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Volume with supplement:

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Article published electronically ahead of the print version: Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002 Nov 15; 100(10):3828-31. Epub 2002 Jul 5.

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Original Article

Validity of Serum Ammonia Level for Diagnosis of Severity of Hepatic Encephalopathy in Children

***Nahar L[1], Karim ASMB[2], Rukunuzzaman M[3], Benzamin M[4], Munmun SR[5], Nahar K[6], Mondal M[7], Sarker MN[8], Hossain ML[9], Sarker M[10], Rahman MM[11]**

Abstract

Hepatic encephalopathy is a broad spectrum neuropsychiatric abnormalities of liver dysfunction. Ammonia level may correlate with the severity of liver failure. The brain is very sensitive to the toxic effects of ammonia. As a result patient may manifests with irritability, slurring of speech, reversal of sleep-awake cycle, flapping tremor, confusion, stupor or even deep coma. This study was aimed to validate the ammonia level in children with liver failure for the assessment of its severity considering hepatic encephalopathy. This cross-sectional comparative study was conducted among 64 children aged 1-15 years of both sexes (study subjects) diagnosed as acute or acute on chronic liver failure in the Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh during the period of November 2017 to September 2019. The subject were divided into two groups for the comparison of ammonia level to assess the severity in contrast to hepatic encephalopathy. In the first group 32 were liver failure with encephalopathy and in the second group 32 were liver failure without encephalopathy. Hepatic encephalopathy was diagnosed on the basis of West Haven Criteria. The analysis was done by the Receiver Operating Characteristic Curve with SPSS-20. Among the 64 patients female were 45% whereas male patients were 55%, male female ratio was 1.2: 1. Regarding etiology, Wilson disease was the most common cause and it was nearly two-third (65.6%) of children, cryptogenic cirrhosis was 10%, Hepatitis A was 9.4%, Autoimmune Hepatitis (AIH) was 3.10%, Hepatitis E, Hepatitis B, Hepatitis C, biliary atresia and lipid storage were 1.60% respectively. This study showed that, ammonia of ≥71 µmol/L is an indicator for presence of hepatic encephalopathy in children. The analysis by the Receiver Operating Characteristic Curve showed area under the curve (AUC) is 0.86 with upper bound 0.96 and lower bound is 0.77. It was observed that about half (48.4%) of the children had positive blood ammonia level (≥71.0 umol/L) and among the children of positive blood ammonia level most of them (80.65%) had hepatic encephalopathy and 19.35% had no encephalopathy. More than half (51.6%) children had negative (<71.0 umol/L) blood ammonia level, among them 21.21% children had encephalopathy and 78.79% patients had no encephalopathy. Sensitivity of blood ammonia was found 78.1%, specificity 81.2%, positive predictive value 80.6%, negative predictive value 78.8% and accuracy 79.7%. In conclusion, high level of ammonia is found with higher grade of encephalopathy and hyperammonia is also found in liver failure without encephalopathy.

Keyword: *Serum ammonia level, hepatic encephalopathy, west haven criteria.*

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INTRODUCTION

Hepatic encephalopathy is characterized by personality changes, intellectual impairment and a depressed level of consciousness[1]. The pathogenesis of hepatic encephalopathy

is not completely understood but ammonia plays a key role among the neurotoxic substances[2]. About 85% of ammonia is detoxified through the liver and excreted in the urine as urea. Whereas 15% is metabolized in the muscle and brain through the synthesis of glutamine from glutamate[3]. Normally the gut produces ammonia as a byproduct of bacterial urease activity, protein digestion, and amino acid deamination. This ammonia in the systemic circulation is regulated by urea cycle in a healthy liver. So, when there is any pathology in liver that causes decreased functioning of urea cycle. It increase the concentration of ammonia in the systemic circulation. This excess ammonia convirt to glutamine in astrocytes, increase intracellular osmolarity that results fluid retention and develop brain edema[4]. However hyperammonia in circulation can also be a result of high protein diet, parental nutrition, and congenital defects in the urea cycle or drugs like sodium valproate[5]. The American and European Associations for the Study of the Liver 2014 practice guidelines recommend that HE will be classified according to four factors: (i) the underlying etiology– Type A, B or C; (ii) severity – using the grading system such as West Haven Criteria; (iii) time course – episodic, recurrent (>1 episode in 6 months) or persistent[1]. (symptoms always present and can have episodes of acute exacerbations); and (iv) non precipitated or precipitated by factors such as infections, medications or electrolyte disorder[6]. Type- A encephalopathy is associated with acute liver failure. Type B HE with portal-systemic bypass and no intrinsic hepatocellular disease. Type C HE with cirrhosis and portal hypertension or portosystemic shunts[7]. Common laboratory testing for hepatic encephalopathy includes assessment of liver and renal function, electrolytes, glucose, complete blood count, cultures and drug screening and ammonia levels may correlate with the severity of hepatic encephalopathy[8]. Blood should be place immediately on ice and centrifuged within 15 min of collection. If left at room temperature the concentration of ammonia can increase about 20% within 1 h and up to 100% within 2 hour[9]. The Pediatric Acute Liver Failure Study Group (PALF) define as follows: (a) evidence of liver dysfunction within 8 weeks of symptoms onset, (b) uncorrectable (6–8 h after administration of one dose of parenteral vitamin K) coagulopathy with international normalized ratio (INR) >1.5 in patients with hepatic encephalopathy (HE) or INR> 2.0 in patients without HE and (c) no evidence of chronic liver disease[10]. The definition of Acute-On-Chronic Liver Failure (ACLF) indicates acute deterioration in patients with chronic liver disease or cirrhosis as a result of an underlying precipitating event[11].

MATERIALS AND METHODS

Study design was cross sectional comparative. Study place was Pediatric Gastroenterology and Nutrition Department of BSMMU, Dhaka Bangladesh. The duration of the study was 22 months from November 2017 to September 2019. Data were collected from children of liver failure with or without encephalopathy attending in the Department of Pediatric Gastroenterology and Nutrition, BSMMU. Sampling technique was Purposive sampling.

Inclusion criteria for cases:

Pediatric patients aged 1-15 years of both sexes diagnosed as acute liver failure or acute on chronic liver failure were selected as the study population.

1. Patients of liver failure with encephalopathy were taken in one group.
2. Patients of liver failure without encephalopathy were taken in another group.

Exclusion criteria:

The following patients were excluded from the study.

Parents who were unwilling to give consent.

2. Encephalopathy other than the liver disease.

Written informed assent from the parents was taken before enrollment of children. Details history was taken and a standard data form was filled up for every children. Past history of illness and any systemic disease was inquired cautiously. A complete physical examination including general physical examination and systemic examination was done. Hepatic encephalopathy was diagnosed on the basis of West Haven Criteria and liver failure on the basis of PALF. After patient selection 3 ml of fasting venous blood was collected, during blood collection fist clenching and tourniquet use was avoided. After collection, blood sent immediately (within 30 minutes) in ice pot to the Department of Biochemistry. Base line investigations along with other investigations to identify the causes of liver failure such as HBV, HEV, HAV, Slit-lamp eye examination, 24 hours urinary copper, Serum ceruloplasmin, CBC with PBF, coomb`s test for Wilson disease and autoimmune screening like ANA, SMA, LKM1 were done. Liver function as prothombine time (PT), Serum albumin, Serum bilirubin were also investigated. Investigations results were collected and recorded in the structured data sheet. Data cleaning validation and analysis was performed using the SPSS (Statistical Package for Social Science) Version 20 (SPSS

Inc., Chicago, IL USA) and graph and chart by MS excel, result was presented in tables in mean, standard deviation (SD) and percentages.

RESULT

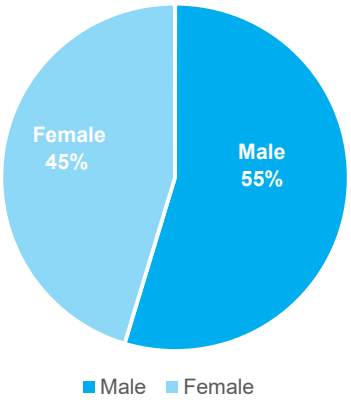

Figure-1: Sex distribution of children with as acute liver failure (n=62)

Figure 1 is shows the sex distribution of the studied patients. Among 64 patients female were 45% whereas male patients were 55%. Male female ratio was 1.2: 1

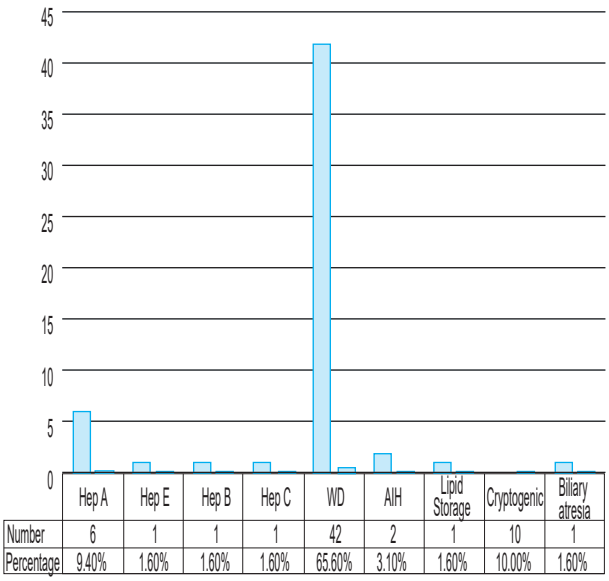

Figure-2: Etiology of acute liver failure in children (n=62)

Figure 2 illustrates the etiology. Regarding etiology Wilson disease was about 65.6%, cryptogenic 10%, Hep A were 9.4%, AIH were 3.10%, Hep E, Hep B, Hep C, biliary atresia and lipid storage were 1.60% respectively among the studied patients.

Table I contains the cut of value of blood ammonia for encephalopathy ≥71.0 (µmol/L); here sensitivity of blood ammonia for encephalopathy found 78.1%, specificity 81.2%, area under the curve (AUC) 0.86 with upper bound 0.96 and lower bound 0.77.

Table- I: Cut of value of blood ammonia level in children with hepatic encephalopathy (n=62)

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
Blood ammonia (µmol/L)	≥71.0	78.1%	81.2%	.862	.770	.955

Table II shows mean ammonia value was 106.3750 µmol/L in children of liver failure with hepatic encephalopathy (HE) and mean ammonia value 53.8438 µmol/L in children of liver failure without encephalopathy.

Table- II Mean value of ammonia in liver failure with and without hepatic encephalopathy (n=62)

HE	N	S. Ammonia Mean	Std. Deviation	Std. Error Mean
Present	32	106.3750	42.71870	7.55167
Absent	32	53.8438	21.60064	3.81849

Figure 3 showing the Receiver Operating Characteristic Curve for ammonia. This study showed that, ammonia of ≥71 µmol/L is an indicator for presence of hepatic encephalopathy in children.

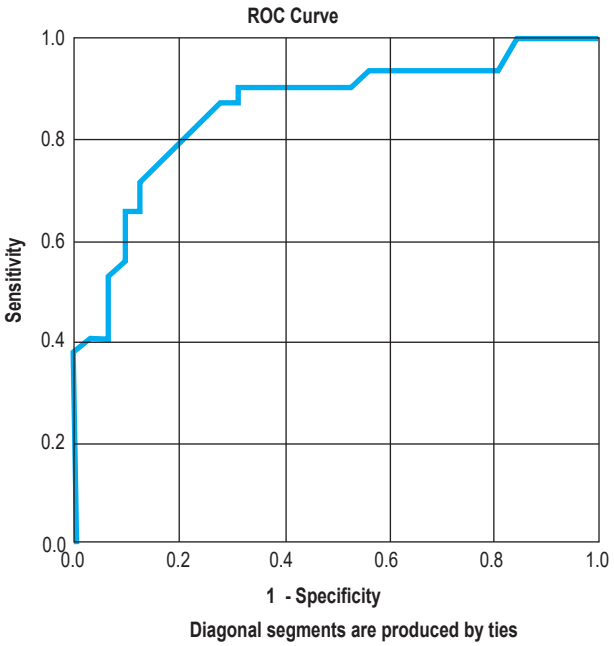

Figure-3: Relationship between ammonia and hepatic encephalopathy (ROC curve)

Table III shows thirty two (32) patients had liver failure with hepatic encephalopathy (HE) and 32 had liver failure without encephalopathy (HE). It was observed that 31 (48.4%) patients out of 64 had positive blood ammonia level (≥71.0 umol/L); among them 25 patients had hepatic encephalopathy and 7 had no encephalopathy. Remaining thirty three (51.6%) patients out of 64 had negative (<71.0 umol/L) blood ammonia level, among them 7 patients had encephalopathy and 26 patients had no encephalopathy. It is found that positive predictive value 80.6%, negative predictive value 78.8% and accuracy 79.7%.

Table- III: Performance of blood ammonia as a diagnostic test for presence of hepatic encephalopathy (n=64)

Blood ammonia	Hepatic encephalopathy		Total
	Present n=32 (%)	Absent n=32 (%)	
Positive ≥71.0	25 (78.1)	06 (18.8)	31 (48.4)
Negative <71.0	07 (21.9)	26 (81.2)	33 (51.6)
Total	32 (100.0)	32 (100.0)	64(100.0)

Sensitivity: 78.1 %
Specificity: 81.2 %
Positive predictive value: 80.6 %
Negative predictive value: 78.8 %
Accuracy: 79.7 %

DISCUSSION

Diagnosis of minimal HE is a challenge for the clinician where needs a sensitive, reliable and easy-to-use diagnostic tool. However neuropsychological evaluation and electrophysiological tests do not fulfill these requirements. So for screening of minimal HE in daily practice, a simple test would be welcome and greatly facilitate the diagnosis and as well as the management of HE[12]. The onset of hepatic encephalopathy in a person with cirrhosis is with poor prognosis and reduced survival if liver transplantation is not done. Overt hepatic encephalopathy also occur approximately 30 to 40% of individuals with cirrhosis. Overt HE need frequent hospitalizations, and pose a burden on the healthcare system. As ammonia has been regarded the key precipitating factor, so plasma ammonia levels are used widely in patients with cirrhosis and altered mental status to diagnose HE. However correlation between ammonia levels and the grading of HE continues to be controversial[8,13]. We found male 55% and female 45%. Different two studies found 63 (63%) males, 37 (37%) females and 85% patients (n = 51) males and 15% (n = 9) females[5,14]. In this study cut of value of ammonia for encephalopathy found ≥71.0 (µmol/L). Gundling et al, (2013) found cut of value of the blood ammonia level ≥ 55 µmol/L to diagnose HE, sensitivity and specificity was 47.2% and 78.3%, respectively. The positive predictive and negative predictive values of ammonia were 77.3% and 48.6%, with an overall diagnostic accuracy of 59.3%. In different two studies, an arterial ammonia level of 124 µ mol/L or higher predicted mortality with 78.6% sensitivity, 76.3% specificity, and 77.5% diagnostic accuracy; and arterial ammonia level higher than 100 µ mol/L (170 µg/dL) predicted the onset of hepatic encephalopathy and intracerebral hypertension with 59% sensitivity, 78% specificity, and 70% diagnostic accuracy[15]. In a retrospective study, grade of HE was found to be correlated with increased ammonia value in 39 patients with acute or acute on chronic liver failure (ACLF)[16]. In this study, some patients had high ammonia level but no encephalopathy, the explanation is that in CLD patients there is colonic dysbiota, that increase ammonia production and decreased ammonia detoxification due to reduced activity of urea cycle enzymes and portosystemic shunting in the liver. Two recent studies highlighted that ammonia levels on admission are important predictive factors for hospital mortality in decompensated cirrhosis[17]. Therefore, patients with advance stage of hepatic encephalopathy and a high

Child-Turcotte-Pugh score at the time of presentation should be considered at a higher risk of having hyperammonemia[18]. Another study shown risk of cerebral herniation increase when ammonia levels reach >200 μ mol/L[19].

CONCLUSIONS

High ammonia levels were a common finding among patients with hepatic encephalopathy. But patient without hepatic encephalopathy may also have raised ammonia level due to underlying CLD, liver dysfunction and high child pugh score.

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Original Article

Gamma-glutamyltransferase (GGT) is a Predictor of NAFLD Activity Score for Diagnosing Non-Alcoholic Steatohepatitis (NASH)

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Abstract

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of conditions ranging from simple steatosis to steatohepatitis, advanced fibrosis and end stage liver disease. Despite the high prevalence and severity of hepatic illness, NAFLD remains underdiagnosed, because of few symptoms, lack of accurate laboratory markers. The study was aimed at to evaluate a bio-chemical score for diagnosing non-alcoholic steatohepatitis. A hospital based cross-sectional observational study was carried out for a period of two years from July 2013 to June 2015 in the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The study was conducted among 50 patients of NAFLD attending at department of Hepatology and underwent for biochemical investigations and liver biopsy with NAFLD Activity Score (NAS). All data were presented as mean ± SD and analyzed by SPSS (version 16). Qualitative data were analyzed by Chi-square test and quantitative data were analyzed by student's t-test. Performance of the test were assessed by sensitivity and specificity test. Statistically significant result were considered when p value < 0.05. Total patients were divided into two groups 25 were NASH and 25 were non- NASH. Mean GGT was found 73.6±48.6 U/L in NASH group and 49.9±25.4 U/L in non-NASH group. There was significant difference in the NAFLD activity score for diagnosing NASH between elevated and normal GGT (P value 0.035). Higher GGT values correlated with higher specificity. The Gamma-lutamyltransferase (GGT) has been proposed as a noninvasive and available marker for assessment of NASH.

Keywords: *Nonalcoholic fatty liver disease, Gamma-Glutamyltransferase, NAFLD activity score, Non- alcoholic Steatohepatitis.*

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a metabolic disorder characterized by excessive triglyceride accumulation in hepatocytes.[1] NAFLD has a multifactorial etiology and a combination of environmental, genetic and metabolic factors play a role in the development of advanced disease. NAFLD consists of a wide spectrum of conditions, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) which can progress to cirrhosis and hepatocellular carcinoma (HCC).[2] The prevalence of NAFLD increases with increasing age. Obesity, diabetes mellitus (DM), insulin resistance are predisposing factors for NAFLD. Although NAFLD is more common in subject with obesity and diabetes mellitus (DM), it also occurs in lean and non-diabetic subject.[3-5] The fatty liver may be diagnosed if the liver echogenicity exceeds that of renal cortex and spleen and there is attenuation of the ultrasound wave, loss of definition of the diaphragm, and poor delineation of the intrahepatic architecture.[6] Although liver biopsy remains the 'gold standard', there are practical limitations, including costs and risk.

AST is a hepatic transaminase that plays a role in diagnosis of steatohepatitis. Up to 3.6% of people in the United States have asymptomatic increase in AST[7]. In Asian studies, AST is considered as an independent marker for severity of hepatic fibrosis if it is at least twice as much as the maximum normal value.[8]

The AST/ALT ratio is approximately 0.8 in normal subjects. The AST is greater than the ALT in alcoholic

hepatitis and a ratio greater than 2:1 is highly suggestive of this disorder. A ratio >1.0 may also suggest the presence of cirrhosis in patients with chronic viral hepatitis.[9]

ALT is a marker of hepatic steatosis or hepatitis[10] and NASH has been associated with slight elevation of liver enzymes[11].Patients typically present with asymptomatic serum aminotransferase elevations of 2-3 times the normal[12].This was also explored by Pulzi et al 2011[13], where majority had mild elevation but less than 5 times upper normal limit and exists in all degree of NAFLD. But Alam et al 2013 showed serum alanine aminotransferase levels were not able to predict NASH.[14]

Excess deposition of fat in the liver is associated with an elevated serum Gamma-Glutamyltransferase and insulin resistance.[15] An increased Gamma-Glutamyl transferase level is a risk factor for advanced fibrosis in non-alcoholic fatty liver disease.[16]

The Gamma-Glutamyltransferase (GGT) has been proposed as a noninvasive and available marker for assessment of NASH.

METHODS AND MATERIALS

This was a observational, cross sectional study. Patients of NAFLD attending at outpatient and inpatient department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from July 2013 to June 2015 were included in this study .Twenty five NASH and twenty five Non-NASH patient confirmed by liver biopsy were included in this study. Nonalcoholic fatty liver disease activity score was constructed according to Kleiner et al.2005[17] with steatosis (0-3), lobular inflammation (0-3), hepatocellular ballooning (0-2) and a separate fibrosis staging (0-4). The proposed non-alcoholic fatty liver disease activity score was the sum of steatosis, lobular inflammation, and hepatocellular ballooning. Non-alcoholic fatty liver disease activity score is a good scoring system. Non-alcoholic fatty liver disease activity score of greater than or equal to 5 correlated with diagnosing of non-alcoholic steatohepatitis and the biopsy with scoring of 1 to 4 was diagnosed as simple steatosis fatty liver. Patient's inclusion criteria were the ultrasonographical evidence of fatty liver and patients of 18 to 60 years of age. Exclusion criteria were the significant alcohol intake (>30 g/day in case of male; >20 g/day in case of female)[18],viral hepatitis (hepatitis B virus, hepatitis C virus), Wilson's disease, autoimmune liver diseases, hereditary hemochromatosis, primary biliary cirrhosis, cirrhosis of liver, pregnancy, comorbid conditions (chronic obstructive airway disease, chronic kidney disease, cardiac failure), hypothyroidism, consumption of drugs causing fatty change in the liver (steroid, oral contraceptive pill, tamoxifen, amiodarone, diltiazem, protease inhibitor). In the American Association for the Study of Liver Diseases Practice Guideline 2018, significant alcohol consumption can be defined as >21 standard drinks per week in men and >14 standard drinks per week in women over 2 years period preceding baseline liver histology. The liver biopsy was done by Trucut liver biopsy needle 14 F,15 cm. The tissue was processed at the Department of Pathology, by standard protocol in automatic tissue processor (BAVIMED 2050, BAVIMED Laborgeneratebau GmBH, Birkeau, Germany). The processed tissue was then properly embedded on the melted paraffin for making blocks and sections. The sections were stained with hematoxylin and eosin for microscopic examination.

After receiving the liver biopsy report, they were grouped as non-alcoholic steatohepatitis and simple steatosis. Consecutive 25 non-alcoholic steatohepatitis patients and 25 simple steatosis patients confirmed by liver biopsy were included in this study.

Statistical Analysis

All data were presented as mean ± SD and were analyzed by SPSS (version 16). The qualitative data were analyzed by Chi-squared test and the quantitative data were analyzed by student's t-test. Performance of the test were assessed by sensitivity and specificity test. Statistically significant result were considered when p value <0.05.

RESULTS

Table-I shows that contains Fifty (50) patients were included in this study. Twenty five were NASH and twenty five were non-NASH. Overall, Thirty four (68%) had normal G-GT. G-GT in NASH group were 73.6±48.6 IU/L and in Non-NASH group were 49.9±25.4 IU/L. In Non-NASH group 10% of elevated G-GT had no NASH. There was significant difference in the NAFLD activity score for diagnosing NASH between elevated and normal G-GT (P value 0.035). Higher G-GT values correlated with higher specificity.

Table -I: Clinical and laboratory characteristics of study patients in two group (n=50)

Variables	Group-I NASH (n=25)		Group-II Simple Steatosis (Non-NASH) (n=25)		*P* Value
	Mean	±SD	Mean	±SD	
Age (years)	41.8	±10.7	39.7	±7.5	0.425^{ns}
Weight (kg)	65.6	±8.6	63.3	±9.7	0.444^{ns}
Height (cm)	159.2	±9.1	157.7	±8.3	0.545^{ns}
BMI (kg/m^2)	26.0	±3.9	25.5	±4.0	0.656^{ns}
Waist circumference (cm)	97.9	±9.0	93.9	±9.8	0.139^{ns}
Systolic blood pressure (mm of Hg)	129.8	±16.9	128.6	±12.2	0.774^{ns}
Diastolic blood pressure (mm of Hg)	80.2	±7.8	81.0	±6.1	0.688^{ns}
Platelet count (x10^9/L)	303.1	±68.7	327.8	±66.8	0.203^{ns}
FBS (mmol/L)	6.6	±2.8	5.9	±2.2	0.330^{ns}
2HABF (mmol/L)	10.0	±4.2	9.1	±4.7	0.478^{ns}
Total cholesterol (mg/dl)	210.0	±48.7	199.9	±38.4	0.419^{ns}
LDL (mg/dl)	126.0	±40.5	119.6	±36.7	0.561^{ns}
HDL (mg/dl)	40.7	±9.1	36.6	±8.9	0.113^{ns}
TG (mg/dl)	209.0	±95.9	222.8	±116.2	0.649^{ns}
AST (U/L)	55.2	±30.1	33.6	±20.0	0.004^{s}
ALT (U/L)	97.0	±51.5	55.5	±28.6	0.001^{s}
AST/ALT	0.6	±0.2	0.7	±0.3	0.171^{ns}
HOMA-IR	2.4	±1.9	2.3	±1.6	0.841^{ns}
GGT (U/L)	73.6	±48.6	49.9	±25.4	0.035^{s}
Serum ferritin(µgm/L)	139.4	±124.5	103.5	±69.9	0.214^{ns}

Group I =Nonalcoholic steatohepatitis (NASH) (NAS ≥5-8)
Group II =Non-NASH fatty liver (Simple Steatosis) (NAS 0-4)

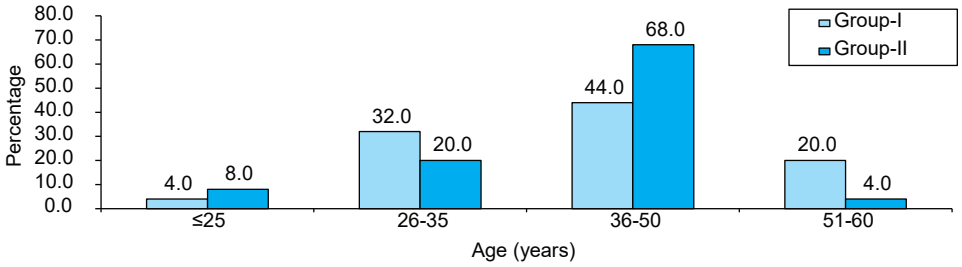

Fig-1: Bar diagram shows age distribution of the study patients.

Figure 1 shows the age distribution of the study patients, here 11(44.0%) patients were in age group 36-50 years in NASH group (Group -I) and 17(68.0%) patient were in age group 36-50 years in Non-NASH group (Group-II). The mean age was found 41.8 ± 10.7 years in NASH group (Group- I) and 39.7 ± 7.5 years in Non-NASH group (Group- II).

Gamma-Glutamyltransferase (G-GT) of the study patients

Table-II shows Mean GGT was found 73.6±48.6 U/L in NASH or group- I and 49.9±25.4 U/L inNon-NASH or group- II. The mean G-GT was statistically significant (p<0.05) between two group.

Table-II : Distribution of the study patients according to GGT (n=50)

GGT (U/L)	Group-I (n=25)		Group-II (n=25)		*P* value
	n	%	n	%	
Male ≤85 U/L, female ≤55 U/L	14	56.0	20	80.0	
Male >85 U/L, female >55 U/L	11	44.0	5	20.0	
Mean±SD	73.6	±48.6	49.9	±25.4	0.035[s]
Min-max	24.0	-209.0	12.0	-121.0	s= significant

DISCUSSION

Non Alcoholic Fatty Liver Disease (NAFLD) is a clinico-pathological entity where fat (predominantly Triglyceride) accumulates in liver without significant alcohol ingestion (male>30g/day, Female >20 g/day) or ingestion of certain drugs observed.[19] It encompasses a spectrum of conditions ranging from simple steatosis to nonalcoholic steato-hepatits (NASH), fibrosis and end stage liver disease.[20]

This study, a hospital based study where most of the patients were from low socioeconomic status. In this study female predominated 30 (60%) out of study population of 50 cases. Among them 16 (32%) were in NASH and 14(28%) non NASH fatty liver (NNFL). Similar female preponderance (57%) was observed in the study conducted in department of Hepatology, BSMMU.[14]. This female preponderance in this study may be due to social conservative attitude which bounded most of females to stay at home for household work leading to sedentary life style and also due to intake of carbohydrate predominant food material.

Mean age of patients were 40.8 (±9.2) years. Majority patients 11(44%) belong to 36 to 50 years range in NASH group. 17(68%) patients of NNFL group belong to 36-50 years range. Similar mean age (40.8 ±10.2 years) was observed in the study conducted in department of Hepatology, BSMMU.[14] Mean GGT in NASH group was 73.6± 48.6 U/L, whereas 49.9 ± 25.4 U/L in NNFL group. Mean Gama-GT differed significantly in NASH patients (p value- 0.035). Gama- GT as a marker of disease severity and diagnosis of NASH was explored.[13]. This value correlates with previous data[14, 21], where GGT had predictive value for NASH.

ETHICAL ISSUE

Ethical clearance for the study was taken from the Institutional Review Board of the Bangabandhu Sheikh Mujib Medical University prior to the commencement of this study. Approval paper was given by 75th Institutional Review Board, Bangabandhu Sheikh Mujib Medical University, meeting held on 30th November 2014 (No. BSMMU/2014/13573).

CONFLICT OF INTEREST

No conflict of interest.

CONCLUSIONS

Gamma-glutamyltransferase (GGT) level has the predictive value for diagnosing NASH in NAFLD patients. We propose the use of GGT in NAFLD patients for the detection of NASH from Non- NASH.

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Original Article

Modified Open Technique for First Port Insertion in Laparoscopic Surgery

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Abstract

Laparoscopy has become the method of excellence for abdominal surgeries in modern age. The significance of a secure and dependable approach for the initial trocar insertion cannot be overstated in this surgical procedure. This preferred method involves employing a modified open technique to access the peritoneal cavity. This study was conducted to evaluate the laparoscopic surgery of modified open technique. This cross sectional follow-up study was conducted in the Department of General Surgery Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from January 2019 to December 2022. The umbilicus was everted to make it tubular, an infra-umbilical incision was given to cut the linea alba for making an opening and advanced bluntly to introduce the first port. A total of 197 patients were studied after completion of surgery. Cholecystectomy was the most common surgical indication. The mean entry time was 3.1±0.6 minutes. Regarding the postoperative complication port site infection was 2.03% and port site hernia was 1%. There was no incidence of pre-peritoneal placement of port, port site seroma, haematoma. No mortality was found during the hospital stay of patients. Modified open technique is a quick and safe procedure for insertion of the first port in laparoscopic surgery.

Keywords: *Open technique, laparoscopy, complications.*

INTRODUCTION

In contemporary surgery, laparoscopy is the established method for abdominal procedures. A crucial initial step in laparoscopic surgery is the secure placement of the first port. This approach offers various advantages, including a faster recovery, shorter hospital stays, and a lower risk of postoperative adhesions compared to open procedures it's noteworthy that the initial port entry poses a higher risk of morbidity compared to laparotomy.[1] Studies suggest that during introduction of initial port approximately 50% of complications occur in laparoscopic surgery.[2]

In minimal invasive surgery the main target of the surgeon is to stay away from unintended damage throughout the time of introduction of the first port, research indicates that laparoscopy-induced intestinal injuries occur at a rate of 3.6%. Over the past two decades, substantial advancements in laparoscopic surgery, such as enhanced optics, electronics, and auxiliary instruments, have contributed significantly to the prevention of complications.[3]

Enhanced surgical skills, specialized training centers, workshops, and online instructional videos play a crucial role in acquiring valuable insights to prevent complications.[4]

Various methods exist for inserting the first port into the abdomen, all of which adhere to two main principles: closed and open techniques. In the closed method, pneumo-peritoneum is established by insufflation of CO2 gas after the veress needle is inserted into the peritoneal space, after that first port is introduced. This closed access technique may have higher chance of inadvertent trauma to major abdominal vessels, bowel and bladder. To address these concerns, the open access technique was introduced by Hasson. In this method, fascia is laid open sufficiently to enter the peritoneal cavity under straight sight where especially devised canula, edgeless obturator and valve with bailer is applied.[4] Regarding the superiority of the open technique over the closed entry method, conflicting evidence exists in various studies, with no consensus opinion.[5] To address this uncertainty, we conducted a study to assess the effectiveness of the altered open access procedure for the introduction of primary port in minimal access surgery.

MATERIALS AND METHODS

This study was conducted in the Department of General Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh during the period of January 2020 to December 2022. Patients who underwent laparoscopic

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surgery by altered open access procedure during the period were included in this study.

Data were considering age, sex, indications for laparoscopic surgery and entry time of the first port, postoperative and intraoperative complications.

OPERATIVE TECHNIQUE

All patients received general anesthesia. To highlight the umbilical tube, upward traction was applied to the umbilicus using a Mayo towel clip on its lateral margins. A small transverse skin incision, approximately the size of the cannula, was made just below the umbilicus. For precise incision diameter estimation, the trocar sleeve was applied to mark the incision site. The trocar sleeve diameter was used to determine the incision size, minimizing the risk of gas leakage. The umbilical tube was prominently visualized in the wound in a longitudinal plane. A scalpel (no. 11) was used to make a nick in the linea alba and extended to the everted umbilical tube, the incision enlarged by medium-sized artery forceps to pierce the peritoneum. The port was then introduced through the raised hole generated by umbilical tube, the trocar being served as a guide. The sleeve was pushed in, and the trocar was withdrawn. Insufflation began after connecting the insufflation tube to the connector valve of the entered cannula. A laparoscope (0/30) was introduced to examine the entire abdominal cavity. The duration of time between the incision given and introduction of the telescope into the peritoneal cavity was regarded as the "time of entry". Closure of the defect was performed using polyglactin 910 OS-6 no. O. A long-acting local anesthetic (0.25% Bupivacaine) was infiltrated around the port site. After the procedure, the abdominal cavity was deflated of gas. The towel clip was reapplied to the umbilicus to recreate the umbilical tube, displacing the fascial access.

RESULTS

A total of 197 patients were included in the study. Individuals with a history of previous abdominal surgeries were excluded from the study.

Table I shows the distribution of patients characteristic and entry time; average age of the study group was 36.52±12.97 and female male ratio was was1.1:1. Surgical indications included appendicitis was 25 (12.7%), cholelithiasis 153 (77.7%), and diagnostic laparoscopy 19 (9.6%). The mean entry time for the procedure was 3.1±0.06 minutes.

Table-I: Patient characteristics and entry time.

Patient characteristics	Frequency	Percentage (%)
Age	36.52±12.97	
Sex		
Male	94	47.7
Female	103	52.3
Indications		
Appendicitis	25	12.7
Cholelithiasis	153	77.7
Diagnostic laparoscopy	19	9.6
Entry time	3.1±0.6	

Table II states the distribution of laparoscopic entry-related complications, here patients with port site infection was 4 (2.03%) and 2 (1.0%) was postoperative port-site hernia. There was no occurrence of pre-peritoneal port placement, port site haematoma or intra-abdominal trauma. No postoperative mortalities were recorded in the study.

Table-II: Laparoscopic entry-related complications.

Complications	Frequency	Percentage (%)
Extraperitoneal port placement	0	00
Intraperitoneal injury	0	00
Failure to enter the abdomen	0	00
Port site seroma	0	0
Port site infection	4	2.03%
Port site hematoma	0	00
Port site hernia	2	1.0
Mortality	0	00

DISCUSSION

More than three decades in the past, various guidelines and strategies have been applied to alleviate the danger related to the introduction of initial port in minimal invasive surgery. There is no procedure or device that can be accepted invariably. Hasson's method and the application of Veress needle are regarded as open and closed techniques respectively that are popularly taken on process in current practice Small laparotomy is employed for entry to the peritoneal space and gas leakage prevented from the pneumoperitoneum applying specially devised canula

along with cone in Hasson's open method .[6] This method is particularly favored for creating a pneumoperitoneum in cases where adhesions are anticipated. In contrast, the Veress needle is inserted through a small skin incision to create a pneumoperitoneum. However, the use of the Veress needle is considered a blind technique, carrying a higher risk of injury. Even the optical trocars, a relatively newer device, are not exempt from the hazards of initial port placement.[7,8]

In practice, every process has difficulties of different grading. Meta- analysis shows that open technique prone to have fewer chances of extensive problem. The challenge of excessive price and limited availability of laparoscopic equipment apart from security measures are evident in least developed states. Therefore, there is a need for a dependable and easily executable technique, using readily available tools, to enhance the effective utilization of laparoscopic surgery.[11]

This study demonstrated the feasibility of a secure open method for the insertion of the first port using readily available equipment. The technique does not necessitate an extensive array of accessory instruments; in fact, a towel clip, middle -sized artery forceps and rational sized trocar were used. Slight less introduction of the needle causes frequent abdominal injuries in traditional veress technique.

Introduction of trocar directly, use of radially expanding trocar, optical trocars and shielded trocars are some alternatives to open and closed methods. Hasson started an open procedure to deduce the risk related to the closed veress technique. The advantage of this approach lies in accessing the peritoneal cavity under direct vision, although it tends to be more time-consuming compared to the closed method.[4,6,9]

Other studies have acknowledged the safety of accessing the abdomen through the umbilical stalk or tube in laparoscopy.[9-12] Moberg et al.outlined a technique where umbilicus was elevated by a towel clip,blunt reusable trocar introduced and S-shaped retractor used specifically in obese patients. [11] For the similar purpose Lal et al.[10] utilized two Alli's forceps,an artery forceps and a small Langenback retractor.

In modified open technique, here positioned an infraumbilical incision to target the point of least resistance for the initial entry port penetration. Sadhu et al. also utilized an infra-umbilical technique in their research.[12]

We opted for a simplified approach to the first port entry to minimize the risk of failure to enter the peritoneum and the challenges associated with extensive dissection. The average time for the first port entry in our study was 3.12±0.06 minutes, which is shorter than the 4.8 minutes reported by Ismaila et al. In our study, the total complications were 4 (2.1%), a rate comparable to the original Hasson's technique (0.5%).[3] Notably, there were no instances of injury to internal organs, extraperitoneal hematoma, port site hematoma, port site hernia, or failure to access the abdominal cavity. The study group did not experience any mortality.

CONCLUSIONS

Safe quick and dependable port entry in laparoscopy is possible in modified open technique. As entry time is less and it was superior to the other technique in terms of complication this method can be used in all cases of laparoscopic surgery.

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Original Article

Clinical, Microbiological Profile and Antibiotics Use in Admitted Patients of Urinary Tract Infection

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Abstract

Urinary tract infections (UTI) can vary from simple cystitis to pyelonephritis with severe sepsis. The objective of this study is to provide information about the clinical and microbiological profile of admitted patients of urinary tract infection, patterns of organisms isolated, antibiotic sensitivity pattern and antibiotics use. It was a prospective observational study conducted on 40 patients age >14 years admitted with diagnosis of UTI based on clinical and microbiological criteria over 8 months at a tertiary care hospital in North India. Data was collected for the clinical, microbiological profile, empirical and definite antibiotics use with duration of stay and outcome of patients. Among 40 cases of UTI; male to female ratio was 1:1 with mean age of 51.3± 16.32 years. Fever was present in almost all (97.5%) of the patients and three-fourth (75%) of them had dysuria. Type-2 Diabetes Mellitus was most common (55%) underlying condition and mean HbA1c was 9.37±2.27 followed by obstructive uropathy (17.50%). Most of cases (82.5%) were of complicated UTI; where Pyelonephritis was 42%, Emphysematous Pyelonephritis 12.5% and Renal Abscess 7.5%. Most common (37.5%) organism isolated from urine/ pus culture was Escherichia coli. More than half of the patients (55%) were given empirical antibiotics injection piperacillin tazobactam and carbapenems was used in more than one third (35%) of patients. The mean duration of antibiotics use was 14.55±4.94 days. Two (5.0%) patients expired out during the study period. Uncontrolled Diabetes Mellitus remains the major underlying condition in cases of complicated UTI. E coli is the most common organism isolated from urine/ pus culture. Most of the patients had favourable outcome with guided antibiotics and interventions.

Keywords: *Urinary tract infection, e-coil, uncontrolled diabetes mellitus*

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INTRODUCTION

Urinary tract infections remains one of the most common bacterial infections in both the community and, in admitted patients.[1] Clinical manifestations may vary from simple cystitis to severe illness like pyelonephritis and severe sepsis. It is broadly classified into uncomplicated and complicated UTI based on underlying structural or neurogenic abnormalities and various immuno- compromised states.[2-5] Most common pathogens causing urinary tract infections are Enterobacteriaceae group like Escherichia Coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, staphylococcus saprophyticus. Organisms causing infection also differs in cases of uncomplicated and complicated UTI. Although E. coli and, other gram-negative organisms remain common causes in complicated UTI pyelonephritis and urosepsis also but percentage of other organisms like Acinetobacter spp, enterococcus spp, fungi, Citrobacter species is significant.[6] In study by Gharbi M et al in 312,896 UTI episodes patients with deferred antibiotics had higher rates of admissions and mortality as compared to those with immediate antibiotic group. These findings were more common in elderly.[7] With ever growing resistance to antimicrobials being described; there is the need for the treating physicians to scrutinize local antimicrobial resistance patterns in order to adequately direct empirical and definitive management. Hence the present study will give us the information about the clinical and microbiological profile of patients of both uncomplicated and complicated urinary tract infection, antibiotic sensitivity patterns in urine culture and usage of antibiotics in these patients.

MATERIAL AND METHODS

It was a prospective observational study undertaken at a tertiary care centre in North India Patients aged >14 years old who were admitted in the internal medicine ward of our institute with clinical, microbiological diagnosis of urinary tract infection and willing to give consent were included in this study. It was conducted over a period over 8 months. Diagnosis of urinary tract infection was based on the clinical symptoms of dysuria, fever, lower pain abdomen, increased frequency of micturition and flank pain with microbiological evidence of UTI which included presence of pus cells in urine or isolation of organism from urine culture with colony count of $>10^5$cfu/ml.Ultrasound abdomen was done in all patients. Computed tomography was done as per clinical condition and decision of the treating team. Other investigations like complete blood counts, biochemistry panel, blood gas analysis, blood cultures, and serum procalcitonin were done in all cases. Fungal markers like beta D glucan and galactomannan test were done as per the clinical status of patient. Ethical clearance was taken from Institutes ethics committee before conducting the study. Participants were further classified into following three groups: 1. Complicated UTI- Complicated urinary tract infections (cUTIs) being defined as those occurring in patients with anatomic or functional abnormalities of the urinary tract or in those with significant medical or surgical comorbidities; 2. Uncomplicated UTI- Uncomplicated UTI is defined as individuals with UTI who are otherwise healthy and without any structural or neurological urinary tract abnormality that predisposes them to infection and 3. Catheter Associated UTI (CAUTI)- Catheter associated urinary tract infection is defined as the new appearance of bacteriuria or funguria with a count of more than 10^3 CFUs/mL occurring in person whose urinary tract is currently catheterized or has been catheterized within the past 48 hrs. Data was recorded on prescribed case record proforma for demographic details, baseline laboratory values, radiology, urine routine examination, urine and blood culture patterns, empirical and definitive antibiotics use, duration of hospital stay in hospital and outcomes.

RESULTS

Statistical Analysis: Data was captured and presented in the form of numbers and percentages. Quantitative data was presented as mean ± SD, minimum and maximum variables were also calculated.

Table I shows the distribution of demographic details, clinical and laboratory parameters of patients as follows- Demographic details: A total of 40 patients with diagnosis of UTI based on clinical, microbiological defined criteria were included in the study. Male and female were equally distributed and the ratio was 20:20. Mean age of patients was 51.3± 16.32 years.

Table- I: Demographic details, clinical and laboratory parameters of patients (n= 40)

S No.	Parameter	Value	Percentage
1.	Male : Female	20:20	
2.	Mean age (yrs)	51.3±16.37	
3.	Fever	39/40	97.5%
4.	Dysuria	30/40	75%
5.	Increased frequency	20/40	50%
6.	Vomiting	13/40	32.5%
7.	Pain abdomen	21/40	52.5%
8.	Altered sensorium	10/40	25%
9.	Oliguria/ anuria	14/40	35%
10.	Type 2 diabetes mellitus	22/40	52.5%
11.	SBP (mm of Hg)	116±16.5	
12.	DBP (mm of Hg)	71.85±8.6	
13.	Pulse (per min)	92.04±12.9	
14.	Temperature (F)	101±0.77	
15.	Haemoglobin (g /dL)	9.6±2.09	
16.	Total leucocyte count (per cm3)	15045.5± 4909.15	
17.	Platelet count (per cm3)	256625.2± 143014.8	
18.	Sodium (meq / L)	132.2±8.4	
19.	Potassium (meq /L)	4.42±0.88	
20.	Blood urea mg %	95.1±77.69	
21.	Serum creatinine mg%	3.36±3.02	
22.	Mean Hba1c(In T2DM patients)	9.37±2.27	

Clinical details: The symptoms of fever were presented in (39/40) 97.5 % of patients during admission, dysuria in (30/40) 75 %; where, pain abdomen and increased frequency of urination were found in 52.5 % and 50 % cases respectively. Other symptoms were vomiting in 32.5 %, decreased urine output in 35%, and altered sensorium in 25%, haematuria in 3 cases (7.5%) pyuria in 3 cases (7.5%). Mean duration of symptoms was 17.85± 17.6 days. Mean duration of stay was 13.62±9.18 days. Most common underlying condition was Type 2 Diabetes Mellitus in 22 cases (52.5%), obstructive uropathy in 7 cases and renal stone disease in 3 cases and catheterisation in 2 cases. Mean HbA1c among diabetics was 9.37±2.27. Out of the 40 cases of UTI; 33 were complicated UTI, 3 were uncomplicated UTI, 2 were catheter associated UTI, 1 prostatic abscess, 1 epididymoorchitis. Among complicated UTI; pyelonephritis constituted 13, 5 cases of emphysematous pyelonephritis, 7 cases of renal abscess and 8 cases of hydroureteronephrosis.

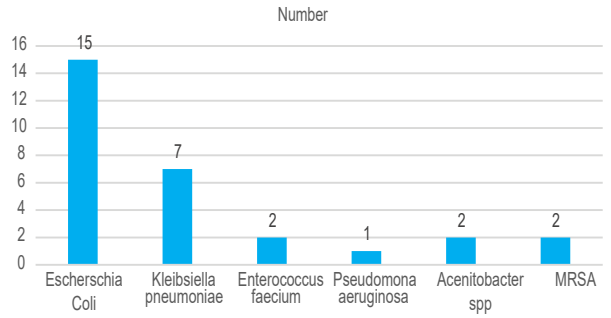

Figure- 1: Organisms isolated from the urine and aspirated pus culture

Figure 1 illustrates the distribution of organisms isolated from the urine and aspirated pus culture. Urine and aspirated pus culture showed growth of organism in 26 (65%) out of 40 cases. There were 14 patients had growth in urine and 12 cases out of 14 patients who underwent single time aspiration of pus or pigtail drainage; had growth of organism. Escherichia coli was identified in 15, Klebsiella pneumoniae in 7, Enterococcus faecium in 2, Pseudomonas aeruginosa in 1, Acinetobacter spp in 2 and Methicillin Resistant staphylococcus aureus in 2 cases. Among the cases 3 patients had growth of more than 1 organism on aspirated pus culture. All patients underwent ultrasound abdomen and showed abnormality in 30 cases. Blood culture showed growth of organism in 2 patients.

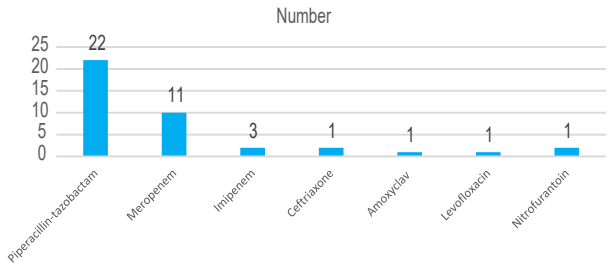

Figure- 2: Empirical antibiotics at the time of admission in patients of UTI

Figure 2 states the distribution of empirical antibiotics at the time of admission in patients of UTI; here piperacillin tazobactam was given in 22 cases (55%) followed by meropenem 11 (27.5%), imipenem in 3 (7.5%) followed by ceftriaxone, amoxycillin clavulanic acid, levofloxacin and nitrofurantoin.

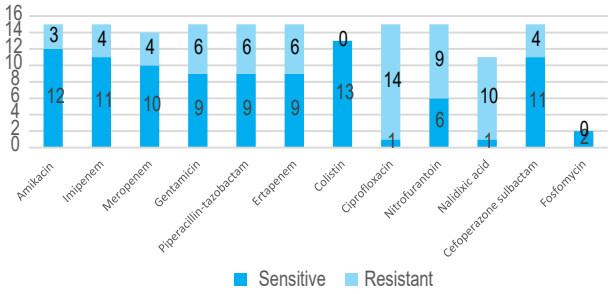

Figure- 3: Antibiotic susceptibility pattern of E. coli for commonly used antibiotics in UTI

Figure 3 contains the distribution of antibiotic susceptibility pattern of E. coli for commonly used antibiotics in UTI; here among the antimicrobial sensitivity pattern of Escherichia Coli; it was found to be sensitive to the most of the drugs used in complicated UTI including carbapenem grp like imipenem, meropenem; aminoglycosides like amikacin, gentamicin; beta lactam antibiotics like piperacillin tazobactam, cefoperazone- sulbactam and colistin. It was found to be resistant to ciprofloxacin, nalidixic acid in more than 90% cases. Antimicrobial susceptibility pattern of Klebsiella pneumoniae isolated in our study was not as consistent as E coli.

Antibiotics: Decision to switch antibiotics was taken based on the urine culture report or clinical condition of the patient. Piperacillin tazobactam was continued in 10 (25 %) patients, carbapenems were continued in 8 (20%) patients as patients had clinical response or culture suggestive of sensitive organisms. Injection Piperacillin tazobactam was used in dose of 4.5 gm iv TID. Injection meropenem was used in dose of 1 gm iv TID and Injection imipenem was used in dose of 1 gm iv TID. Renal modification of the drugs was done as per the eGFR. One patient had radiological evidence of fungal pathology; she was given amphotericin B for total dose of 2 gm and she responded. Switch over of antibiotics was done from piperacillin tazobactam to carbapenems in 8 (25 %) patients and to aminoglycosides in 2 (5%) patients. In rest of patients; antibiotics were upgraded based on the clinical and radiological evidence of the disease progression as per unit's policy. 6 (15%) patients required multiple antibiotics ≥ 3 (like piperacillin-tazobactam, carbapenems and colitis) based on the clinical symptoms, urine culture, blood culture and radiological investigations.

Hospital course and outcomes: 14 patients had undergone aspiration of the collection with pigtail insertion or single time aspiration. Seven patients underwent haemodialysis as per the protocol for kidney

injury. Total duration of antibiotics was 14.55±4.94 days; which was same as per guidelines of treatment of complicated UTI. Two patients expired out of 40 (5%).

DISCUSSION

Urinary tract infections are one of the frequent infections to occur in communities and health care settings. They are divided based on- (i) site of infection as upper UTIs like pyelonephritis and lower UTIs like cystitis, prostatitis and (ii) depending upon underlying conditions and functional or anatomical abnormalities; uncomplicated or complicated UTI. Proper knowledge and recognition of these clinical syndromes will lead to appropriate antibiotics; which can ward off fatal complications and antibiotic misuse.Excessive and needless use of the antimicrobial agents is one of the main causes of antimicrobial resistance. It is one of the major public health issues encountered worldwide. Infections due to resistant microorganisms do not respond to antibiotics because of the limited therapeutic choices; which results in extended period of sickness and higher risk of death. Failure of treatment also leads to lengthier days of infectivity. It can result in increased numbers of infected people in the society. It leads to exposure of general public to the resistant strain of microorganisms.

Most common underlying risk factor for complicated UTI in our study was Type 2 Diabetes mellitus which goes in agreement with previous studies.[3,8] Like the previous studies in UTI; Escherichia coli was the most common organism isolated (57.7%) in our study followed by Klebsiella pneumoniae, as per the last annual report of antimicrobial resistance research and surveillance network from January 2020 to December 2020 across India; Enterobacteriaceae constitutes 75.7 % of the isolates from urine culture.[9,10]E coli is followed by Klebsiella pneumoiniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus aureus, Enterococcus spp and Proteus mirabilis.

Majority of the antibiotic use in our study was as per the Institute and local guidelines for antibiotic use in common syndromes.[11] Most of the patients (80%) in our study were of complicated UTI with 67.5 % patients with kidney injury. All of them were started on either intravenous piperacillin tazobactam or carbapenem; recommended as per the hospital guidelines and other guidelines. As most of the cases in our study were of complicated UTI; duration of antibiotics was 14.55±4.94 days.In patients with complicated UTI like renal abscess, emphysematous pyelonephritis and obstructive uropathy; interventions along with antibiotics play major role in treatment outcomes.

In our study sensitivity pattern of E coli for commonly antibiotics was good, fosfomycin (100%), amikacin (80%), imipenem (73%), meropenem (71%), ertapenem (60%), piperacillin tazobactam (60%). ARRS network from India showed similar findings with good susceptibility to meropenem (77%), amikacin (77%), imipenem (73%) and ertapenem (72%), followed by nitrofurantoin (68%) and piperacillin-tazobactam (63%).[10]

Effective AMSP succeeds through a multidisciplinary style encompassing a variety of experts like hospital administration, microbiologist, pharmacologist, pharmacist, internist, infectious disease specialist and nursing staff. [11]

Appropriate antibiotic use and escalation and de-escalation reduces the hospital stay, costs and may improve outcomes in patients of complicated UTI.[12,13]Study by Spoorenberg V et al showed proper antibiotic use in patients with a complicated UTI seems to reduce the length of hospital stay by more than 2 days and therefore favors patient outcome and healthcare costs.[12,13]

CONCLUSION

Uncontrolled Diabetes Mellitus and obstructive uropathy remains the most common causes of complicated UTI. Escherichia Coli is the most common organism isolated from urine/pus culture. Majority of the patients received appropriate empirical and definite antibiotics therapy. Majority of patients (95%) had favourable outcome.

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Original Article

Serum Vitamin D Level in Inflammatory Bowel Disease (IBD) and it's Association with IBD Activity

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Abstract

Vitamin D influences innate immunity, which is believed to be the imbalance of it involved in the pathogenesis of Inflammatory Bowel Disease (IBD). Evidence exists on the association between vitamin D deficiency and inflammatory bowel disease (IBD). To assess the serum vitamin D concentration in patients with inflammatory bowel disease and to study the relationship of vitamin D level with disease activity in the patients with inflammatory bowel disease. This case-control study was carried out in the department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU). Total 40 IBD cases, diagnosed on clinical background and 40 apparently healthy control group of similar age and sex were taken. Blood samples were collected and serum vitamin D level was measured with Chemiluminescent Microparticle Immunoassay (CMIA) method in Biochemistry laboratory of BSMMU. The result were analyzed by statistical package for social sciences (SPSS) version 22. Vitamin D deficiency and insufficiency were defined as serum concentration of ≤20 ng/ml and 21–29 ng/ml respectively. Disease activity were evaluated using the Harvey Bradshaw Index for Crohn's Disease, Truelove and Witt's Index for Ulcerative colitis. The vitamin D levels were correlated with disease activity in IBD patients comparing with control group. Mean (±SD) serum vitamin D levels were 16.27 ± 5.16 ng/ml in IBD group and 24.25 ± 6.69 in controls (p <0.001). Almost all (97 %) of IBD patients had low serum vitamin D in comparison to controls; more than three-fourth (77.5%) of the patients of IBD exhibited deficiency (<20 ng/ml), one-fifth (20%) had insufficiency (21-29 ng/ml) of serum vitamin D, whereas in the controls 30% had deficiency, 42.5% had insufficiency, and 27.5% had sufficient serum vitamin D. There was highly significant inverse correlation between vitamin D level and disease activity in IBD patients. The study showed that IBD patients had significantly lower serum vitamin D levels in comparison to controls. Serum vitamin D concentration is inversely correlated with disease activity in IBD patients. The study suggests that inadequate vitamin D level, along with other factors, probably contributes to the development of active disease in patients with IBD.

Keywords: *Serum Vitamin D Level, IBD, crohn's disease, ulcerative colitis*

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INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD) is a chronic idiopathic inflammatory disorder of the gastrointestinal tract with a typically relapsing and remitting course[27,46]. Crohn's disease (CD) is a chronic inflammatory disorder that may involve any part of the alimentary tract from mouth to anus, with a propensity for the distal small intestine and proximal large bowel.[10]

UC is a chronic, relapsing disease characterized by diffuse mucosal inflammation of the colon.[44] It is thought to be caused by an inappropriate inflammatory response to the gut contents in genetically predisposed individuals.[1]

UC almost invariably involves the rectum and it may extend proximally in a continuous pattern to affect part of the colon or the entire colon. Clinical manifestations of active disease include bloody diarrhea (with or without mucus), urgency, tenesmus, abdominal pain, weight loss, fever, and malaise. Acute complications such as severe bleeding and toxic megacolon may occur, which can lead to perforation. There is an increased risk of colorectal cancer in UC patients. Risk factors include long duration of disease, extensive colonic involvement, severe inflammation and epithelial dysplasia, and childhood onset disease.[17]

Environmental factors such as smoking, medications such as non-steroidal anti-inflammatory drugs, stress and

psychological factors such as depression, nutritional factors and even air pollution increase risk of IBD.[2,3,4,5,50,65]

Another environmental factor involved in the patho-physiology of IBD is vitamin D deficiency.[47] Vitamin D is a major regulator of calcium and phosphorus metabolism and key in maintaining bone health.[50] There is evidence that vitamin D plays a role in immune regulation.[50] Vitamin D receptors are expressed by immune cells, including antigen presenting cells, natural killer cells, B and T lymphocytes (Yap *et al.,* 2015).

Vitamin-D inhibit proliferation of T-helper cells and secretion of IL-2, IFN-γ and IL-5, while increasing production of IL-4 by Th2 cells. Thus, vitamin D seems to modulate T-cell differentiation, driving cells towards the Th2 phenotype and inhibiting Th1development.[48]

Recent studies support the role of vitamin D in the pathogenesis, clinical course, and also the potential treatment of autoimmune diseases such as multiple sclerosis[51], systemic lupus erythematous.[40] and IBD.[51] Vitamin D regulates epithelial cell integrity[12,20,48] and its deficiency leads to intestinal barrier dysfunction, mucosal damage, and susceptibility to infectious agents (Kong *et al.,* 2008, Assa *et al.,* 2014). It also affects the mucosal and systemic immune system activities, generally with regulatory and anti-inflammatory properties.[667] There is also evidence on the role of vitamin D on the gut microbiome, which is implicated in the pathogenesis and clinical course of IBD.[12,20,48] Accordingly, it is possible that vitamin D affects the severity of inflammation and disease course in IBD patients.[50]

MATERIALS AND METHODS

This case control was carried out in the department of Gastroenterology, BSMMU, from November 2017 to February 2019. Adult patients with IBD diagnosed on the basis of compatible history, clinical features, laboratory findings and endoscopy with histopathology were enrolled in study group. Equal number of age-sex matched apparently healthy individuals selected from employees of the university or post graduate students those who voluntarily agreed and fulfilled the eligibility criteria was included as controls. We excluded patients with pregnancy, history of gastrointestinal surgery, female patients on hormonal contraception, chronic kidney disease, diabetes mellitus, history of hypoparathyroidism, metastatic bone disease or other malignancies and patients taking vitamin D supplements that can be associated with vitamin D deficiency. Total eighty (80) participants, 40 were apparently healthy control and 40 patient fulfilling the inclusion criteria of inflammatory bowel disease (IBD), who were admitted or came for follow-up in IBD clinic in the Department of Gastroenterology at BSMMU were enrolled. Demographic and clinical characteristics were recorded. According to Harvey Bradshaw Index (HBI) for Disease Activity of Crohn's Disease patients were classified as Mild disease (5-7), Moderate disease (8-16), Severe disease (>16). Ulcerative colitis patients are classified as mild, moderate, severe by Truelove and Witts' severity index. Blood samples were purposively collected for serum Vitamin D in active disease group and age- gender matched healthy controls. Serum vitamin 25 (OH) D concentrations was measured with Architect ci 4100 using the Chemiluminescent microparticle immunoassay* (CMIA) method In the Biochemistry Department of BSMMU.

Data were analyzed using SPSS version 22.0 software. Descriptive statics like frequency and corresponding percentage for qualitative data, mean and standard deviation for quantitative data were calculated. While the data presented on categorical scale were compared between groups using Chi-square (x2). The data presented on continuous scale were compared between groups with the help of unpaired t-Test. Quantitative data in three groups were compared by one way ANOVA test. P values of < 0.05 was considered significance.

RESULTS

From November 2017 to February 2019 with 40 patients with diagnosis of crohn's disease or ulcerative colitis were consecutively enrolled as cases and 40 apparently healthy adult individuals as controls. Twenty of the IBD patients had CD and 20 had UC. Mean age of IBD patients was 32.10 ± 9.99 years and 32.63 ± 10 years of control group and age range was 18 - 60 years in both groups.

Table I states the distribution of the age in case and control groups; among the IBD patients 33 (82.5%) were in age group 17 -40 years and 7 (17.5%) were >40 years, whereas in the control 32 (80.0%) were in age group 17 -40 years and 8 (20.0%) were >40 years.

Table-I: Distribution of the age in case and control (n=80)

Age (years)	Case (n=40)	Control (n=40)	P value
17 - 40	33 (82.5)	32 (80.0)	
>40	7 (17.5)	8 (20.0)	
Mean±SD	32.10 ± 9.99	32.63 ± 10.00	0.815

Unpaired t test was done to measure the level of significance

Table II shows the distribution of the sex in case and control groups; among the IBD patients 25 (62.5%) were males and 15 (37.5%) were females, whereas in the control 25 (62.5%) were males and 15 (37. 5%) were females.

Table-II: Distribution of the sex in case and control groups (n=80)

Gender	Case (n=40)	Control (n=40)	p-value
Male	25 (62.5)	25 (62.5)	1.000
Female	15 (37.5)	15 (37.5)	

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

Table III states the distribution of vitamin D level both in case and control groups; In IBD patients 31 (77.5%) had deficiency, 8 (20%) had insufficiency, and 1 (2.5%) had sufficiency of serum vitamin D level, whereas in the control group, 12 (30%) had deficiency, 17 (42.5 %) had insufficiency, and 11 (27.5%) sufficiency in serum vitamin D level. IBD patients had significantly lower mean serum level of vitamin D as compared to the control group (16.27± 5.16 vs. 24.25 ±6.69) respectively and P value <0.001).

Table- III: Distribution of vitamin D level in case and control groups (n=80)

Vitamin D	Case (n=40)	Control (n=40)	p-value
≤20 (Vit-D deficiency)	31 (77.5)	12 (30.0)	21-29
(Vit-D insufficiency)	8 (20.0)	17 (42.5)	
>29-100 (Sufficient Vit-D)	1 (2.5)	11 (27.5)	<0.001
Mean±SD	16.27±5.16	24.25±6.69	

Unpaired t test was done to measure the level of significance

Table IV contains the distribution of the duration of illness of the IBD patients; here duration of illness of 24 (60%) patients were > 4 weeks (established case), 16 (40%) were ≤ 4 weeks (new case) duration.

Table -IV: Duration of illness of the IBD Patients (n=40)

Duration of illness (months)	Frequency (n)	Percentage (%)
≤4 weeks	16	40.0
>4 weeks	24	60.0
Mean±SD (years)	2.45 ±3.73 (0.08 - 20)	

Table V shows the distribution of type of IBD and its severity. Here both Cron's disease and ulcerative colitis was equal in number (50%).

Table -V : Type of IBD and its severity (n=40)

Severity of disease	Crohn's disease (n=20)	Ulcerative colitis (n=20)	Total
Mild	4 (20.0)	5 (25.0)	9 (22.5)
Moderate	6 (30.0)	5 (25.0)	11 (27.5)
Severe	10 (50.0)	10 (50.0)	20 (50.0)

Table VI shows the comparison of lab parameters between Crohn's disease and Ulcerative colitis. No significant difference of vitamin D level, Hb%, ESR and CRP were found between Crohn's disease and Ulcerative colitis patients (15.50 ± 4.26 vs 17.05 ± 5.94, p=0.349), (11.25 ± 2.84 vs 11.65 ± 2.66, p=0.649), (26.80 ± 17.01 vs 43.00 ± 30.64, p=0.046) and (26.85 ± 37.18 vs 24.10 ± 34.70, p=0.810) respectively.

Table- VI: Comparison of lab parameters between Crohn's disease and Ulcerative colitis (n=40)

	Crohn's disease (n=20)	Ulcerative colitis (n=20)	p-value
25(OH)D level	15.50±4.26	17.05±5.94	0.349
Hb%	11.25±2.84	11.65±2.66	0.649
ESR	26.80±17.01	43.00±30.64	0.046
CRP	26.85±37.18	24.10±34.70	0.810

Unpaired t test was done to measure the level of significance

Table VII shows the 25(OH)D level according to severity of IBD; as Crohn's Disease activity increased, the level of serum vitamin D decreased (21.0 ±1.41 , 17.17±22.93, 12.30±2.50) reciprocally and P value <0.001. Also as the disease activity of Ulcerative colitis increased, the level of Vitamin D decreased (25.0 ±3.08, 17.40±1.67, 12.90± 3.84) reciprocally and P value <0.001.

Table -VII: 25(OH)D level according to severity of IBD (n=40)

Type of IBD	Mild (n=20)	Moderate (n=20)	Severe	Total
Crohn's disease (n=20)	21.00 ± 1.41	17.17 ± 2.93	12.30 ± 2.50	<0.001
Ulcerative colitis (n=20)	25.00 ± 3.08	7.40 ± 11.67	12.90 ± 3.84	<0.001
Total	23.22 ± 3.15	17.27 ± 2.33	12.60 ± 3.17	<0.001

ANOVA test was done to measure the level of significance

Table VIII shows the 25(OH)D level according to duration of IBD; here, no difference of Vitamin D was found between newly diagnosed patients with established cases both in CD group (17.33 ± 4.12 ng/mL vs 14.00 ± 3.92, p value 0.081) and UC group (16.57 ± 5.96 vs 17.30 ± 6.15, p value 0.80) .

Table- VIII: 25(OH)D level according to duration of IBD (n=40)

Type of IBD	< 1 months (n=20)	≥ 1 months (n=20)	Total
Crohn's disease (n=20)			
<20	8 (88.9)	10 (90.9)	
21 - 29	1 (11.1)	1 (9.1)	
Mean±SD	17.33 ± 4.12	14.00 ± 3.92	0.081
Ulcerative colitis (n=20)			
<20	5 (71.4)	9 (69.2)	
21 - 29	2 (28.6)	3 (23.1)	
30 - 100	0 (0.0)	1 (7.7)	
Mean±SD	16.57 ± 5.96	17.30 ± 6.15	0.800

Unpaired t test was done to measure the level of significance

Table IX illustrate the distribution of serum Vitamin D level among IBD and controls by age; here in male 10 (40%) had insufficiency, 9(36%) had sufficiency and 6(24%) had deficiency of serum vitamin D level. IBD patients had significantly lower serum vitamin D level as compared to the control group (16.27± 5.16 vs. 24.25 ± 6.69, P value <0.001). The difference was significant.

[In IBD patients 13(86.66%) had deficiency, 1(6.66%) had insufficiency and 1(6.66%) had sufficiency of serum vitamin D level].

Table-IX: Distribution of IBD and controls by age (n=80)

Age	Deficiency (≤20)	Insufficiency (21 – 29)	Sufficiency (>29)	p-value
IBD				
17 – 40	26 (81.3)	6 (85.7)	1 (100.0)	0.862
>40	6 (18.8)	1 (14.3)	0 (0.0)	
Control				
17 – 40	8 (66.7)	16 (94.1)	8 (72.7)	0.148
>40	4 (33.3)	1 (5.9)	3 (27.3)	

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

Table X states the distribution of serum Vitamin D level among IBD and controls by sex; in male 19 (76%) had deficiency, 6(24%) had insufficiency of serum vitamin D level. In the healthy control females, 7 (46.66%) had insufficiency, 6(40%) had deficiency and 2 (13.33%) had insufficiency in serum vitamin D level.

Table-X: Distribution of IBD and controls by gender (n=80)

Gender	Deficiency (≤20)	Insufficiency (21 – 29)	Sufficiency (>29)	p-value
IBD				
Male	19 (59.4)	6 (85.7)	0 (0.0)	0.182
Female	13 (40.6)	1 (14.3)	1 (100.0)	
Control				
Male	6 (50.0)	10 (58.8)	9 (81.8)	0.266
Female	6 (50.0)	7 (41.2)	2 (18.2)	

Table XI illustrate the distribution of Crohn's disease severity and Vitamin D status; in Crohn's disease patients, half 10 (50%) had severe disease activity (>16), followed by 6 (30%) moderate disease activity (8-16) and 4 (20%) mild disease activity (5-7).

Table-XI: Distribution of Crohn's disease severity and Vitamin D status (n=20)

Level of 25 (OH)D	Mild (n=4)	Moderate (n=6)	Severe (n=10)	Total
<20	2 (50.0)	6 (100.0)	10 (100.0)	
21 - 29	2 (50.0)	0 (0.0)	0 (0.0)	
Mean±SD	21.00±1.41	17.17±2.93	12.30±2.50	<0.001

ANOVA test was done to measure the level of significance

Table XII illustrate the distribution of ulcerative colitis severity and Vitamin D status; in ulcerative colitis patients, half 10 (50%) had severe disease activity, followed by 5(25%) moderate disease activity and 5 (25%) mild disease activity.

Table-XII: Distribution of Ulcerative colitis severity and Vitamin D status (n=20)

Level of 25 (OH)D	Mild (n=5)	Moderate (n=5)	Severe (n=10)	Total
<20	0 (0.0)	5 (100.0)	9 (90.0)	
21 - 29	4 (80.0)	0 (0.0)	1 (10.0)	
30 - 100	1 (20.0)	0 (0.0)	0 (0.0)	
Mean±SD	25.00±3.08	17.40±1.67	12.90±3.84	<0.001

ANOVA test was done to measure the level of significance

Table XIII shows the distribution of IBD by ESR and vitamin D; there were statistically significant association between vitamin D levels and erythrocyte sedimentation rate (36.31 ± 27.63 vs 26.29 ± 15.70 vs 50.00 ± 0.00 , p value <0.001).

Table-XIII: Distribution of IBD by ESR and vitamin D (n=40)

ESR	Deficiency (≤20) (n=32)	Insufficiency (21 - 29) (n=7)	Sufficiency (>29) (n=1)	p-value
>30	15 (46.9)	2 (28.6)	1 (100.0)	
≤30	17 (53.1)	5 (71.4)	0 (0.0)	
Total	36.31±27.63	26.29±15.70	50.00±0.00	<0.001

ANOVA test was done to measure the level of significance

Table XIV shows the distribution of IBD by CPR and vitamin D; there were statistically significant association between vitamin D levels and serum C-reactive protein (27.88 ± 35.28 vs 18.00 ± 39.73 vs 1.00 ± 0.00, p vale <0.001).

Table-XIV: Distribution of IBD by CRP and vitamin D (n=40)

CRP	Deficiency (≤20) (n=32)	Insufficiency (21 - 29) (n=7)	Sufficiency (>29) (n=1)	p-value
>6	26 (81.3)	2 (28.6)	0 (0.0)	
≤6	6 (18.8)	5 (71.4)	1 (100.0)	
Total	27.88±35.28	18.00±39.73	1.00±0.00	<0.001

ANOVA test was done to measure the level of significance

DISCUSSION

In recent years, vitamin D has attracted a significant amount of scientific attention (Bruyn et al., 2013). Along with function of regulating the phosphocalcic metabolism, growing evidence point its anti-inflammatory, anti-proliferative and anti-apoptotic functions.[63] It is estimated that as many as one billion people worldwide suffer from vitamin D deficiency or insufficiency and this was shown to be prevalent across all age groups, genders, and geographic regions.[19,31,32] So, it is important to emphasize that vitamin D deficiency is a current public health issue that has been increasing, including in healthy individuals of all ages in developed and developing countries.

The present case-control study was carried out with the aim to determine the prevalence of vitamin D concentration in Inflammatory Bowel Disease and to compare them with that of apparently healthy controls and correlate with disease activity of IBD patients.[28]

The present study included forty inflammatory bowel disease (IBD) patients (15 females and 25 males) and forty (age and sex matched) healthy control participants**.** In this study we have seen significantly lower mean serum vitamin D levels in IBD patients compared to controls, (16.27±5.16 ng/ml) vs (24.25±6.69 ng/ml) respectively with p value<0.001. These finding are consistent with research finding of[21] who reported mean vitamin D levels in IBD patients was 24±10 ng/ml and in controls 31±13 ng/ml. The difference was significant, p<0.05.

When IBD patients and control subjects were classified according to Vitamin D status, among 40 IBD cases, 39 cases (97.5%) had low vitamin D concentration (<30 ng/ml); only one case (2.5%) had sufficient vitamin D concentration (≥30 ng/ml). Out of 39 low vitamin D patients, 31 cases (77.5%) were deficient (≤20 ng/ml) and 8 cases (20.0%) were insufficient (21-29 ng/ml). Among 40 control subjects, 29 participants (72.5%) were found to be low vitamin D (<30ng/ml) while in 11 participants (27.5%) vitamin D level were sufficient .This means that vitamin D deficiency is more prevalent in IBD patients than control subjects.

In the present study, however 1 out of 40 IBD patients and 11 out of 40 control subjects had sufficient vitamin D concentration. This was also similar with result of with results of [63,22] who confirmed lower levels of vitamin D among IBD patients as compared to the controls. The result of this study, however dissimilar with results of Ko *et al.*,(2019) who found that there was no significant difference in vitamin D levels between groups. This may be due to demographics, physical activity, and nutritional status.

In our study no difference was found in the prevalence of low vitamin D between CD and UC patients. This agrees with the results of study by.[39,22] However this study result do not agree with the result of[43] They reported that mean 25(OH)D levels were lower in CD patients compared with UC patients.

In the present study, as regard to age, there was no significant difference between IBD patients with different vitamin D status (Vitamin D deficiency and Vitamin D insufficiency). This finding is similiar with the finding of.[56] However, the results of this present study did not agree with results of[62] who reported younger patient were more Vitamin D deficient.

In our study there was no significant difference between IBD patients with different vitamin D status (vitamin D deficiency and vitamin D insufficiency) as regard to gender with p value = 0.182. Our observations are consistent with the findings of Hassan *et al.*,(2013) . However, the results of our study did not agree with results of[39,68] who reported the prevalence of low vitamin D was higher in males.

In the present study there was no significant difference between vitamin D level and disease duration (new case vs established case, p value 0.081). This however, did not agrees with the result of study by[63] who reported more vitamin D deficiency in patients with longer disease duration and[21] who reported newly diagnosed IBD patients had lower Vitamin D levels than established cases.

In our study there was a significant difference between different vitamin D status (vitamin D deficiency and insufficiency) as regard to HBI in Crohn's disease and Truelove and Witt's severity in Ulcerative colitis. It was also found that vitamin D correlated inversely with IBD disease activity. These findings are similar with study by[68] who also reported the association between higher disease activity and lower vitamin D levels.[9] reported vitamin D levels decreased with increased disease activity in ulcerative colitis patients.[9,21,38] reported significant correlation between vitamin D levels and crohn's disease activity but no significant correlation with ulcerative colitis disease activity. However[22] reported that serum vitamin D levels are not affected by disease severity in IBD patients (both UC and CD patients).

CONCLUSION

In this case-control study, we observed that average serum vitamin D concentration of IBD patients were significantly low in comparison to controls. In our study, vitamin D concentration inversely correlated with disease activity and not significantly correlated with age and disease duration. The study suggests that inadequate vitamin D level, along with other factors, probably contributes to the development of active disease in patients with IBD.

Limitation

Only a small number of IBD patients and controls were enrolled. The participants were from one centre, so result can't be generalized to reference population. Dietary intake of vitamin D, nutritional status of study participants not studied. Seasonal variation, time spent in sunlight were not studied.

Recommendation

Further large scale studies should be considered to strengthen the study and establish the relationship of vitamin D levels with IBD along with other cofounders.

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Original Article

Nutritional Status of Under-Five Children in the Climate Vulnerable Area of Bangladesh

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Abstract

Children, due to their physiological and metabolic vulnerabilities, are particularly sensitive to climate-related changes. Factors such as heat waves, extreme weather events, temperature variations, increased precipitation, and drought directly impact food and nutrition. This cross-sectional study was aimed to assess the nutritional status of under-5 children in a flood-prone district in northern Bangladesh. A total of 207 children aged 24-59 months were conveniently selected for the study. Data collection involved face-to-face interviews and observations using a semi-structured questionnaire. Data analysis was performed using SPSS version 16.0. Demographic information, educational background, immunization status, breastfeeding practices, health history, and dietary intake were considered for assessing nutritional status. More than half (55.6%) of the children was in age group 48-59 months, and the male-female ratio was 1.25:1. Most of the (70%) children belonged to nuclear families and more female children (53.6%) had completed their primary education than male (44%). All children were immunized, where three-fifth (60.4%) of the mothers acknowledged breastfeeding after birth, and three-fourth (75.4%) had completed exclusive breastfeeding. The majority were not ill in the month preceding the data collection. Dietary assessment revealed that most of the (94%) children consumed rice in the morning as breakfast, 97% at midday as lunch, and 94% at night as dinner. Among the children all of them had experienced flooding (100%) and significant proportion had experienced river bank erosion (97.6%). According to measurements, 81.2% were normal by MUAC, 62.8% by height for age Z scores, 71% by weight for age Z scores, and 83.1% by weight for height Z scores. The study identified higher proportions of underweight and severe wasted cases in male children, severe stunted cases with mothers having primary education, and severe wasted cases in extended families. Although certain trends were observed, the relationships between nutritional status and variables such as gender, maternal education, family type, and duration of residence were not statistically significant. Given the potential long-term impact of malnutrition, early intervention, and prioritization of nutritional considerations during the under-five age group are imperative.

Keywords: *nutritional status, under-5 children, climate vulnerable area of Bangladesh*

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INTRODUCTION

Nutrition is concerned primarily with the part played by nutrients in body growth, development, and maintenance.[27] Malnutrition comprises four forms- under nutrition, over nutrition, imbalance, and specific deficiency. Malnutrition begins quite commonly in womb and ends in the grave.[27] Nutritional status is influenced by three broad factors: food, health, and care. These factors directly influence nutrient intake and the presence of disease. The interaction between under nutrition and infection creates a potentially lethal cycle of worsening illness and deteriorating nutritional status.[6.35,36,37,38,39] In modern age malnutrition continues to be a serious public health problem.[6.35,36,37,38,39] Despite the economic growth observed in developing countries, malnutrition and particularly under-nutrition is still highly prevalent.[23] In children, malnutrition is synonymous with growth failure. Malnourished children are shorter and lighter than they should be for their age. [6.35,36,37,38,39] Assessment of nutritional status is the current body status, of a person or a population group, related to their state of nourishment (the consumption and utilization of nutrients). The nutritional status is determined by a complex interaction

between internal/ constitutional factors and external environmental factors: i) Internal or constitutional factors like: age, sex, nutrition, behavior, physical activity and diseases; ii) External environmental factors like: food safety, cultural, social and economic circumstances. An ideal nutritional status occurs when the supply of nutrients conforms to the nutritional requirements or needs.[33] Anthropometric measurements remain the most practically useful means for the assessment of the nutritional status of a population.[18] Anthropometry is the measurement of body height, weight, and proportions. It is used to evaluate both under and over nutrition.[33] Anthropometric measurement is an almost mandatory tool in any research to assess health and nutritional condition of children. Physical measurement like body weight, height, circumference of arm, triceps, skin fold etc. and mainly Z-score are extensively used to determine the nutritional status of children. Based on age, height, and weight, a number of indices such as height for age Z-score (stunting), weight for age Z-score (underweight), weight for height Z-score (wasting) and BMI for age (Thinness) have been suggested.

Climate is the statistics of weather over long periods of time. It is measured by assessing the patterns of variation in temperature, humidity, atmospheric pressure, wind, precipitation, atmospheric particle count and other meteorological variables in a given region over long periods of time. Climate differs from weather, in that weather only describes the short-term conditions of these variables in a given region.

Communities across the globe are already experiencing the impacts of more extreme weather events, temperature changes and disease outbreaks. Though no one will be immune to the effects of climate change, children are particularly vulnerable. The types of climate risks confronting children are diverse, ranging from direct physical impacts, such as cyclones, storm surges and extreme temperatures, to impacts on their education, psychological stress and nutritional challenges. Higher temperatures have been linked to increased rates of malnutrition, cholera, diarrhoeal disease and vector-borne diseases like dengue and malaria. Yet children's underdeveloped immune systems put them at far greater risk of contracting these diseases and succumbing to their complications. [6.35,36,37,38,39]

Climate change impacts are also projected to increase the numbers of children affected by natural hazards, from an estimated 66.5 million per year in the late 1990s to as many as 175 million per year (globally) in the coming decade. [6.35,36,37,38,39] Under nutrition remains one of the world's most serious but least addressed socioeconomic and health problems, hitting the poorest the hardest, especially women and children. The number of people suffering from hunger stood at 925 million in 2010, and maternal and child under nutrition persists. In developing countries, nearly one-third of children are underweight or stunted, and under nutrition is the cause of more than one-third of deaths among children under 5 years of age.[19]

Urbanized areas of Bangladesh are expanding, but only 34% of the total population lives in urban areas. The remainder lives in rural areas and towns. This may seem like a large amount.[41] Malnutrition is one of the principle public health problems, affects large numbers of children in developing countries. Nutritional assessment in the community is essential for accurate planning and implementation of intervention programmers to reduce mortality and morbidity associated with malnutrition. Malnutrition which refers to an impairment of health either from a deficiency or excess or imbalance of nutrients is public health significance among children all over the world specifically in developing countries.[2]

Two billion people in the world suffer from various forms of malnutrition (IFAD/FAO/WFP, 2011). Malnutrition is an underlying cause of death of 2.6 million children each year, which is a third of child deaths globally.[9,6.35,36,37,38,39] One in four of the world's children are stunted.[10] In developing countries this is as high as one in three. Under nutrition accounts for 11% of the global burden of disease and is considered the number one risk to health worldwide.[9]

Calorie availability in 2050 is likely to decline throughout the developing world resulting in an additional 24 million undernourished children.[40] Global land temperatures in the past decade, 2006-2015, were 1.0◦C (1.8◦F) warmer than the twentieth-century average.[30] Lower respiratory tract infections, diarrhea, and malaria are responsible for > 50% of childhood deaths and these disease categories could worsen with climate change. Diarrheal disease is primarily attributable to environmental factors, specifically contaminated food and drinking water, and is affected by changing temperature and precipitation events. Thirty-five percent of excess child mortality is secondary to malnutrition, a risk factor also expected to worsen with climate change because of increasing food insecurity.

Micronutrient deficiencies, common with malnutrition, can exacerbate infectious disease morbidity.[28] Intergovernmental Panel on Climate Change (IPCC) reinforced adaptation needs. Over coming years for health adaptation in developing countries such as Bangladesh Community-based strategic interventions will be needed. In low-income countries the number of studies is very limited than developed countries. Bangladesh has topped the IPCC's risk index since 2007 for climate change.[17]

MATERIALS AND METHODS

This community based cross sectional study was conducted to assess the nutritional status of under-5 years of children. The Study was carried out in Chauhali upazilla in Sirajgonj district. This area was selected because it is a climate vulnerable which was prone to flood and river erosion. The study was conducted for a period of 12 months from 1stJanuary to 31st December and data were collected from 24th August to 20th September 2017. Study population was 207 children aged 24 to 59 months of both sexes. Parents or legal guardians were interviewed on behalf of children as respondents.

Convenient sampling was carried out to select the samples from the communities and fulfilled the selection criteria were interviewed and observed. A pretested semi-structured questionnaire in Bengali and checklist were used for data collection instruments. Data collection tools includes weighing scale, measuring tape and MUAC (Mid-upper arm circumference) measuring tape were used for anthropometric measurement. Data were collected by face-to-face interview of respondents, observation and reviewing record.

Data processing and analysis

After data collection, the questionnaires were checked for consistency and completeness. The data were entered, cleaned and re-coded using Statistical Package for Social Sciences (SPSS) version 16. Missing data were checked through frequency run and an analysis plan was made. Descriptive statistics was used and statistical significance of association was analyzed by the chi-square test. The level of significance was set as 0.05.

Ethical Consideration

A letter of informed written assent in Bengali was used to take from the respondents (parents or legal guardian). Before starting the interview, the respondents were informed about the purpose and objectives of the study. Respondents were assured about the confidentiality of the data. They were informed about the full rights to participate or to refuse in this study at any time.

RESULTS

This study was conducted to assess nutritional status of 207 under five children. Data has presented in following ways: Socio demographic characteristics of children, immunization history, exclusive breast feeding, illness history, dietary pattern, climate vulnerability condition, nutritional status of the children. All children (207) under this study were immunized (100% coverage rate).

Table 1 states the distribution of socio-demographic characteristics of children; among 207 children, 38.2%, 35.3% and 26.6% were in age group 48-59, 24-36 and 36-48 months, where male female ratio was 1.25:1 and 70% of them were from nuclear family. The range of monthly family income of 62.8% children's family was 10000-30000 BDT. Among the children 97.6% lived in kancha house and 53.6% mothers and 44% fathers of the children had completed primary level of education.

Table-I: Socio-demographic characteristics of respondents (N=207)

Characteristics	Frequency	Percent
Age of the respondents (in months)		
24-36	73	35.3
36-48	55	26.6
48-59	79	38.2
Mean ±SD	41.33(10.915)	
Sex of the Respondents		
Male	115	55.6
Female	92	44.4
Religion of the Respondents		
Islam	206	99.5
Hindu	1	0.5
Type of Family		
Nuclear	145	70
Extended	62	30
Total number of family members		
≤5	129	62.3
6≥	78	37.7

Table-I *(Cont'd)* **: Socio Demographic characteristics of respondents (N=207)**

Characteristics	Frequency	Percent
Monthly Family income		
<10,000	76	36.7
10,000-30,000	130	62.8
>30,000	1	0.5
Mean+ SD	11466.18(4566.27)	
Types of houses		
Semi-pacca	4	1.9
Pacca	1	0.5
Kacha	202	97.6
Mothers Education		
Illiterate	54	26.1
Primary	111	53.6
Secondary	25	12.1
Higher Secondary and above	17	8.2
Father's Education		
Illiterate	69	33.3
Primary	91	44
Secondary	25	12.1
Higher Secondary and Above	18	8.7
Non-formal education and others	4	1.9

Respondents' exclusive breast-feeding status and Illness within 1 year

Table II shows the distribution of exclusive breast feeding and illness within one year among the children. Result shows that majority 156 (75.4%) children had continued exclusive breast feeding and rest 51 (24.6%) did not maintain continuous breast feeding. About 94.2% of children had no illness during the last 1 month. Among the ill children 5 (2.4%) had breathlessness, 3 (1.4%) had measles, 2 (1%) faced diarrhoea and 2 (1%) had malnutrition problems.

Table- II: Respondents' exclusive breast-feeding status and Illness within 1 year (n=207)

Continuing breast feeding	Frequency (f)	Percent (%)
Yes	156	75.4
No	51	24.6
Total	207	100
Illness within 1 year		
Diarrhoea	2	1.0
Breathlessness	5	2.4
Measles	3	1.4
Malnutrition	2	1.0
Total illness	12	5.8
No illness	195	94.2
Total	207	100

Childrens' 24 hours recall of food consumption

Table III shows the distribution of children regarding 24 hours recall of food consumption; in the morning 74% eat rice, 69% leafy vegetables, 49% Pulses, 43% milk. Mid-day 97% take rice, 94% leafy vegetables, 92% pulses and 43% egg. At night the respondents used to take rice 94%, leafy vegetables 92% and pulse 43%.

Table- III: Distribution of children regarding 24 hours recall of food consumption

Food	Morning		Mid-day		Night	
	Yes	No	Yes	No	Yes	No
Rice	152 (74%)	55 (26%)	200 (97%)	7 (3%)	194 (94%)	13 (6%)
Bread	53 (26%)	154 (74%)	7 (3%)	200 (97%)	13 (6%)	194 (94%)
Leafy Veg	142 (69%)	65 (31%)	194 (94%)	13 (6%)	190 (92%)	17 (8.2%)
Non-leafy veg	52 (25%)	155 (75%)	119 (58%)	88 (43%)	90 (43%)	117 (57%)
Fruits	55 (27%)	152 73%)	10 (4.8%)	197 (95%)	2 (1%)	205 (99%)
Pulses	102 (49%)	105 (51%)	190 (92%)	17 (8.2%)	90 (43%)	117 (57%)
Fish	2 (1%)	205 (99%)	94 (46%)	113 (55%)	55 (27%)	152 (73%)
Meat	2 (1%)	205 (99%)	20 (10%)	187 (90%)	52 (25%)	155 (75%)
Milk	90 (43%)	117 (57%)	2 (1%)	205 (99%)	10 (4.8%)	197 (95%)
Egg	10 (4.8%)	197 (95%)	90 (43%)	117 (57%)	2 (1%)	205 (99%)
Milk Product	12 (6%)	195 (94%)	2 (1%)	205 (99%)	2 (1%)	205 (99%)

Climate vulnerability condition

Table IV states distribution of respondents by their duration of stay in the locality; here mmajority of respondents (67.6%) were residing there for less than 30 years, 26.6% were staying in that area for more than 30 years.

Table-IV: Distribution of respondents by their duration of stay in the locality (n=207)

Staying period in years	Frequency (f)	Percent (%)
<30	140	67.6
30	12	5.8
>30	55	26.6
Total	207	100

Table V contains the ddistribution of respondents by natural calamity which they faced; among 207 respondents, 100 respondents faced flood, 202 faced river bank erosion, 58 faced cyclone and only 6 faced earthquakes.

Table-V: Distribution of respondents by natural calamity which they faced (n=207)

Natural Calamity	Flood		Drought		Cyclone		Earthquake		River Bank erosion	
	f	%	f	%	f	%	f	%	f	%
Yes	207	100	184	88.9	58	28	6	2.9	202	97.6
No	0	0	23	11.1	149	72	201	97.1	5	2.4
Total	207	100	207	100	207	100	207	100	207	100

Nutritional status of under-five children

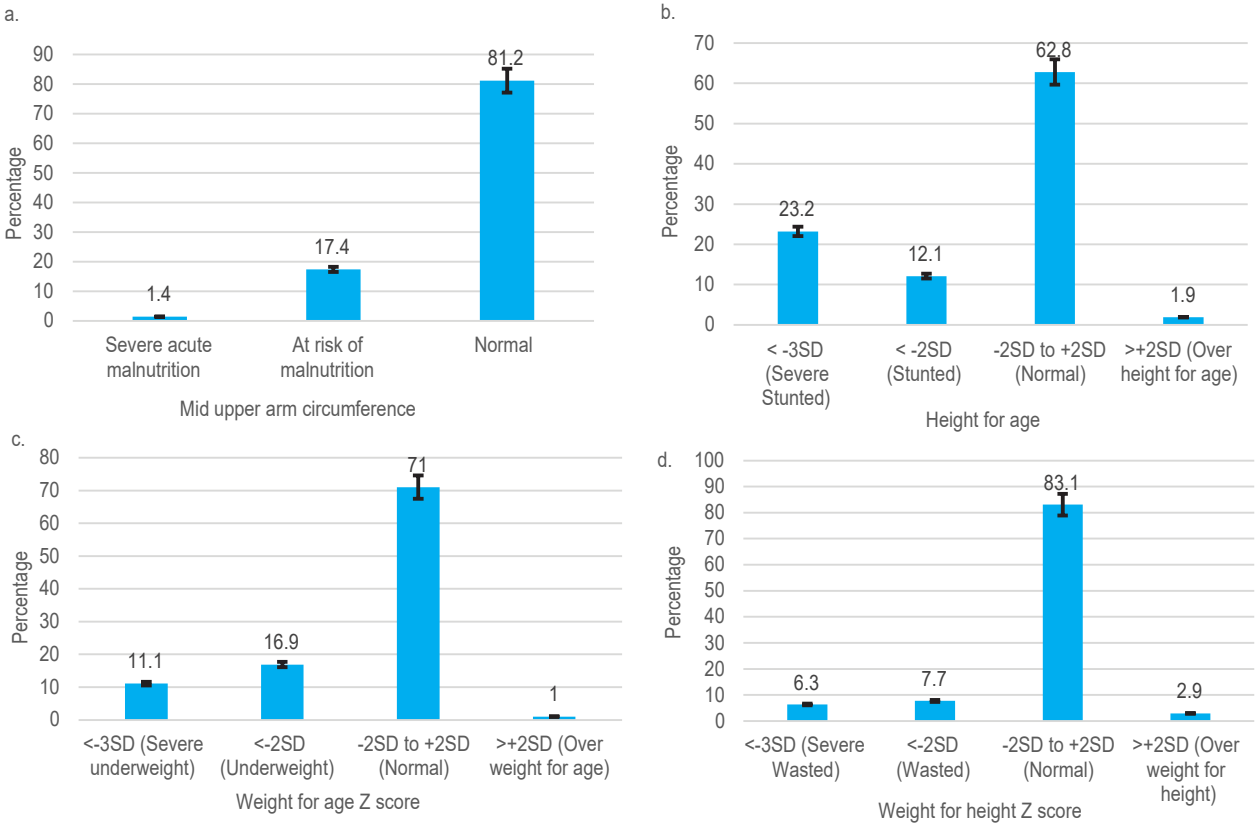

Figure 1. Malnutritional status of the under-five children in the climate vulnerable area of Bangladesh

Figure 1 represents the under-five children's nutritional status. In the mid upper arm circumference measurement, only 3 (1.4%) were at severe acute malnourished, 36 (17.4%) were at risk or moderate and majority 168 (81.2%) were normal (Figure 1.a). According to height for age z score, the majority 130 (62.8%) were normal height for age Z score, 48 (23.2%) were severe stunted, 25 (12.1%) were stunted and 4 (1.9%) were over height for age Z score (Figure 1.b). According to weight for age z score, a maximum 147 (71%) were with normal weight for age Z score, 35 (16.9%) were underweight, 23 (11.1%) were severe underweight for age Z score and only 2 (1%) were overweight for age Z score (Figure 1.c). According to weight for height z score, 172 (83.1%) were normal weight for height Z score, 16 (7.7%) were wasted, 13 (6.3%) were severe wasted and 6 (2.9%) were overweight for height Z score (Figure 1.d).

Socio-demographic variation of children's weight for age

Table VI shows that most male (67.8%) and female (75%) respondents had a normal weight-for-age z score, with higher underweight prevalence (20.9%) among males. Chi-square analysis revealed no significant association ($p > 0.05$). Children with normal weight-for-height z scores often had mothers with higher secondary education or above, while severe underweight was prevalent among children of mothers with similar education levels, showing no significant association with father's education ($p > 0.05$).

Table-VI: Socio-demographic variation of children's weight for age z score

Characteristics	Severe underweight, f(%)	Underweight, f(%)	Normal f(%)	Overweight f(%)	Test statistics f(%)
Sex of Children					
Male	13 (11.3)	24 (20.9)	78 (67.8)	0(0)	$\chi2$=4.817
Female	10 (10.9)	11 (12)	69 (75)	2 (2.2)	p=0.150*
Mothers' education					
Illiterate	7 (13)	7 (13)	139 (72.2)	1 (1.9)	$\chi2$=9.487
Primary	11(9.9)	20 (18)	79 (71.2)	1 (0.9)	p=0.346*
Secondary	1 (4.0)	3 (12)	2 (84)	0 (0)	
Higher secondary and above	4 (23.5)	5 (29.4)	8 (47.1)	0 (0)	
Fathers' education					
Illiterate	7 (10)	13 (18.8)	13 (18.8)	47 (68.1)	$\chi2$=12.23
Primary	16 (11)	13 (14.3)	68 (74.7)	0 (0)	p= 0.416*
Secondary	1(4%)	6 (24.0)	18 (72)	0 (0)	
Higher secondary and above	5 (27.8)	3 (16.7)	16 (55.6)	0 (0)	
Non-formal Education & others	0 (0)	0 (0)	4 (100)	0 (0)	

*Fisher's exact test

Socio-demographic variation of children's height for age

Table VII reveals that the majority of male and female respondents had a normal height-for-age z score, with higher severe stunting (24.3%) observed in males. No significant association was found between sex and height-for-age z score ($p > 0.05$). Children with severe stunting often had mothers with only primary education, and a similar trend was noted with fathers, but without a significant association with parental education levels ($p > 0.05$).

Table-VII: Socio-demographic variation of children's height for age

Characteristics	Severe Stunted f(%)	Stunted, f(%)	Normal, f(%)	Over Height f(%)	Test statistics
Sex of Children					
Male	28 (24.3)	12 (10.4)	75 (65.2)	0(0)	χ2=5.64
Female	20 (21.7)	13 (14.1)	55 (59.8)	4 (4.3)	p=0.119*
Mothers' education					
Illiterate	9 (16.7)	9(16.7)	35 (64.8)	1 (1.9)	χ2 =5.038
Primary	30 (27)	13 (11.7)	66 (59.5)	2 (1.8)	p=0.824*
Secondary	5(20)	2(8)	17 (68)	1(4)	
Higher secondary and above	4 (23.5)	1 (5.9)	12 (70.6)	0 (0)	
Fathers' education					
Illiterate	12 (17.4)	13 (18.8)	42 (60.9)	2 (2.9)	χ2=8.85
Primary	25 (27.5)	8 (8.8)	57 (62.6)	1 (1.1)	p=0.710*
Secondary	6 (24)	3 (12)	15 (60)	1 (4)	
Higher secondary and above	4 (22.2)	1(5.6)	13 (72.2)	0 (0)	
Non-formal Education & other's	1 (25)	0 (0)	3 (75)	0(0)	

*Fisher's exact test

Socio-demographic variation of children's weight for height

Table VIII depicts the socio-demographic variation in children's weight-for-height z scores. The majority of male and female respondents exhibited a normal weight-for-height z score, but the prevalence of severe wasting (7.8%) was higher in males than females. No significant association was found between sex and weight-for-height z score (p-value > 0.05). However, there was a significant association between mother's education and weight-for-height z score (p > 0.05), with children experiencing more wasting when mothers had completed higher secondary education or above.

Table-VIII: Socio-demographic variation of children's weight for height z score

Characteristics	Severe Wasted, f(%)	Wasted, f(%)	Normal, f(%)	Overweight, f(%)	Test statistics
Sex of Children					
Male	9 (7.8)	10 (8.7)	95 (82.6)	1(0.9)	χ2=4.697
Female	4(4.3)	6 (6.5)	77(83.7)	5 (5.4)	p=0.193*
Mothers' education					
Illiterate	3 (5.6)	7(13)	41(75)	3(5.6)	χ2 =17.07
Primary	5 (4.5)	6 (5.4)	98 (88.3)	2 (1.8)	p= 0.019*
Secondary	1 (4.0)	0(0%)	23 (92)	1(4)	
Higher secondary and above	4 (23.5)	3 (17.6)	10 (58.8)	0 (0)	

*Fisher's exact test

Socio-demographic variation of children's mid upper arm circumference

Table IX illustrates the socio-demographic variation in children's mid-upper arm circumference. The majority of male (82.6%) and female (79.3%) respondents had a normal mid-upper arm circumference, and a chi-square test revealed no significant association ($p > 0.05$). Children at risk of moderate malnutrition (24%) were more likely to have mothers with a secondary level of education, although no significant association was found between mid-upper arm circumference and mother's education ($p > 0.05$).

Table-IX: Socio-demographic variation of children's Mid upper arm circumference

Characteristics	Severe Acute Malnutrition, f(%)	At risk or moderate Malnutrition, f(%)	Normal, f(%)	Test statistics
Sex of Children				
Male	1 (0.9)	19 (16.5)	95 (82.6)	$\chi2$=0.882
Female	2(2.2)	17 (18.5)	73(79.3)	p=0.639*
Mothers' education				
Illiterate	0 (0)	11 (20.4)	43 (79.6)	$\chi2$ =3.443
Primary	3(2.7)	16 (14.4)	92 (82.9)	p= 0.736*
Secondary	0(0)	6 (24)	19 (76.0)	
Higher secondary and above	0 (0)	3 (17.6)	14 (82.4)	

*Fisher's exact test

DISCUSSION

Good nutritional status is an indispensable requirement for maintaining good health[7]. Any compromise to nutritional status and health during childhood can lead to significant harm and adverse health consequences, creating unavoidable circumstances. The study involved 207 respondents, aiming to assess the nutritional status of under-five children in a climate-vulnerable area. The majority of respondents fell within the age range of 48-59 months, and a significant proportion belonged to Muslim families (70%), with 62.3% having a family size of less than or equal to 5 members.

The educational status of parents, as revealed in this study, indicated that 53.5% of mothers and 44% of fathers had completed primary education[7]. Notably, all children in the study had achieved complete immunization status, aligning with the national statistics reported by the Bangladesh Demographic and Health Survey. Breastfeeding practices also mirrored national trends, with 60.4% of children positively experiencing breastfeeding after birth. However, 18.8% resorted to alternatives like sugar and honey instead of breast milk.

Regarding health indicators, the study reported a low incidence of illness, with 94.2% of respondents not experiencing any health issues in the month preceding data collection. Those who were ill presented with various conditions, such as breathlessness, measles, diarrhea, and malnutrition problems. The study emphasized the impact of climate vulnerability on the health of the population, particularly in an area like Sirajganj, where 67.6% of respondents had resided for less than 30 years, facing challenges such as floods, river bank erosion, cyclones, and displacement[7].

Globally, child malnutrition remains a critical issue, with stunting affecting 26% of under-5 children.[6,35,36,37,38,39] In Bangladesh, the prevalence of stunting, wasting, and underweight[7], aligns closely with the findings of this study. The study identified cases of severe acute malnutrition, stunting, underweight, and wasting based on various anthropometric measurements. Notably, the study observed higher rates of underweight and severe wasting in males, with variations in malnutrition rates based on maternal and paternal education levels and family types. However, these relationships were not statistically significant ($p>0.05$).

The discussion highlighted the improvements in child nutritional status over the past decade, with a decline in stunting from 51% in 2004 to 36% in 2014. While

wasting increased initially and then gradually declined, underweight decreased from 43% in 2004 to 33% in 2014[7]. The study reinforced the importance of proven interventions, such as women's education, increasing community awareness, and ensuring proper nutrition, to address stunting and undernutrition among children. Overall, these findings underscore the complex interplay of factors influencing child nutrition in a climate-vulnerable area and emphasize the need for targeted interventions to mitigate adverse health outcomes.

Several limitations were identified in the study. Firstly, a notable limitation stemmed from the lack of enthusiasm among some participants to engage in the study, which may have introduced a potential selection bias. Additionally, the study's scope was confined to assessing the nutritional status of under-5 children in a specific sub-district of a selected district, which may not adequately represent the diverse climate vulnerabilities across the entirety of Bangladesh. The study's focus on a single time points without follow-up or comparison with a control group hindered the establishment of causal relationships between malnutrition and various contributing factors. To enhance the study's generalizability and strengthen causal inferences, future research should consider a larger sample size and a more comprehensive approach that includes follow-up assessments and comparisons across different regions.

The findings of the study underscore the need for comprehensive actions. Firstly, it is recommended that a large-scale study be conducted, encompassing a more substantial sample size, to enhance the generalizability of the results. Secondly, given that the current study focused on a specific locality, it is imperative to extend the research to different regions to capture the diversity of nutritional challenges faced by under-5 children across Bangladesh. Furthermore, there is a crucial call for a broad-spectrum evaluation of the nutritional status of under-5 children by both governmental and private sectors in Bangladesh. This comprehensive assessment is essential for informing and implementing preventive and curative measures at a national level to address the identified nutritional issues effectively. Such multifaceted efforts are pivotal in safeguarding the health and well-being of the vulnerable under-5 age group in the face of climate-related challenges.

CONCLUSION

In this study, MUAC children with normal nutritional status were found more than malnourished children. The Study revealed that proportion of underweight and severe wasted were more in male than female proportion of underweight and severe wasted were more in extended family than nuclear family. These relationships were not found as statistically significant ($p>0.05$). Multidimensional approach is needed to prevent the malnutrition in this area.

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Review Article

An Update Review on Childhood Interstitial Lung Diseases (chILD)

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Abstract

In recent times, we have encountered several cases of childhood Interstitial Lung Disease (chILD) in our clinical practice in Bangladesh. In developed world, there has been tremendous progress in the approach to chILD, with particular recognition that chILD in infants is often distinct from the forms that occur in older children and adults. Confirmation of diagnosis is challenging because of the rarity of ILD and the fact that the presenting symptoms of ILD often overlap those of common respiratory disorders. There are few case reports and almost no study on chILD in Bangladesh from net search. A growing part of the etiologic spectrum of chILD is being attributed to molecular defects. The pathogenesis of the various chILD is complex and the diseases share common features of inflammatory and fibrotic changes of the lung parenchyma that impair gas exchanges. We are trying to diagnose chILD by excluding methods of suspected children in our aspects. However, in developed nations, clinical practice guidelines emphasize the role for high resolution computed tomography (HRCT) of chest, genetic testing, and lung biopsy in the diagnostic evaluation. Despite improvements in patient management, the therapeutic strategies are still relying mostly on corticosteroids although specific therapies are emerging. Larger longitudinal cohorts of patients are being gathered through ongoing international collaborations to improve disease knowledge and targeted therapies. Thus, it is expected that children with ILD will be able to reach the adulthood transition in a better condition.

Keywords: *Review, childhood, interstitial lung diseases*

INTRODUCTION

The term chILD that are associated with significant morbidity and mortality. Rare lung diseases in children comprise a variety of pulmonary disorders that include cystic fibrosis, primary ciliary dyskinesia, congenital malformations of the lung, pulmonary hypertension, abnormal ventilatory drive and chILDs. The latter is, by itself, a heterogeneous group of very rare lung diseases with an overall estimated prevalence of 1.6–46 per million depending on the few available reports.[1] Thus, they appear to be around 10 times rarer than in adults, covering different aetiologies with some of them being extremely severe.[4] Most general practitioners and paediatricians will face none or one of these patients in their whole career and even paediatric pulmonologists may manage only a few cases of chILD. Unspecific and often inconspicuous, clinical signs could also delay the diagnosis and worsen the prognosis for child.[2]. When an ILD in a child is suspected, further investigations should be performed by experienced radiologists, geneticists and pathologists. Despite an exhaustive workup, a proportion of 6–12% of chILD remains unexplained or undefined.[5]

Chronic ILD in children – "the presence of respiratory symptoms and/or diffuse infiltrates on chest radiograph, abnormal pulmonary function test with evidence of restrictive ventilatory defect and/or impaired gas exchange, and persistence of any of these findings for >3 months."

Clement, 2004.[8] Diffuse lung disease – "a heterogeneous group of uncommon disorders characterized by impaired gas exchange and diffuse infiltrates by imaging.[7]

chILD – "a heterogeneous group of respiratory disorders that are mostly chronic and associated with high morbidity and mortality. These disorders are characterized by inflammatory and fibrotic changes that affect alveolar walls. Typical features include diffuse infiltrates on chest radiograph, abnormal pulmonary function tests with evidence of a restrictive ventilatory defect (in older children) and/or impaired gas exchange.[2]

chILD syndrome – diffuse lung disease in children < 2 years of age with common causes of diffuse lung diseases excluded as the primary diagnose as the presence of at least three of a) respiratory symptoms b) respiratory signs c)hypoxia d) diffuse abnormalities on CXR or CT scan.[13]

EPIDEMIOLOGY

The prevalence of ILDs in children in Bangladesh is not well-established. ILDs are generally considered rare, and specific epidemiological data are limited. We have found

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some cases of chILD form our clinical practice and published them as case report in Bangladesh. Environmental factors, including air pollution (indoor and outdoor), exposure to biomass fuels, and other pollutants, may contribute to the development or progression of ILDs in children in Bangladesh. Epidemiology of ILDs in children can vary within S outh East Asia based on regional and socioeconomic factors, access to healthcare, and environmental exposures. Due to the rarity of pediatric ILDs, larger-scale studies, collaboration among healthcare professionals, and establishment of dedicated registries can help improve our understanding of the epidemiology and management of ILDs in children in these countries.

Overall, ILD is rare in children. Studies have estimated a prevalence of 3.6 cases per million in the United Kingdom and Ireland,[10] and 1.32 cases per million in Germany,[11] 4 cases per million in Denmark. There is no data in Bangladesh from net search.

CLASSIFICATION

Many different approaches have been used for the classification of chILD. According to Kabra it is classified into 2 groups, below 2 years age of children and above. Below 2 years these are a) Diffuse Developmental disorders b) Alveolar growth abnormalities c) Neuroendocrine Hyperplasia of Infancy (NEHA) d) Pulmonary Interstitial Glycogenesis (PIG) e) Surfactant Protein Deficiency Disorders f) Disorders related to systemic illnesses g) Disorders of normal immune responces h) Disorders of immuno compromised host i) Disorders masquerading as interstitial disease j) Aspiration syndromes.

chILD above 2 years are a) Hypersensitivity pneumonitis b) Usual Interstitial Pneumonitis (UIP) c) Recurrent pulmonary hemorrhage d) Lymphocytic Interstitial Pneumonitis (LIP)

The 2004 report of the ERS Task force on chronic ILD in immuno-compitant children presented the 1st classification system for children that was closely linked to the classification system in adult.[15] In 2007, pathologists, together with clinicians, proposed a classification system based on the history of lung tissue for children <2 years of age.[5] This system was later extended to all paediatric age groups.

DIAGNOSIS

Diagnostic approach depends upon many factors. Over the past decade, USA and European Union work groups have proposed some diagnostic approaches.[13,14] The first was in 2013 based on a careful family screening for ILD, followed by the elimination of other diagnoses before proceeding to more specific chILD investigations such as CT scan, genetic tests and lung biopsy.[13]At that time, the number of involved genes was limited to surfactant-related genes (SFTPB, SFTPC, ABCA3 and NKX2-1), pulmonary alveolar proteinosis genes (CSF2RA and CSF2RB) and FOXF1 for diffuse abnormalities of lung development. Two years later, on behalf of the chILD-EU working group proposed another flowchart for the diagnosis of chILD, primarily based on CT scan and placing blood tests, especially genetic testing, before more invasive tests such as bronchoalveolar lavage and lung biopsy.[14] The genetic evolution reflected the expansion and the wider availability of new molecular techniques allowing the study of a panel of genes (next-generation sequencing (NGS) and whole-exome sequencing (WES)) instead of one by one (Sanger sequencing). This led to the discovery of new genetic entities in chILD, such as MARS mutations, other cytosolic aminoacyl-tRNA synthetase (ARS) mutations or OAS1 in pulmonary alveolar proteinosis.[19,20] COPA and STING1 mutations for ILD related to autoinflammatory disorders, and many other even rarer diseases related to mutations in FLNA, TBX4, NHLRC2 or ZNFX1. [17,21,22]

HISTORY

Meticulous history taking and clinical examination is important to diagnose a case of chILD. This remains the first and major step of chILD workup as valuable information can be retrieved from the patient and their family history. Establishing a genealogical tree, also called a pedigree chart, is mandatory in all chILD. It is estimated that up to 20–30% of chILDs are due to monogenic diseases, some of them being associated with extrapulmonary involvement. Thus, collecting information on relatives and siblings can be highly useful: oxygen therapy, lung transplantation, neonatal respiratory distress or unexplained death, neurological issues such as hypotonia, developmental delay, chorea (NKX2-1), cerebral aneurysms (FARSA and FARSB), sensorial defects (ARS), peripheral hypothyroidism (NKX2-1), autoimmune diseases or general symptoms such as fever, skin lesions, joint pains (autoinflammatory disorders, connective tissue diseases), age and cause of death of older generation family members may be of interest. The age at onset of the ILD is crucial information. Now well documented that almost all chILD can occur at any age, some diagnoses are much more frequent in newborns, infants or older children.[23,24]

INVESTIGATIONS

Radiology and imaging (CXR, HRCT)

In the initial stages, CXR may be normal. Subtel radiological findings may be missed. In advanced stages, may find ground glass haziness and prominent interstitial shadows. HRCT play as a vital role for chILD diagnosis. If the diagnosis of chILD is suspected, a high-resolution CT (HRCT) scan is the first-line investigation to be performed.[25,26] The HRCT scan will allow to confirm ILD and to identify the ILD pattern.[27,28] The use of intravenous contrast is indicated if lymphadenopathies, gross structural abnormalities, or associated cardiac or vessel abnormalities need to be differentiated. The lung parenchyma analysis will search for elementary lesions of ILD such as ground-glass anomalies, consolidations, thickening of the bronchovascular interstitium, thickening of the interlobular septa, visualisation of intralobular lines, cystic lesions and micronodules or nodules. Their association, distribution, extent as well as the presence of signs of fibrosis will be sought.[29, 30] The CT pattern observed varies depending on the age of the child. Infants most often present with diffuse ground-glass anomalies associated or not with other abnormalities/ findings. Older children may have more cystic, nodular or even fibrosing abnormalities.

Lung Function Test and Gas exchange

Oxygen saturation at rest, during sleep and with exercise, the absence or presence of clinical signs, and pulmonary hypertension are used in the Fan severity score for chILD {rated 1 (low severity) to 5 (high severity)}.[31] Blood gas may be of interest to determine impairment of gas exchange. The 6-min walk test is particularly interesting in chILD because of its high sensitivity and ease of use from the age of 4– 5 years.[32] The first pulmonary function tests (PFTs) should be performed as soon as possible after chILD diagnosis, if the child's condition allows it and depending on their age.[33,35]

ILD is often characterised by a restrictive ventilatory disorder, with a decrease in total lung capacity and vital capacity. Measurement of diffusing capacity of the lung for carbon monoxide (DLCO) should be systematically performed according to the age of the child. Additionally, measurement of pulmonary compliance is done exceptionally to complete the evaluation.[34] In infants, PFTs can only be performed during sleep and therefore require the use of chloral pre-medication, the use of which is unauthorised in some countries and subject to signed informed consent in others. Between the ages of 3 and 6 years, PFTs require active cooperation. After the age of 6–8 years, exploration approaches that of adults. Functional residual capacity is the most common measurement.

Fiber Optic Bronchoscopy (FOB) and Broncho Alveolar Lavage (BAL)

Flexible bronchoscopy with bronchoalveolar lavage (BAL) should be performed and it allows cytological and microbiological analysis (bacteria, viral and fungi). Collected alveolar fluid will provided information regarding: 1) the volume and appearance of the fluid, 2) cell count and staining for cellular morphology, 3) Perls to detect the presence of iron-containing cell samples, 4) Periodic acid–Schiff (PAS) to detect polysaccharides such as glycogen, glycoproteins, glycolipids and mucins, and 5) targeted staining (Ziehl and Grocott) to detect mycobacteria and fungi, respectively. A global increase of the BAL cell count in the presence of a proven case of chILD and after exclusion of an infection may reflect alveolitis.[36, 39] The cytological examination makes it possible to search for pathogenic agents, viral inclusions, unusual macrophages, foreign bodies and abnormal cell populations.[40] These results, together with those of the HRCT scan, allow a definite chILD diagnosis.[64]

Cardiac ultrasound

Cardiac ultrasound must be carried out early and systematically as part of the severity assessment. It has three main purposes in the evaluation of chILD: 1) the search for pulmonary hypertension, which is an important prognostic factor and part of the Fan severity score items,[13] but can also guide toward specific aetiologies such as diffuse developmental disorders of the lung and surfactant disorders in newborns,[41] 2) the search for a left-sided heart pathology, and 3) the search for cardiac involvement in the context of a general illness).

Genetic study

A genetic cause is currently identified in ~20% of patients with chILD . Genetic analysis is recommended for all paediatric patients with chronic ILD, whether sporadic or familial with no identified cause.[42,44] The analysis must be carried out by specialised genetics centres, and the detection of a genetic.[71,73] The majority of patients in whom a genetic abnormality related to chILD is identified have a mutation in the genes encoding proteins of surfactant metabolism.[46] Mutations in the SFTPB and SFTPC genes, encoding surfactant protein (SP)-B and

SP-C, the surfactant transporter ABCA3 (ATP binding cassette subfamily A member 3), and the transcription factor NKX2-1 (or TTF1 (thyroid transcription factor 1) are most often implicated.[46,47] SFTPA1 and SFTPA2 (SP-A1 and SP-A2) and FLNA (filamin A) mutations have also very rarely been involved in chILD (but more often in adult ILD).[49,50] If alveolar proteinosis is suspected, the genes MARS (methionyl-tRNA synthetase), particularly when elevated liver values are noted, and CSF2RA and CSF2RB (subunits α and β of the receptor) are studied.[51,52] Other ARS (FARSA, FARSB, YARS, IARS and LARS) mutations have also been associated with rare cases of syndromic child.[53,54] Genetic abnormalities responsible for autoinflammatory diseases with autoimmunity have also been described in early chILD such as SAVI syndrome (STING-associated vasculitis of infancy) related to mutations in TMEM173 and COPA syndrome due to mutations in COPA) [55,56].

Lung biopsy

The indications for lung biopsy are currently declining with the progress of genetic diagnostics. Previously considered as the gold standard for chILD diagnosis, it is now discussed as a last line of investigation.[13,14] Microscopic examination is carried out on standard stains (haematoxylin/eosin), special stains (Perls, PAS, Grocott, reticulin and Masson's Trichrome) and immunostaining (TTF-1, bombesin, surfactant proteins and vascular markers). In the case of chILD with extrapulmonary involvement, the diagnosis may be obtained by biopsy of an organ that is easier to access than the lung. This is the case, for example, for sarcoidosis (salivary glands, adenopathy, liver, etc.) or dermatomyositis (skin, muscle, etc.) .[57]

Treatment

In general, supportive care, including oxygen and ventilator therapy when needed, nutritional intervention, prevention of infection, and conditioning and rehab are of utmost importance. Corticosteroids remain the first-line therapy for a number of these disorders, including the surfactant dysfunction disorders, idiopathic interstitial pneumonias, hypersensitivity pneumonia, eosinophilia pneumonia, alveolar haemorrhage, and connective tissue diseases. Use of intravenous pulse steroids. Steroid-sparing agents with anti-inflammatory properties, such as hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, and intravenous immunoglobulin, have also been used with some success.[27] Lung transplantation is an option for children with end stage diffuse lung disease, with long-term outcomes that appear to be comparable to those with CF and pulmonary hypertension.[28]

Supplemental oxygen and ventilator support, nutritional support, proper immunizations, and avoidance of harmful environmental exposures. Lung transplantation is an option for children with end-stage lung disease.[28] Genetic counselling and family support are also important components of care.

CONCLUSIONS

The disorders that together constitute the group of diseases known as chILD are extremely heterogeneous and associated with high morbidity and mortality. The chILD diagnostic process can be simple and relatively short if a systematic two-step approach is followed. The role of the general paediatrician is crucial in untangling the personal and family medical history and the clinical signs, and in referring the patient to specialised centres when chILD is suspected. Even if easily accessible, the HRCT scan should be performed in a specialised centre to optimise its profitability. Lung biopsy is being dethroned by the fantastic progress in molecular diagnostics. However, a low number of expert geneticists may induce a prolonged delay in getting the results. Thus, for each patient, a multidisciplinary case-by-case discussion based on coherent algorithms could minimise chILD diagnostic delay and reduce the proportion of undefined chILD, allowing a maximum of these young patients to receive personalised treatments and to benefit from an improved prognosis.

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Obituary news May 2023

BMA would like to express deep condolence on deaths of the following notable physicians in recent past:

Sl. No.	Name	Date of Death
1	Dr. Shawkat	06/01/2023
2	Dr. Md. Nasir Uddin	06/01/2023
3	Dr. Ananta Anchita Sayeed	08/01/2023
4	Dr. Mirja Istiaq Ahmed Prince	14/01/2023
5	Dr. Swapon Kumar Ghosh	15/01/2023
6	Dr. Monirul Islam Monir	16/01/2023
7	Dr. Minhaj Ul Karim Bhaiya	18/01/2023
8	Dr. N. K. Natasha	19/01/2023
9	Dr. Jahanara	05/02/2023
10	Dr. Simran Ashfaq	16/03/2023
11	Dr. Md. Asadul Haque	27/03/2023
12	Dr. Jafrullah Chaudhary (Freedom Fighter)	11/04/2023
13	Dr. Sayla Rahman	13/04/2023
14	Dr. Md. Riyaz Uddin	26/04/2023

May Allah bless the departed souls.
Our heartiest commiseration to the deceased's family, our prayers are with them during this difficult moment of their life.

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