and 13.3% were females and ratio were 6.5:1. The mean age of the patients were 59.41±2.89 years.Out of the 120 patients, 100 patients (83.3%) had history of smoking in their life time and 20 patients (16.7%) were non-smoker. In case of male, majority of patients were smokers (82.5%) and in case of female, majority of patients (12.5%) were non -smokers. Among smokers, squamous cell carcinoma (44.1%) was the most common histological type followed by adenocarcinoma (6.7%). In case of non -smokers, the status was entirely different and here adenocarcinoma was the most common type and which constituted 11.7% and squamous cell carcinoma in non-smokers was less and only 1.7%. Among male patients 45% had squamous cell carcinoma which was higher than other histological types of cancer. In case of female patients 10.83% had adenocarcinoma, which was higher than other histological types of lung cancer.*

Conclusion: *In male smokers, squamous cell carcinoma is still the most frequent histological type of bronchial carcinoma in present study. In case of females and non-smokers adenocarcinoma is the predominant histological type.*

Key words*: Histological Pattern, Bronchial carcinoma.*

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Introduction:

Among all human cancers, carcinoma of the lung has the highest mortality rate and is the leading cause of all cancer deaths. Lung cancer is a leading cause of morbidity and mortality globally, accounting for 2,094 million cases and 1.8 million deaths per year.[1]Lung cancer is the most common malignant disease in developed countries, causing more deaths than breast, colorectal, prostate and pancreatic cancer combined. It is one of the health problems in Bangladesh of which smoking plays the most vital role. Lung cancer mainly originates from the basal epithelial cells and is mainly classified into two types, non-small cell lung cancer and small cell lung cancer. Among these non-small carcinomas is more common and which accounts for around 85% of lung cancer cases.[2] The main histological types of lung cancer are adenocarcinoma, squamous cell carcinoma, large cell carcinoma and small cell carcinoma.[3] All the diverse histological types are somehow associated to tobacco smoking. However, the intensity of association between smoking and adenocarcinoma is much lesser than between smoking and squamous cell carcinoma or small cell carcinoma. In the mid-1900s lung carcinoma was an uncommon disease. Now it is in relevant proportions and is presently the prominent cause of cancer related deaths in the western countries.[4,5] In the recent decades, the percentage of squamous cell carcinoma (which was predominant) has decreased and the trend shows an increase of adenocarcinoma in both genders.Histological gradation of the bronchial carcinoma in order of frequencies were squamous cell carcinoma 54.7 %, small cell carcinoma 24.1%, adenocarcinoma 16.9% and large cell carcinoma 4.3%.[6] In another study, squamous cell carcinoma was found 31.7%, adenocarcinoma 30.9%, and large cell carcinoma 26%.[7]Although squamous cell carcinoma has for many years been the most common. Adenocarcinoma has been increasing in incidence over last 20 years.[8]Adenocarcinoma has become today the most frequent histological type of lung cancer and is responsible for 50% of all lung cancers.[9]However, it is also possible that the increase in lung adenocarcinoma cases, in fact, may be caused also by increasing smoking prevalence. A direct association between smoking and various histologic types of lung cancer has been observed for measures of intensity, duration and dose. Studies conducted in the USA, Western Europe and China observed a higher smoking related risk of squamous cell carcinoma and small cell carcinoma than that of adenocarcinoma of the lung. The largest of these studies suggested that intensity of cigarette exposure has less distinct effect on all cell type than duration of use with duration more strongly associated with SQCC and SMCC than adenocarcinoma. The distribution of lung cancer by histological type differs between smokers and non- smokers and even among smokers, is different for man and woman. In both sexes adenocarcinoma is much more common among non-smokers than smokers.[10] But regardless of smoking status, squamous cell carcinoma is much more common among men and adenocarcinoma is more common among women.[11] Lung cancer has a tremendous impact on US mortality, with an estimated total 142670 deaths in 2019 in men and women combind.[12]It is the common malignant disease in developed countries, there approximately 228150 new patients per year in the USA and 85000 patients per year in the UK; the incidence is increasing rapidly in developed countries. The disease is more common in men than women, although this difference has become smaller; in USA and the UK the male/female ratio was approximately 2.5:1.[13] But in 2019 in USA male/female ratio was around 1.04:1.Risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day and is diminished by discontinuing smoking. In the United States, current estimates indicate that 87% of all cases of lung cancer are directly attributable to cigarette smoking. This includes 51.03% of lung cancer in men and 48.96% of cases in women. The lifetime risk for developing lung cancer in a nonsmoker is probably about 1% less. Environmental, or secondhand, tobacco smoke, is also implicated in causing lung cancer. Environmental tobacco smoke has the same components as inhaled mainstream smoke, although in lower absolute concentrations, between 1% and 10%, depending on the constituent. It has been estimated that cigarrete smokers are 8-20 times more likely to develop lung cancer than life long nonsmokers and the extent of this risk correlates closely with the number of cigarettes smoked.[14]In Bangladesh out

of all cancer patients, 8.2% is newly diagnosed with lung cancer, the number might seem insignificant but that is about 12,374 people. A new study suggests that cases of lung cancer have been on the rise in Bangladesh, with the number of smokers and air pollution levels rising. The report claimed that from January 2015 to December 2017, a total 5,887 people with lung cancer were admitted in National Institute of Cancer Research and Hospital. Their study also reported that 81.56% lung cancer in male smoker. Squamous cell carcinoma was most frequent type among the males and smokers, but adenocarcinoma more in females and nonsmokers.[15]Data on histological pattern of bronchial cancer is limited in Bangladesh pointing out to the need of more researches for prevention and treatment. Therefore, this study was aimed to identify histological pattern of bronchogenic carcinoma in tertiary care hospital in Bangladesh.

Materials and methods:

This was a cross-sectional type of Descriptive study, was conducted in the Department of Respiratory Medicine, National Institute of the Diseases of the chest & Hospital (NIDCH), located in the Mohakhali, Dhaka-1212, Bangladesh, duringthe period of 1 year (January 2020-December2020).Total 120 patients were enrolled consecutively who was confirmed as a case of bronchial carcinoma. The information regarding bronchial carcinoma was collected from each patient in whom the diagnosis was confirmed by CT guided FNAC of chest and FNAC of the cervical lymph nodes, biopsy reports. Exclusion criteria were 1. Patients who refused to be part of the study.2. Patients having major concomitant diseases i.e., recent MI, CVD, serious cardiac dysrhythmias, unstable angina etc.3.Patients having bleeding diathesis.4.Sputum positive for acid-fast bacilli (AFB).Written informed consent was obtained from patient. Before requesting consent, the individual was explained in an understandable language about the aims of the study, the methods of conduct, expected duration of subject participation,benefits, foreseeable rights or discomfort, the extent of investigators responsibility, the right to refuse to participate and withdraw from the study without affecting further medical care. All information were properly documented in the data sheet. All questionnaires were checked for completeness, accuracy and consistency to exclude missing or inconsistent data. Data were checked, cleaned and edited properly before analysis and for this analysis recent version of worldwide well accepted statistical software SPSS (Statistical Package for Social Science) were used. During analysis, age, sex and other baseline characteristic differences were analyzed by Z test, t test and chi-square test whenever necessary. Results were presented by choosing variable form of tables, graph, percentage, and chart. In all cases, p-value <0.05 was considered statistically significant.

Results:

In this study 120 patients with bronchial carcinoma, squamous cell carcinoma (44.1%) was the most common histological type among the smokers followed by adenocarcinoma (6.7%). In case of non -smokers, the status was entirely different and here adenocarcinoma was the most common type and which constituted 11.7% and squamous cell carcinoma in non-smokers was less and only 1.7%. Among male patients 45% had squamous cell carcinoma which was higher than other histological types of cancer. In case of female patients 10.83% hadadenocarcinomawhich was higher than other histological types of lung cancer.

Table-I

Age and sex distribution of study respondents (n=120)

Age (in years)	Male		Female		Total		P value
	Number	%	Number	%	Number	%	
35-44	7	5.8	2	1.7	9	7.5	
45-54	22	18.33	10		8.3	32	26.7
55-64	35	29.17	2	1.7	37	30.83	0.00001
65-74	34	28.33	1	0.83	35	29.1	
75-84	6	5	1	0.83	7	5.83	
Total	104	86.7	16	13.3	120	100.0	

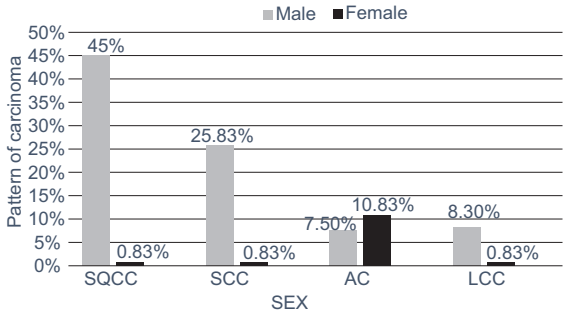
[Analysis done by t test and SPSS. P value-0.00001]

It is observed that most of the male patients were in the age range of 55-64 years 35(29.17%), followed by 65-74 years 34(28.33%), 45-54 years 22(18.33%) and 75-84 years 6(5%). Among female patients majority were in the age range of 45-54 years 10(8.3%) followed by 65-74 years and 75-84 years 1(0.83%); 35-44 years and 55-64 years 2(1.66%). The mean age of the patients were 59.41 years with SD±2.89. In case of male the mean age of the patients were 60.46 years with SD ±3.11& in case female the mean age of the patients were 52.62 years with SD ±9.07; Male: Female were 6.5:1. It was evident that statistically significant age difference was found between male and female patients ($p<0.05$).

Figure 1- It was found that major proportion of squamous cell carcinoma 54(45%) were in male respondents and majority 13(10.83%) adenocarcinoma were found in female respondents.

The table shows distribution of study subjects by histologic pattern and age of the patients. It was found that among squamous cell carcinoma majority 20(16.7%) were in the age group of 55-64 years and 5(4.1%) were found in large cell carcinoma in the same age group. Among the patients of small cell carcinoma 12(10%) were found 65-74 years age group, adenocarcinoma 11(9.1%) were found in 45-54 years age group.

Figure '!I- It was found that majority 55(45.83%) respondents had squamous cell carcinoma, followed by 32(26.7%) had small cell carcinoma, 22(18.33%) had adenocarcinoma, 11(9.2%) had large cell carcinoma.



[SQCC-Squamous Cell Carcinoma, SCC-Small Cell Carcinoma, ACC-Adenocarcinoma, LCC-Large Cell Carcinoma]

Fig.-1: *Distribution of the respondents by histologic pattern and sex of the patients.*

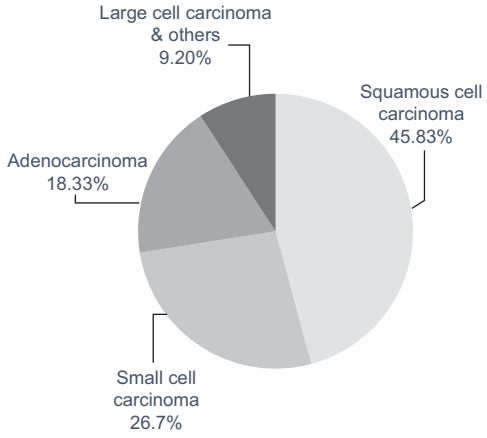


Fig.-1: *Distribution of the respondents by histologic patterns of carcinoma*

Table-II

Distribution of the respon	Pattern of carcinoma				Total	P value
	SQCC	SCC	AC	LCC		
35-44	5(4.1)	2(1.7)	1(0.83)	1(0.83)	9(7.5)	
45-54	12(10)	7(5.8)	11(9.1)	2(1.7)	32(26.7)	
55-64	20(16.7)	10(4.3)	2(1.7)	5(4.1)	37(30.83)	0.847
65-74	15(12.5)	12(10)	6(5)	2(1.7)	35(29.2)	
75-84	3(2.5)	1(0.83)	2(1.7)	1(0.83)	7(5.83)	
Total	55(45.83)	32(26.7)	22(18.3)	11(9.1)	120(100)	

[Analysis done by t test and SPSS. P value-0.847]
[SQCC-Squamous Cell Carcinoma, SCC-Small Cell Carcinoma, ACC-Adenocarcinoma, LCC-Large Cell Carcinoma]

Discussion

It has been observed by different studies that in both developed and developing countries, tobacco smoking is widely prevalent. It is found in all classes of people from very high to low class, which is one of the important preventable causes of premature death. In developing countries, it has been estimated that nearly 50% of man are dependent on some form of tobacco use whereas less than 50% of women are smokers.[12,16]The main objective of present study was to find out the different histological types of lung cancer in tertiary care hospital in Bangladesh. This was a cross-sectional type of descriptive study conducted in the NIDCH Dhaka during the period of January 2020-December 2020.A total of 120 histologically proven primary lung cancer patients were included in the study.

In this study, out of 120 patients, 104 (86.7%) were male and 16 (13.3%) were female and Male: Female ratio was 6.5:1. The number of female patients were small in this study which can be explained by the fact that in our country females are dependent mostly on husband and or guardian, religious and social grounds act as a barrier; over and above bronchogenic carcinoma is uncommon in females of our country. In the Jonathan M S, Erika A T study showed that male and female ratio among smokers was 32:1 and among non-smokers 1:1.9.[17] In Navin P, Balbin M study found that male and female ratio was 5:1.[13] The frequency of tobacco habits among females is very low compared to male. The increasing percentage of smoking in males was consistent with the study reports from developing countries.[18] These studies were almost similar with present study. But it was not similar with the statistics of the American Cancer Society in 2019which reveals that among 235760 new cases of lung cancer-119,100 (50%) were found in men and 116,660 (49%) in women. This might be due to fact that tobacco smoking in women of this country (USA) became increasingly popular day by day.[12]

In the present study, it was found that most of the patients belonged to the age range of 55-64 years among smokers 35(29.1%) and in case of non-smokers majority 12(10%) of the patients belonged to the age range of 45-54 years. These findings were consistent with the Tsugaway, Hashimoto K study which showed that out of 473 patients 51% were above 50-60 years of age. Lung cancer mainlyoccurs in older people. Most of the patient were diagnosed with lung cancer above 60 years of age, a very small number of patients were diagnosed below 45 years of age.[16]

In the present study, it was found that among the smoker patients highest percentage were among the farmers (32.5%). This was because more than 70% of the population of our country belong to cultivation. Among the non-smokers, most of the patients were housewives (10.8%). These findings were almost similar with the Dubey N, Julka Arti study which showed that most of the smoker patients were farmers (72.3%) and non-smokers were housewives.[18]

In the present study, out of 120 patients among the smoker patients 68(56.7%) had monthly family income below 20,000 BDT followed by 27(22.5%) between 20,000-40,000 BDT. Among the non-smoker patients, 10(8.3%) had monthly family income between 20,000-40,000 BDT, followed by 5(4.1%) had monthly family income below 20,000 BDT. This was quite similar with Elahi MQE, Razzak MA study. They found that majority of smoker patient's (85.93%) monthly family income was below 10,000 BDT,[19]

In the present study, highest percentage of patients had squamous cell carcinoma 55(45.8%) followed by small cell carcinoma 32(26.7%) and adenocarcinoma 22(18.3%). It was observed that among the smoker patients majority of bronchial carcinoma were squamous cell carcinoma 53(44.1%) followed by small cell carcinoma 32(26.7%) and adenocarcinoma 22(18.33%). Among the non-smoker patients, most of the bronchial carcinoma were adenocarcinoma 14(11.7%), followed by squamous cell carcinoma 2(1.7%). Similar findings were observed in C. Muhas, Palur Ramakrishnan Anand Vijaya Kumar study. They found among the smoker patients, squamous cell carcinoma (63.25%) was the most common histological type followed by adenocarcinoma (22.89%). In case of non-smoker patients, the status was entirely different and here adenocarcinoma was the most common type which constituted 66.67% and the presence of squamous cell carcinoma in non-smokers were very less only 15.27%.[20]

In the present study, it was found that major proportion of squamous cell carcinoma 54(45%),

small cell carcinoma 31(25.8%) were higher in male respondents whereas adenocarcinoma 13(110.8%) was proportionately higher among female respondents. In C. Muhas, Palur Ramakrishnan study, it was observed that in case of male patients squamous cell carcinoma was the predominant histologic type of lung cancer (55.84%) followed by adenocarcinoma (29.95%) and small cell carcinoma (10.15%). In case of female patients, adenocarcinoma was the most prevalent histologic type (65.85%) and squamous cell carcinoma was 14.63%.[20]These findings were similar with the present study.

In the present study it was found that mean number of smoking was 22.79±1.4 sticks/day. The mean number of smoking 26.89±1.9 sticks/day for squamous cell carcinoma, followed by 21.16±2.7 sticks/day for small cell carcinoma, 24.61±4.8 sticks/day for large cell carcinoma. It was almost similar with Yelena Y, Kevin Mc Donnell study which showed that number of smoking more than 30 sticks/day for squamous cell carcinoma and 20 to 29 sticks/day smoking for small cell and large cell carcinoma.[21]

It was observed in the present study that among squamous cell carcinoma majority 20(16.7%) were in the 55-64 years age group and 5(4.1%) were found in large cell carcinoma in the same age group. Among the patients of small cell carcinoma 12(10%) were 65-74 years age group, adenocarcinoma 11(9.1%) were found in 45-54 years age group. These findings were consistent with AL. Hashimi MMY, C. Muhus, Rahul G study. These studies found increasing number of lung cancer patients were in older age group, particularly in the sixth and seventh decades of life. Highest percentage of squamous cell carcinoma were in the 61-80 years age group.[20,22,23]

In the present study, it was found that highest percentage of squamous cell carcinoma 30(25%) and small cell carcinoma 27(22.5%) had monthly family income below 20,000 BDT, whereas large cell carcinoma 5(4.2%) patients had monthly family income between 20,000-40,000 BDT, adenocarcinoma 12(10%)monthly family income above 40,000 BDT. These findings were almost similar with Rahul G, Ishfaq C study. These studies found smokers of low socioeconomic status (low household income) were associated with an increased risk of squamous cell carcinoma.[23]

In the present study, it was found that squamous cell carcinoma was more frequent in male smoker respondents in 55-64 years age group and adenocarcinoma was more in non-smokers and female respondents in 45-54 years age group. These findings were supported by SEER Cancer statistics 2017 and WHO 2019.[24,25,26]

Conclusion:

In this present study, out of 120 respondents 104 patients were males and 16 patients were females and ratio were 6.5:1. It was found that among the smokers, most of the patients belonged to the 55-64 years age group and in case of nonsmokers majority were 45-54 years age group. Out of 120 respondents, 100 patients had history of smoking in their life time and 20 patients were nonsmoker. It was found that among the smoker patients highest percentage were the farmers. Among the nonsmokers, most of the patients were housewives. Among the smokers, squamous cell carcinoma was the most common histological type of cancer. In case of nonsmokers adenocarcinoma was the most common type of cancer. Among male patients 45% had squamous cell carcinoma which was higher than other histological types of lung cancer. In case of female patients 10.83% had adenocarcinoma which was higher than other histological types of lung cancer.

Data of the present study confirmed a marked relationship between smoking and all histological types of lung cancer under the study and also showed that squamous cell carcinoma is more frequent among male smokers and adenocarcinoma in non-smoking females. However, the association of smoking and adenocarcinoma remain unclear at the moment. Further work in this field should be encouraging.

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ORIGINAL ARTICLE

Change of CRP and D-dimer Level of COVID-19 Patients: An Observational Prospective Study

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Abstract:

Background: *COVID-19 is a global pandemic causing million of death during last two years, so it became a global health and economic burden right now. COVID-19 is a Novel infectious disease, for which there is no definite curable treatment till now. It is therefore necessary to explore biomarkers to determine the extent of lung lesions and disease severity. CRP levels are elevated in patients with COVID-19 and may be different with severity of the disease. Elevated plasma D-dimer is a hallmark to determine cardiovascular complications related to patients.*

Objective: *The primary objective of the present study was to evaluate the changes of CRP and D-dimer level of COVID-19 patients in respect to severity of the disease.*

Methods: *This prospective observational study was conducted in Private set up and OPD, National Institute of Diseases of the Chest & Hospital, Mohakhali, Dhaka, between January 2020 to July 2020. A total of 49 patients with COVID-19 were included in the study. Diagnosed case of RT-PCR positive patients with or without respiratory symptoms were assessed by CRP and D-dimer level on the first visit. After 7 days CRP and D-dimer levels were collected to compare with baseline levels. All other clinical, laboratory, and outcome data were documented using a standardized data collection form.*

Results: *In this study 49 patients with COVID-19, majority 22(44.9%) patients belonged to age 41 to 60 years. The mean age was 53.3±14.7 years. Male patients were predominant 41(83.7%) with male female ratio was 5.1:1. More than one third 17(34.7%) patients had hypertension followed by 15(30.6%) had diabetes mellitus, 4(8.2%) had COPD, 3(6.1%) had asthma and 2(4.1%) had CKD. Co-morbidity was significantly higher in respiratory symptoms than without respiratory symptoms. CRP level was significantly reduced after 7 days compared with baseline (10.1±13.0 mg/L vs39.6±54.6 mg/L). Twenty three (46.9%) patients were found D-dimer >3.0 gm/dl in baseline and 14(28.6%) in after 7 days, that was not significant (p=0.066).*

Conclusion: *At the early stage of COVID-19, CRP levels were positively correlated with lung lesions. Co- morbidity was significantly associated with respiratory symptoms. This study found significant reduced CRP levels after 7 days compared with baseline. D-dimer levels also reduced but not significant. CRP levels and D-dimer could reflect disease severity and should be used as a key indicator for disease monitoring.*

Key words: *COVID-19, CRP and D-dimer*

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Introducton:

Coronavirus disease 2019 (COVID-19), caused by the Severe acute respiratory syndrome coronavirus 2, was first recorded in Wuhan, the capital of Hubei province of China in December 2019.1 While COVID-19 is primarily a respiratory illness, it can affect multiple organ systems including gastrointestinal, hepatic, cardiac, neurological, and renal systems.[2] COVID-19 is usually characterized by lower respiratory tract symptoms with fever, dry cough, and dyspnea, a manifestation similar to those of two other diseases caused by coronaviruses, severe acute respirato ry syndrome (SARS) and Middle East respiratory syndrome, MERS.[3] The reported overall case-fatality rate (CFR) for COVID-19 by now was 2.3%, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR.4 In some patients, severe pulmonary and extra-pulmonary complications may lead to respiratory failure and life-threatening events.

CRP is an acute-phase, nonspecific marker of inflammation or infection and has been found to broadly correlate with disease severity and treatment response across a variety of infectious and noninfectious conditions.[5] Elevated CRP levels have been previously reported in severe acute respiratory syndrome, Middle East respiratory syndrome, H1N1 influenza.[6-8] Recent studies have reported that CRP levels are elevated in patients with COVID-19 and may correlate with severity of disease and disease progression.[9] As such, CRP holds promise as a potential prognostic biomarker.

Coagulopathy was reported, and D-dimer elevations were seen in 3.75–68.0% of the COVID-19 patients.[10-12]

Previous studies in community-acquired pneumonia (CAP) and chronic obstructive pulmonary disease (COPD) patients have shown that D-dimer level is higher in severe cases and may be used as a prognostic biomarker[13-15], and D-dimer > 1 ìg/ml is one of the risk factors for mortality in adult inpatients with COVID-1912. However, the role of D-dimer in COVID-19 patients has not been fully investigated. A comprehensive description of trajectories of change in D-dimer levels in COVID-19 patients is lacking, and whether early levels and/or the early rate of change in D-dimer levels are predictive of risk of VTE or death remain unknown.[16] In our experience, biomarkers, which can identify thrombus formation at earlier stages, might be used to evaluate the formation of thrombus and response to treatment. D-dimers are fibrin degradation products which have been shown to be useful in a clinical decision rule for ruling out pulmonary embolism[17], highlighting its role as a potentially helpful biomarker. However, the relationship between CRP and D-dimer of COVID-19 and the level changes during disease development were not fully reported. In this study, we evaluate the changes of CRP and D-dimer level of COVID-19 patients and explored its association with markers of inflammation.

Methods:

This prospective observational study was conducted in Private set up and OPD, National Institute of Diseases of the Chest & Hospital, Mohakhali, Dhaka, between January 2020 and July 2020. The diagnosis of COVID-19 was according to World Health Organization interim guidance and confirmed by RNA detection of the SARS -CoV-2 in onsite clinical laboratory. A total of 49 participants who had a CRP and D-dimer levels on first visit and had a definite outcome were enrolled. All clinical, laboratory and outcome data were extracted using a standardized data collection form. Blood samples were collected on first visit to perform routine laboratory tests, such as blood count, coagulation profile, serum biochemical tests (including renal and liver function) et al in onsite laboratory. Baseline CRP levels were collected. D-dimer was determined on CS5100 automatic coagulation analyzer (Sysmex, Kobe, Japan) by utilizing a latex-enhanced photometric immunoassay (Siemens, Marburg, Germany, The laboratory reference range was 0-0.5 ìg/ml. The D-dimer result was expressed in ìg/ml FEU (Fibrinogen Equivalent Unit). All measurements were done within 2 hours after blood sampling. After 7 days CRP level s and D-dimer levels were collected for compared with baseline

levels.Collected data were compiled and appropriate analyses were done. Qualitative variables were expressed as percentage. Chi-Square test was used to analyze the categorical variables, shown with cross tabulation. Paired t-test was used for continuous variables. P values <0.05 was considered as statistically significant.

Results:

Out of 49 COVID-19 patients, majority 22(44.9%) patients belonged to age 41 to 60 years. The mean age was 53.3±14.7 years. Forty one (83.7%) patients were male with male: female ratio was 5.1:1 (Table-1). Seventeen (34.7%) patients had hypertension followed by 15(30.6%) had diabetes mellitus, 4(8.2%) had COPD, 3(6.1%) had asthma and 2(4.1%) had CKD (Table-2). Twenty five (51.0%) patients had respiratory symptoms (Table-3). Co- morbidity was significantly higher in respiratory symptoms than without respiratory symptoms (Table-4). Mean CRP was found 39.6±54.6 mg/L in baseline and 10.1±13.0 mg/L in after 7 days. The difference was statistically significant (p<0.05) between baseline and after 7 days groups (Table-5). Twenty three (46.9%) patients were found D-dimer >3.0 gm/dl in baseline and 14(28.6%) in after 7 days. The difference was not statistically significant (p>0.05) between baseline and after 7 days (Table-6). CRP and D-dimer were not statistically significant (p>0.05) between age groups (Table-7).

Table-I

Demographic characteristics of the study patients (n=49)

	Frequency	Percentage
Age (years)21-40	9	18.4
41-60	22	44.9
61-80	18	36.7
Mean±SD	53.3+14.7	
Range (min-max)	21.0-75.0	
Sex		
Male	41	83.7
Female	8	16.3

Table-II

Co-morbidity of the study patients (n=49)

Co-morbidity	Frequency	Percentage
No	27	55.1
Yes	22	44.9
Hypertension	17	34.7
Diabetes mellitus	15	30.6
COPD	4	8.2
Asthma	3	6.1
CKD	2	4.1

Table-III

Respiratory symptoms of the study patients (n=49)

Respiratory symptoms	Frequency	Percentage
Present	25	51.0
Absent	24	49.0

Table-IV

Association between respiratory symptoms with co-morbidity (n=49)

Co-morbidity	Respiratory symptoms				P value
	Present		Absent		0.030s
	n	**%**	**n**	**%**	
Yes	15	60.0	7	29.2	
No	10	40.0	17	70.8	

s= significant
P value reached from chi square test

Table-V

CRP in different follow up (n=49)

CRP (mg/L)	Baseline		After 7 days		P value
	n	%	n	%	
<6.0	12	24.5	36	73.5	
>6.0	37	75.5	13	26.5	
Mean±SD	39.6±54.6		10.1±13.0		0.001s
Range (min-max)	5.0-302.4		3.0-69.7		

s= significant
P value reached from paired t-test

Table-VI

D-dimer in different follow up (n=49)

D-dimer (gm/dl)	Baseline		After 7 days		P value
	n	%	n	%	
<0.5	8	16.3	17	34.7	
0.5-3.0	18	36.7	18	36.7	0.066ns
>3.0	23	46.9	14	28.6	

ns= not significant
P value reached from chi square test

Table-VII

Association between baseline CRP and D-dimer with age (n=49)

	Age (years)						P value
	21-40		41-60		61-80		
	n	%	n	%	n	%	
CRP (mg/L)<6.0	3	33.3	5	22.7	4	22.2	0.792ns
>6.0	6	66.7	17	77.3	14	77.8	
D-dimer (gm/dl)							
<0.5	0	0.0	3	13.6	5	27.8	
0.5-3.0	6	66.7	9	40.9	3	16.7	0.094ns
>3.0	3	33.3	10	45.5	10	55.6	

ns= not significant
P value reached from chi square test

Discussion:

Coagulation dysfunction in COVID-19 patients insidiously drives progression to severe illness and fatal outcome, and is characterized by elevated D-dimer and thrombi in the veins and arteries.18 The high level of D-dimer in COVID-19 is triggered by excessive clots and hypoxemia. In addition, D-dimer elevation is frequently observed in COVID-19 patients with severe disease, and correlates significantly with mortality.12,19 CRP levels were positively correlated with lung lesion and disease severity. This suggests that in the early stage of COVID-19, CRP levels could reflect lung lesions and disease severity.[20]

In this study 49 patients with COVID-19 majority 22(44.9%) patients belonged to age 41 to 60 years. The mean age was 53.3±14.7 years with age range 21 to 75 years. In a study done by Yuet al.[21] observed that for COVID-19 patients, the median age was 65 years (IQR 54–72). Zhang et al.22 reported that the median age was 62 years (IQR,

48-69 years), ranging from 18 years to 92 years. 37.6% (129/343) patients were older than 65 years. Sharifpour et al.[23] described that the mean age of the cohort was 63±15 years. Another study done by Poudel et al.[24] demonstrated that the mean age of enrolled participants was 58.16±15.65 years.Present study observed that 41(83.7%) patients were male with male: female ratio was 5.1:1. In a study conducted by Poudel et al.24 reported that 113 (62.1%) were males and 69 (37.9%) were females. Sharifpour et al.[23] had observed that 63.6 patients were men and 44.4% were women. Another study done by Creel-Bulos et al.16 described that 61.0% were males and 41.0% females.

Regarding co-morbidity, observed that 17(34.7%) patients had hypertension followed by 15(30.6%) had diabetes mellitus, 4(8.2%) had COPD, 3(6.1%) had asthma and 2(4.1%) had CKD. Yu et al.21 demonstrated that 20(35%) patients had hypertension, 9(16%) had diabetes mellitus, 4(7%) had cardiovascular diseases, 1(2%) had CKD and

1(2%) had pulmonary disease. Sharifpour et al.[23] found hypertension (197 [73.5%]), obesity (141 [52.6%]), diabetes mellitus (118 [44.0%]), and a history of tobacco use (72 [26.8%]) were the most common comorbidities. Yao et al.[25] showed nearly one third of the patients had comorbidities, with

hypertension being the most common (31.5%), followed by diabetes mellitus (17.7%). Creel-Bulos et al.16 also found hypertension was present in 83(72%) and diabetes in 60 (52%).

This study found that 25(51.0%) patients had respiratory symptoms. Co-morbidity was significantly higher in respiratory symptoms than without respiratory symptoms. Bangladeshi study, Rahman et al.26 observed that majority of COVID-19 patients 300(60.0%) were symptoms free during follow-up and 40.0% had persistent respiratory symptoms.

This study observed that mean CRP was found 39.6±54.6 mg/L in baseline and 10.1±13.0 mg/L in after 7 days. The difference was statistically significant ($p<0.05$) between baseline and after 7 days groups. In a study done by Yu et al.21 reported that the specific relationship between D-dimer levels and CRP levels in COVID-19 patients, and found that both CRP levels and D-dimer levels decreased after treatment. They analyzed their relationship before and after treatment stratified by untreated CRP quartiles, as expected, after therapy, CRP levels were significantly decreased in the 2nd, 3rd and 4th quartiles of untreated CRP. Wang20 showed that CRP levels and the diameter of the largest lung lesion increased as the disease progressed. CRP levels were positively correlated with lung lesion and disease severity. Sharifpour et al.23 had described that the median CRP during hospitalization for the entire cohort was 130 mg/L (IQR 82–191 mg/L), and the median CRP on ICU admission was 169 (IQR 111–234). The hospitalization- wide median CRP was significantly higher amongst the patients who died, compared to those who survived [206 mg/L (157–288 mg/L) vs 114 mg/L (72–160 mg/L), $p<0.001$]. CRP levels increased in a linear fashion during the first week of hospitalization and peaked on day 5. Within the first 7 days, the maximum CRP was significantly higher in patients who died [median 309 mg/L (246–387 mg/L)] compared to those who survived [median 234 mg/L (148–312 mg/L), $p = 0.01$]. The slope of change in daily CRP levels within the first 7 days was also greater in patients who died [22.6, (5.12–41.7)] compared to those who survived [-0.84, (-18.4–13.4), $p<0.001$].

This study found that 23(46.9%) patients were found D-dimer >3.0 gm/dl in baseline and 14(28.6%) in after 7 days. The difference was not statistically significant ($p>0.05$) between baseline and after 7 days. Huang et al.2 showed D- dimer levels on admission were higher in patients needing critical care support than those who did not require it (median: 0.5 ìg/ml). Therefore, a recent guidance on recognition and management of coagulopathy in Covid-19 from International Society of Thrombosis and Haemostasis (ISTH) "arbitrarily defined markedly raised D-dimers on admission as three-four folds increase".[27] Yao et al.[25] also reported that D-dimer elevation (e" 0.50 mg/L) was seen in 74.6% (185/248) of the patients.

Limitation of the present study was the small sample size. Further clinical studies with larger sample size are required. Multiple-parameter prediction model including CRP, D-dimer and other variables might provide better predictive ability for COVID-19 patients.Conclusion:

At the early stage of COVID-19, CRP levels were positively correlated with lung lesions. Co-morbidity was significantly associated with respiratory symptoms. This study found significant reduced CRP levels after 7 days compared with baseline. D-dimer levels also reduced but not significant. There was no significant association between CRP and D-dimer with different age group. CRP and D-dimer levels could reflect disease severity and should be used as a key indicator for disease monitoring.

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ORIGINAL ARTICLE

Role of Vitamin D Supplementation on Patients of Severe COPD to Reduce Exacerbations

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Abstract:

Background: *Vitamin D deficiency is prevalent among patients with chronic obstructive pulmonary disease (COPD) and comes to be more frequent with increased disease severity. Low serum 25-hydroxyvitamin D (25-[OH]D) levels have been associated with lower FEV_1, impaired immunologic control and increased airway inflammation which causes frequent exacerbations of COPD patients.*

Aims: *To evaluate the role of vitamin D supplementation on patients of severe COPD to reduce exacerbations.*

Materials & Methods: *This study was prospective observational study conducted at the Department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital from December, 2019 to March, 2021. Total 94 severe COPD patients were enrolled in this study, out of which 46 patients were taken in group A that include vitamin D deficiency (<20 ng/ml) group and 48 in group B that include vitamin D insufficiency (20-30 ng/ml) group.*

Results: *Mean vitamin D level – initial (25.1±2.7 vs 10.9±3.8 ng/ml), at 3rd month (39.4±3.9 vs 32.5±3.2 ng/ml) and at 9th month (34.0±4.5 vs 22.7±4.9 ng/ml) were significantly (p<0.05) higher in group B than group A. Mean vitamin D level - at 9th month were statistically significant (p<0.05) within the group A and group B compare with initially. At 3rd month and at 9th month exacerbation were significantly higher in group A than group B.*

Conclusion: *We concluded that vitamin D level was significantly increased at nine month in both group A and group B respectively. In both group, exacerbation was significantly reduce at nine month follow up than initially. So early supplementation of Vitamin D in exacerbation of severe COPD patients can reduce number of further exacerbation.*

Keyword: *Chronic obstructive pulmonary disease (COPD), Serum 25-hydroxyvitamin D, Exacerbation.*

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Introduction:

Chronic obstructive pulmonary disease (COPD) remains a major public health problem.[1]

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease and parenchymal destruction (emphysema). 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.[2] Airflow limitation is usually measured by spirometry as this is the most widely available and reproducible test of lung function.

Vitamin D is a fat soluble hormone precursor that plays an important role in bone metabolism and seems to have anti-inflammatory and immune-modulating properties. Vitamin D is present in two forms. Ergocalciferol or vitamin D2, is present in plants and some fish. Cholecalciferol or vitamin D3, is synthesized from 7-dehydrocholesterol in the skin by sunlight.

Vitamin D deficiency is prevalent among patients of COPD and comes to be more frequent with increased disease severity.[3] In participants with severe vitamin D deficiency at baseline, supplementations may reduce exacerbations.[4]

Recent studies show that a substantial proportion of patients with chronic obstructive pulmonary disease have deficient vitamin D levels (<20 ng/mL).[3,5] Few studies have measured the significance of vitamin D deficiency in COPD by calculating serum levels of 25-hydroxyvitamin D (25-[OH]D), which is the important circulating vitamin D metabolite and recognized as the finest short-term biomarker of entire contact to vitamin D. With disease development, marked by decay in FEV_1, patients grow systemic significances and became prone to infectious exacerbations which are precipitated by concomitants vitamin D deficiency.[3]

Vitamin D supplements halve the number of exacerbations of chronic obstructive pulmonary disease (COPD) in people with low levels of the vitamin, from two per year to one per year. The supplements do not affect exacerbations of COPD in people who are not deficient.[6]

In this study, we have aimed to evaluate the role of vitamin D supplementation on patients of severe COPD to reduce exacerbations.

Methods:

This study was prospective observational study was carried out in the Department of Respiratory Medicine of National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period from December, 2019 to March, 2021. Pulmonary disease other than COPD, malignancy, advanced renal disease, COPD with history of diseases (nephrolithiasis, hypercalciuria, malignancy, tuberculosis, sarcoidosis, Paget's disease, malabsorption syndromes), pregnant women, alcoholics, HIV seropositivity and use of active metabolites of vitamin D within 6 months of screening were excluded.

Of 102 patients with COPD vitamin D deficiency which fulfilled the inclusion and exclusion criteria during the study period. Out of them 1 patient died & 4 patients were lost to follow up in group A (vitamin D <20 ng/ml) and 3 patients were lost to follow up in group B (vitamin D 20-30 ng/ml). Finally, 46 patients were taken in group A and 48 in group B. Both groups of patients received oral vitamin D 40000 IU weekly for 8 weeks followed by 2000 IU daily for 1 month.Vitamin D level was measured at 3 month and 9 months and exacerbation of COPD was recorded.

Statistical Package for Social Science (SPSS) version 23 for windows was used to analyze the data. Chi square test was used for categorical variables as shown cross tabulation. Unpaired t-test and paired t-test was used for continuous variables. A p value d"0.05 was considered to be significant.

Results:

The mean age was found 60.2±10.2 years in group A and 58.2±10.3 years in group B. Majority (87.0%) patients were male in group A and 43(89.6%) in group B. The difference were not statistically significant (p>0.05) between two groups (Table-1).

Mean vitamin D level - initial, at 3rd month and at 9th month were significantly (p<0.05) higher in group B than group A. Mean vitamin D level - at 9th month were statistically significant (p<0.05) within the group A compare with initially. Mean vitamin D level - at 9th month were statistically significant (p<0.05) within the group B compare with initially (Table-2).

At 3rd month, 25(54.3%) patients were found exacerbation in group A and 16(33.3%) in group B. At 9th month, 28(60.9%) patients were found exacerbation in group A and 13(27.1%) in group B. The difference were statistically significantly (p<0.05) between two groups (Table-3).

Table-I

Demographic characteristics of the study patients (n=94)

Demographic characteristics	Group A(n=46)		Group B (n=48)		P value
	n	%	n	%	
Age (years)	41-50	9	19.6	13	27.1
	51-60	17	37.0	17	35.4
	61-70	15	32.6	12	25.0
	71-80	4	8.7	6	12.5
	>80	1	2.2	0	0.0
Mean±SD	60.2	±10.2	58.2	±10.3	[a]0.346[ns]
Range (min-max)	42.0	-85.0	41.0	-80.0	
Sex					
Male	40	87.0	43	89.6	[b]0.692[ns]
Female	6	13.0	5	10.4	

ns= not significant

[a]P value reached from unpaired t-test

[b]P value reached from chi square test

Table-II

Vitamin D level in different follow up (n=94)

Vitamin D level (ng/ml)	Group A(n=46) Mean±SD	Group B (n=48) Mean±SD	P value
Initial	10.9±3.8	25.1±2.7	[a]0.001[s]
Range (min-max)	6.0-19.1	20.1-29.9	
At 3rd month	32.5±3.2	39.4±3.9	[a]0.001[s]
Range (min-max)	24.6-38.0	32.4-47.2	
At 9th month	22.7±4.9	34.0±4.5	[a]0.001[s]
Range (min-max)	15.3-34.2	24.2-44.1	
P value (Initialvs at 9th month)	[b]0.001[s]	[b]0.001[s]	

s= significant

[a]P value reached from unpaired t-test

[b]P value reached from paired t-test

Table-III

Exacerbation in different follow up (n=94)

Exacerbation	Group A (n=46)		Group B (n=48)		P value
	n	%	n	%	
Initial					
Present	46	100.0	48	100.0	
Absent	0	0.0	0	0.0	
At 3rd month					
Present	25	54.3	16	33.3	0.040[s]
Absent	21	45.7	32	66.7	
At 9th month					
Present	28	60.9	13	27.1	0.001[s]
Absent	18	39.1	35	72.9	

s= significant

P value reached from chi square test

Discussion:

This study was Prospective Observational study carried out with an aim to evaluate the role of vitamin D supplementation on patients of severe COPD to reduce exacerbations among the patients in the Department of Respiratory Medicine, NIDCH. Of 102 patients with COPD vitamin D deficiency which fulfilled the inclusion and exclusion criteria during the period from December, 2019 to March, 2021 were included in this study. Out of them 1 patient died & 4 patients were lost to follow up in group A (vitamin D <20 ng/ml) and 3 patients were lost to follow up in group B (vitamin D 20-30 ng/ml). Finally, 46 patients were taken in group A and 48 in group B. The present study findings were discussed and compared with previously published relevant studies.

In this study it was observed that mean age was found 60.2±10.2 years in group A and 58.2±10.3 years in group B. The difference were not statistically significant (p>0.05) between two groups. In a study done by Pourrashid et al.[7] reported mean age was 62.73±8.26 years in vitamin D group and 64.06±8.77 years in placebo group, that was not significant (p=0.54).

In the present study it was observed that most of the patients were males in both groups that (87.0%) group A and 43(89.6%) in group B. Whereas, female was 6(13.0%) and 5(10.4%) in group A and group B respectively. The difference were not statistically significant (p>0.05) between two groups. Rezk et al.[8] observed that 86.7% patients were male and 13.3% were female. Male to female ratio was 6.5:1.

Regarding vitamin D level in different follow up it was observed that mean vitamin D level – initial (25.1±2.7 vs 10.9±3.8 ng/ml), at 3rd month (39.4±3.9 vs 32.5±3.2 ng/ml) and at 9th month (34.0±4.5 vs 22.7±4.9 ng/ml) were significantly (p<0.05) higher in group B than group A. Mean vitamin D level - at 9th month were statistically significant (p<0.05) within the group A compare with initially. Mean vitamin D level - at 9th month were statistically significant (p<0.05) within the group B compare with initially. Pourrashid et al.[7] consisted that at baseline, mean±SD of serum 25(OH)D levels were 10.59±3.39 ng/mL and 11.12±3.17 ng/mL in vitamin D and placebo groups respectively and did not differ in between groups comparison ($p = 0.82$). Vitamin D supplementation resulted in a statistically significant increase in serum 25(OH)D levels in vitamin D group (36.85±11.80 ng/mL) versus placebo group (12.30±3.66 ng/mL), by day 120 [$p = 0.000$, (CI -30.0, -18.90)]. Rezk et al.[8] observed that mean vitamin D was found 11.8±2.4 nmol/L in before vitamin D replacement and 55.3±5.65 nmol/L in 1 year after vitamin D replacement (p <0.001).

In the present study it was observed that at 3rd month, 25(54.3%) patients were found exacerbation in group A and 16(33.3%) in group B. At 9th month, 28(60.9%) patients were found exacerbation in group A and 13(27.1%) in group B. The difference were statistically significantly (p<0.05) between two groups. Khan et al.[9] reported that at baseline, exacerbation was present all patients in both groups. Whereas, at 2nd month follow up exacerbation present 39(65.0%) patients in group A and 40(66.7%) in group B. At 6th month follow up exacerbation was not found in group A but 4(6.7%) found in group B. According to a recent meta-analysis, the benefits of supplementation were only present when baseline 25-OHD levels are very low (<10 ng/ml).[10]

Conclusion:

We concluded that vitamin D level was significantly increased at nine month in group A and group B respectively. In both group, exacerbation was significantly reduce at nine month follow up than initially. Exacerbation rate was significantly higher in group A than group B. Vitamin D can be beneficial in reducing exacerbations in patients with severe COPD.

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ORIGINAL ARTICLE

Factors Affecting Antibiotic Resistance Among Patients With Community Acquired Pneumonia In A Tertiary Care Hospital

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Abstract:

Background: *Community Acquired Pneumonia (CAP) is a major health problem leading to significant morbidity and mortality worldwide. Bacteriological profile of CAP is different in different countries and changing with time within the same country. Bacterial resistance to antibiotics is also an increasing problem, which may cause infection that is difficult to treat.*

Aims: *To identify the factors affecting antibiotic resistance among indoor patients of NIDCH.*

Materials & Methods: *This cross sectional, observational study conducted at the Department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital from May 2019 to September 2020. Of 195 patients with CAP, 87 patients with positive sputum bacterial growth were enrolled in this study.*

Results: *A total number of 87 patients with community acquired pneumonia were selected and among them, majority patients were male 65(74.7%), male to female ratio was 2.9:1. The mean age was found 50.6±16.7 years with range from 18 to 85 years. Among the co morbidities diabetes mellitus was the highest 34(39.1%) followed by hypertension 23(26.4%), chronic obstructive pulmonary disease (COPD) 20(23.0%). Most frequent pathogens were* Klebsiella pneumoniae *35(40.2%) followed by* Streptococcus pneumoniae *15(17.2%),* Pseudomonas aeruginosa *11(12.6%). In this study it was observed that multidrug-resistant pathogens was found 54(62.1%) with 95% CI 51.9 to 72.3%. In multivariate logistic regression analysis, previous antibiotic use, history of self medication and history of previous hospitalization were found to be independent predictors for multidrug resistance.*

.***Conclusion:*** *Gram negative bacteria are the main pathogenic bacteria in CAP. Identification of bacteriological profile and susceptibility pattern of pathogens could enable accurate diagnosis and treatment of CAP. The growing prevalence of multidrug resistant bacteria represents an important issue in choosing empiric antimicrobial management in hospitalized patients. The widespread antibiotic resistant microorganisms necessitate the implementation of antibiotic stewardship strategies, to ensure that antibiotics are used only when necessary and appropriate.*

Keywords: *Factors Affecting, Antibiotic Resistance, Multi Drug Resistance (MDR), Community Acquired Pneumonia.*

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Introduction:

Pneumonia is broadly defined as acute infection and inflammation of lung parenchyma[1]. Pneumonia can be classified as- community acquired pneumonia (CAP), nosocomial pneumonia, aspiration pneumonia and pneumonia in immunocompromised host[2].

Infectious Diseases Society of America (IDSA) defines CAP as "an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia in a patient not hospitalized or residing in a long-term care facility for more than 14 days before onset of symptoms[3-5].

Bacterial resistance to the effects of antibioti-cs is an increasing problem around the world. Multi-drug resistant organisms (MDRO), which in de-veloped countries would result in the selection of an alternative treatment but in poor countries, may cause infections that are difficult to treat[6] .

Unfortunately, the three major bacterial respiratory pathogens; *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae*; have increasing prevalence of antibiotic resistance in developed world[5,7,8].

Moreover, resistance surveillance data from parts of the developing world remain poor. Relatively few surveillance data are available for countries in South-East Asia[9].

We are living through an antibiotic resistance crisis, mainly because antibiotics tend to lose their efficacy over time due to the emergence and dissemination of resistance among bacterial pathogens, principally caused by the overuse and inappropriate use of antibiotics, as well as the extensive use of antibiotics in agriculture and the food industry.

Risk factors for the spread of resistant bacteria in hospitals and the community are overcrowding, lapses in hygiene or poor infection control practices, unnecessary use of antibiotics for conditions where they are not indicated, such as common colds or viral pharyngitis, non compliance and inadequate duration or dosage, veterinary use of antibiotics[10]. Prior hospitalization, previous colonization, history of antibiotic use, non ambulatory status, prior use of inhaled corticosteroid are the risk factors associated with drug resistant organism of community acquired pneumonia[11,12].

Identification of patients with drug-resistant pathogens at initial diagnosis is also essential for treatment of pneumonia[11].

Hence, this study was conducted to address the factors associated with antibiotic resistance among patients admitted in Inpatient Department of NIDCH.

Methods:

This cross-sectional observational study was conducted in National Institute of Diseases of the Chest and Hospital (NIDCH), Dhaka, Bangladesh. This study was carried out from May 2019 to September 2020. Community acquired pneumonia patients admitted in Inpatient Department of NIDCH fulfilling the inclusion and exclusion criteria were included in this study.

The patients were selected by non-randomized purposive sampling method. Community acquired pneumonia patients with positive sputum bacterial growth admitted in Inpatient Department of NIDCH were included.

The patients with co-infection with Tuberculosis and those who refused to enroll in the study were excluded.

Patients of community acquired pneumonia were selected by history, clinical examination and radiological examination from the Inpatient Department of Respiratory Medicine of NIDCH according to inclusion and exclusion criteria.

Early morning sputum samples were collected in a sterile container and sent to International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) for Gram staining, culture sensitivity test. Sputum for AFB, sputum for Gene X-pert MTB/RIF were sent to Department of Microbiology of NIDCH. For scanty sputum production, sputum was collected after nebulization by hypertonic saline (3% sodium chloride).

All the data were recorded systematically in a preformed data collection sheet and analyzed by descriptive and analytic techniques. Chi square test was used for categorical variables. Multivariate logistic regression was performed to assess independent relationship between factors.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 23 for windows.

Sputum samples were collected from all patients enrolled in the study. Representative sputum originated from the lower respiratory tract was defined as that containing >25 granulocytes and <10 epithelial cells per low power field microscopic view. Validated sputum was cultured in blood agar, chocolate agar and McConkey's agar media. Isolation and identification of microorganism was done by semiquantitative method.

Antibacterial susceptibility testing was done by using modified Kirby-Bauer disk diffusion method[13] and interpreted according to Clinical and Laboratory Standard Institute guideline.

Results:

Table-I

Socio-demographic distribution of the study respondents (n=87)

Demographic characteristics	Number of patients	Percentage
Sex		
Male	65	74.7
Female	22	25.3
Mean age (years)	50.6	±16.7
Range (min-max)	18.0	-85.0
Marital status		
Married	78	89.7
Unmarried	9	10.3
Residence		
Rural	36	41.4
Urban	51	58.6
Educational status		
Illiterate	13	14.9
Primary	19	21.8
Secondary	41	47.1
College	9	10.3
University	5	5.7

Table I shows that male patients were predominant 65(74.7%) and female was 22(25.3%), male female ratio was 2.9:1. The mean age was found 50.6±16.7 years with range from 18 to 85 years. Married patients were found 78(89.7%), 41(47.1%) patients completed secondary education level. Other results are depicted in the table.

Table-II

Distribution of the respondents according to risk factors (n=87)

Risk factors	Number of patients	Percentage
Previous antibiotic use	63	72.4
History of self medication	40	46.0
Sharing of antibiotic with others	24	27.6
Use of left over antibiotics	21	24.1
History of non adherence to antibiotic	47	54.0
History of previous hospitalization	48	55.2
Vaccination is status against *S. pneumoniae*	4	4.6
Use of inhaled corticosteroid	25	28.7

Regarding risk factors, 63(72.4%) patients had history of previous antibiotic use, 48(55.2%) had history of previous hospitalization, 47(54.0%) had history of non adherence to antibiotic, 42(46.0%) had history of self medication, 24(27.6%) sharing of antibiotic with others, 21(24.1%) used of left over antibiotics and 25(28.7%) used inhaled corticosteroid.

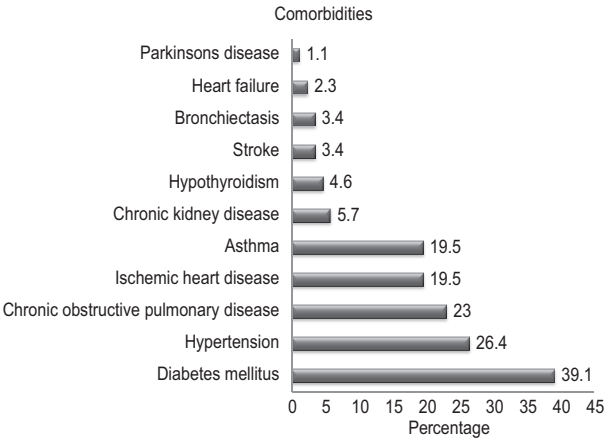

Fig.-1: *Comorbidities of the study respondents (n=87)*

Figure 1 shows that among the comorbidities diabetes mellitus was the highest 34(39.1%), followed by hypertension 23(26.4%), chronic obstructive pulmonary disease (COPD) 20(23.0%), ischemic heart disease 17(19.5%), asthma 17(19.5%), chronic kidney disease 5(5.7%),

Table-III

Distribution of the respondents according to isolated bacteria (n=87)

Name of the bacteria	Number of patients	Percentage
Single bacterial agent		
Klebsiella pneumoniae	35	40.2
Streptococcus pneumoniae	15	17.2
Pseudomonas aeruginosa	11	12.6
Acinetobactor	4	4.6
Haemophilus influenzae	4	4.6
Staphylococcus aureus	3	3.4
E. coli	2	2.3
Staphylococcus haemolyticus	2	2.3
Serratia	1	1.1
Mixed bacterial agent		
Klebsiella pneumoniae+ Acinetobactor	3	3.4
Acinetobactor+ Pseudomonas aeruginosa	2	2.3
Acinetobactor+ Staphylococcus aureus	1	1.1
Klebsiella pneumoniae+ Enterobactor	1	1.1
Klebsiella pneumoniae+ Enterococcus faecium	1	1.1
Klebsiella pneumoniae+ Staphylococcus haemolyticus	1	1.1
Pseudomonas aeruginosa+ Strptococcus pneumoniae	1	1.1

hypothyroidism 4(4.6%), stroke 3(3.4%), bronchiectasis 3(3.4%), heart failure 2(2.3%) and parkinson's disease 1(1.1%).

Table III shows that the most frequent pathogens were *Klebsiella pneumoniae* 35(40.2%), *Streptococcus pneumoniae* 15(17.2%), *Pseudomonas aeruginosa* 11(12.6%), *Acinetobactor* 4(4.6%), *Haemophilus influenzae* 4(4.6%), *Staphylococcus aureus* 3(3.4%), *E.coli* 2(2.3%), *Staphylococcus haemolyticus 2(2.3%) and Serratia* 1(1.1%). Regarding mixed(dual) pathogens *Klebsiella pneumoniae+ Acinetobactor* were 3(3.4%), *Acinetobactor+ Pseudomonas aeruginosa* 2(2.3%). Other results are depicted in the table.

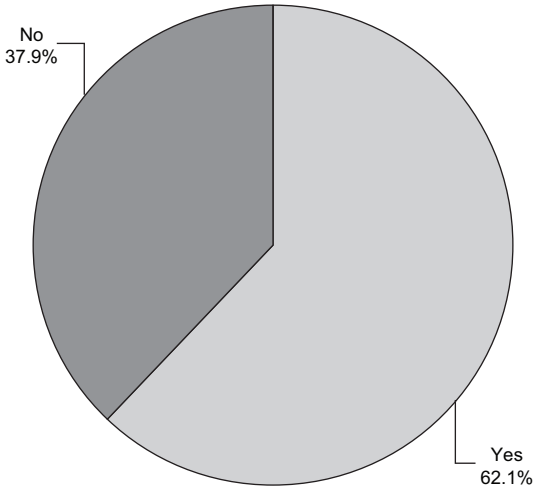

Fig.-2: *Multidrug resistance of the study respondents (n=87)*

Multidrug resistant organism (MDRO): non susceptibility to at least one agent in three or more antimicrobial categories. Figure 2 shows that multidrug resistance was found 54(62.1%) with 95% CI 51.9 to 72.3%.

Table IV shows that hypertension, chronic obstructive pulmonary disease, previous antibiotic use, history of self medication, sharing of antibiotic with others, use of left over antibiotics, history of non adherence to antibiotic, history of previous hospitalization, vaccination status against *S. pneumoniae* and antibiotic prescribed by pharmacy were significantly associated with multidrug resistance. However, other risk factors were not significantly associated with multidrug resistance.

In multivariate logistic regression analysis, previous antibiotic use, history of self medication and history of previous hospitalization were found to be independent predictors for multidrug resistance.

Table-IV

Association between Multidrug resistance with risk factors (n=87)

Risk factors	Multidrug-resistance				P value
	Yes (n=54)		No (n=33)		
	n	%	n	%	
Age (>60 years)	18	33.3	9	27.3	0.364^{ns}
Male	42	77.8	23	69.7	0.400^{ns}
Smoking	34	63.0	20	60.6	0.826^{ns}
Consumption of broiler chicken	51	94.4	28	84.8	0.132^{ns}
Consumption of pasteurized packet milk	31	57.4	13	39.4	0.103^{ns}
Diabetes mellitus	25	46.3	9	27.3	0.078^{ns}
Hypertension	19	35.2	4	12.1	0.015^{s}
Chronic obstructive pulmonary disease	18	33.3	2	6.1	0.003^{s}
Ischemic heart disease	10	18.5	7	21.2	0.759^{ns}
Asthma	8	14.8	9	27.3	0.155^{ns}
Chronic kidney disease	4	7.4	1	3.0	0.368^{ns}
Hypothyroidism	2	3.7	2	6.1	0.490^{ns}
Stroke	3	5.6	0	0.0	0.234^{ns}
Bronchiectasis	3	5.6	0	0.0	0.234^{ns}
Heart failure	2	3.7	0	0.0	0.383^{ns}
Using inhaled steroid	15	27.8	10	30.3	0.800^{ns}
Previous antibiotic use	47	87.0	16	48.5	0.001^{s}
History of self medication	34	63.0	6	18.2	0.001^{s}
Sharing of antibiotic with others	21	38.9	3	9.1	0.003^{s}
Use of left over antibiotics	19	35.2	2	6.1	0.002^{s}
History of non adherence to antibiotic	37	68.5	10	30.3	0.001^{s}
History of previous hospitalization	42	77.8	6	18.2	0.001^{s}
Vaccination status against *S. pneumoniae*	0	0.0	4	12.1	0.018^{s}
Antibiotic prescribed by pharmacy	21	46.3	3	9.1	0.040^{s}

s= significant, ns= not significant
p-value reached from chi square test

Table-V

Multivariate logistic regression analysis for Multidrug resistance

	Adjusted	95% CI		P value
	OR	Lower	Upper	
Hypertension	12.261	0.466	82.788	0.133^{ns}
Chronic obstructive pulmonary disease	0.547	0.022	13.800	0.714^{ns}
Previous antibiotic use	22.708	2.542	92.846	0.005^{s}
History of self medication	4.352	1.250	15.151	0.021^{s}
Sharing of antibiotic with others	0.936	0.024	36.946	0.972^{ns}
Use of left over antibiotics	18.182	0.374	82.768	0.143^{ns}
History of non adherence to antibiotic	0.264	0.017	4.182	0.345^{ns}
History of previous hospitalization	10.257	1.537	68.456	0.016^{s}
Vaccination is status against *S. pneumoniae*	1.025	0.447	2.349	0.954^{ns}
Antibiotic prescribed by pharmacy	1.721	0.262	11.288	0.572^{ns}

s= significant, ns= not significant
p-value reached from multivariate analysis by binary logistic regression analysis
OR=Odd's Ratio

Discussion:

This cross sectional observational study was carried out with an aim to identify the bacteriological profile of community acquired pneumonia and their antibiotic susceptibility pattern among patients admitted in Inpatient Department of NIDCH. This study also to find out the multidrug resistance and factors affecting multidrug resistance.

Of 195 patients with community acquired pneumonia, 87 fulfilled the inclusion and exclusion criteria during the period from May 2019 to September 2020 were included in this study. Community acquired pneumonia patients with positive sputum bacterial growth and patient willing to participate were enrolled in this study. Patients suffering from co-infection with active pulmonary tuberculosis and patient not willing to be included in this research were excluded from the study. The present study findings were discussed and compared with previously published relevant studies.

Regarding risk factors in this study it was observed that 63(72.4%) patients had history of previous use, 48(55.2%) had history of previous hospitalization, 47(54.0%) had history of non adherence to antibiotic, 42(46.0%) had history of self medication, 24(27.6%) sharing of antibiotic with others, 21(24.1%) used of left over antibiotic. Ishida et al.[14] had observed that previous antibiotic treatment was found 31.4%. Gross et al.[15] consisted that antibiotic use in the last 90 days was found 31.9%. Another study documented by Lauderdale et al.[16] which showed antibiotic used 16.1%.

Regarding history of antibiotic use of the respondents, majority 32(50.8%) respondent 1st time complete full course and 7(77.8%) respondent 4th time demand of antibiotic. 16(25.4%) respondent 1st time prescribed by registered doctor.

In this study it was observed that among the comorbidities diabetes mellitus was the highest 34(39.1%) followed by hypertension 23(26.4%), chronic obstructive pulmonary disease (COPD) 20(23.0%), ischemic heart disease 17(19.5%), asthma 17(19.5%), chronic kidney disease 5(5.7%), hypothyroidism 4(4.6%), stroke 3(3.4%), bronchiectasis 3(3.4%), heart failure 2(2.3%) and parkinsons disease 1(1.1%). In a study conducted by Jeong et al.[17] where they found diabetes was 23.0%, cerebrovascular disease 19.0%, chronic heart disease 8.0%, chronic kidney disease 6.0%, chronic liver disease 8.0%. Prina et al.[18] reported that COPD was 35.0%, bronchiectasis 11%, diabetes mellitus 23.0%, chronic kidney disease 16.0%, neurologic disease 19.0%. Ishida et al.[14] consisted that congestive heart failure 32.1%, chronic obstructive pulmonary disease 21.6%, bronchiectasis 15.7%, chronic kidney disease 11.8%, cerebrovascular disease 22.9% and diabetes 13.7%. Gross et al.[15] had observed COPD was 27.6%, congestive heart failure 16.5% and diabetes 28.4%. Another study conducted by El-Sokkary et al.[19] which showed that diabetes mellitus was 31.48%, hypertension 25.93%, COPD 18.52%, ischemic heart disease 16.67%.

In this present study it was observed that multidrug-resistant pathogens was found 54(62.1%) with 95% CI 51.9 to 72.3%. In a study of El-Sokkary et al.[19] reported that overall, 76.2% of isolates showed a multidrug resistant phenotype. Another study conducted by Prina et al.[18] which showed although MDR pathogens were more frequently isolated in HCAP (26.6%), they were also detected in CAP (8.6%).

In my study it was observed that hypertension, chronic obstructive pulmonary disease, previous antibiotic use, history of self medication, sharing of antibiotic with others, use of left over antibiotics, history of non adherence to antibiotic, history of previous hospitalization, vaccination is status against and antibiotic prescribed by pharmacy were significantly associated with multidrug-resistant pathogens. However, other risk factors were not significantly associated with multidrug-resistant pathogens. Gross et al.[15] reported that statistically significant associations with MDRO included the following: history of cerebrovascular accident, congestive heart failure, presence of HCAP, number of days hospitalized in the previous 180 days, antibiotic use in the previous 90 days.

In multivariate logistic regression analysis in this study it was observed that previous antibiotic use, history of self medication and history of previous

hospitalization were found to be independent predictors for multidrug resistance. In a study of Luan et al.[20] had observed that prior multiple antibiotic treatment was the only independent risk factor for MDRCAP (OR: 3.542; 95% CI: 1.141–14.827, P=0.002) Although frequent use antibiotics might significantly inhibit bacterial growth, it also might lead to frequent bacterial mutation and drug resistance. When more than one antimicrobial agent is present in the microorganism environment, pressure from these antimicrobial agents results in selection of bacteria using multiple or polyvalent resistance mechanisms. Therefore, bacteria optimize one resistance mechanism to survive in variable environments or increase mutational events during situations of bacterial stress[21]. Self medication commonly associated with inappropriate drug use practices include- short duration of treatment, inadequate dose, sharing of medicines, and avoidance of treatment upon the improvement of disease symptoms[22]. This may be the cause of antibiotic resistance in self medication.

Prina et al.[18] showed that the following six independent factors were described for MDR pathogens: prior hospitalization; immuno-suppression; previous antibiotic use; use of gastric acid–suppressive agents; tube feeding; and nonambulatory status. Moreover, they defined some additional risk factors for MRSA (including chronic dialysis during the preceding 30 days, positive MRSA history within the previous 90 days, and congestive heart failure). Gross et al.[15] reported that in the propensity score-adjusted multivariate logistic regression analysis, duration of previous hospitalization in the last 90 or 180 days, *P. aeruginosa* colonization/infection in the previous year, antimicrobial use in the last 90 days, and admission from a nursing home were all predictors of MDRO. Another study conducted by Jeong et al.[17] where they found logistic regression analysis identified 5 variables that were independently associated with the identification of PDR pathogens. Recent history of hospitalization for e" 2 days in the preceding 90 days (adjusted OR 2.324 and 95% CI 1.241–4.352, p = 0.008) and recent antibiotic therapy within the past 30 days (adjusted OR 2.699 and 95% CI 1.366–5.334, p = 0.004) were independently associated with PDR pathogens. Chronic lung disease (adjusted OR 1.970 and 95% CI 1.075–3.612, p = 0.028) were also independently associated with the recovery of PDR pathogens.

Conclusion:

In multivariate analysis, previous antibiotic use, history of self medication and history of previous hospitalization were found to be independent predictors for multidrug resistance. The growing prevalence of multidrug resistant bacteria represents an important issue in choosing empiric antimicrobial management in hospitalized patients. The widespread antibiotic-resistant microorganisms necessitate the implementation of antibiotic stewardship strategies. Microbiological profile of community acquired pneumonia varies geographically. There is a need to conduct regular prevalence and antibiogram studies to develop empirical guidelines for treatment of community acquired pneumonia in that particular region.

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Author Contributions: Dr.Mohammad Zannatul Rayhan had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Dr. Mohammad Zannatul Rayhan contributed to study conception and design, data collection, analysis and interpretation of data, drafting of the manuscript and critical revisions of the article.

Prof. Krishna Chandra Ganguly, contributed to case selection, critical revisions & section writing of the manuscript. Bipul Kanti Biswas, Most Mehenaz Alam, Tazrin Farhana also contributed to critical revisions of the manuscript.

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ORIGINAL ARTICLE

Risk Factors for Multidrug Resistant organisms in Exacerbation of COPD

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Abstract:

Background & Objective: *Bacterial infections are the major cause of acute exacerbation of COPD (AE-COPD). The natural history of chronic obstructive pulmonary disease is characterized by frequent exacerbations. Majority of exacerbations are infectious and bacteria responsible for 30-50% of these cases. Appropriate use of antibiotic reduce mortality, hospital stay, subsequent exacerbations, further lung damage and also prevention of development of antibiotic resistance.*

Patients & Methods: *This cross sectional observational and analytical study conducted at the Department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital from July 2019 – June 2020. A total of 102 patients with acute exacerbation of COPD were enrolled in this study. Early morning Sputum were examined for bacteriological culture and sensitivity. Multidrug-resistance was determined according to European Centre of Disease Prevention and Control classification.*

Result: *One hundred and two exacerbations were included and microorganisms were isolated in 50 cases.* Pseudomonas aeruginosa*15(30%),*Klebsiella pneumoniae*14(28.0%) and Acinetobacter 11(22%) were more frequent. Multidrug-resistant pathogens were found in 35(70%) cases. In multivariateanalysis,preevious hospitalization (Odds ratio2.19,95% CI 1.22-3.91), frequent antibioticuse (OR 3.136, 95% CI 1.37-7.15) and chronic kidney disease (7.560,95%CI 1.82-31.33) were found to be independent predictors for MDR pathogens. Irregular use of antibiotics ($p<0.007$) among the frequent antibiotic users favored growth of MDR pathogen.*

Conclusion: *Recent hospitalization, frequent antibiotic users particularly indiscriminate use of antibiotics and chronic kidney disease were seemed to be the risk factor for multidrug resistant bacteria.So special attention should be warranted in these groups regarding use of antibiotics.*

Key words: *Multidrug Resistant Organism, Exacerbation of COPD, Risk factors*

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Introduction:

Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory condition of the airways, which is associated with significant morbidity and mortality. According to World Health Organization (WHO), COPD will be the third-leading cause of death worldwide by 2030[1,2]. Based on BOLD and other large scale studies, it is estimated that the number of COPD cases was 384 million in 2010, with global prevalence of 11.7% (95% CI 8.4% - 15%)[2]. The overall prevalence of COPD in Bangladesh is 4.3% and in adults with age >40 years is 21.24% with total burden of COPD patients is about 6 million (BOLD-BD, 2007). Globally, there are around three million deaths annually and by 2030 COPD will be the 5th leading cause of loss in DALYs globally, where it was only number 13 in 2004[3].

ATS/ERS guidelines define Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) as an event characterized by an increase in patient's daily symptoms of dyspnea, cough, and/or sputum beyond normal day-to-day variability and severe enough to require a change in management[4].About 50-78% of acute exacerbations of COPD are caused by respiratory infections[5]. Bacteria as cause of AECOPD are reported from 30% up to 55% and common bacterial pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and in patients with more severe COPD also *Pseudomonas aeruginosa and Klesiella pneumonae*[6].

So, identification and appropriate treatment of these organisms is an essential part in management of AE-COPD.

Optimal antibiotic use is crucial, especially in an era of rising antibiotic resistance and lack of new antimicrobial development[7]. Overprescribing and misprescribing antibiotics are undoubtedly contributing to the growing challenges posed by antibiotic resistant bacteria, and epidemiological studies have clearly demonstrated direct relationships between antibiotic consumption and the emergence and dissemination of resistant strains in hospitals[8].

Infections caused by MDR gram-negative organisms are associated with high morbidity and mortality[9]. Moreover, the financial burden of antimicrobial resistance can be significant as a result of prolonged hospitalizations due to antibiotic treatment failures. The economic impact of antibiotic resistance can be measured not only through direct health care expenses but also through health burden to the individuals affected and to the society[9]. Leaders in world health have described antimicrobial-resistant bacteria as "nightmare bacteria" that account for a substantial number of excess deaths and catastrophic healthcare spending[10].

It is necessary to find out the resistant pathogens so that treatment can be planned accordingly which may decrease the mortality and morbidity.

Materials and Methods:

This cross-sectional analytical study was carried out in the Department of Respiratory Medicine, National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka over a period of one year between July 2019 to June 2020.Adult patients presented with exacerbation of COPD admitted to the inpatient Department of Respiratory Medicine were the study population. Patients with concomitant pulmonary tuberculosis were excluded from the study. A total of 102 cases were taken in the study. Study samples were selected by purposive sampling.

Results:

Out of 102 patients with acute exacerbation of exacerbation of COPD mean age was 62.0±8.5 years with range from 42 to 84 years. Male patients were predominant 88(86.3% with M:F 6.3:1. Smoker was found in 89(87.2%). Among them majority 81(79.5%) patients took e"20 pack per year. The mean BMI was found 23.0±1.9 kg/m$^{2.}$

Sputum for C/S showed bacterial growth in 50(49.0%) with multidrug-resistant organism in 35 (70%) cases.

Majority 47(46%) patients used frequent antibiotic, 15(14.7%) had previous exacerbation in last year, and 10(9.8%) patients required hospital admission and I/V antibiotics. 25(24.5%) had DM and 15(14.7%) had CKD.

According to Winnipeg criteria 14 (13.7%) patients were in mild group, 53 (52.0%) were in moderate

and 35 (34.3%) were in severe exacerbation group. 26(52%) in moderate and 15(30%) in severe exacerbation group showed growth of organism which was insignificant (p>0.05).

Patients presented with no respiratory failure were 22 (21.5%) and rest 80 (78.5%) with respiratory failure of which 45 (44.1%) presented with non-life threatening and 35 (34.4%) with life threatening failure. 5 (10%) patients in no respiratory failure and 45 (90%) in respiratory failure group had growth of organism which was statistically significant (p<0.005).

In univariate analysis, previous exacerbation, recent hospitalization, frequent antibiotic use, diabetes mellitus and chronic kidney disease were found to be independent predictors for MDR pathogens.

In multivariable analysis, recent hospitalization, frequent antibiotic use and chronic kidney disease were found to be independent predictors for MDR pathogens.

Table-I

Demographic Characteristics of the Study Cases (n=102)

Demographic characteristic	Number of patients	Percentage
Sex		
Male	88	86.3
Female	14	13.7
Mean age (years)	62.0	±8.5
Range (min-max)	(42.0-84.0)	
Economic status		
Low	69	67.6
Lower middle	11	10.8
Upper middle	20	19.6
High	2	2.0
Smoker		
No	13	12.8
Yes	89	87.2
<20 pack/yr	8	7.7
>20 pack/yr	81	79.5

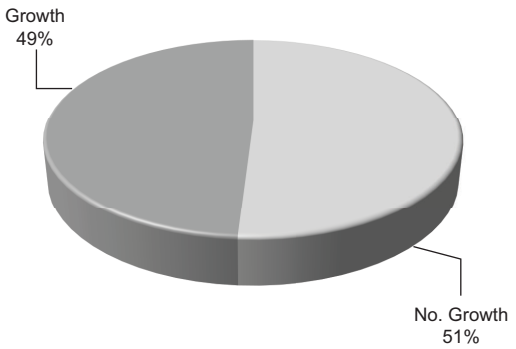

Fig.-1: *Sputum for C/S of the study patients*

Table 7 showed 14 (13.7%) patients were in mild group, 53 (52.0%) were in moderate and 35 (34.3%) were in severe exacerbation group according to Winnipeg criteria. 52% in moderte and 30% in severe exacerbation group showed growth whereas 53% and 35% didn't show any growth respectively. The chi-square statistic is 0.326. the p value is 0.568 and not significant at p <0.05.

Table III showed patients presented with no respiratory failure were 22 (21.5%) and rest 80 (78.5%) with respiratory failure of which 45 (44.1%) presented with non-life threatening and 35 (34.4%) with life threatening failure. 5 (10%) patients in no respiratory failure and 45 (90%) in respiratory failure group had growth of organism.

Chi square statistics was 7.7592 and p value is 0.0053. p value was significant (<0.01) for growth of organism between respiratory failure and no respiratory group which indicated respiratory failure favored growth of organism in this study.

In univariate analysis, previous exacerbation, recent hospitalization, frequent antibiotic use, diabetes mellitus and chronic kidney disease were found to be independent predictors for MDR pathogens

Table VI showed multivariable regression analysis using age, sex, smoking status, past exacerbation, past hospitalization, frequent use of antibiotics, presence of respiratory failure, DM and CKD for growth of MDR pathogens. P value was significant (p<0.05) for patients with previous hospitalization, frequent antibiotic use and presence of concomitant CKD.

Table II

Exacerbation of COPD according to Winnipeg criteria and growth of organisms (n=102)

Severity	Growth of organism				Total	P value
	Yes (n=50)		No (n=52)			
	N	%	N	%		
Mild	9	18.0	5	9.6	14(13.7%)	
Moderate	26	52.0	27	51.9	53(52.0%)	0.568[ns]
Severe	15	30.0	20	38.5	35(34.3%)	

ns= not significantP-value reached from chi square test

Table III

Association between growth of organism with exacerbation according to respiratory failure (n=102)

Exacerbation according to respiratory failure (GOLD guideline-2019) of organism	Growth				Total	P value
	Yes (n=50)		No (n=52)			
	n	%	N	%		
Acute respiratory failure- non life threatening	27	54.0	18	34.6	45(44.1%)	0.285[ns]
Respiratory failure (life threatening)	18	36.0	17	32.7	35(34.4%)	0.005[s]
No respiratory failure	5	10.0	17	32.7	22(21.5%)	

s= significant P-value reached from chi square test

Table-IV

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

Risk factors	Number of patients	Percentage
Previous exacerbation in last year	15	14.7
Hospitalization in last year	10	9.80
Frequent antibiotic use	47	46.0
Previous I/V antibiotics in last year	10	9.80
Diabetes mellitus	25	24.5
Chronic kidney disease	15	14.7

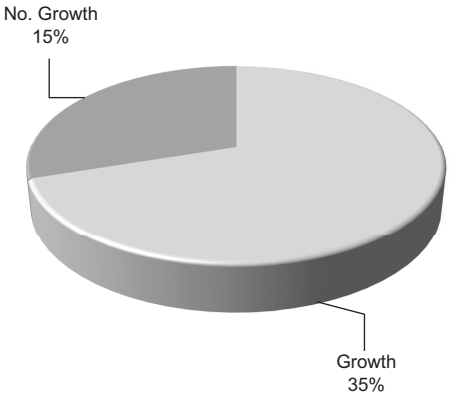

Fig.-2: *Distribution of Multidrug-resistant Pathogens of the Study Cases (n=50)*

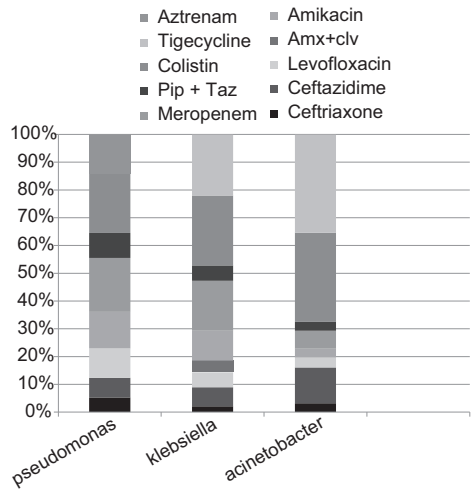

Fig.-3: *Antibiotic sensitivity of predominantly isolated organisms in component bar chart.*

Table-V

Univariate regression analysis for MDR pathogens

	Adjusted OR	95% CI		P value
		Lower	Upper	
Previous exacerbation	4.380	1.327	14.452	0.015[s]
Recently hospitalization	3.733	1.905	7.318	0.001[s]
Frequent antibiotic use	4.079	2.043	8.142	0.001[s]
Diabetes mellitus	3.451	1.762	6.759	0.001[s]
Chronic kidney disease	8.857	2.555	30.707	0.001[s]

s= significantP-value reached from univariate analysis by binary logistic regression analysis

Table-VI

Multivariable regression analysis for MDR pathogens

	Adjusted OR	95% CI		P value
		Lower	Upper	
Age (>60 years)	0.622	0.221	1.749	0.368[ns]
Male	1.224	0.493	3.039	0.663[ns]
Smoker	1.548	0.626	3.828	0.344[ns]
Previous exacerbation	1.434	0.358	5.745	0.610[ns]
Previous hospitalization	2.192	1.228	3.914	0.008[s]
Frequent antibiotic use	3.136	1.375	7.152	0.007[s]
Respiratory failure	0.879	0.263	2.935	0.834[ns]
Diabetes mellitus	1.781	0.774	4.098	0.175[ns]
Chronic kidney disease	7.560	1.824	31.331	0.005[s]

s= significant, ns= not significant
P-value reached from multivariate analysis by binary logistic regression analysis

Discussion:

This cross sectional observational and analytical study was carried out with the aim to identify the possible risk factors for the development of multidrug resistant pathogens. In this study, the age of the patients ranged from 42 years to 84 years with a mean of 62.0±8.5yearswith male predominance (86.3%) which was consistent with results found in another studies[11].

Smoker was found in 89(87.2%). Among them majority 50(49.0%) patients taken e"20 pack per year. Similar results were found in other studies[12].

In this present study it was observed that there was no significant association between growth of organism with exacerbation according to Winnipeg criteria. It was found that the number of patients in severe exacerbation were lower as compared to mild and moderate grade, the growth percentage of a pathogenic organism was found to be highest (71.4%) in severe exacerbation followed by moderate (55.9%) and least (35.2%) in mild exacerbation cases and this difference was found to be statistically significant (p = 0.004)[13].

In this study it was observed that 45(44.1%) patients had acute respiratory failure-non life threatening, 15(14.7%) had respiratory failure (life threatening) and 42(41.2%) were no respiratory failure. Respiratory failure slightly higher than other studies as only hospital admitted patients were considered[14,15]. In this study it was observed that presence of respiratory failure was statistically significant (p<0.05) when compared between growth of organism and no growth of organism group which was similar to other study[15].

This study showed bacterial growth found in 50 cases (49.0%). These results are comparable with previous studies[6,7,14,15] and are not supported by the study[13] where bacteriological isolation was found in 35% of cases.

In this study multidrug-resistance was found in 35 (70%) while it was 20.1% in another study[18].

This study also showed hospitalization in last year 9(66.7%) and chronic kidney disease 13(87.0%) were found in multi-drug resistance, which were statistically significant ($p<0.05$) when compared between multidrug-resistant and non multi drug-resistant pathogens. Another study[19]reported that exacerbation in last year was 87.5%, hospitalization in previous year was 81.2%, long term oral antibiotics use was 12.5%, Diabetes mellitus was 21.9%, Renal disease was 21.9 %. Hospitalization in previous year and renal disease was statistically significant ($p<0.05$) between groups.

This study observed that in univariate analysis, previous exacerbation, recent hospitalization, frequent antibiotic use, diabetes mellitus and chronic kidney disease were found to be independent predictors for MDR pathogens. Another study[12] documented MDR pathogens were more frequently encountered in patients with more chronic conditions and in those required prior hospitalization.

In multivariate analysis, previous hospitalization (Odds ratio (OR)2.92, 95% CI 1.23-3.91), frequent antibiotic use (OR 3.136, 95% CI 1.37-7.15) and chronic kidney disease (OR 7.56, 95%CI 1.82-31.33) were found to be independent predictors for MDR pathogens. Another similar study[20] found three independent MDR risk factors: chronic renal disease (Odds ratio (OR), 7.60, 95% CI 1.92-30.09), hospitalization in the previous year (OR, 3.88 95% CI 1.37-11.02) and prior multidrug-resistant isolation (OR, 5.58, 95% CI 2.02-15.46).

Limitations of the study:

Adequate past treatment history of patients was not available due to lack of records. It was necessary to evaluate the reason for such high antibiotic resistance pattern observed in this study.Also,atypical organisms and viruses could not be detected due to unavailability of serological tests.

Conclusion:

Presence of multidrug resistant bacteria were very high 35 (75%) in admitted cases. Previous hospitalization, repeated use of antibiotics, DM and CKD were found as important predictors for development of multi-drug resistance.

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CASE REPORT

5 Months Old Baby with Tension Pneumatocele - A Case Report

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Abstract :

Pneumatoceles are thin walled air-filled pulmonary cysts which commonly develop as a complication of pneumonia. They are known to resolve spontaneously over several weeks or months. Rarely, they may result in complications of tension, infection, and rupture which may be life threatening and requires prompt attention.Tension pneumatocele enlarges significantly compressing adjacent lung and mediastinum resulting in cardiovascular collapse and may need definitive treatement. A case of 5 months old boy baby with tension peumatocele in right lower lobe underwent lobectomy has been described here.

Keywords : *Pneumatocele, pneumonia,S.aureus, tension, lobectomy.*

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Introduction :

Pulmonary pneumatoceles are thin-walled, air-filled cysts that develop within the lung parenchyma. They can be single emphysematous lesions but are more often multiple, thin-walled, air-filled, cystlike cavities. Most often, they occur as sequelae to acute pneumonia, commonly caused by Staphylococcus aureus. Pneumatoceles are generally observed soon after the development of pneumonia but can be observed on the initial chest radiograph[1]. In all cases of pediatric pneumonia, the incidence of postinfectious pulmonary pneumatocele is about 2–8%. In a study by Kunyoshi et al.[2] ,more than 70% of those cases occurred in children younger than the age 3 years. In adults, the incidence of pneumatoceles is much lower, with only a few reported cases in the literature[3]. Since the 1950s, multiple theories have been proposed as to the exact mechanism of pneumatocele formation; however, the exact mechanism remains controversial.Carrey suggested that the initial event is inflammation and narrowing of the bronchus, leading to the formation of an endobronchial ball valve[4]. Ultimately, this bronchial obstruction leads to distal dilatation of the bronchi and alveoli. In 1972, Boisset concluded that pneumatoceles are caused by bronchial inflammation that ruptures the bronchiolar walls and causes the formation of "air corridors" Air dissects down these corridors to the pleura and forms pneumatoceles, a form of subpleuralemphysema[5]. We describe a case report of 5 months old boy baby with tension peumatocele in right lower lobe underwent lobectomy by right postero-lateral thoracotomy.

Case Report :

Baby boy Rihan 5 months old son of Md. Mainul Islam and Mrs.Fatematuzzahura presented with respiratory distress and occationalcough from his birth. Baby,s mother told, Sometimes this distress was very severe and needed oxyzen inhalation and also nebulization. Mild dry cough was noticed

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during severe respiratory distress and associated with chest indrawing. Mother gave H/O, antenatally she experienced 4 times per vaginal bleeding but no other any illness or problems. Due to severe P/V bleeding H/O LUCS at 31 weeks of gastation on 02/07/20. At birth, baby,s weight was only 2.1 kg and response was delayed. For severe respiratory distress, he was admitted in NICU at that time and treated about 20 days.When he was NICU, done echo and found cardiac problems like ASD,VSD,PDA. After that his condition was stable but problems was not resolved completely at home. He was suffering from respiratory distress, fever, cough and visited to various doctors and again underwent echo which revealed no cardiac problems those found previously and treated as a pneumonia. Lastly about 20 days ago, he admitted Dhaka shishu hospital for 10 days and done CXR, CT scan chest and diagnosed as a pneumatocele. For better and definitive treatement he was reffered to NIDCH (reg.-4968/6).His father and mother had no co-morbidity. He came from middle class family. His feeding, bowel and bladder habit was normal. Already started vaccination according to EPI schedule. He had no other congenital abnormalities. On examination, baby looked healthy and had normal response. His respiratory rate was fast and found chest indrawing during distress. Breathsound was diminished in right lower part of chest.

Chest x-ray showed hyper translucent area in Rt. Lower zone and right lung also hyper inflated, mediastinam shifted to left side.

CT scan revealed multiple thin walled cavitary lesion in postero-basal segment like peumatocele in right lower lobe with hyper inflated Rt. Lung.All other routine investigations found within normal limit.

So we planned for right lower lobectomy Under G/A with one lung ventilation. Patient underwent thorough pre anesthetic check up and surgery was performed. During procedure,there was no collection within thoracic cavity, adhesions were visualized between visceral pleura and chest wall in the right upper lobes and middle lobe of the lung by fibrous band. All adhesion were freed meticulously and then inspected all around . That lung found hugely hyper inflated and a cavitary lesion containing mainly air found in lower lobe.

Right lower lobe was mobilized. After ligation of all vessels,lower lobectomy was done .Then checked air leak and lung expansion properly. After sequiredhaemostsis,a chest drain kept in situ and wound closed in layers. Obtaining materials were send for histological analysis. Pneumatocele was confirmed histopathologically in our case. Post operative recovery was uneventful. On 6th POD chest drain removed and then discharged later.

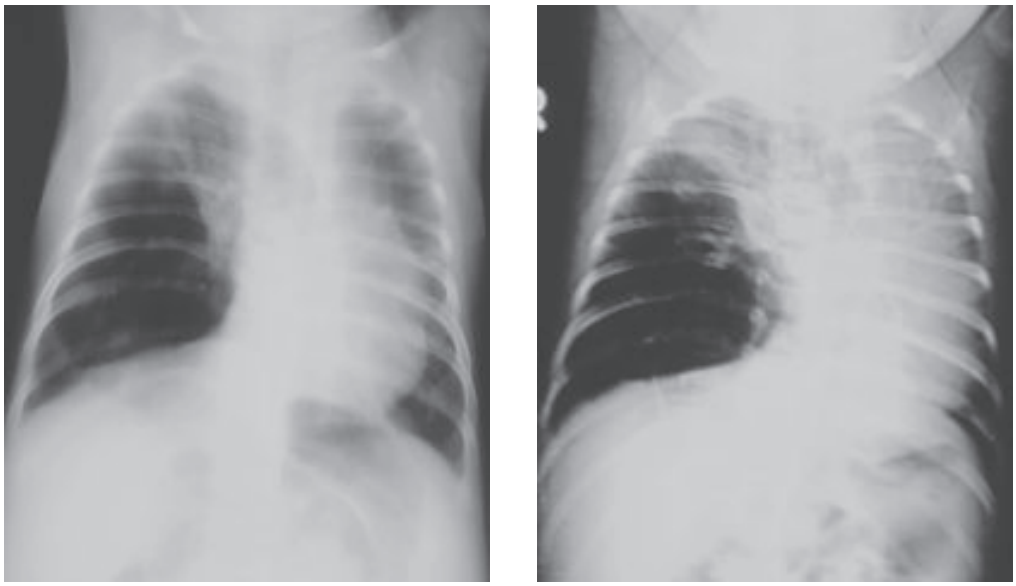

Fig.-1: *X-ray Chest P/A view (pre-operative)*

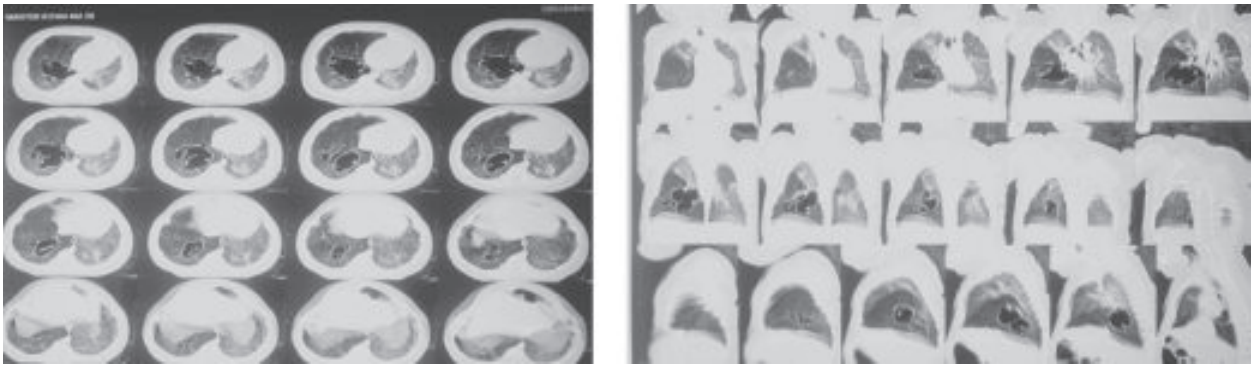

Fig.-2: *CT scan of the chest.*

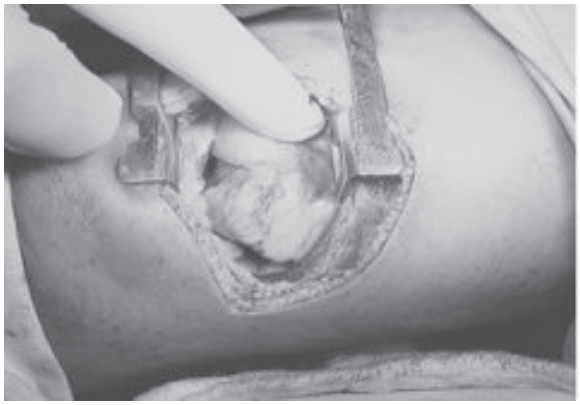

Fig.-3: *Lesion in Lower lobe (Rt.)*

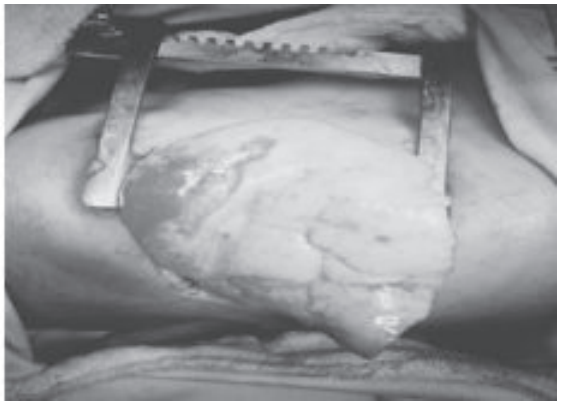

Fig.-4: *Hyperinflated lower lobe*

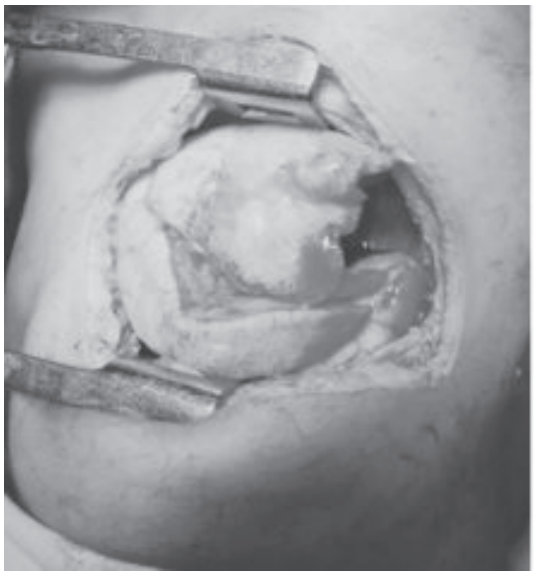

Fig.-5: *Re-expansion of remaining two lobes.*

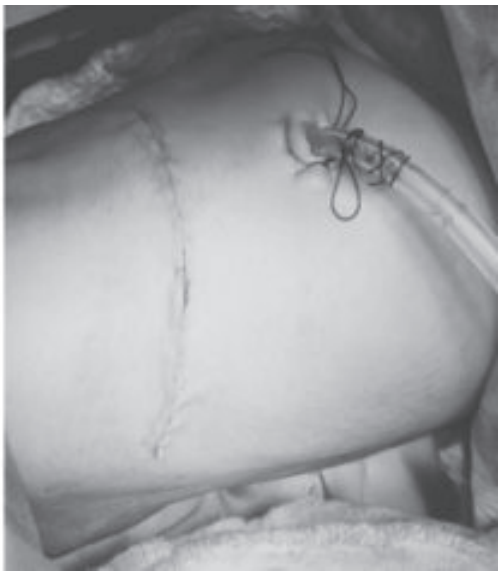

Fig.-6: *Post. Operative wound*

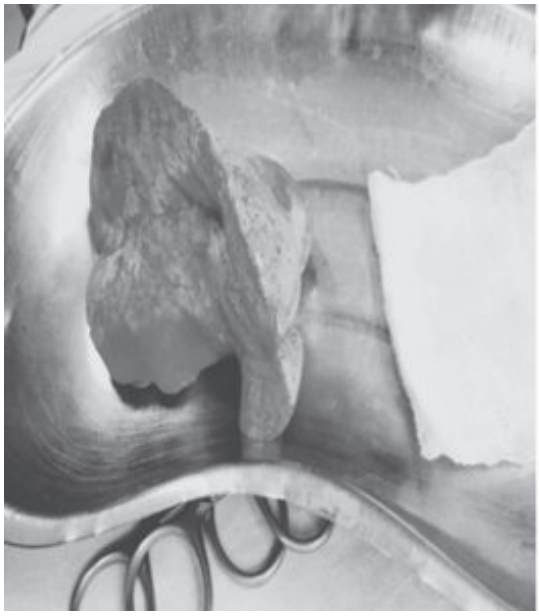

Fig.-7: *Excised rt. Lower lobe*

Fig.-8: *Cavaty within that lobe*

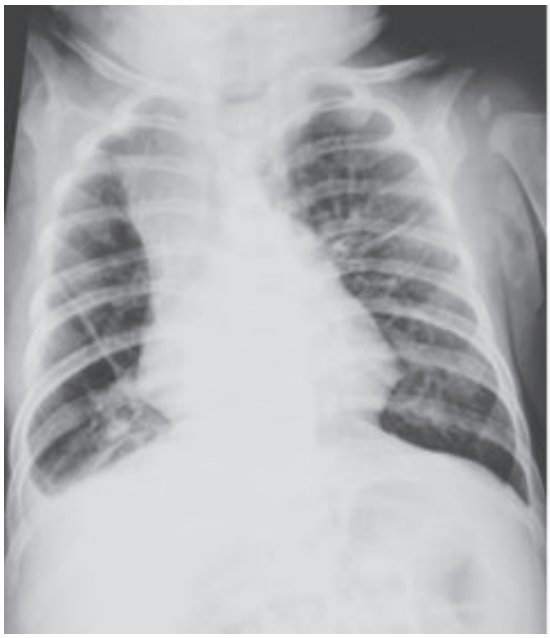

Fig.-9: *Post operative x-ray*

Fig.-10: *During went to home*

Discussion :

Pulmonary pneumatoceles are air collections in the interstitium of the lung. Pneumatoceles can occur at all ages from infants to adults and may be solitary or multiple lesions. However, it is interesting that the predominant location of pneumatoceles is still in the right lung especially the right lower and middle lobes; and the peak time of occurrence remains around the 7th day of life. It is twice as common in males as in females.Mostly, they occur as sequelae to acute bacterial pneumonia, reported as Staphylococcus aureus, Streptococcus pneumoniae, Proteus mirabilis, Escherichia coli or Acinetobacter

calcoaceticus. Noninfectious etiologies include hydrocarbon ingestion, trauma, and secondary to positive pressure ventilation[6]. A study published in Australia detected pulmonary involvement in 82% of patients with staphylococcal sepsis and 21.9% of them presented pneumatocele [7]. In the U.S., in a study on 493 children with pneumonia, the frequency of pneumatocele was 2.4% [8]. The physiopathogenesis of pneumatocele is still unknown. The most widely accepted hypothesis suggests that in necrotizing pneumonias, tissue destruction leads to structural defect in small bronchioli and parenchyma that allow air passing to the interstitial space, resulting in an intraparenchymal ventilated cyst with thin walls. The valve mechanism related to secretion and necrotic material causes increased pressure in the defect region. This raise in pressure leads to expansion of the necrotic area inside the cavity. Air passage may increase pressure inside the pneumatocele, resulting in its expansion and compression of adjacent areas with cardiovascular and respiratory impairment (hypertensive pneumatocele). The pneumatocele may rupture into the pleural space causing pneumothorax and/or bronchopleural fistula[9].The presence of a pneumatocele is an independent risk factor for pneumothorax in patients with Pneumocystis carinii pneumonia, and sudden pneumothorax as a result of ruptured pneumatocele has resulted in reported mortality[10].Most pneumatoceles do not cause severe symptoms and resolve spontaneously within weeks or months by treating the primary condition, and with no clinical or radiological sequelae. Children present with typical features of pneumonia, including cough, fever, and respiratory distress. No clinical findings differentiate pneumonia with or without pneumatocele formation. However, pneumatoceles complicated by rupture, hypertension or infection are very severe and require immediate treatment. There is no algorithm established to treat pneumatoceles so far. Tension pneumatocele enlarges significantly compressing adjacent lung and mediastinum resulting in cardiovascular collapse[11].Diagnosis can be made using chest X-ray; the lesion shows up as a small, round area filled with air. Computed tomography (CT) can give a more detailed understanding of the lesion. Lung ultrasonography (LUS) is a promising technique used to investigate neonatal pulmonary diseases. LUS showed a multilobed cyst with a thin hyperechoic wall and a hypoechoic central area. Repeated LUS demonstrated a progressive reduction of the cyst's size for follow-up.In laboratory studies : If findings are positive, blood culture helps to guide antibiotic therapy in patients with pneumatocele. If sputum is available, this is a good noninvasive method to discover potential pathogens. If effusion is present, culturing pleural fluid from thoracentesis can be a direct method to identify the causative organism. Tests for bacterial antigen detection can be performed on blood, urine, and pleural fluid.Many modalities of treatment have been described in the literature. Image-guided percutaneous drainage, compression, catheter drainage and tube drainage as well as lung resection surgery (lobectomy and pneumonectomy) are effective treatment modalities of pneumatocele[12]. Our baby had symptomatic tension pneumatocel in right lower lobe with shifting of mediastinum to the left which was treated conservatively first and then surgical management done successfully with symptomatic improvement of baby's condition and complete expansion of right lung.

Conclusion :

Complicated pneumatocele is a severe disease especially in younger age groups.In a resource-limited center like ours, there is a role for tube thoracostomy in the management of tension pneumatocele; however, if they do not resolve or if they aremore than 2, lung resection surgery becomes the preferred modality of management.

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INSTRUCTION TO AUTHORS ABOUT UNIFORM MANUSCRIPT WRITING

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Cancer in South Africa (editorial). S Afr Med J 1994; 84-15.

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

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