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Diabetes Prevention Program Research Group.

Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension. 2002;40(5): 679-86 No author given:

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184

Volume with supplement:

Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. Headache. 2002;42 Suppl 2:S93-9.

Issue with supplement:

Glauser TA. Integrating clinical trial data into clinical practice. Neurology. 2002;58(12 Suppl 7):S6-12.

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.

2. Books and Other Monograph Personal author(s):

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

3. Other Published Material MaterialNewspaper article:

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Clinical Spectrum and Management of Ovarian Masses in Children and Adolescent up to 20 Years of Age

Khatoon F[1], Begum SA[2], Choudhury N[3], Yeasmin S[4], Begum M[5]

Abstract

Pathological type as well as management of ovarian tumor in the pediatric population are different than adult women. We performed a retrospective analysis of clinical and diagnostic aspects of ovarian tumors and tumor-like lesions in girls in order to identify characteristics associated with malignancy and it's clinical management which is different from adult women. This is a descriptive type of cross sectional study was condunted among seventy nine female children and adolescent admitted in Bangabandhu Sheikh Mujib Medical University (BSMMU) with ovarian mass from January 2017 to December 2020. Secondary data were collected from hospital record review. The demographic data, diagnostic procedure, management and histopathological analysis of the ovarian tumor were recorded. Mean age of study population was 16.7±3.1 and age range was 8-20 Years. Benign and malignant ovarian tumor was 40.50% and 59.49% respectively. The main symptom and sign were abdominal pain and palpable mass were found in 51% and 50% cases respectively. Malignant lesion appeared as cystic in 22.44%, solid 44.89% and mixed in 32.65% cases. But benign ovarian tumor was found predominantly as cystic in 70% cases preoperatively. More than three fourth (75.51%) of malignant ovarian tumor showed one or more positive tumor marker whereas one third (33.33%) benign tumor had raised tumor marker. Large lesions in both benign and malignant cases were found in almost similar number of cases and these were 80% and 81% respectively. In the group of solid tumors, positive tumor marker results occurred more frequently in patients with malignant tumor (57.14%). Elevated serum alpha feto protein (AFP), Human Chorionic Gonadotrophin (HCG) and high Lactate Dehydrogenage (LDH) value associated more often with malignant tumor. Laparotomy was performed in all cases of study population. Among 49 malignant ovarian tumour 34 (69.3%) underwent ovary preserving surgery. All patient with benign ovarian tumor undergone conservative surgery. Predominantly solid structures noted on imaging studies, large dimension and positive tumor markers are clinical predictors of malignancy. Multicenter prospective studies are needed to improve and unify the ovarian preservation rates across the world.

Keywords: *Ovarian masses, alpha-feto protein, fertility preserving surgery*

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INTRODUCTION

Ovarian masses in girls represent a wide pathological spectrum ranging from tumor-like conditions to highly aggressive malignant tumors. Malignant ovarian tumors (MOT) in children and adolescents are rare, accounting for 0.9% of all malignancies.[1,3,5] It is estimated that almost 10-30% of all the ovarian neoplasms occurring in girls up to 17 years of age are malignant.[2] In premenarchal girls, up to 40% of ovarian neoplasms are malignant.[3,4,5] However, the true incidence of MOT in the pediatric population is unknown, as only few studies, case reports and case series have been published. Germ cell tumors (GCT) are the most frequent malignant tumor of childhood, this contrasts with adults, in whom epithelial malignant tumors (EMT) account for most malignant ovarian neoplasm. Mature cystic teratoma is the most frequent neoplastic tumor of children and adolescents, accounts for more than one half of ovarian neoplasms in women younger than 20 years of age.[1,3,4] Females under the age of 20 years with ovarian masses are unique in terms of clinical symptoms, pathological subtypes and the treatment required.

Tumour markers, including CA 125, AFP, LDH, CEA, and beta hCG, are essential tools in the diagnosis and follow up of specific malignancies in childhood. In children and adolescents, the estimation of serum AFP and B-HCG levels is essential in the evaluation of adnexal

masses. LDH, inhibin, and CA 125 levels may also be useful markers for ovarian tumors that do not produce AFP or b-HCG [11, 8] Management of ovarian lesions varies with demographic, hospital, and physician factors. International treatment guidelines dedicated to children are still not established, causing a great difficulty in making appropriate therapeutic decisions (a search of PubMed: English language; 1966–2017; search terms: "ovarian neoplasms" and "child"/ "ovarian masses" and "child"). This in turn poses a threat to the patient's life and fertility in the future. Recently, efforts are being made to promote ovary-sparing surgery in the appropriate setting. [9,5,7] The rarity of this condition prompted us to conduct this study and share our experience on the clinical aspects and management of different ovarian tumors in girls up to 20 years of age operated at our instituition in last 3 years.

MATERIAL AND METHOD

We reviewed the records of 79 females of the age 20 and below with adnexal masses who were treated at the Gynaecological Oncology department of BSMMU from 2017 to 2020. Sampling was nonrandom purposive sampling. Patients demographics and clinical characteristics, results of laboratory and diagnostic studies especially ultrasound findings and tumor marker were extracted from the hospital database for each cases. Tumor markers, including serum alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-HCG), LDH, cancer antigen 125 (CA-125), carbohydrate antigen 19–9(CA 19–9) and carcino embryonic antigen (CEA) were tested in most cases. The stages of malignant ovarian tumors were done after histopathological report and classified according to FIGO staging. Operative procedure, and histopathology report of and clinical outcome (including preservation rate), of the patients were recorded. All clinical characteristics were reviewed to test their association with malignancy. Patients were followed-up for an average of 17 month (range: 1 to 6 months for benign masses; 1 month to 3 years for malignant neoplasms). Demographic and clinical characteristics of patients in our at-risk cohort were described with frequencies and percentages for categorical variables and medians and interquartile ranges for continuous variables. Descriptive statistics for prevalence and age-wise prevalence was done. Bivariate relationships between patient characteristics and malignancy were assessed using Chi-square, Fisher's exact, and Wilcoxon-Mann-Whitney U tests where appropriate.

The study group was divided into two subgroups of patients; girls with tumor-like lesions combined with benign tumors (non-malignant group) and malignant tumors. A p value of less than 0.05 was required to reject the null hypothesis. For statistical purposes, we included the non-neoplastic cases comprising of corpus luteal cyst, follicular cyst and endometriotic cyst in benign cases. The borderline surface epithelial tumours are included in the malignant category for the same reason. An ovarian lesion was described arbitrarily as large when its diameter was 10 cm or more. Such classification obtained from the previous experiences of other Authors. [9,10]

RESULT

This study was conducted among 270 patients of ovarian tumor by reviewing record of last 3 years period. Among them, 79 cases of girls up to 20 years of age were included for this study purpose.

Table I shows, 67.1% of the patient belong to >15 years age group, 30.4% were between 10-15 years and only 2.5% were from below 10 years age group.

Table-I: Distribution of respondents according to age (n=79)

Age Group (in Years)	Frequency	Percent
<10 Years	2	2.5
10-15 years	24	30.4
>15 years	53	67.1
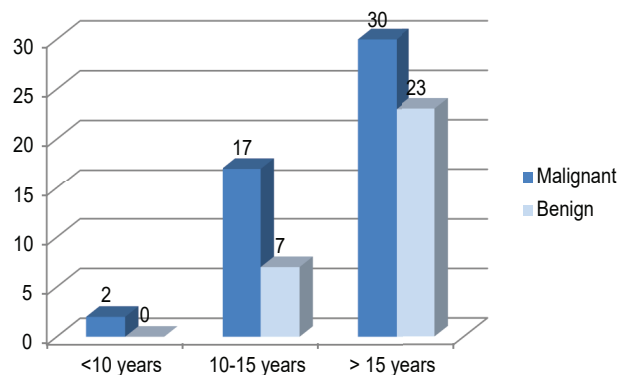
Figure 1: Bar diagram showing frequency of tumors type in different age group

Figure 1 shows, the distribution of types of ovarian tumor (OT) in different age group. Among 79 ovarian tumor, benign ovarian tumor (BOT) were 40.50% and MOT were 59.49%. BOT and MOT in >15 years age group

were 76.66% and 61.22% respectively .On the other hand , In 10-15 years age group BOT and MOT were 23.33% and 34.69%. All cases below 10 years were malignant.
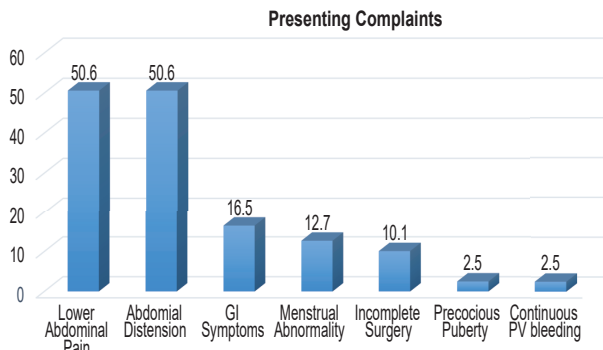
Figure 2: Bar diagram showing distribution of presenting complaints

Figure 2 shows, the most common presenting complain; here both abdominal pain and abdominal distension were 50.6%. GI symptom and menstrual abnormality were 16.5% and 12.7%. Incomplete surgery in MOT were 10.1%. Precocious puberty and P/V bleeding both were 2.5% in frequency.

Table II Shows the distribution of different histopathologic type ; distribution of GCT, epithelial tumor and sex cord stromal tumor were 35 (44.30%) ,28(35.44%) and 5(6.32%) respectively. Non-neoplastic lesion were 11(13.92%). Among GCT, dysgerminoma were 11 (23.40%), Endodermal Sinus tumor were 9 (19.14%) and immature teratoma were 8(17.02%). Among epithelial tumor, Mucinious cystadenocarcinoma were 9 (19.14%) and serous cystadenocarcinoma were 7 (14.89%). Benign Serous and Mucinious tumor were 9(11.39%) and 3(3.79%) respectively.

Table -II: Distribution of Histopathologic type of tumor and age group (n=79)

Histopathologic Type	Age Groups (in Years)			Total
	< 10 Years	10 to 15 years	>15 years	
Germ Cell Tumor(GCT)				35
Mature Teratoma	0	2	5	7
Immature Teratoma	1	2	5	**8**
Dysgerminoma	0	4	7	**11**
Endodermal Sinus Tumor	1	4	4	**9**
Epithelial Tumor				28
Benign Mucinous Tumor	0	0	3	**3**
Malignant Mucinous Tumor	0	3	6	**9**
Benign Serous Tumor	0	2	7	**9**
Malignant Serous Tumor	0	1	6	7
Sex Cord Stromal Tumor				5
Juvenile Granulosa Cell Tumor	0	3	2	**5**
Non Neoplastic Lesion				11
Corpus Luteal Cyst	0	1	0	**1**
Endometriotic Cyst	0	2	5	7
Paraovarian Cyst	0	0	2	**2**
Functional Cyst	0	0	1	**1**
Total	**2**	**24**	**53**	**79**

Table III Shows the comparision of clinical and peroperative findings in BOT and MOT; sonographically 70 %, 23.33% and 6.66% BOT were cystic, mixed and solid in nature. In contarary MOT, were cystic, mixed and solid in 32.65%, 22.44%, and 44.89% cases. The mean ovarian tumor volume was 15.2 (+-8.1) cm (range 2 to 40 cm). Per-operatively 81.63% MOT (40/49) and 80%

(24/30) BOT were >10 cm. Among MOT 67.2% were unilateral 33.3% were bilateral. Torsion was found in 14.3% of MOT and 30.0% of BOT. Metastasis were present in 38.8% of MOT. Age, size and laterility of tumor had no statistical significance with malignancy status of the patient (P=0.262,P=0.579,P=0.059). Only free fluid is statistically significant (p=0.00).

Table-III: Comparison of clinical data in benign and malignant tumor (N=79)

Variables		Malignant Frequency (%)	Benign Frequency (%)	P value
Age Groups (in Years)				
	< 10	2 (4.1)	0 (0.0)	p=0.262
	10 to 15	17 (4.7)	7 (23.3)	
	>15	30 (61.2)	23 (76.7)	
USG Findings				
	Cystic Mass	11 (22.44)	21 (70)	p=0.176
	Solid Mass	22 (44.89)	2 (6.66)	
	Mixed Mass	16 (32.65)	7 (23.33)	
Per-operative findings:				
Size of the tumor (in cm)				
	< 10	9 (18.4)	6 (20.0)	p=0.579
	10 to 15	18 (36.7)	14 (46.7)	
	>15	22 (44.9)	10 (33.3)	
Laterality				
	Unilateral	45(91.8)	23 (76.7)	p=0.059
	Bilateral	4 (8.2)	7 (23.3)	
Consistency				
Cystic		7 (14.28%)	19 (63.33)	P=0.456
Solid		25 (51.02)	0 (00)	
Mixed		17 (34.69%)	11 (36.66)	
Torsion				
	Yes	7 (14.3)	9 (30.0)	p=0.092
	No	42 (85.7)	21 (70.0)	
Free Fluid				
	Yes	22 (44.9)	4 (13.3)	p=0.004
	No	27 (55.1)	26 (86.7)	
Metastatic Deposit				
	Yes	19 (38.8)	6 (20.0)	p=0.082
	No	30 (61.2)	24 (80.0)	

Table IV Shows the various tumor marker status in both BOT and MOT; AFP and both LDH and B-HCG were raised in 15 and 14 cases of MOT. CA-125 were raised in 21 (80.8%) MOT and in 5 (19.2%) BOT. CA-19-9 and CEA were elevated in 14 (77.8%) and 6 (85.7%) MOT, 4(22.2%) and 1(14.3%) cases of BOT. Both large size and raised marker (any one) were found in 70% (28/40) of MOT 45.83% (11/24) of BOT. All solid tumor along with elevated marker 57.14% (8/14) were malignant.

Table V Shows the according to FIGO, Stage distribution of different Histological type; Among 11 cases of Dysgerminoma, 7 cases presented at stage I only 1 cases at stage IV. Among 9 Endodermal sinus tumor tumor 4 cases presented in advanced stage (stage III). 5 cases of Immature teratoma were found in stage I and 3 cases in stage III. All juvenile granulosa cell tumor found in stage I. Seven cases Malignant mucinious cystadenocarcinoma mostly found stage I. Only I cases is found in advanced stage. 4 cases of serous cystadenocarcinoma found in early stage and 2 cases in advanced stage. (Table-V)

Table-IV: Results of tumor marker (n=79)

Variables	Malignant f(%)	Benign f(%)
AFP	15 (100%)	00(00%)
LDH	14 (100%)	00 (00%)
B-HCG	14 (100%)	00 (00%)
CA 125	21(80.8%)	5 (19.2)
CA-19-9	14(77.8)	4 (22.2)
CEA	6 (85.7)	1 (14.3)
Large lesion with positive marker	28/40 (70%)	11/24 (45.83%)
Solid lesion (in USG) with positive marker	8/14(57.14%)	0/5(0%)

Table-V: Distribution of Histological type according to FIGO stage

Histologic type of tumor	Stage of tumor				
	Stage I	Stage II	Stage III	Stage IV	Total
Dysgerminoma	7	2	1	1	11
Endodermal Sinus Tumour	3	2	4	0	9
Immature Teratoma	5	0	3	0	8
Juvenile Granulosa Cell Tumour	5	0	0	0	5
Mucinous Cystadenocarcinoma	7	1	1	0	9
Serous cystadenocarcinoma	4	1	2	0	7

Table VI Shows the modalities of treatment offered in BOT and in MOT; 69.3% MOT and 100% of BOT had ovary preserving surgery. Cystectomy were done in 43.3% of BOT. Unilateral SO (salphingo-ophorectomy) and Unilateral SO with infracolic omentectomy were done in 57.1% and 12.2% cases of MOT and 50.0% and 3.3% cases of BOT . 29.6% MOT underwent radical surgery. Among radical surgery TAH with BLSO with infracolic omentectomy, PCS, SCS and ICS were done in 14.2%,10.2%,4.1% and 2% cases of MOT consecutively. Adjuvant Chemotherapy were given in 31 cases of malignant ovarian tumor. All patient with benign ovarian tumor undergone conservative surgery.

Among the 48 malignant cases we followed up 30 patient for 3 years. Among them 7 girls were found dead. Among them 2 cases were serous cystadenocarcinoma stage III, died at 8-month post-surgery. Two were mucinious cystadenocarcinoma, one died at 1 month and 18 month of follow up. One patient with stage IV dysgerminoma died at 6 month follow up. One yolk sac tumor of stage III and one immature teratoma of stage III died respectively at 19 month and 5 month follow up.

Table-VI: Distribution of respondents according to treatment given n=79

Type of Treatment	Malignant Frequency (%)	Benign Frequency (%)
Ovary Preserving Surgery	34 (69.3%)	30(100%)
Cystectomy (Unilateral / Bilateral)	0 (0.0)	13 (43.3)
Unilateral SO with Cystectomy	0 (0.0)	1 (3.3%)
Unilateral SO	28 (57.1)	15 (50.0)
Unilateral SO with Infracolic Omentectomy	6 (12.2)	1 (3.3)
Radical Surgery	15(29.6%)	00(00%)
TAH with BLSO with Infracolic Omentectomy	7 (14.3)	0 (0.0)
Primary Cytoreductive Surgery(PCS)	5 (10.2)	0 (0.0)
Secondary Cytoreductive Surgery(SCS)	2 (4.1)	0 (0.0)
Interval Cytoreductive Surgery(ICS)	1 (2.0)	0 (0.0)
Adjuvant CT	31 (63.3)	00 (00%)

DISCUSSION

In this study, patient ranged in age from 8 years to 20 years, with a mean age of 16.8(+-3.2) at the time of presentation. which is nearly similar with previous study.[12] Ovarian malignancy accounts for 1% of all the childhood tumors in previous studies but incidence is found as high as 6% and 11.2% in some other studies.[2,11,13] Another study reported 34.8% of all ovarian tumor were malignant, in contrast we found 59.49% were malignant ovarian tumor in paediatric and adolescent adnexal masses.[12] The high frequency of malignant ovarian tumour in our study may be due to our one is a referral hospital where suspected malignancy are reffered.

Regarding age distribution some contradictory observation was found among girls with malignant tumors in the literature.[14,15,16] One study in a large group of 1037 patients noted that most girls with malignant lesions were between 15 and 19 years of age, while another study in a group of 424 patients found the highest incidence of malignancy between 1 and 8 years of age.[10, 17] In our study we noted the mean age of malignant ovarian tumor 16.4 years (+-3.3) and the highest incidence was in the group aged 15 to 20 years. Mean age for benign ovarian tumor was 17.4 (+-2.6).

Germ cell tumor were seen to be three times more than epithelial tumours in younger age group in literature.[18] The frequency of germ cell tumor is reported to vary from 67% to 85% in previous studies.[19] In contrast we found germ cell tumor at a frequency of 44.30 . Second most common was epithelial ovarian tumor at a frequency of 35.44%. Similar frequency of surface epithelial tumor was seen in a study (12). But contrast result regarding surface epithelial was observed, about 15 – 20% [20]. This finding could possibly be explained by the fact that our study population included girls up to 20 years of age when a lot of girls have achieved menarche and are already going through the various hormonal surges giving rise to these tumours.

Dysgerminoma is commonest malignant tumour in our study, which is in accordance with other studies.[2,21]

Sex cord stromal tumor constitute 10-25% of all paediatric ovarian neoplasm.[22] In this study we reported only 6.32% sex cord stromal tumour ,all were Juvenile granulosa cell tumor, similar frequency (5.1%) were observed in previous study.[23]

As regards clinical presentation of ovarian pathology in children we noted another discrepancy between various clinical series in the literature. In our series of patient, Abdominal pain was in frequency of 50% which is in concordance with other study, which shows 45.5%[12] Palpable adnexal mass was 51% which is in contrast with other study , where adnexal mass was 24% in frequency. [22] At the time of initial examination, in this study malignant ovarian tumor was found to be large in 81.01% . Such clinical presentation may indicate significant delay in seeking of medical consultation by the patients and their

parents. Other symptoms, incidental diagnosis (2.53%) and precocious puberty was reported 2.5% in our study, but other study shows 4.6% and 6.2% respectively[22]. There is no strict correlation between the size of ovarian mass and its histology. But study reveals that a large ovarian mass should always raise a concern and should be treated as a risk factor for malignancy [10,24,25]

The gold standard for diagnosing ovarian masses is ultrasound (1). Sonographically we categorise the lesion as cystic, solid mixed. We observed that sonographically mixed masses (32.65%) had more tendency to being malignant .Most of the solid tumor (22/24) were malignant. although previous study did not show any specific relation with large or complex mass.[26,27]

USG continues to be the primary imaging modality used to identify and characterize adnexal masses. USG demonstration of a solid component within a cystic mass is the most important predictor of malignancy and conversely malignancy is very unlikely in the absence of a solid component.[27] but there is pitfall in USG finding which lead to diagnostic problem. Solid component can be seen with benign, as well as borderline and malignant tumor [3,26.]

Regarding gross feature in our study, Apart from the size, the structure of the tumor and its characteristics found very important in preoperative evaluation. Reviewing the data of other authors and our own series it may be concluded that a solid lesion must always be viewed as potentially malignant. But in our series we also found cystic lesion to be malignant, which is also reported by other authors [28]

Tumor marker is an important step in a preoperative assessment of a girl with a pelvic mass. Although many studies have confirmed association of their elevated levels with malignancy, there are some that highlight their limited diagnostic accuracy.[10,29, 30] AFP particularly are increased in patients with tumour with yolk sac components [29]. Our results also revealed their positive role in predicting histology of ovarian lesions. We found , Among the elevated AFP, nine were Yolk sac tumor , 2 were immature teratoma, 2 dysgerminoma,1 juvenile granulosa cell tumor and one was serous cystadeno-carcinoma. Our results revealed all the tumor with elevated AFP were malignant. In a recent study, high serum AFP separated benign from malignant tumors in children and adolescents with a specificity of 89% and with sensitivity of 50% [29] In this study all yolk sac tumor except 2 exibit 2 or 3 marker elevation along with alpha fetoprotein either

LDH or B HCG. One yolk sac tumor show very high level >20,000 iu/ml which was in FIGO stage IIB.

Similarly in our study Raised HCG (14 cases) were observed in three were yolk sac tumor (range from 1000 to 5000iu/), five immature teratoma (ranges 50-10,000 iu/l) and in five dysgerminoma. The same observation was made other study.[15] Our study shows neither CA-12 5, nor CA19-9, is very specific as these were the positive markers in non-malignant lesion too. But when positive markers are correlated with the size, structure and level of tumor marker, they provide very important diagnostic clue. Because tumor marker levels can be high in both benign and malignant tumors, it has been recommended to perform frozen-section analysis before radical surgery and not to rely solely on tumor marker levels in decision -making.[30,31]

In this study. Among malignant ovarian tumour (34/49) 69.3% underwent ovary preservation surgery. The preservation rate was reported in other series vary between the studies (24-82.9%) [32, 24, 33, 34] .There were some reviews indicating lower rates of Oophorectomy when a gynecologic surgeon was present [25,28, 32,33,34]. As fertility preserving procedure are a priority in the constant aging society, we had every attempt to do that. We were dealt with all suspected malignant ovarian tumor and all cases were undergone open laparotomy with frozen section facility. Therefore decision were taken according to the per-operative finding and frozen section report, that may explain the high rate of preservation surgery in our series. The ovarian-sparing technique has been widely adopted in pediatric surgical centers in girls with benign lesions. However,it requires verification based on a long-term follow-up review [9,28,33,31,15,17].Although ovary preserving surgery was done in majority of malignant tumor, adjuvant treatment was given regardless of extent of surgery rather on the basis of histopathological findings. 63.3% of patient got adjuvant chemotherapy. Many studies showed that oncologic treatment such as chemotherapy and radio-therapy increase infertility.[33,34] So it is crucial to diagnose these lesion in early stage.

In summery, We presented important descriptive data from a referral institution where suspected malignancies are referred. The incidence of ovarian tumor increased with age, being most common in patients older than 14 years of age. Abdominal pain is the most common presenting complaint of young adolescent girls with adnexal masses. So the index of suspicion should be kept high and prompt

investigations like ultrasound must be performed to rule out such adnexal masses. AFP is the most useful diagnostic marker for ovarian tumors in young females. Germ cell tumors are the most common ovarian neoplasms in adolescent girls, but fair no. of surface epithelial tumors was observed in our study. Which may be due to inclusion of adolescent up to 20 years.

CONCLUSIONS

The rate of malignant ovarian tumour in children and adolescent is high, 59.49% in this study. More than three fourth 75.51% ovarian tumour showed one or more positive tumour marker. Screening of ovarian tumour might serves girls from malignancy. Treatment guidelines for ovarian lesions in children should be established on the basis of multicenter prospective studies and introduced as soon as possible in order to improve and unify the ovarian preservation rates across all gynecologist. There is need for bigger population studies with larger sample size.

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Original Article

Radionuclide Renogram Findings in Different Kidney Diseases Referred to Institute of Nuclear Medicine and Allied Science (INMAS)

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Abstract

Renal function evaluation with the use of radio nuclide scanning is a very helpful technique. Renogram is a routine procedure in the Institute of Nuclear Medicine and Allied Sciences (INMAS), Sylhet. This is a tertiary referral hospital to north east part of the country. The aim of this study was to analyze the renal disease pattern and outcome of diuretic renogram of different types of renal diseases. This retrospective study was conducted among 223 patients who underwent 99mTc-DTPA renogram from February to October 2018 in INMAS, Sylhet. Mean age of the patients was 30.04 ± 18.52 year with age range 1 to 80 years, male to female ratio 1.5:1. USG. Clinical information and other adjuvant findings along with the ultrasound findings were collected to categorize the study subject. Most common indication for the renogram was hydronephrosis (HDN) 80.27%, followed by smaller kidney 7.17%, renal parenchymal disease 3.14%, nephrolithiasis 3.14% and others (renal cysts and renal artery stenosis). The mean and standard deviation of serum creatinine was 0.9 ± 0.51, range from 0.30 to 4.50. Among the 179 HDN patients, mild, moderate and severe cases were 37 (20.7%), 44 (24.6%) and 81 (45.3%) respectively. Most common site of involvement was left kidney (n=90, 41.3%), followed by both kidneys (n=67, 30.7%). Overall renographic findings showed obstructive disease in 144 (66.05%) patients and non-obstructive disease in 74 (33.94%) patients. It concluded that isotope renogram is very important in the evaluation of renal function especially differentiate between obstructive from non-obstructive pathology.

Keywords: *Radionuclide renogram, 99mTc DTPA (diethylene-triamine-pentaacetic acid), diuretic challenge, renal diseases*

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INTRODUCTION

Renal scan using 99mTc diethylenetriamine pentaacetate (99mTcDTPA) has proved to be a noninvasive, widely available test that can evaluate renal function and urine transit in a single procedure.[1] It also provides the information about the perfusion and function of individual kidney to determine the differential renal function. This sensitive gold standard nuclear imaging study is available in nuclear medicine centers of different areas of the country and offer functional information and anatomic details as well required for thorough evaluation. Tc-99m-DTPA is filtered by the glomerulus and may be used to measure the glomerular filtration rate (GFR), making it theoretically the best (most accurate) choice for kidney function imaging.[2] The burden of radiation hazard is much lower than other radiological modalities[3] in diagnosis and management of various nephro-urological conditions. The aim of this study was to analyze the disease pattern of outcome of diuretic renogram of different types of renal diseases at INMAS, Sylhet like obstructive & non-obstructive renal disease, chronic renal parenchymal disease, nephrolithiasis and others with their functional information along with drainage pattern which are necessary for a justified management protocol.

MATERIAL AND METHODS

This retrospective study was conducted in the Institute of Nuclear Medicine and Allied Sciences (INMAS), Sylhet. Study subjects comprised of 223 patients between ages 1 to 80 years, with mean age of 30.04 ± 18.52 years who underwent 99mTc-DTPA renogram from February 2018 to October 2018. Among them male and female patients were 136 (61%) and 87 (39%) respectively. The method of

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99mTc-DTPA was used for evaluation of renal function was as following. Patients stay well hydrated and then void before starting procedure. First we calculation of full syringe count. Then the patients are placed in supine position in a single photon emission computed tomography (SPECT) digital dual head gamma camera (e-cam series, Siemens from Germany) with detector placed behind. A low-energy high-resolution parallel hole collimator was used, with matrix size 64 x 64, energy peak 140 Kev, and window width 20%. After administration of an intravenous bolus injection of 3-5 mCi 99mTc-DTPA for adult patient and 1-2 mCi 99mTc-DTPA for children, perfusion images are obtained in every 01 second for the first minute followed by acquisition of dynamic images in every 20 seconds for the next 29 minutes. Diuretic is administered intravenously to adult patient according to patient's serum creatinine level within $10^{th} - 15^{th}$ minute after tracer injection and for children it is administered along with the tracer at 0 (zero) minute. In a dilated system, prolonged retention of contrast or radiopharmaceutical is seen because of a reservoir effect. The addition of furosemide (diuretic) to the protocol allows accurate identification of patients affected by obstruction. If mechanical obstruction is present, the narrowed lumen prevents augmented washout; prolonged retention of tracer proximal is seen and can be quantified on the time-activity curves were also calculate the empty syringe count. Time–activity curves from the region of interests are computed and corrected for physical decay. Processing units of gamma camera software measured 99mTc-DTPA renogram clearance for the determination of glomerular filtration rate (GFR). Software also calculate differential renal function (DRF) or split function (SF). In general, in a normally functioning kidney, a half-time of less than 10 minutes from the time of diuretic effect constitutes a normal response. A rapid washout of the isotope in a dilated pelvicalyceal system is considered non obstructed. Persistence of the isotope suggests that the system is not only dilated but also obstructed. The statistical analyses were done by IBM SPSS Statistics (version 25).

RESULTS

Table I Shows the distribution of socio-demographic characteristics of the study population. Among the 223 individuals age of the patients ranged from 1 to 80 years with the mean age of 30.04 ± 18.5 year. Among them 80 (35.9%) patients were in 1-20 years' age group and lowest number 15 (6.7%) were in 61-80 years' age group. Distribution of sex shows that 61% were males and the remaining 39% were females. The mean and standard deviation of age for male and female were 27.79 ± 19.27 years and 33.55 ± 16.78 years respectively.

Table I: Age and sex distribution of the study subjects (n=223)

Parameters		Frequency	Percentage
Age (years)	1-20	80	35.9
	21-40	76	34.1
	41-60	52	23.3
	61-80	15	6.7
Sex	Male	136	61
	Female	87	39

Table II Shows the distribution of common indication for renogram among the study population. Among the study subjects (80.3%). Were indicated for HDN followed by smaller kidney (7.2%), renal parenchymal disease (3.14%), nephrolithiasis (3.14%) and others (renal cysts and renal artery stenosis). The mean and standard deviation of serum creatinine was 0.9 ± 0.51, range from 0.30 to 4.50. Among the 179 HDN patients, mild, moderate and severe cases were 37 (20.7%), 44 (24.6%) and 81 (45.3%) respectively.

Table II: Distribution of common indication for DTPA renogram

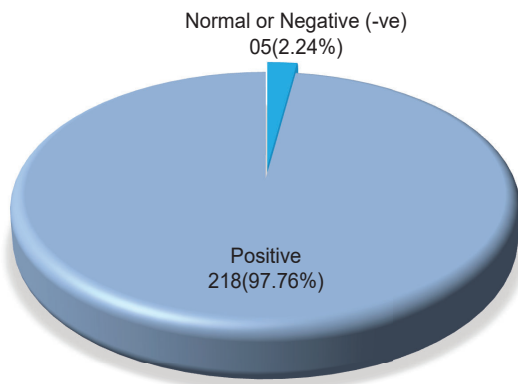| Indications	Frequency	Percent
Hydronephrosis	179	80.3
Nephrolithiasis	7	3.1
Renal parenchymal disease	7	3.1
Smaller kidney	16	7.2
Non visualized	2	0.9
Ectopic	5	2.2
Post pyeloplasty	5	2.2
Renal cyst	1	0.4
Renal artery stenosis	1	0.4
Total	223	100.0

Figure 1: *Radionuclide renogram findings*

Figure-1 Shows the radionuclide renogram findings, among 223 cases, 218 (97.76%) had positive findings on renogram while rest were normal.
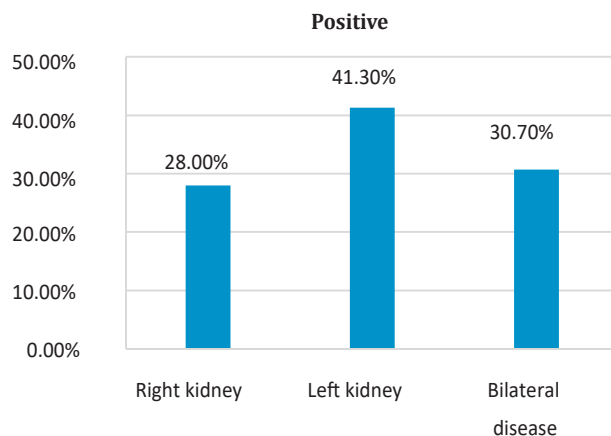
Figure 2: *Site of distribution of renal disease in the study population (n=223).*

Figure-2 Shows the site of distribution of renal disease; the whole group based on site of involvement in renogram was divided as right, left, both kidneys, 90 (41.3%) involvement was in left kidney followed by 61 (28.0%) in right kidney and both kidneys was 67 (30.7%)
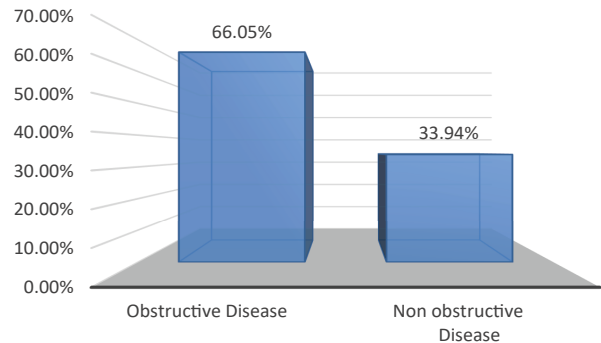
Figure 3: *Renogram findings (in percentages) according to nature of involvement (n=218)*

Figure 3 Shows two main groups as obstructive disease (obstructive uropathy and obstructive nephropathy) and non-obstructive disease (non-obstructive HDN; parenchymal impairment and nonfunctioning kidney). Here obstructive disease was found in 144 (66.05%) patients and non-obstructive disease in 74 (33.94%) patients

Table III Shows the pattern of renogram findings in five groups. In the right kidney (n=61), obstructed nephropathy (obstruction with parenchymal impairment) was 39.3% and others OU, NO, PI and NF were 11.5%, 1.6%, 36.1% and 11.5% respectively ; whereas in the left kidney obstructed uropathy was 33.3% kidney (n=90) and others ON, NO, PI and NF were 30.0%, 3.3%, 22.2% and 11.1% In case of bilateral disease involvement, obstructed nephropathy was (67.2%), others OU, NO, PI, and NF were 16.4%, 00%, 16.4%, 00% respectively.

Table III: Pattern of renogram findings

Site of involvement	Pattern of renogram findings					Total
	Obstructed uropathy (OU)	Obstructed nephropathy (ON)	Non Obstructed (NO)	Parenchymal impairment (PI)	Non-functioning (NF)	
Right kidney	7(11.5%)	24(39.3%)	1(1.6%)	22(36.1%)	7(11.5%)	61(100)
Left kidney	30(33.3%)	27(30.0%)	3(3.3%)	20(22.2%)	10(11.1%)	90(100)
Bilateral	11(16.4%)	45 (67.2%)	0	11(16.4%)	0	67(100)

DISCUSSION

A renogram is simply a time-activity curve that provides a graphic representation of the uptake and excretion of a radiopharmaceutical by the kidneys. Renogram curve can be revealed easily in patients with suspected renal diseases, with disturbances of the renal circulation, with functional obstruction of the upper urinary tract, and specially in the impairment of tubular function. Renogram objectively measures individual renal function and it is considered as the imaging modality of choice for the assessment of the individual renal function[5]. The importance of isotope renogram for evaluating individual kidney's function were previously reported.[6,7]

In this study, distribution of gender showed that 61% were males and the remaining were females. Age ranged from 1 to 80 years. The mean and standard deviation of age was 30.04 ± 18.52 years. These findings are similar to previous study.[9] The range of serum creatinine was 0.30 – 4.50 mg/dl (mean 0.9 ± 0.51). Hosen et al.[8] reported serum creatinine range from 0-5 -12.9 mg/dl (mean 1.75 ± 12.1) that differ from this study could be due to presence of outlier.

This study showed 97.76 % (n=218) cases had positive findings on renogram while rest were normal. Hosen et al.[8] reported normal cases of about 14.29% that is higher than current study might be due to selective referral of the renal patients.

This study revealed that most common site of involvement was left kidney (41.3%, n=90), followed by both kidneys (30.7%, n=67) (figure I). Hosen M et al.[8] reported that 42.86% had pathology in right kidney, 24.49% had in left kidney, 18.37% had bilateral disease and 14.29% had normal findings. This difference of involvement may be due to different method of analysis.

In our institute prior to renogram, renal US is routinely done. HDN is defined as a significant increase in the diameters of the collecting system on US.[9] We classified HDN into three groups according to ultrasound measurement of the renal pelvis diameter: mild (Anterior posterior diameter (APD) 5–9.9 mm), moderate (APD 10–14.9 mm) and severe (APD ≥ 15 mm). The degree of HDN is used to assist in decision making with regard to management and some prognostic information. However, controversy exists over size cutoffs and significant pathology.

In this study, US revealed HDN in 179 (80.3%) patients, smaller kidneys in 16 (7.2%) patients, nephrolithiasis 7 (3.1%) patients, renal parenchymal disease in 7 (3.1%) and others (ectopic kidney, post pyeloplasty, non-visualized kidney etc.). Among the 179 HDN patients, mild, moderate and severe cases were 20.7% (n=37), 24.6% (n=44) and 45.3% (n=81) respectively. By reviewing all the laboratory investigations, the causes of HDN was identified pelvi-ureteric junction obstruction (PUJO) was 46 (25.7%), calculus was 14 (7.8%) and unknown 119 (66.5%).

Overall renographic findings in 218 patients showed obstructive disease in single or both kidneys in 144 (66.05%) patients and non-obstructive disease in 74 (33.94%) patients which is slightly more than Hosen M et al.[8] possibly due to selected group of patients

Diuretic renogram is a dynamic, noninvasive test which was developed to distinguish between the dilated non-obstructed and the dilated obstructed upper urinary tract. [10]. Renogram curves which show an obstructed pattern can be subjected to an increased flow rate as a consequence of the IV administration of a diuretic. Differential renal function (DRF) is the contribution of each kidney to sum of both left and right renal activities, normally ranging from 45% to 55%.[11], although ranges of 42–58% have also been reported in normal adults for 99mTc-MAG 3 imaging[12,13]. A DRF <40% or a decrease of DRF of >5% on successive diuretic renogram studies is indicative of renal function deterioration.

The results were classified into five groups. Among the right kidney (n=61), most common findings were obstructed nephropathy (obstruction with parenchymal impairment) (39.3%), whereas obstructed uropathy (33.3%) in the left kidney(n=90). In bilateral disease involvement, obstructed nephropathy was the common findings (67.2%) (Table –III).

CONCLUSIONS

Evaluation of different renal pathologies & functions by 99mTc-DTPA at INMAS, Sylhet reveals various pattern of nephro-urological disorders. This study analyses the outcome of different renographic findings; mostly unilateral or bilateral obstructive or non-obstructive pattern, parenchymal impairment, functional assessment. The association of our study & clinical presentation of the patients can be sufficient for the clinicians to establish a causal link for the better management of the patients.

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Faecal Calprotectin in Differentiating Inflammatory Bowel Disease (IBD) from Irritable Bowel Syndrome (IBS)

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Abstract

Inflammatory bowel disease (IBD) is a chronic idiopathic inflammatory disorder of the gastrointestinal tract with relapsing and remitting course. Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by altered bowel habit in association with abdominal discomfort and pain. Faecal biomarker may be used an accurate tool in the differentiation of IBD and IBS. The aim of this study was to measure faecal calprotectin (FC) level in patients with IBD and IBS and compare between them. This cross-sectional observational study conducted at the department of Gastroenterology, BSMMU, Dhaka, Bangladesh. Patients with IBD were diagnosed on the basis of compatible history, clinical examination, laboratory, radiological and endoscopic findings, where IBS patients were selected by using the Rome IV criteria. Quantitative faecal calprotectin enzyme-linked immune sorbent assay (ELISA), BÜHLMANN Quantum Blue® test was done and compared between IBD and IBS patients. In this study, Ninety (90) patients were enrolled, 45 patients with IBD and 45 patients with IBS. Mean age of the IBD patients was 32.24±9.76 years and IBS patients was 33.80±9.70 years. There were 28 (62.2%) male and 17 (37.8%) female patients with IBD and 30 (66.7%) male and 15 (33.3%) female patients with IBS. We found faecal calprotectin (FC) level was 445.68 ± 237.35μg/g in IBD patients and 39.16 ± 17.31μg/g in IBS patients. There was a significant difference of faecal calprotectin level between IBD and IBS patients (p-value < 0.001). The sensitivity and specificity of faecal calprotectin to differentiate IBD from IBS was 91.1% and 86.7% respectively. The test accuracy was 88.9%. Area under ROC was 0.959 (95% CI, 0.909 to 1.0). This study showed that faecal calprotectin appears to be clinically useful, non-invasive, rapid and reliable marker to differentiate IBD from IBS.

Keywords: Inflammatory bowel disease, irritable bowel syndrome, faecal calprotectin.

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INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn'sdisease (CD) are chronic idiopathic inflammatory disorders of the gastrointestinal tract with a typically relapsing and remitting course. Peak incidence of UC and CD occurs in second to fourth decade of life. Genetic susceptibility and a number of environmental factors such as smoking, drugs, diets and infectious gastroenteritis are related to IBD.[1] Crohn's disease (CD) is a chronic inflammatory disorder that may involve any part of the alimentary tract from mouth to anus. It can involve all layers of intestine from mucosa to serosa. Patients usually present with diarrhoea, abdominal pain and weight loss. Common complications include stricture and fistula. Numerous extra intestinal manifestations also may occu.[2] Ulcerative colitis (UC) is a chronic relapsing amd remitting disease characterized by diffuse mucosal inflammation of the colon.[3] The exact

etiology of UC is unknown however, it is thought to be caused by inflammatory response to the gut contents in genetically predisposed individuals.[4] The cardinal symptoms of UC are rectal bleeding with passage of mucous and bloody diarrhoea. In severe or extensive UC, acute complications such as severe bleeding , toxic megacolon and perforation may occur. Colorectal cancer is common in UC patients compared to the general population; risk factors include long duration of disease, extensive colonic involvement, severe inflammation and epithelial dysplasia, and childhood-onset disease.[5] There is no single test which allows the diagnosis of IBD. Diagnosis of IBD and differentiation between CD and UC which can be made accurately in most patients based on the patient's history and physical examination, ileocolonoscopic examination, biopsy, double contrast barium enema examination and microbiology.[6] Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by altered bowel habit in association with abdominal discomfort and pain in the absence of detectable structural and biochemical abnormalities.[7] Visceral hypersensitivity, altered gastrointestinal motility , post infectious reactivity, brain-gut interactions, alteration of faecal microflora, bacterial overgrowth, food sensitivity, carbohydrate malabsorption, and intestinal inflammation all have been implicated in the pathogenesis of IBS.[8] IBS is diagnosed solely on the basis of patient-reported symptoms when obvious biochemical and anatomical pathology have been excluded since no biomarkers have been identified to date.[9] The use of recognized diagnostic criteria does allow for a certain degree of standardization in patient characteristics and Rome III are useful resources for this purpose.[10] Rome III criteria cannot exclude IBD before the diagnosis of IBS. Till date there are only few researches about Rome III criteria for diagnosing IBS which is the most commonly used criteria in the world. It has modest value to diagnose IBS. Recently, it showed that Rome IV criteria is much superior to the Rome III criteria, although the clinical relevance of this is uncertain.[11]

IBS is a chronic functional gastrointestinal disorder that affects about 23% of the population across the world. Patients who are seeking health care related to IBS is by far the largest subgroup seen in gastroenterology clinics in primary health care settings.[12] In Bangladesh, its prevalence is reported at 20.6% in men & 27.7% in women.[13] Women present with IBS more commonly than men with a ratio of 2:1.[14] Though, this syndrome is not life threatening, it can significantly impair quality of life

resulting in high health care costs.[15] This economic burden adds to the importance of accurately diagnosing and managing IBS in both primary and secondary healthcare.Lower GI endoscopy was done in most of the patients presented with chronic diarrhoea. IBS is a chronic functional GI disorder. But, if IBD is missed then, several life threatening complications may occur such as, toxic megacolon, intestinal perforation, intestinal obstruction and colonic malignancy. Due to lack of simple clinical or laboratory mean, we do colonoscopy for all. Most of colonoscopic findings are negative, but we do it to ensure that IBD is not missed.[16] We routinely use the inflammatory marker, C-reactive protein (CRP), to track inflammation in our IBD patients, but in our experience, it lacks sufficient sensitivity to make the diagnosis.[17] In several conditions serum markers of intestinal inflammation can be raised. Faecal markers of inflammation in the absence of enteric infection would be more specific for IBD.[18]

Usually faecal biomarkers provide a reliable and simple noninvasive means in the differentiation of IBD and IBS, calprotectin appears to represent the most accurate marker to differentiate between IBD and IBS.[19] Calprotectin is probably the most promising markers for various reasons. Most of the cytosolic proteins in neutrophils is calprotectin. Calprotectin in faeces can therefore be considered directly proportional to neutrophil migration to the gastrointestinal tract. [20]

Calprotectin is stable in stool samples for up to seven days at room temperature and one sample of less than 5 gm is sufficient for a reliable measurement.[21] It is difficult to distinguish IBD from IBS using symptoms and signs only. Most patients with IBS are evaluated by endoscopy and radiographic imaging to exclude a diagnosis of IBD as clinical differentiation remains challenging and may delay effective treatment. This not only exposes patients to the inheretent risks associated with this procedure, but also increases their economic burden.[19] Endoscopic evaluation is often not comfortable but also expensive and has some significant risk such as perforation.[22] Radiological imaging also has drawbacks with observer variability and does not allow histological sampling.[23] Therefore, in this situation a simple, rapid, non-invasive and inexpensive test in discriminating IBD from IBS is of great importance. Environmental and genetic factors are implicated in IBD pathogenesis. Several studies were done in western population regarding faecal calprotectin. But, only limited data are available in Bangladesh in this regard. So, this

cross-sectional observational study was done in Bangladeshi population to see the value of faecal calprotectin level to differentiate IBD from IBS.

MATERIALS AND METHODS

This was a cross-sectional study done in the department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from May 2017 to August 2018. IBD patients were selected on the basis of compatible history, clinical examination, and laboratory, radiological and endoscopic findings.[24,25] IBS patients were selected using the Rome IV criteria. [26] A total of 45 IBD and 45 IBS patients were enrolled purposively aged 18-50 years. IBD and IBS patients diagnosed based on aforementioned criteria were enrolled. Patients with microscopic colitis, indeterminate colitis, infectious colitis, colorectal carcinoma, intestinal tuberculosis, intestinal lymphoma, colonic polyp, history of taking NSAIDs, pregnancy were excluded. IBS patients having alarm features such as anemia, fever, weight loss, melena, family history of colon cancer, thyroid disease, and Diabetes mellitus were excluded. Complete blood count, erythrocyte sedimentation rate (ESR), CRP, RBS, serum albumin, stool R/M/E, stool culture, celiac serology, thyroid function test, abdominal ultrasound and ileocolonoscopy was done. Barium follow through or enteroscopy was also done case by case basis where needed to confirm the diagnosis. Quantitative faecal calprotectin ELISA test was performed. The study was performed after taking ethical clearance from Institutional Review Board (IRB) of BSMMU. Data obtained from the study was used only for the research purpose and the confidentiality of all study information was maintained strictly.

Estimation of faecal calprotectin

For estimation of faecal calprotectin less than 1 gram of native stool was collected in plain tubes without any chemical or biological additives. Samples were stored in refrigerator at 2-8 degree Celsius. Quantitative measurement of faecal calprotectin was done in the department of microbiology, BSMMU. A cut off value ≥50 microgram/ gram was considered positive as per manufacturer's guide.

Sample collection:

For estimation of faecal calprotectin less than 1 gram of native stool was collected in plain tubes without any chemical or biological additives. Samples were stored in refrigerator at 2-8 degree celsius. All patients were requested to provide a stool sample in a container supplied to them.

Test Procedure:

The test was designed for the selective measurement of calprotectin antigen by sandwich immunoassay. A monoclonal capture antibody (mAb) being highly specific for calprotectin is coated onto the test membrane. A second monoclonal detection antibody conjugated to gold colloids is deposited onto the conjugate release pad and released into the reaction system after addition of the extracted diluted stool sample. The Calprotectin/ anti-calprotectin gold conjugate bind to the anti-calprotectin antibody coated on the test membrane and the remaining free anti-calprotectin gold conjugate binds to the goat anti-mouse antibody coated on the test membrane (control line: control band). The signal intensities of the test line and control line are measured quantitatively by the BUHLMANN Quantum Blue Reader. The color intensity is directly proportional to the concentration of calprotectin in the test sample.

Statistical analysis: Numerical variables were presented as mean ± SD. Categorical variables were expressed in percentage. A p-value ≤ 0.05 were considered statistically significant. Only age was normally distributed. All other numerical variables were non-normally distributed. During comparison of two independent numerical variable, student's t test and Mann Whitney U test were used for normally and non-normally distributed data respectively. Two set of categorical variables were tested using Chi-Square test. Sensitivity and specificity was calculated for each test by 95% confidence interval.

Ethical consideration:

Before starting this study, the research protocol was submitted to the institutional review board (IRB) of BSMMU, Dhaka and IRB clearance was obtained. All participants were informed about the objectives, methodology and purpose of the study in easily understandable way. Verbal and written consents were obtained from all participants without any influences prior to sample collection. Data obtained from the study was used only for the research purpose and the confidentiality of all study information was maintained strictly.

RESULTS

A total of 90 patients were enrolled, among them 45 were IBD patients and 45 were IBS patients. Mean age of the IBD patients was 32.24±9.76 years and IBS patients was 33.80±9.70 years. Twenty eight (62.2%) male and 17 (37.8%) female patients with IBD and 30 (66.7%) male

and 15 (33.3%) female patients with IBS. Demographic variables are shown in Table 1. Hemoglobin level was significantly lower in IBD patients than IBS patients (p ≤ 0.001). ESR and CRP was significantly higher in IBD group (Table 1).Faecal calprotectin level was 445.68 ± 237.35µg/g in IBD patients and 39.16 ± 17.31µg/g in IBS patients (p ≤ 0.001)(Table 2). Distribution of the patients according to level of faecal calprotectin at a cut off value 50 µg/g of stool is shown in table 3.No significant difference of faecal calprotectin was found between ulcerative colitis (UC) and crohn's disease (CD) (Table 4). The sensitivity and specificity of faecal calprotectin to distinguish between IBD and IBS using a cut-off value 50 µg/g was 91.1% and 86.7% respectively, with a negative predictive value 90.7% and positive predictive value 87.2%.The test accuracy was 88.9%. Area under ROC was 0.959 (95% CI, 0.909 to 1.0) which is close to 1. It indicates that classifier was very good and difference between the test results of the IBD and IBS was highly significant (p-value <0.001); shown in table 5 and figure 1.

Table I Shows the demographic and biochemical factors in IBD and IBS patients. There were 28 (62.2%) male and 17 (37.8%) female patients with IBD and 30 (66.7%) male and 15 (33.3%) female patients with IBS .The mean difference of hemoglobin level, ESR and CRP level between the patients of IBD and IBS patients were statistically significant (p value < 0.001).

Table I: Demographic and biochemical factors (n=90)

		IBD group	IBS group	P
Age in years (mean ± SD)		32.2 ± 9.8	33.8 ± 9.7	0.450[a]
Gender n (%)	Male	28 (62.2)	30 (66.7)	0.660[b]
	Female	17 (37.8)	15 (33.3)	
Hb (gm/dl)		9.9 ± 0.9	13.4 ± 1.1	<0.001[c]
ESR (mm in 1st hour)		47.5 ± 16.8	15.9 ± 9.9	<0.001[c]
CRP(mg/L)		21.1 ± 11.8	4.2 ± 1.1	<0.001[c]

n= number, %= percentage

P < 0.05 considered significant

a-Students t-test, b- Chi-square test, c- Mann-Whitney U test

Table II shows the faecal calprotectin was 445.68 ± 237.35µg/g in IBD patients and 39.16 ± 17.31µg/g in IBS patients. The p-value was <0.001. The mean difference of faecal calprotectin level was statistically significant between IBD and IBS patients

Table II: Faecal Calprotectin level in IBD and IBS patients (n=90)

Parameter	Groups		p-value
	IBD (n=45)	IBS (n=45)	
Faecal Calprotectin (µg/g) (Mean±SD)	445.68±237.35	39.16±17.31	<0.001c

P < 0.05 considered significant

c- Mann-Whitney U test

Table III shows the distribution of patients of IBD and IBS at a cut off value of 50µg/g faecal calprotectin level. There were 41 (91.1%) patients of IBD and 6 (13.3%) patients of IBS with faecal calprotectin level ≥ 50µg/g of stool and 4 (8.9%) patients of IBD and 39 (86.7%) patients of IBS had faecal calprotectin level < 50 µg/g of stool. The p-value was <0.001.

Table III: Distribution of the patients according to level of faecal calprotectin level at a cut off value 50 µg/g of stool (n=90)

Faecal Calprotectin (µg/g of stool)	Groups		Total	p-value
	IBD (45)	IBS (45)		
≥50	41 (91.1)	6 (13.3)	47 (52.2)	<0.001b
<50	4 (8.9)	39 (86.7)	43 (47.8)	
Total	45 (100.0)	45 (100.0)	90 (100.0)	

P < 0.05 considered significant

b- Chi-square test

Table IV Shows mean±SD of faecal calprotectin level in patients of IBD. In Crohn's disease patients the faecal calprotectin level was 413.91 ± 230.24µg/gm and in patients of Ulcerative colitis was 478.90 ± 245.43µg/gm. The mean difference among the patients of CD and UC was not statistically significant.

Table IV: Faecal Calprotectin level in CD and UC patients (n=45)

Parameter	Groups		p-value
	CD (n=23)	UC (n=22)	
Faecal Calprotectin (µg/gm) [Mean±SD]	413.91 ± 230.24	478.90 ± 245.43	< 0.358[c]

< 0.05 considered significant

c- Mann-Whitney U test

Table V Shows the performance of diagnostic test of faecal calprotectin at a cut-off value 50 µg/g. The sensitivity was 91.1%, Specificity was 86.7% in differentiating IBD from IBS. The PPV was 87.2%, NPV was 90.7% and test accuracy was 88.9%.

Table V: Performance of diagnostic test of faecal calprotectin at a cut off value 50 µg/g

Performance of diagnostic test	%	95%CI	
		Min	Max
Sensitivity	91.1	81.7	96.6
Specificity	86.7	77.3	92.2
PPV	87.2	78.2	92.5
NPV	90.7	80.8	96.5
Accuracy	88.9	79.5	94.4

PPV-positive predictive value,

NPV-Negative predictive value

Performance of diagnostic test of faecal calprotectin at a cut-off value 50 µg/gm to differentiate IBD from IBS.

ROC (Receiver Operator Characteristic) Curve:

The curve was generated by plotting the relationship of true positive versus false positive rate as the threshold value for classifying an item as 0 or is increased from 0 to 1.

ROC Curve

Diagpnal segments are produced by ties
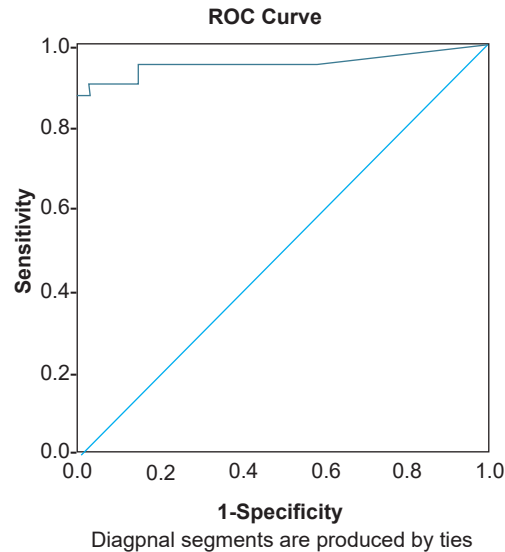
Figure 1: The figure shows AUC score of 0.959 (0.909-1.000) with 95% CI which is close to 1. It indicates that classifier was very good and difference between the test results of the IBD and IBS were highly significant (p-value <0.001).

DISCUSSION

The mean age of the patients with IBD was 32.24 ± 9.76 years and IBS patients was 33.80 ± 9.70 years. Mehrjardi et al.[27] conducted a similar study and found the mean age of the IBD patients was 35.4±8.6 years and the mean age of the IBS patients was 32.3±6.8 years. The mean age of the patients of this study was close to our study. Considering gender distribution, among the IBD patients28 (62.2%) were male and 17 (37.8%) were female. On the other hand 30 (66.7%) were male and 15 (33.3%) were female in IBS patients. Male patients were predominant in both groups in our study. Mehrjardiet al.[27] showed majority of patients in both groups were female. This dissimilarity may be due to easy health care access for male is in our country.

For estimation of faecal calprotectin we used the BUHLMANN Quantum Blue Reader in this study. Same method was used by other authors like Sharbatdaran M. *et al*[28], Dhaliwal *et al.*[29], Chang *et al.*[30]and Kotze et al.[31]. In this current study, low hemoglobin and high ESR and CRP was found in IBD patients. On the other hand, normal hemoglobin and low ESR and CRP was found in IBS patients (p<0.001). This finding was similar as studied by said *et al.*[32], whereas no difference of ESR was found in two groups of patients as studied by Chang *et a*[30]

In our study, we found mean faecal calprotectin level was 445.68±237.35 µg/g in IBD patients and 39.16 ± 17.31 µg/g in IBS patients. Significant difference of faecal calprotectin level between IBD and IBS patients was found (p-value <0.001). Faecal calprotectin at a cut-off value 50µg/g showed sensitivity 91.1%, specificity 86.7% to differentiate IBD from IBS, PPV 87.2%, NPV 90.7% and test accuracy was 88.9%. Consistent result was found in another study done by Kotze et al.[31]in 2015 .They found faecal calprotectin level in Crohn`s disease was 405µg/g and in Ulcerative colitis was 457µg/g and in IBS patients was 50.5µg/g. A significant difference of faecal calprotectin level was found between IBD and IBS patients with p value <0.001. Another study done by Dhaliwal *et a*[298]in 2015 had shown that faecal calprotectin level was 674.0±480.0µg/g in active IBD patients and 34.0±69µg/gin IBS patients. Sensitivity and specificity of faecal calprotectin to differentiate IBD from IBS using a cut off value of 50µg/g was 88% and 78% respectively. A study in Tiawan by Chang et al[30]. in 2014 found mean faecal calprotectin level in IBD patients was 694.8±685.0µg/g and 85.8±136.1µg/g in IBS patients (p <0.001).In comparison of our study, close results were seen regarding difference of faecal calprotectin level in IBD and IBS patients in previous two studies. But faecal calprotectin level was higher in IBD patients in comparison to our study. This could be explained by most patients in our study were previously diagnosed and most of them getting treatment for long time. But, in above mentioned studies all patients were newly diagnosed and faecal calprotectin level was measured before treatment started. Langhorstet al.[33]and Xiang et al.[34]showed significant difference of faecal calprotectin between IBD in relapse and IBD in remission.

There were 6 patients with elevated faecal calprotectin level in IBS which may be due to subtle inflammation or post-infectious IBS as explained by David *et al.*[35] whereaspatients of IBD had <50µg/g of faecal calprotectin level which may be due to IBD in remission as shown by Said*et al.*[32],Erik *et al.*[36]and Dhaliwal et *al*[29].In our study, faecal calprotectin level was significantly higher in IBD patients in comparison to IBS patient, which is similar that of other studies conducted by Tibble *et al.*[37], Antonio et *al.*[38]and Schoepfer*et al*[39].Schoepferet al.[39]measured faecal calprotectin by using another kit and their findings were similar with our study results. C-reactive protein and ESR are commonly used inflammatory markers used by clinicians to discriminate organic gastrointestinal diseases from functional GI disorder. Sensitivity and specificity of

ESR and CRP is much lower than faecal calprotectin. Faecal calprotectin is more superior to CRP and ESR to differentiate IBD from IBS[40].

CONCLUSIONS

In conclusion, based on our study findings and previous study results, estimation of faecal calprotectin is a simple, rapid, accurate and noninvasive test to differentiate inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS).

Limitation

Healthy controls were not taken in the study population.

All patients were recruited in this study from a single tertiary level hospital which does not reflect the whole country.

Clinical Significance

Faecal calprotectin can be used as a screening tool before selection of patients for colonoscopy in adjunct with other clinical examinations to differentiate IBD from IBS.

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Original Article

Clinicopathological Profile of Head and Neck Cancer Patients in a University Hospital, Bangladesh.

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Abstract

In Bangladesh, the head and neck cancer is one of the most prevalent cancers. The goal of this study was to assess at the clinicopathological characteristics of individuals with head and neck cancer. This descriptive, cross-sectional study was conducted from July to December 2018, 286 patients with head and neck cancer were included at Bangabandhu Sheikh Mujib Medical University (BSMMU), Department of Clinical Oncology. A pre-made questionnaire was used to collect data from patients during face-to-face interviews. The mean age of the patients was 56.27 (±12.23) years. The bulk of the cases (77.6%) were male, and the most of the patients consumed tobacco (86%). The most common histological type among the patients was squamous cell carcinoma (92%). In terms of primary tumor location, the oral cavity (36%) was the most prevalent. Patients were most often found in stages III (32.2%) and IV (34.6%). In conclusion, head and neck cancer occurs mainly in males and tobacco users. Squamous cell carcinoma is the most frequent histological form, with the oral cavity as the main location of tumors. The majority of the patients are in advanced stages.

Keywords: *Clinicopathological, head and neck cancer.*

INTRODUCTION

Head and neck cancer refers to cancer of the upper aerodigestive tract, which includes the lips, oropharynx, larynx, oral cavity, hypopharynx, salivary glands and sinonasal cavities. The great majority of them develop from the surface epithelium and hence are squamous cell carcinoma (approximately 90%) or one of its variations.[1]

Each year, more than 887,000 new cases of head and neck cancer are diagnosed worldwide (representing 5.2 percent of all new cancer cases), with 453,000 fatalities.[2] In Bangladesh, the new cases of head and neck cancer were more than 30,000 in 2018. Lip and oral cavity cancers were the most prevalent, with 13,401 new cases, followed by hypopharyngeal cancers (7,099), laryngeal cancers (4,996), oropharyngeal cancers (3,667), salivary gland cancers (849), and nasopharyngeal cancers (845).[3] In our country, there are no comprehensive statistics on head and neck cancer. Only institute-based studies account for the majority of demography. In 2014, our NICRH's outpatient department saw a total of 18,856 newly diagnosed cancer patients. There were 1238 individuals with lip, oral cavity, and pharyngeal cancer among them, accounting for 11.1 percent of the total. There were 245, or 2.2 percent of all patients, having cancer in the cheek and buccal mucosa. Males had 148 cases of tongue cancer, accounting for 2.4 percent, and 109 cases of laryngeal cancer, accounting for 1.8 percent. They were one of the top five malignancies in males when they were all together. The number of females with cheek and buccal mucosa malignancies was 140, making it the sixth most frequent malignancy.[4]

Head and neck cancer epidemiology is closely linked to exposure to specific environmental factors, notably cigarettes and alcohol. There is a clear causal link between smoking and oral cavity cancer. In 80 percent to 90 percent of patients, smoking is established as an independent risk factor.[5,6] Alcohol and tobacco usage together may have a synergistic effect on carcinogenesis.[7]

Head and neck cancer is most commonly diagnosed after 40 years of age.[1] Nearly 60% of all patients with head and neck cancers attend the oncology department in the advanced stages.[8] The majority of people with head and neck cancer have discomfort, trouble swallowing, and a lump in their neck.[9] In this study, we looked at the epidemiological and clinicopathological features of individuals with head and neck cancer.

MATERIALS AND METHODS

This descriptive, cross-sectional study was conducted from July to December 2018, 286 patients with head and neck

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cancer were included at Bangabandhu Sheikh Mujib Medical University's Department of Clinical Oncology. Before collecting data, each patient provided informed consent. The approach of consecutive sampling was followed. A pre-made questionnaire was used to collect data from patients during face-to-face interviews. Age, gender, economic background, primary locations of cancer, clinical stage, histological type, risk factor, and presenting symptoms were study variables. The data was analysed using the SPSS software program for Windows, version 13.0.

RESULT

Table I shows this study included 286 individuals who were diagnosed with head and neck cancer. The mean age of the patients was 56.27 (±12.23) years. Head and neck cancer was most common in 51-60 age group (26.9%). Males cases were 222 (77.6 %) and the female patients were 64 (22.4%). The male-to-female ratio was 3.47:1. The majority of the patients were from lower (37.1%) and middle-class families (49.3%). There were 246 tobacco users (86%) and 40 non-users (14%) among the total number of patients.

Table I: Distribution of patients according to demographic characteristics

Variables	Number of patients
Age (mean± SD)	56.27 (±12.23)
Age groups (%)	
21-30	07 (2.4%)
31-40	22 (7.7%)
41-50	68 (23.7%)
51-60	77 (26.9%)
61-70	63 (22.0%)
>70	49 (17.1%)
Sex (%)	
Male(M)	222(77.6%)
Female(F)	064(22.4%)
M: F (Ratio)	3.47:1
Economic Status (%)	
Lower	106(37.1%)
Middle	141(49.3%)
Upper	039(13.6%)
Tobacco use (%)	
Yes	246(86.0%)
No	40(14.0%)
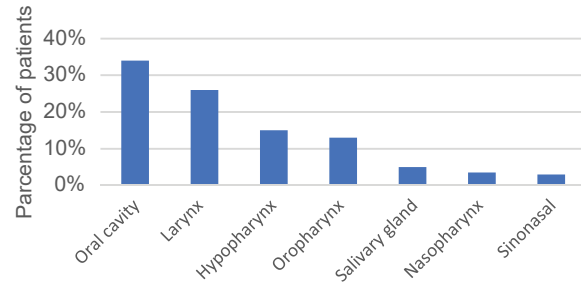
Figure1: Distribution by primary sites

Figure 1 shows the patients' primary sites were the oral cavity (34%) and the larynx (26%). Hypopharynx (15%), oropharynx (12%), salivary gland (6%), nasopharynx (4%), and sinonasal cancer (3%) are among the others.
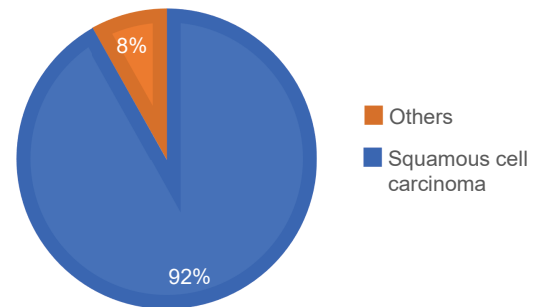
Figure 2: Distribution by histopathological type

Figure 2 shows the individuals squamous cell carcinoma on histopathology (92%). Adenocarcinoma, adenoid cystic carcinoma, acinic cell carcinoma and mucoepidermoid carcinoma, are the other histological categories (8 percent)
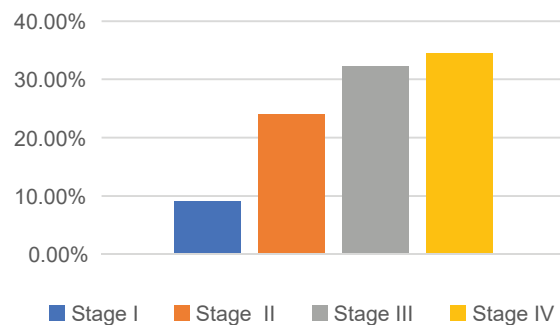
Figure 3: Distribution by stages

Figure 3 shows the patients in different stages of carcinoma, stages III 32.2% and stage IV 34.6% and IV was 34.6%.

Table II shows the most common symptom was neck swelling 197(68.9%) and the second most common symptom was pain in throat and or oral cavity 114(39.9%)

Table II : Distribution of patients according to major complaints

Presenting complaints	Number of patients (%)
Hoarseness of voice	65 (22.7%)
Pain in throat and/or oral cavity	114 (39.9%)
Difficulty in deglutition	77 (26.8%)
Difficulty in taking food	91 (31.8%)
Neck node swelling	197 (68.9%)
Oral ulcer	85 (29.7%)

DISCUSSION

In Bangladesh, the new cases of head and neck cancer were more than 30,000 in 2018. Lip and oral cavity malignancies were the most frequent.[3] In 80 to 90 percent of patients, smoking is established as an independent risk factor.[5,6] The vast majority of people with head and neck cancer are detected at a late stage.[8] A total of 286 patients were studied for this study in order to assess the epidemiological and clinicopathological features of head and neck cancers.

The mean age of the patients was 56.27 (±12.23) years. This finding is comparable to one reported in a Brazilian study.[10] The majority of the patients (89.7%) were diagnosed after the age of 40. This finding is consistent with DeVita et al. that the majority of the patients were over 40 years old.[1] Most of the patients were lower and middle-class, which might be due to the trend of upper-class patients seeking treatment in the private sector or overseas.

The majority of the patients (77.6%) were men, with a male-to-female ratio of 3.47:1, which is consistent with several studies.[10-12] Tobacco use has been identified as the most prevalent risk factor in earlier research.[5-7, 10-12] Tobacco is hazardous in all forms, and there is no such thing as a safe level of tobacco exposure. Cigarette smoking is the most frequent method of tobacco consumption in the world. Waterpipe tobacco, pipe tobacco, different smokeless tobacco products, cigars, roll-your-own tobacco, bidis, kreteks and cigarillos are among the other tobacco products available.[13] We also found that the majority of the patients in our research consumed tobacco (86%). Squamous cell carcinoma (92%) was the most prevalent

histological type we found in this study, which correlates with previous studies.[10-12] Adenocarcinoma, adenoid cystic carcinoma, acinic cell carcinoma and muco-epidermoid carcinoma are among the other histological categories (8%). The oral cavity (34%) was the most frequent primary tumor location, followed by the larynx (26%), hypopharynx (15%), oropharynx (13%), salivary gland (5%), nasopharynx (4%), and sinonasal (3%). India, Bangladesh, Sri Lanka, and Pakistan are the countries with the highest rates of oral cancer.[14] The habit of chewing tobacco, betel, and nuts in these nations is the cause of this high prevalence.[15] The oral cavity was also the most prevalent primary site in several additional investigations.[4,9] The majority of the patients in this study were in advanced stages, which is consistent with Halperin et al.[8] The most frequent symptom was neck swelling (68.9%), followed by pain in the throat or oral cavity (39.9%), and difficulty in taking food (31.8%). Walden and Aygun also found that the majority of patients with head and neck cancer have pain, swallowing difficulties, and swellings in their neck.[9]

CONCLUSIONS

According to the findings, head and neck malignancies are more common in middle-aged men who consume tobacco. Squamous cell carcinoma was the most frequent histological type, with the oral cavity and larynx being the most affected locations. The bulk of the patients were in advanced stages of the disease, necessitating early detection to prevent the disease from progressing.

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Correlation of Long Term Proton Pump Inhibitors (PPI) Use with Iron and Vitamin B12 Deficiency Anaemia

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Abstract:

The Suppression of gastric acid by long term use of PPI may decrease iron and vitamin B12 absorption and might be causing iron and vitamin B12 deficiency anaemia. This comparative cross-sectional study was conducted among patients with peptic ulcer disease from November 2017 to March 2020; attending in the Internal Medicine department of Bangabandhu Sheikh Mujib Medical University (BSMMU). A total of 80 patients were included and divided into group-A (PPIs user) and group-B (non-PPI user), each group containing 40 patients each. The group-A included patients who were taking PPIs for more than one year and aged from 18 to 70 years and group-B the control group who were not taking PPIs for atleast 1(one) year. The data were analysed by Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). The study shown that male were 18(45%) and 19(47.5%) in group A and B respectively and female were 22(55%) and 21(52.5%) in group A and B respectively. The mean age of male and female was (year) 45.35 ± 12.46, 44.85 ± 15.24, respectively. Most of the patient took omeprazole 62.5% follwed by, esomeprazole 20%, pantoprazole 12.5%, rabeprazole 5%. About 47.5% of the patient took PPI for more than 2 years, and 52.5% took between 1-2 years. The mean (±SD) haemoglobin (Hb) level was 10.93±2.00 g/dl amongst group-A and 13.16±1.68g/dl in group-B, the difference is statistically significant (P<0.001). The mean serum iron of the PPI users (group-A) was 46.43±22.79, and of non-PPI users (group-B) was 84.95±33.18, the difference between iron level between two groupd was satistically significant (odds ratio -6.38 ; CI-2.28-17.84 and P-value <0.001). The PPI user group, mean vitamin B12 was 449±166.99 and in non-PPI group it was 432.85±175.93, which was statistically nonsignificant (P-value -1.00). Amonst all the participant low serum concentrations of iron, ferritin and transferrin were found 23(57.5%), 18(45%) and 27(67.5%), respectively in

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Group-A (PPI user group) and 7(17.5%), 7(17.5%) and 8(20%) respectively in Group-B (PPI-non user). The difference was statistically significant (p<0.05) between the two groups. But the value of TIBC was found to be high in 36 (90.0%) participants in both groups, which was statistically non-significant(p=0.33). Hematocrit (HCT) were low in 35 (87.5%) participants in Group-A and 25(62.5%) in Group-B. The difference was statistically significant (p<0.05). Low MCV was found in 10(25%) in the PPI user group and 4(10%) in the non-user group, whish was statistically non-significant. No significant differences in vitamin B12 concentrations (pg/ml) 449±166.99 vs 432.85±175.93 were found between groups A and group B, respectively. There was a weak negative Pearson's correlation shown in ascatter diagram between duration of PPI use, and the iron level of group A (n=40) (r=-.311, p=.051). A negligible Pearson's correlation was seen in the scatter diagram between the duration of PPI use, and vitamin B12 level of group A (r=+.05 p=.977). This study showed a significant decrease in haemoglobin, haematocrit, iron, ferritin, transferrin saturation in participants taking PPIs for more than one year, compared with age and gender-matched controls. No significant change of MCV, TIBC (Total Iron Binding Capacity) and vitamin B12 were noticed between groups. In conclusion,the study found a significant decrease in hematologic indices and iron profile among patients receiving PPIs for longer than one year. There was no substantial change of Vitamin B12 levels was detected between long-term PPIs users and non PPIs user groups. So, from the study it is suggested that judicial prescription of long-term PPIs must be practiced. However, the small sample size and short study duration were the limitation of the study.

INTRODUCTION

Anaemia has long been recognized as a significant global health problem affecting a considerable proportion of the world's population. Iron deficiency is thought to be the most common cause of anaemia, but other nutritional deficiencies like vitamin B12 can cause anaemia.[1] The anaemia is defined as a fall of haemoglobin concentration below a statistically defined threshold lying at two standard deviations below the median of a healthy population of the same age, sex, and stage of pregnancy.[2] According to world health organization(WHO), about 500 million to 1(one) billion individuals representing 15-20% of the world population are presently affected by nutritional anaemia, and half of these have iron deficiency.[3] Nutrition survey of rural Bangladesh during 1975-76 reveals that about 70% of the Bangladeshi population suffers from anaemia with a

mean haemoglobin value of 9.7 gm/dl. The data on the aetiology of anaemia reveal that iron deficiency may be a substantial cause of anaemia in the Bangladeshi population.[1] While epidemiological findings indicate the enormous extent of the problem globally, the developing countries are the most affected areas. It remains a significant problem with serious public health, social and economic consequences and undermines human potential. The prevalence of anaemia in developing countries is predictably three to four times higher than in industrialized countries.

Since their advent in the late 1980s, proton pump inhibitors (PPIs) have become widely used to treat many upper gastrointestinal disorders, including gastro-esophageal reflux disease, peptic ulcer disease, and stress ulcer prophylaxis. The use of proton pump inhibitors (PPIs) in treating gastrointestinal diseases has evolved over recent years. Initially intended for short-term use, PPIs are increasingly being used, often inappropriately, as long-term maintenance medications. Overutilization of PPIs is also well documented. [4] In one series of hospitalized patients, rates of PPI use increased six-fold from admission to discharge, presumably because of failure to discontinue PPIs started for stress ulcer prophylaxis. The absorption rate of non-heme iron is extremely poor without gastric acid. It has long been known that iron absorption is poor under conditions of gastric acid deficiency, such as that observed in patients with atrophic gastritis.[5] Gastric acid plays a vital role in iron and vitamin B12 absorption; the long-term use of PPIs suppresses gastric acid production and has been shown to increase the risk of vitamin B12 deficiency.[6] The study's objective was to explore the association of long-term proton pump inhibitor use with iron and vitaminB12 deficiency anaemia.

MATERIALS AND METHOD

This was a comparative cross-sectional study oconducted among 80 patients of peptic ulcer (PUD), where 50% of them were taking PPIs (Proton Pump Inhibitor) for more than one year, at least 20 or more per month ageing from 18 to 70 years and rest were using medication other them PPIs attended inpatient or outpatient Department of Internal Medicine at Bangabandhu Sheikh Mujib Medical University from November 2017 to March 2020. The patients consented to study participation and were recruited at the first visit. Data collection was accomplished by maintaining adequate privacy and confidentiality without any physical harm abiding by the Helsinki declaration. Patient with gastrointestinal bleeding, excessive menstrual bleeding, strict vegetarian, known case of chronic kidney disease and dialysis, chronic liver disease, smoking, pregnancy, history of intestinal surgery,

malabsorption, malignancy, connective tissue disease, the patient receiving drugs like prolonged ecosprin, NSAIDs, erythropoietin, vitamins, iron or folic acid preparations anticoagulation with coumarin or low-molecular-weight heparin, antiepileptics users, bleeding disorders were excluded from the study.

This study was done in two groups involving group A and group B. Patients who received PPIs for at least one year were enrolled as group A. Age and sex-matched controls were identified using the same inclusion and exclusion criteria as group B. The primary exposure of interest was PPIs use for more than one year. Duration and dose of medication and medication changes were recorded and tabulated after at least one year of PPI therapy. Data collection sheet was filled up from comprehensive history, including deworming, medical records, physical findings, and laboratory reports. Dates of laboratory results were recorded to assess the length of time between collection and initiation of PPIs therapy.

Biochemical assay:

Hematologic indices (including haemoglobin, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, and platelet count) were measured using Automated Haematology Analyzer Pentra ABX-120DX. Additional laboratory data, including iron, TIBC, Serum Ferritin, vitamin B12, were measured using the ARCHITECT Plus ci4100 autoanalyzer manufactured by Abbott, Ilinois, USA.

Cut-off values:

The cut-off values for anemia, in male: haemoglobin level<13 mg/dl, female: haemoglobin level<12 mg/dl (WHO, 2011). Baseline reference ranges for s.iron male 55-160 μg /dl, Female 40-155 μg/dl (Gomella, 2007). Baseline reference ranges for s.ferritin male 30-200 ng/L and female 30-150 ng/L (Isanaka et al., 2012). The level of total iron-binding capacity (TIBC) of serum 155-300μg/dl and serum vitamin B12 is considered 239-931 pg/ml pg/ml according to BSMMU Biochemistry Lab using the ARCHITECT Plus ci4100 autoanalyzer manufactured by Abbott, Ilinois, USA.

Statistical analysis:

The numerical data obtained from the study were analyzed, and the significance of differences was estimated by using statistical methods. Continuous variables were expressed as mean values ± standard deviation and compared using Student's t-test. Categorical variables were expressed as frequencies with percentages and compared using the Chi-square test or Fisher's exact test when & where appropriate. P values less than 0.05 were considered

statistically significant. Data were compiled and analyzed using SPSS version 20.0(SPSS Inc., Chicago, IL, USA).

RESULT

Table- I shows a total of 80 participants were selected for this study. The participants were divided into groups; each group included 40 participants, Group-A who received PPIs (patients who have a history of taking PPIs for at least one year) such as esomeprazole, omeprazole, pantoprazole, and rabeprazole) either single or in combination and Group B (control, PPI non-users). Amongst the participants, male were 18(45%) & 19(47.5%) in group A & B respectively, female were 22(55%) & 21(52.5%) in group A & B respectively. Mean age(year) of male & female were 45.35 ± 12.46, 44.85 ± 15.24 respectively. The average BMI(Kg/m²) in groups A & B were 23.55 ± 4.45, 22.15± 3.63, respectively

Table I: Demographic characteristics of the participant of Group-A and Group -B (N=80)

Characteristics	Group A (n = 40) Frequency n (%) Mean±SD	Group B (n = 40) Frequency n (%) Mean±SD	P-value
Age(year)	45.35 ± 12.46	44.85 ± 15.24	0.873
Male	18 (45%)	19 (47.5%)	0.81
Female	22 (55%)	21 (52.5%)	
BMI (Kg/m²)	23.55 ± 4.45	22.15± 3.63	0.80

Data are expressed as frequency and percentage,
Independent-Samples T-Test is done for quantitative data,
Chi-square test is done for qualitative data

Table-II shows most of the patient (62.5%) took Omeprazole follwed by, Esomeprazole 20%, Pantoprazole 12.5%, Rabeprazole 5%. Among PPI users, 47.5% of patients took PPI more than 2 years, and 52.5 % took PPI between 1-2 years

Table - II: Distribution by categories & duration of Proton pump inhibitor (PPI) use (N=40)

PPI generics & duration	Frequency (N)	Percentage
Omeprazole	25	62.5
Esomeprazole	08	20
Pantoprazole	05	12.5
Rabeprazole	02	05
1 to 2 year	21	52.5
More than 2 year	19	47.5

Table- III shows in this study ,the mean haemoglobin level was 10.93±2.00 in group-A and 13.16±1.68 in group-B , which is statistically significant (OR [Male 8.38 (1.77-39.7) & Female 4.33 (1.19-15.69)] & P-value< 0.001). There was significant difference of haematocrit (HCT) level between the two groups(HCT level was 34.84±6.33 vs 41.04±5.62 in group-A vs group-B, respectively, OR -4.2(1.35-13.06),p-value <0.001). The mean corpuscular volume (MCV) was 84.92±10.11 vs 88.31±6.15 in group-A and group-B, respectively(OR 3 :0.85-10.54 & p-value-0.074). The study has also shown a significant difference between groups in term of concentration of serum iron (46.43±22.79 vs 84.95± 33.18 in group-A vs group-B, OR-6.38 (2.28-17.84), P-VALUE <0.001) ; in serum ferritin level (45.64±37.99 vs 90.13±66.51 in group-A vs group-B, OR-6.38 (2.28-17.84), P-VALUE<0.001) and transferrin saturation (12.96±6.95 vs 24.63.±8.88 in group-A vs group-B, OR-8.31 (3-23.01),p-value<0.001). But, there was no significant difference in between two groups for total iron binding capacity(TIBC) (357.18.±59.37 vs 345.33±48.31 in group-A vs group-B, OR- 1 (0.23-4.31),P-value-0.331), and for vitamin B12 concentration(449±166.99, vs 432.85±175.93, in group-A vs group-B, OR- 1 (0.13-7.47) p value-0.675)

Table III: Comparison of hematologic indices, iron profile and vitamin B12 between two groups (N=80)

Variables	Group A (n=40) Mean±SD	Group B (n=40) Mean±SD	Odds Ratio (CI)	P-value
Hb (g/dL)	10.93±2.00	13.16±1.68	Male 8.38 (1.77-39.7) Female 4.33 (1.19-15.69)	<0.001
HCT %	34.84±6.33	41.04±5.62	4.2(1.35-13.06)	<0.001
MCV (fL)	84.92±10.11	88.31±6.15	3 (0.85-10.54)	0.074
Iron (µg/dL)	46.43±22.79	84.95±33.18	6.38 (2.28-17.84)	<0.001
Ferritin (ngm/L)	45.64±37.99	90.13±66.51	3.86 (1.38-10.76)	<0.001
TIBC (µg/dL)	357.18.±59.37	345.33±48.31	1 (0.23-4.31)	0.331
Tsat %	12.96±6.95	24.63.±8.88	8.31 (3-23.01)	<0.001
Vit B12 (pg/ml)	449 ±166.99	432.85±175.93	1 (0.13-7.47)	0.675

Data were expressed as mean±SD; P-value reached from chi-square test

Table- IV Shows among all the participant ,low serum concentrations of iron, ferritin and transferrin were found 23(57.5%), 18(45%) and 27(67.5%), respectively in PPI Group-A and 7(17.5%), 7(17.5%) and 8(20%) respectively in Group-B.The difference was statistically significant (p<0.05) between the two groups. But the value of TIBC was found to be increased in 36 (90.0%) participants in both groups, which was statistically non-significant

Table- V Shows the HCT concentrations were low in participants in both Group-A (87.5%) & in Group-B (62.5%) (OR:4.2(1.35-13.06;p value-0.010). The difference was statistically significant (p<0.05). Low MCV was found in 10(25%) in the PPI user group and 4(10%) in the non-user group, which is statistically not significant(OR:3 (0.85-10.54; p value-0.115). There was no significant differences in vitamin B12 concentrations (pg/ml) in between two groups (449 ±166.99 vs 432.85±175.93 in group-A vs group-B, respectively,OR: 1 (0.13-7.47;p value-1.00)

Table IV: Comparison of iron profile status between GroupA and Group B (N=80)

Variables		Group A (n=40)	Group B (n=40)	Odd ratio(CI)	P value
Serum iron concentration (μ/dl)	<50	23(57.5%)	7 (17.5%)	6.38 (2.28-17.84)	<0.001
	50-150	17(42.5%)	33 (82.5%)		
S. Ferritin (ng/mL)	<30	18(45.0%)	7 (17.5%)	3.86 (1.38-10.76)	<0.001
	30-200	22(55.0%)	33 (82.5%)		
S. TIBC (μ/dl)	150-300	4 (10.0%)	4 (10.0%)	1 (0.23-4.31)	0.331
	>300	36(90.0%	36 (90%)		
S. Transferrin saturation (%)	<16	27(67.5%)	8 (20%)	8.31(3-23.01)	<0.001
	>16	13(32.5%)	32 (80%)		

P-value reached from chi-square test

Table V: Comparison of haematocrit(HCT), mean corpuscular volume(MCV) and Vitamin B12 between Group A and Group B (n=80)

Variables		Group A (n=40)	Group B (n=40)	Odd ratio(CI)	P value
HCT %	<45	35 (87.5%)	25 (62.5%)	4.2(1.35-13.06)	.010
	>45	5 (12.5%)	15 (37.5%)		
MCV (fl)	<80	10 (25.0%)	4 (10.0%)	3 (0.85-10.54)	0.115
	>80	30 (75.0%)	36 (90%)		
Vitamin B12 (pgm/ml)	<230	2 (5.0%)	2 (5.0%)	1 (0.13-7.47)	1.00
	>230	38 (95.0%)	38 (95.0%)		

P-value reached from chi-square test
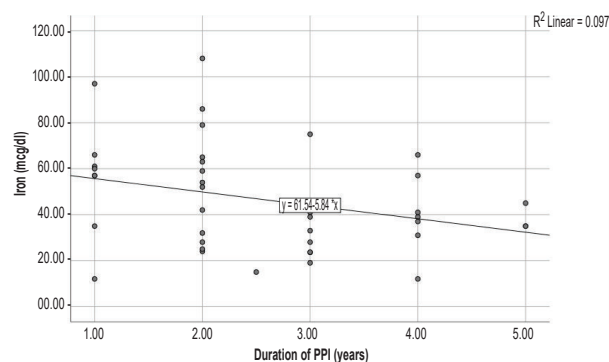
Figure 1A: Scatter diagram showing duration of PPI use and iron level of group A (n=40) has weak negative Pearson's correlation (r=-.311, p=.051)

There was a weak negative Pearson's correlation shown in a scatter diagram between duration of PPI use, and the iron level of group A (n=40) has (r=-.311, p=.051) (Figure- 1A).
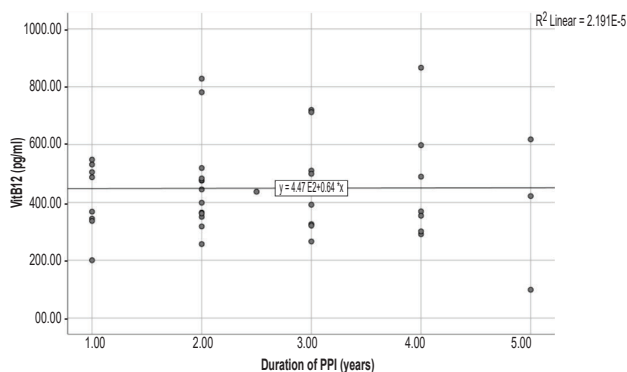

Figure 1B: Scatter diagram showing duration of PPI use and vitamin B12 level of group A (n=40) has negligible Pearson's correlation (r=+.05 p=.977)

A negligible Pearson's correlation was seen in the scatter diagram between the duration of PPI use, and vitamin B12 level of group A (n=40) has (r=+.05 p=.977) (Figure- 1B).

DISCUSSION

This comparative cross-sectional study was conducted in the Department of Internal Medicine in Bangabandhu Sheikh Mujib Medical University to observe the effects of long-term use of PPIs on haematological indices, iron profile, and vitamin B12. About Forty participants with a history of taking PPI for at least one year (including esomeprazole, omeprazole pantoprazole, rabeprazole were included in group-A and a forty participant of age and gender-matched controls were included in group-B. This present study observed that the mean age of the PPI user group was 45.35±12.46 years, ranging from 19 to 70 years, and non-PPI users were was 44.85±15.23 years, ranging from 18 to 70 years. Analysis revealed that difference between the two groups was not statistically significant (p>0.05). The mean age of the current study was very similar to a cross-sectional study done in California.[7]

This study observed that 45% of male and 55% of the female participants belonged to the PPI user group. In the non-PPI user group, 47.5% were male, and 52.5% were female. The difference was statistically not significant between the two groups. A study done by Lam, Schneider, Zhao, and Douglas (2013) found almost similar results in their study.[8]

There was no significant difference in the mean BMI between group-A and group-B (P= 0.80). Den Elzen and his colleagues conducted a study in 2008, and their finding was similar to this study.[9]

In this study, it was observed that among PPI-users, 62.5% used omeprazole, 20% used esomeprazole, 12.5% used pantoprazole, 5% used rabeprazole. A retrospective cohort study conducted by Sarazynski et al.(2011) found similar findings.[10] Roy and his colleagues conducted a study in 2016, and their conclusion is similar to this study .[11] In this present study, it was observed that among the PPIs user group, 52.5% of the participants used PPI for 1 to 2 years, and 47.5% used for more than two years.

The mean Hb was 10.9±2.00g/dl among PPIs users, and mean Hb was 13.16±1.68g/dl in PPIs non-user, which was significantly lower in PPIs user group A (P<0.001), which was consistent with a study done by Krieg et al.[12] Among the male PPI users, 11 subjects (61.1%) had a haemoglobin <13 g/dL who used PPIs for more than a year. The odds ratio (OR) for a <13 g/dl decrease was 8.38 (95% CI, 1.77–39.7). The study conducted by Shikita and her colleagues found the mean haemoglobin level in the PPIs user group was lower than the mean haemoglobin level in the PPIs non-user group.[13] This present study observed that 16 subjects (72.7)% of female PPIs users had a haemoglobin <12 g/dL while on PPIs for more than a year. The odds ratio (OR) for a <12 g/dl decrease was 4.33 (95% CI, 1.19–15.69), had 4.33 times significantly increased chance to develop anaemia in the PPIs user group compared to the non-user group. The study conducted by Sarazansky and associates shown a significant decrease in both haemoglobin and hematocrit in patients taking PPIs for more than one year which is consistent with this study.[10] Lam et al. (2017) showed that PPIs taken for longer than two years were associated with iron deficiency.[7] There was no decrease in the body iron stores or iron deficiency was observed in patients with Zollinger-Ellison syndrome who received continuous omeprazole therapy for up to 12.5 years.[14] There was a strong negative Pearson's correlation of Hb (r=-.729), moderate negative Pearson's correlation of hematocrit (r=-.67), weak negative Pearson's correlation (-.318) of transferrin saturation was found with the duration of long term PPI use. The risk of iron deficiency increased with more prolonged use of PPIs, with over four-fold increased risk among PPI users who took >1.5 pills/d for at least 10years.[7]

In this study, the PPI user group,the mean vitamin B12 was 449 ±166.99, mean vitamin B12 was 432.85±175.93 in the non-PPI user group which was statistically not significant. A similar observation was found in a study done by DenElzenet al. (2008), where they showed that there were no differences in mean serum levels of vitamin B12 between the long-term PPI users and PPI non-user groups and the prevalence of vitamin B12 deficiency (serum level <150 pM) was similar in both the groups: four (3%)in PPI users and three (2%) in non-PPI user group which were consistent with our study. Valuck et al. (2004) found that the current use of PPIs for 12 or more months was associated with vitamin B12 deficiency.[15] Two studies conducted by Ter Helde et al. (2001) and Toliaet al.(2008) in children reported there was no association between PPI use and vitamin B12 deficiency like the current study.[16,17]

CONCLUSIONS

PPIs have long been used to improve gastrointestinal disorders; however, the risks of the long-term use of these drugs have recently been taken into account. There was a significant decrease in hematologic indices and iron profile among patients receiving PPIs for longer than one year. No substantial change of Vitamin B12 levels was observed between long-term PPIs users and non PPIs user groups. We recommend that judicial prescription of long-term PPIs should be made; otherwise, it may cause iron deficiency anaemia. However, the sample size was small; the study was done for a limited period of time & it was a

single center study; hence it may not represent the whole community population. The systemic diseae were excluded clinically and specific investigation was not done . Most of the participants did not show documentation of taking PPIs, so there was a chance of recall bias. Further study should be undertaken with a larger sample size & in multiple centres to find out the real picture .

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Ethical Issue:

The Institutional Review Board of Bangabandhu Sheikh Mujib Medical University approved the protocol for this study.

Conflict of Interest:

The authors declare no conflict of interest.

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Morbidity Pattern among Under Five Children in a Selected Upazilla Health Complex

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Abstract

A descriptive type of cross sectional study was conducted to find out the morbidity pattern of under five children from February to March 2018. Sick child up to 5 years of age attending Sonarganon Upazila Health Complex, Narayangonj were included in this study. Total 250 respondents were selected by purposive sampling method. Data were collected through structured questionnaire by face to face interview and anthropometric measurement by cheklist. Out of 250 respondents, maximum mother 96(38.4%) were in the age group 20-24 year, only 10 (4%) were above 40 years of age. Most of the respondents (94%) were Muslims, one third of them (34%) had non formal education and nearly one third (32%) had completed primary education. About three forth of the respondents (73.6%) were house wives and 40% live in kacha houses. Monthly family incomes 12000TK of the (36.8%) respondent and more than (67%) two third had sanitary latrine. Majority of the children (59.6%) were within the age group of 12 months or less and mean age ± SD was 15 ± 12.8 months and majority were female child (51.2%). Mean weight ± SD and mean height ± SD of the children were 7.84 ± 2.76 kg and 67.77 cm ± 13.5 cm respectively. Among the morbidity it was found that 26.4% were ARI followed by diarrhoea 18.8%, fever 18% pneumonia 13.6%, skin diseases 6.8%, helminthiasis 6.4%, anemia 4.8%, mumps 3.6% and malnutrition 1.6%. Majority of the children (60%) completed immunization.

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Diarrhoea was found more common among illiterate and non-formal educated mothers (55.58%). Acute respiratory infection (ARI) was more prevalent in children who lived in kacha house. Pneumonia was more common among the children of business women (33.3%). This study reveals the existing morbidity pattern of under 5 children and would be helpful for development of health services of under 5 children.

INTRODUCTION

Morbidity can be defined as the condition of being diseased, the rate of disease in a population is a morbidity. Disease state, disability and poor health all together mean morbidity.[1] Morbidity impedes body's metabolism and retards the response. The poor appetite of a malnourished child leads to a fall in dietary intake and indicates a morbid condition. Morbidity reveals impairment in the immune competence of an organism and may cause death at one early stage of life. The common morbidities in Bangladesh are Pneumonia, Diarrhoea, other infections, prematurity, neonatal sepsis, perinatal asphyxia, accidents and poisoning, Pertussis, Measles, Tetanus, Meningitis & Malaria. These morbid conditions often take a heavy toll of every year.[2] The under-5, infant and neonatal mortality rate in our country are 28, 21, and 15 per thousand live births respectively. Although these have been reduced a lot from before, they are still very high when compared with the developed world.[3]

Most often the children living in a developing country like ours reside in a hostile environment, like poverty, overcrowding, lack of easy access to treatment, lack of sanitation and malnutrition. This makes the under -5 age group the frequent victims of infectious diseases & other morbidities. There are some common diseases from which children under 5 are suffering. These are ARI, Diarrhoea, Malnutrition, Helminthiasis, and skin diseases. These diseases are mostly preventable. The morbidities are reducible by improving socio economic conditions, changing some habits and improving macro environment. In the most areas of the country, especially in the lower socio-economic class, water supplies are unprotected & unclean. Latrine & other facilities for disposal of excreta

are inadequate and impoverished. Houses hold rubbish, and garbage is usually dumped in the dwelling places or in the water supply which contaminates the source of water. As a result, high incidence of diarrhoeal diseases does occur. Diarrhea prevalence is usually high among under-five children and it is significantly prevalent among children aged between one to two years.[6]

Homes are poorly ventilated and overcrowded.[5] Smoke from the cooking stoves pollutes the air inside the house, and the polluted air, in turn, causes ARI.[6] ARI causes 23% of infant (0-1yrs) death and 25% death of 1-5 yrs age group. Respiratory infections account for 6% of the total global burden of disease which is a higher percentage compared with the burden of diarrheal disease, cancer, human immunodeficiency virus (HIV) infection, ischemic heart disease or malaria.[7]

Low levels of parental education increases morbidities. Mothers' education, and household economic status are significantly associated with childhood diarrhea.[4] There are also evidence available for a link between maternal education and child health in low and middle-income countries.[8] However, vaccination is playing an important role in giving the children the strength to fight off diseases and disabilities.

MATERIALS AND METHODS

A descriptive type of cross-sectional study was carried out to find out the morbidity pattern among under five children at Sonargaon Upazilla Health Complex. The total study period was from February to March, 2018. Sample was selected purposively and a total of 250 under five children were included in this study. All the under five children attending the hospital were considered as sample. A questionnaire was developed for collecting information for this study. For the collection of anthropometric data, measuring tape and weighting scale were used. The data was collected in every ward and outpatient department of the hospital where under five children were available. The data was collected by interviewing the mother, father or any attending guardian capable of providing necessary information.

RESULT

Total number of 250 under five children were examined to findout their morbidity pattern.

Table I, shows the distribution of mothers by age, among the mothers 38.4% were at the age of 20 to 24 years followed by 23.6% at the age of 25 to 29 years. There were 4% respondents at the age of 40 and above years. A total 94% were Muslims & only 6% were Hindus. Total

number of non-formal educated persons were 34%. The next group was the respondents with primary education which was 32% and graduate & above was 4.4%. Among the respondents 73.6% were housewives, followed by 14.8% garments workers, 5.2% service holders, 4% day labourers and 2.7% were business woman. It was observed that 46.8% respondent were living in pucca houses, 40.8% in kacha houses and 12.4% in tin-shed houses.

Table I   Sociodemographic characteristics of respondents (n=250)

| Attributes	Groups	Number	Percentage %
Age of the Mother (in year)	<20	48	19.2
	20 to 24	96	38.4
	25 to 29	59	23.6
	30 to 34	24	9.6
	35 to 39	13	5.2
	40 and above	10	4
Religion	Islam	235	94
	Hindu	15	6
Education level of the Mother	Illiterate	6	2.4
	Non-formal	85	34.0
	Primary	80	32.0
	Secondary	68	27.2
	Graduate and above	11	4.4
Occupation of the mother	Housewives	184	73.6
	Garments worker	37	14.8
	Service holder	13	5.2
	Day labourer	10	4
	Business woman		2.7
Housing of the respondents	Kacha house	102	40.08
	Pucca house	117	46.8
	Tin shed house	31	12.4
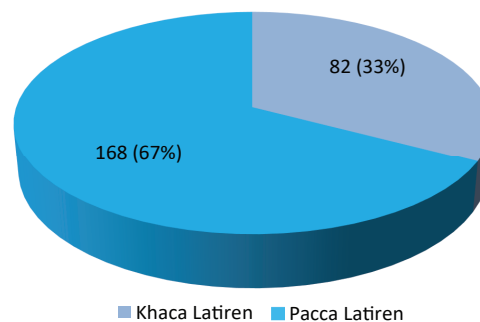
Figure-1: Distribution of respondents by sanitary facilities (n=250).

Regarding sanitary facilities the distribution of respondentrs by sanitary facilities 67% were using sanitary latrine and 33% were using kacha latrine.
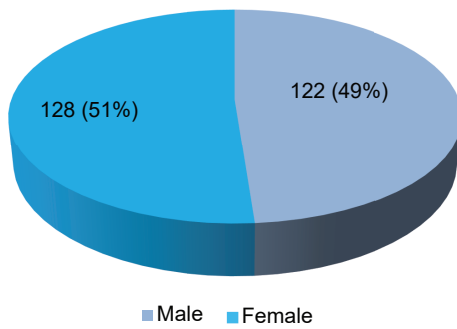
Figure-2: Distribution of the children by Gender (n=250)

Figure 2 shows about 128 (51.2%) children were girls and 122 (48.8%) children were boys.

Table II shows distribution of children, among the 250 children 59.6% belonged to less than 12 months age group, followed by 23.6% in 13 to 24 months age group. Mean±SD age of the children was 15.01±12.76 months. It was observed that 25.2% children were within 61 to 70 cm height, 22.4% within 51 to 60 cm height and 20.8% within 71 to 80 cm height.. Mean height±SD of the children were 67.77±13.50 cm. Among the children 49.2% were of 6.1 to 9 kg weight, followed by 23.6% of 3.1 to 6 kg weight, 2.8% were of 3 kg or less weight. Mean weight ± SD of the children were 7.84±2.76 kg.

Table II Distribution of the children by age, height and weight (n=250)

Attributes	Groups	Number	Percentage %
Age	12 months or less	149	59.6
	13 to 24 months	59	23.6
	25 to 36 months	20	8
	37 to 48 months	17	6.8
	49 to 60 months	05	2
	Mean=15.01 months SD=+12.76 Months		
Height	50 cm or less	27	10.8
	51 to 60 cm	56	22.4
	61 to 70 cm	63	25.2
	71 to 80 cm	52	20.8
	81 to 90 cm	42	16.8
	90 cm and above	10	4
	Mean=67.77 cm SD= + 13.50 cm		
Weight	3 kg or less	07	2.8
	3.1 to 6 kg	59	23.6
	6.1 to 9 kg	123	49.2
	9.1 to 12 kg	45	18
	12.1 to 15 kg	16	6.4
	Mean=7.84 kg SD= + 2.76 kg		
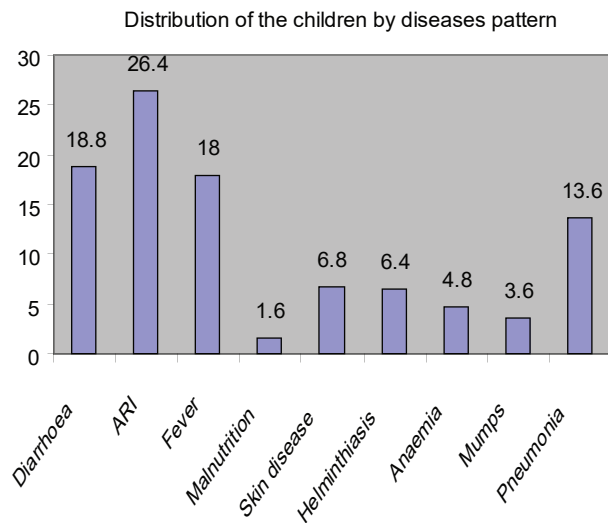
Figure 3: Distribution of the children by diseases pattern (n=250)

Figure 3 shows the distribution of children by disease patterns, 26.4% children suffered from ARI, 18.8% from Diarrhoea, 18% from fever and 13.6% from Pneumonia. There were children who suffered from skin disease (6.8%), Helminthiasis (6.4%), Anaemia (4.8%), Mums (3.6%) and malnutrition (1.6%) respectively.

Table III shows 94.8% respondents had adequate knowledge about breast feeding, 5.2 % had not adequate knowledge. About 28.8% took rice as their supplementary food. This was followed by suji (26%), milk (22.4%), Khichuri (21.8%) and 1.2% took fruits as their supplementary food.

Table III Knowledge of breast feeding and type of supplementary food of children (n=250)

Attributes	Groups	Number	Percentage %
Knowledge about breast feeding	Inadequate knowledge	13	5.2
	Adequate knowledge	237	94.8
Supplementary food	Khichuri	54	21.6
	Shuji	65	26
	Rice	72	28.8
	Fruits	03	1.2
	Milk	56	22.4
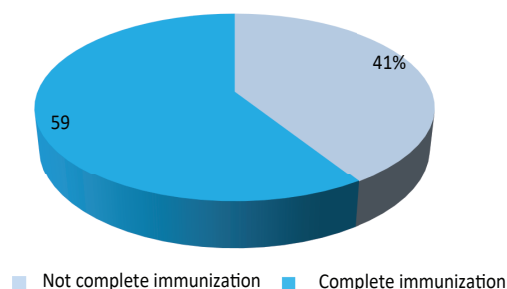
Figure 4: Distribution of the children by immunization status

Figure 4 shows the immunization status of children, 58.8% children were completely immunized and 41.2% were incomplete immunization.

Table IV shows that 33.33% and 16.25% children of illiterate and primary educated mothers respectively suffered from diarrhoea. The children of higher secondary and graduate mothers suffered 15.4% and 9%. Prevalence of ARI was 29.4% among the children living in Kacha house, 25.8% living in tin-shed house and 23.9% living in pacca houses. The occurrence of pneumonia was 33.3% among the children of business women and 31% in children of service holder and 13% aong children of house wives.

**Table IV: Relationship between morbidity of children and mothers' factors**

Factors	Morbidity	
Educational Status	**Diarrhoea Present**	**Diarrhoea Absent**
Illiterate	2 (33.33%)	4(66.66%)
Non formal education	19 (22.35%)	66(77.65%)
Primary	13 (16.25%)	67(83.75)
Up to class X	7 (24%)	22(76%)
Secondary	3 (11.5%)	23(88.5%)
Higher, Secondary	2(15.4%)	11(84.6%)
Graduate and above	1 (9%)	10(91%)
Type of housing	**ARI Present**	**ARI Absent**
Kacha House	30(29.4%)	72(70.6%)
Pacca	28(23.9%)	89(76.1%)
Tin-shed	8(25.8%)	23(74.2%)
Occupation of mother	**Pneumonia Present**	**Pneumonia Absent**
Housewife	24(13%)	160(87%)
Service	4(31%)	9(69%)
Garments workers	4(10.8%)	33(89.2%)
Day labor	0(0%)	10(100%)
Business	2(33.3%)	4(66.7%)

DISCUSSION

In this study when demographic data were analyzed it was found that among 250 respondents 102 (40.8%) resided in Kacha house, 117 (46.8%) in pacca house and only 31(12.4%) in Tin shed house. According to a survey report of Bangladesh Bureau of Statistics, more than half of the countries total population live in Kacha houses.[9] Regarding sanitary facility majority 168(67%) were using Sanitary facilities using sanitary latrine and rest 82(33%) were using khacca latrine. According to the Bangladesh Bureau of Statistics (BBS) and UNICEF, the proportion of households using sanitary latrines in rural areas was 49.9% in 2009.[10]

Male female ratio of children in 61:64. Mean height of child were 67.77 $\pm$ 13.5cm. Majority 63(25.2%) were belong to 61 to 70 cm of height and lonely 10(4%) were belong to 90cm and above. Mean weight of children were 7.84 $\pm$ 2.76 kg. Maximum 123 (49.2%) belong to the wt. 6.1 to 9 kg only 16 (6.4%) were belong to weight 12.1 to 15 kg. Maximum 143(58.8%) child had completed Immunization and 103 (41.2) were not completed immunization. A study conducted from Secondary dataset from Bangladesh Demographic and Health Survey shows about 86% of the children were fully immunized which is much higher than our finding.[11]

In this study, it was found that ARI is the major cause of morbidity among under five children, 66(26.4%) followed by dirarrhoea.[9] 47(18.8%) which supports the WHO. WHO report from state of world children's 98 shows that annual death of under five children by main causes are ARI (30%) and dirarrhoeal diseases (28%).[12] Another report from WHO bulletin 1996-97 shows that, ARI accounts for 30% to 50% of pediatric hospitalization in most developing countries. 33% of deaths of under five children in 1995 were due to ARI, pneumonia.[13] The study observed that, major cause of under-five morbidity is Diarrhoea, ARI, Fever, pneumonia, which was also found in WHO report explaining the most common enemies of the world children includes several diseases that kill over 8 million children a year in developing countries. These are diarrhoea, Pneumonia, measles, ARI, malnutritional etc. Out of 8 million under five child deaths, 4.5 million die from ARI, 2.5 million die from diarrhoea and 0.6 million die from other diseases. Considering the occurrences of diseases among under five children, it was found that, ARI, diarrhoea, fever, pneumonia, helminthiasis, fever. were the major causes of their illness .A morbidity study carried out in 350 children below 5 years, in a sindhi colony in Raja

Park of Jaypur city India, Sharma et al [14] showed that, a majority of children (78%) suffered from one or more diseases like ARI, diarrhoea, pneumonia and helminthiasis which were leading causes of illness.

The majority of children in this study were under 12 month's age group indicating higher morbidity in lower age group. It is supported by a hospital-based study by Amin R et al who showed that 55% of total morbidity occurred in 0-12 months of age and highest mortality was due to ARI (23.7%), diarrhoeal disease (34.6%) and fever (2%) also prevalent among this age group. The study found higher incidence of diarrhoea among lower educational status. [15]

A study done in Ghana on factors associated with childrens' Diarrhoea and ARI shows Children under-5 years old whose mothers had a secondary or higher education had a lower prevalence of diarrhoea compared to children whose mothers had no formal education.[16]

It was found that children of illiterate mothers suffered more from diarrhoea 13(22%) than the literate mothers. A study among 0-4 years children of urban community of Abidjan by Domande et al revealed that low literacy and poor socioeconomic condition and lack of water supply within the house were the associated factor responsible for occurrence of diseases such as diarrhoea, ARI etc.[17]

The study observed higher incidence of ARI in lower living condition (Kacha house) I,e 29% . A longitudinal study by Mitra N was carried out in West Bengal on ARI among rural under-fives showed that overall incidence density rate of ARI episodes was 19.57/100 person months at risk. Risk ratio analysis showed that, low socio-economic class, low birth weight, malnutrition of the children, low standard of living and indoor smoke pollution were significantly associated with increasing number of ARI episodes.[18] The study showed that, the occurrence of pneumonia was more among the children of service holder mothers (33.3%) and Business women (33.3%) than the children of house wives (13.2%). It indicates that lack of care was responsible for the occurrence of disease among children. The study revealed that major causes of morbidity among under five children were ARI 46 (26.4%) and diarrhoea 33(19%) which supports another study by Anandhi CL et al. who conducted a cross sectional study on acute morbidity in under five children in a rural area of Haryana, India found that out of 980 under five children 81 had diarrhoea and 78 had ARI. These two diseases are more prevalent among under five children.[19]

CONCLUSIONS

Study shows that most of the mothers was young adult and are Muslims. Most of them were housewives, primary educated, residing in kacha houses and used sanitary latrine. Maximum children were below one year of age and female child. Most of the children completed immunization. ARI was most common morbid condition followed by diarrhoea, fever, pneumonia and others. ARI was more prevalent in children who lived in Kacha houses and pneumonia was more common among the children of business women. Findings of this study may be a useful basis for future research.

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Post Traumatic Stress Disorder among the Forcibly Displaced Rohingya Population from Myanmar Nationals in Bangladesh

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Abstract

Forcibly Displaced Myanmar Nationals (FDMN's) specially Rohingya population considered as a maltreated minority. They suffered physical brutality that conse- quences are physical, sexual and psychological trauma. This community based cross-sectional study was carried out to ascertain the prevalence rate and associated factors of post traumatic stress disorder (PTSD) among the 363 adult Rohingyas in the Kutupalong and Nayapara refugee camps, Cox's Bazar, Bangladesh by a semi-structured questionnaire through face-to-face interviews during the study period of June 2018 to November 2018. Among the 363 study participants, 60.33% had probable PTSD. The prevalence of PTSD was found higher in female (64.7%) in comparison to male (53.52%) and a statistically significant association (P=0.03) found between sex and PTSD. Married people had a higher prevalence of PTSD (64.62%) in compared to unmarried people and a significant association (P=0.003) found with the presence of PTSD. The prevalence of PTSD was very high (72.55%) among the respondents those faced sexual exploitation. Among the exploitations related variables, having previous experience of sexual exploitations were found statistically significant associated (P=0.039) with PTSD. Hypertension had a statistically significant association (P=0.02) with PTSD and the prevalence of PTSD among Hypertensive patients was 71.79%. Probable PTSD was highly prevalent among the Rohingya population in Bangladesh. Measures should be taken by trained healthcare professionals and mental healthcare providers.

Keywords: PTSD, Rohingya FDMN, sexual exploitations, medical conditions, Cox's Bazar, Bangladesh.

INTRODUCTION

Forced displacement or forced immigration is the coerced movement of a person away from home or region. In some cases, the forced immigrant may become a refugee, as the term has a certain definition.[1-2] Refugee crisis is an emerging global problem, United Nations High Commissioner for Refugees (UNHCR) reporting an intense increase of forcibly displaced populations from 59.5 million in 2014 to 65.3 million in 2015.[3] About 10 million stateless people and 1.5 million people who are refugees in addition to being stateless.[4,5]

UNHCR reported, an estimated 389,000 Rohingyas had fled since the last spell of violence exploded in Northern Rakhine state on August 25, 2017.[5] Kutupalong and Nayapara refugee camp are two government-run refugee camps in the Cox's Bazar area of southern Bangladesh have around 77,000 FDMN's, and it is increasing with time.[5,6] These enormous outflows of refugees were followed by huge deportation to Burma. Repatriation has been considered the desired solution to the refugee crisis. Since the influx of Rohingya over international borders has never ceased, and it has not ascertained a definite solution. The root causes of this unprecedented evacuation are not effectually resolved for this crisis.[6]

Rohingya FDMN's considered as a persecuted minority in the world. The majority is not considered to be citizens by the Myanmar Government, and live in a statelessness condition.[7] They have been fleeing Myanmar in huge numbers, often to nearby developing countries- specially in Bangladesh to avoid conflict and persecution.[8] Compatibly, the refugee crisis in Bangladesh has reached critical levels, with the number of unregistered Rohingya population estimated 200,000 to 500,000.[9]

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The Rohingya situation in Bangladesh becomes one of the most protracted in the world, with more than twenty years of continuous camp settlements. Due to unstructured refugee policies in Bangladesh and politicization of the refugee situation, integration of Rohingyas becomes a challenge. The Government declared national policy for managing the Myanmar refugees in 2014. Whether residing in camp or non-camp areas, the Rohingya FDMN's have been issued to the miserable living conditions marked by scarcity of basic needs, exposure to various types of violence, restricted movement, local aggression, and various forms of discernment.[10]

However, these victims of this forced migrant often suffer from physical brutality, those results in physical, sexual and psychological trauma. Due to their vulnerability, they run the health risk of sexually transmitted diseases, hepatitis, tuberculosis and other communicable diseases; unwanted pregnancy, teen pregnancy, forced abortion and abortion-related complications; rape and other physical exploitation. There are also several mental and emotional health conditions such as nightmares, insomnia, alcohol and drug abuse, suicidal ideation and attempt, even suicide and homicide.

MATERIAL AND METHODS

Study design

A community based cross sectional study was carried out to ascertain the prevalence rate and associated factors of PTSD among the Forcibly Displaced Rohingya population from Myanmar nationals in Bangladesh. The study sample was selected purposively who satisfied the inclusion criteria of the study during the period of June 2018 to November 2018. Suffering from any severe physical or psychological diseases before force migration were excluded from the study.

Study places

Total 363 adult Rohingya peoples (≥18 years) were selected, living in the Kutupalong and Nayapara refugee camps, Cox's Bazar, Bangladesh.

Data collection

A pre-tested semi-structured questionnaire was used for data collection through face-to-face interviews after obtaining informed written consent from each participant.

Data analysis

The data were checked and cleaned followed by making a template, categorizing data, coding and recoding into IBM SPSS v23. The analysis was carried out by using both descriptive and inferential statistics, and presented with frequency tables and chart.

Ethical approval

The study was approved by the North South University Ethical Review Committee (NSU-ERC).

RESULTS

Table I shows, presents the socio-demographic state of the Rohingya population. Among 363 Rohingya around two-third (60.88%) were female and three-fourth (76.4%) were married. The study participants were between 18-60 years old, whereas more than half (52.07%) were aged 40 years or higher. Most of them (67.91%) were learned the Quran from informal Arabic schools and only 8.76% of Rohingya people were received formal education through school. Among the study participants around two-third (62.26%) had more than 6 members in their household. When they were staying in Myanmar, regarding occupation most of them (42.42%) was homemaker and more than 95% had a permanent residence and about their average monthly family income, 53.99% had less than 500 USD.

Table 1: Socio-demographic state of the Rohingya population (n=363)

Variables		n(%)
Age	≥40 years	189 (52.07)
	<40 years	174 (47.93)
Sex	Female	221 (60.88)
	Male	142 (39.12)
Marital status	Married	277 (76.40)
	Others	86 (23.60)
Education	No education	85 (23.33)
	Arabic (Quran)	246 (67.91)
	Formal education	32 (8.76)
Past occupation	Agriculture	102 (28.10)
	Business	58 (15.98)
	Homemaker	154 (42.42)
	Others	49 (13.50)
Current household members	≤6 members	137 (37.74)
	>6 members	226 (62.26)
Had permanent residence	Yes	345 (95.04)
	No	18 (4.96)
Past average monthly family income	≥500 USD	167 (46.01)
	<500 USD	196 (53.99)

Table II Shows, demonstrates the exploitations faced by Rohingya FDMN's before entry in the Bangladesh. The prevalence of sexual exploitations was 16.8% and physical exploitations were 14.05%. Other types of exploitations like threat, economic and land-house related damage were also faced by 28.65% of participants.

Table II: Exploitations faced by the Rohingya population before entering in Bangladesh (n=363)

Exploitations faced		n(%)
Sexual	Yes	61 (16.81)
	No	302 (83.19)
Physical	Yes	51 (14.05)
	No	312 (85.95)
Others	Yes	104 (28.65)
	No	259 (71.35)

Table III Shows, represents the distribution of physical factors of the Rohingya population. The prevalence of Hypertension (21.49%) was higher than Diabetes mellitus (9.37%) among the study participants and prevalence of physical disabilities were found in only 3.3% of participants. Three-fourth (74.38%) participants reported that they received medical supports as required.

Table III : Physical factors of the Rohingya population (n=363)

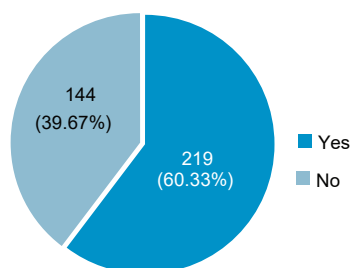| Physical factors		n(%)
Diabetes mellitus	Yes	34 (9.37)
	No	329 (90.63)
Hypertension	Yes	78 (21.49)
	No	285 (78.51)
Physical disabilities	Yes	12 (3.30)
	No	351 (96.70)
Getting medical supports	Yes	270 (74.38)
	No	93 (25.62)

Figure 1: Prevalence of PTSD among the Rohingya population (n=363)

Figure 1 Shows, illustrates the prevalence of PTSD among Rohingya communities in Bangladesh. Among the 363 study participants, three-fifth (60.33%) had probable PTSD.

Table IV Shows, interprets the prevalence of PTSD varies in different characteristics of the study participants. The prevalence of PTSD was found higher in females (64.7%) in comparison to males (53.52%) and a statistically significant association (P=0.03) found between sex and PTSD. The statistical association between age (P=0.27) and education (P=0.88) with PTSD were not revealed, though the prevalence of PTSD was higher among the individuals who are less than 40 years old. People those had a formal education showed a lower prevalence of PTSD (56.25%) in compared to other educational categories. Marital status was found significantly associated (P=0.003) with the presence of PTSD. Married people had a higher prevalence of PTSD (64.62%) in comparison to unmarried peoples. Past occupation (P=0.25), permanent residence (P=0.36), current number of household members (P=0.104) and past average monthly family income (P=0.12) did not reveal any statistically associated with PTSD.

Exploitations related variables having previous experience of sexual exploitations were found statistically significant associated (P=0.039) with PTSD. The prevalence of PTSD was very high (72.55%) among the respondents those faced sexual exploitations. The prevalence of PTSD was also high among the participants those faced physical exploitations (72.55%) and other exploitations (67.31), however here statistically significant associations were not observed. Regarding the disease and medical conditions related variables considered, Hypertension had a statistically significant association (P=0.02) with PTSD and the prevalence of PTSD among hypertensive patients was 71.79%. Those have diabetes and did not get regular medical support to have also a higher prevalence of PTSD. Diabetes mellitus (P=0.36), physical disabilities (P=0.88) and getting medical supports (P=0.23) did not reveal any statistically significant association with PTSD.

Table IV: Probable PTSD prevalence by characteristics of the Rohingya FDMN's and their associations

		Probable PTSD		Chi-square	P
		Yes (n=219)	No (n=144)	(χ²)	value
Age	≥40 years	103 (54.50)	86 (45.50)	1.22	0.27
	<40 years	116 (66.67)	58 (33.33)		
Sex	Female	143 (64.70)	78 (35.30)	4.52	0.03*
	Male	76 (53.52)	66 (46.48)		
Marital status	Married	179 (64.62)	98 (35.38)	8.99	0.003*
	Others	40 (46.51)	46 (53.49)		
Education	No education	52 (61.68)	33 (38.82)	0.25	0.88
	Arabic (Quran)	149 (60.57)	97 (39.43)		
	Formal education	18 (56.25)	14 (43.75)		
Past occupation	Agriculture	64 (62.75)	38 (37.25)	3.28	0.35
	Business	39 (67.24)	19 (32.78)		
	Homemaker	91 (59.09)	63 (40.91)		
	Others	25 (51.02)	24 (48.98)		
Current household members	≤6 members	90 (65.69)	47 (34.31)	2.64	0.104
	>6 members	129 (57.08)	97 (42.92)		
Had permanent residence	Yes	210 (60.87)	135 (39.13)	0.84	0.36
	No	9 (50.00)	9 (50.00)		
Past average monthly family income	≥500 USD	108 (64.67)	59 (35.33)	2.43	0.12
	<500 USD	111 (56.63)	85 (43.37)		
Sexual exploitations	Yes	44 (72.13)	17 (27.87)	4.27	0.039*
	No	175 (57.95)	127 (42.05)		
Physical exploitations	Yes	37 (72.55)	14 (27.45)	3.70	0.054
	No	182 (58.33)	130 (41.67)		
Other exploitations	Yes	70 (67.31)	34 (32.69)	2.96	0.08
	No	149 (57.53)	110 (42.47)		
Diabetes mellitus	Yes	23 (67.65)	11 (32.35)	0.84	0.36
	No	196 (59.57)	133 (40.43)		
Hypertension	Yes	56 (71.79)	22 (28.21)	5.45	0.02*
	No	163 (57.19)	122 (42.81)		
Physical disabilities	Yes	7 (58.33)	5 (41.67)	0.02	0.88
	No	212 (60.40)	139 (39.60)		
Getting medical supports	Yes	158 (58.52)	112 (41.48)	1.44	0.23
	No	61 (65.59)	32 (34.41)		

*Statistically significant

DISCUSSION

PTSD is one of the most important psychopathological public health concerns experiencing after any major form of trauma or disaster. In this study, it was revealed that some types of exploitation had a negative impact on exposed individuals' mental health in terms of housing, income, jobs and family problems etc. A number of people met the criteria for post-trauma stress symptomatology found this study. Among the 363 participants, 60.33% had probable PTSD. Our finding is almost similar with study findings 48% in South Sudan, 75.6% in Rana Plaza building collapse victims in Bangladesh, 57% in Saudi Arabia, 83.7% in Croatia, Germany and UK, 59.4% in Fukushima nuclear disaster, Japan.[11-17,23,32-34] However, our study was inconsistent from the findings of studies on people exposed to natural disasters, such as 36.3% among earth quack victims in Kerman, 35.4% Syrian refugees in Lebanon, 34.9% in Turkey and 34.3% among the bombing victims of Oklahoma City, USA.[18-24] The reason of difference is using of different instruments and cut-off points to measure PTSD, exposures to multiple trauma, study design, and nature and magnitude of the occurrence.

When staying in Myanmar females was mostly (42.42%) were homemakers and more than 95% of the participants had a permanent residence. The greater likelihood of PTSD among woman than men in our work was similar to the reports of other studies, because females experience sexual assaults and child sexual abuse more than males.[19,25-29] Hence, being exposed to such trauma involves more risk than other trauma in causing PTSD.[8,23,28,30]

The prevalence of sexual exploitation was 16.8% and physical exploitations were 14.05%. The prevalence of PTSD was found higher in female (64.7%) in compared to male (53.52%) participants. A statistically significant association found between sex and PTSD (P=0.03). Statistically significant association between age, education and PTSD were not revealed though the prevalence of PTSD was higher among the individuals those are less than 40 years old. People who had a formal education showed lower prevalence of PTSD (56.25%) in compared to other educational categories.[8,31-32] Marital status was found significantly associated with the presence of PTSD (P=0.003). Married people had a higher prevalence of PTSD (64.62%) compared to unmarried people. This finding is similar to the studies.[23,30,33-34]

Exploitations related variables having previous experience of sexual exploitations were found statistically significant associated (P=0.039) with PTSD. The prevalence of PTSD was very high (72.55%) among the respondents those faced sexual exploitations. Some studies, also found a relevant association.[23,33-35]

Regarding the disease and medical conditions related variables considered, Hypertension had a statistically significant association (P=0.02) with PTSD, and the prevalence of PTSD among hypertensive patients was 71.79%. Those have diabetes and did not get regular medical support to have also a higher prevalence of PTSD. Diabetes mellitus (P=0.36), physical disabilities (P=0.88) and getting medical supports (P=0.23) did not reveal any statistically significant association with PTSD. Moreover, experiencing physical injury was also a stronger predictor of PTSD compared with those who had not experienced any such injuries in the incident. The finding is similar to the studies.[29,34-36]

CONCLUSION

The prevalence of PTSD was high in the adult Rohingya population. This study confined that some types of exploitations (sexual exploitation) had a harmful impact on the mental health of affected individuals. It is recommended that a PTSD-focused early regular screening by trained healthcare professionals and linkage with mental healthcare providers. It is necessary to give emphasis to individuals with a family history of mental illness, women and history of mental illness of those who experienced physical trauma during coming to Bangladesh.

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Relation of Serum Uric Acid Concentrations with Etiology and Severity in Patients with Cirrhosis of Liver

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Abstract

Hyperuricaemia is now an established factor to cause oxidative stress, insulin resistance and systemic inflammation. So it is likely that hyperuricemia might be involved in hepatic necroinflammation and destruction which are the common underlying pathophysiology of cirrhosis. On the other hand, as uric acid is the end product of cellular degradation, increased hepatocyte destruction due to any etiology increases the level of serum uric acid which might further aggravate hepatic necroinflammation, cirrhosis and complications. The aim of this study is to assess serum uric acid concentrations in patients of cirrhosis of liver and its relation with cirrhosis of different etiology, disease severity and liver enzymes. This cross sectional observational study was carried out in the Department of Gastroenterology, Banghabandhu Sheikh Mujib Medical University, Bangladesh during the period of September 2015 to October 2016. A total of 220 diagnosed cases of cirrhosis of liver due to any cause from inpatient and outpatient Department of Gastroenterology were enrolled as the study population. Serum uric acid level was measured in each patient and its relationship with different etiology of cirrhosis, severity of cirrhosis and liver enzymes were assessed. The mean age was found to be 47.8 ± 14.6 years and male: female ratio was 1.9:1. Majority patients (52.3%) belonged to Child-Turcotte-Pugh Class C. The mean (±SD) value of serum uric acid was 6.19 (±3.25mg/dl) and hyperuricemia (>7 mg/dl) was detected in 27.73% patients. Among all etiologies of cirrhosis, the higher mean (±SD) level of serum uric acid was found in Non-alcoholic Fatty Liver Disease (19.54 ±2.20 mg/dl). There was positive correlation of serum uric acid with liver enzymes. Mean serum uric acid level increased gradually as the cirrhotic patients progressed to higher CTP classes and there was positive correlation of serum uric acid with liver enzymes. It requires further large scale multicenter studies with increased sample size & prolong follow-up to establish serum uric acid as a risk factor of cirrhosis of liver.

Keywords: *Cirrhosis, NAFLD, serum uric acid, liver enzymes*

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INTRODUCTION

Cirrhosis is a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal regenerative nodule.[1] Cirrhosis may be compensated; or decompensated when complicated by one or more of the following features: jaundice, ascites, hepatic encephalopathy and raised prothrombin time. Cirrhosis is irreversible. Unless the underlying cause of cirrhosis is removed and the person takes measures to treat the condition, the liver will continue to incur damage, eventually leading to liver failure, ammonia toxicity, gastrointestinal hemorrhage, kidney failure, hepatic coma, and death.[2]. Continued inflammatory process and hepatocyte destruction due to the activity of underlying etiology (i.e. chronic hepatitis B &/or chronic hepatitis C virus, alcohol etc) is responsible for advancement of the cirrhotic process and leads decompensation and occurrence of complications. In humans and higher primates, uric acid (UA) is the final oxidation product of purine metabolism and is excreted in urine.

Hyperuricemia is defined as a serum uric acid concentration greater than 7 mg/dl (416 μmol/L), the approximate level at which urate is supersaturated in plasma.[3] Hyperuricemia has long been recognized as a cause of gouty arthritis and kidney stones.[4] In recent years, hyperuricemia has also been implicated in the development of many other diseases. Obvious correlation

has been found in hypertension, kidney disease, metabolic syndrome, and cardiovascular disease.[5,6] The underlying mechanisms include induction of endothelial dysfunction, insulin resistance, oxidative stress, and systemic inflammation by hyperuricemia. [5,6]

Hyperuricemia is now an established factor to cause oxidative stress, insulin resistance and systemic inflammation. So it is likely that hyperuricemia might be involved in hepatic necro-inflammation.[4] In fact, different studies across the world have found correlation between hyperuricemia and cirrhosis. Benerji et al. (2013) conducted comparative study of ALT, AST, GGT & uric acid levels in liver diseases and found association between serum uric acid levels and the incidence of cirrhosis-related hospitalization or the presence of elevated serum ALT or GGT. These associations were largely independent of other known liver disease risk factors. According to their study, the elevated serum uric acid level might be a risk factor for the incidence of chronic liver disease. In an observational study by Paul et al. (2013) found significantly high serum uric acid level in certain cases of CLD i.e. chronic viral hepatitis and autoimmune hepatitis. Uric acid levels were higher in higher CTP score and it was also linked with mortality. Serum uric acid level showed correlation with parameters of CLD i.e. SGOT and INR. Lee et al. (2010) showed in a study on Korean adults with non-alcoholic fatty liver disease that Serum uric acid is independently associated with the presence of NAFLD, and uric acid may be a useful additional measure in assessing the risk of NAFLD in the clinical setting. These associations remained even after adjustment for other surrogate markers of NAFLD, such as AST, ALT, GGT and CRP. Petta et al. (2011) carried out a study on a cohort of patients with histological diagnosis of NAFLD and showed an independent link between hyperuricemia and the severity of liver damage. In particular, they found that hyperuricemia was independently associated with the severity of steatosis and lobular inflammation. Petta et al. (2011) carried out another study on a cohort of mostly overweight or obese patients with histological diagnosis of chronic hepatitis C and found that hyperuricaemia was independently associated with steatosis, its severity and also a factor involved in the progression of liver disease.

A crucial question was raised in different studies as to whether hyperuricaemia plays any role in directly causing hepatic necroinflammation and cirrhosis or whether it is a marker for an adverse metabolic profile that leads to NAFLD/NASH or promotes progression of viral or alcoholic hepatitis.[10] The aim of the study was to assess uric acid concentrations in patients of cirrhosis of liver and its relation with etiology & severity.

MATERIAL AND METHODS
Patients

This cross sectional observational study was carried out in the Department of Gastroenterology, BSMMU, Bangladesh during the period of September 2015 to October 2016. A total of 220 diagnosed cases of cirrhosis of liver due to any cause from inpatient & outpatient Department of Gastroenterology, BSMMU were enrolled as the study population. Serum uric acid level was measured in each patient and its relationship with different etiology of cirrhosis, severity of cirrhosis and liver enzymes were assessed. Patients were excluded below the age 18, known malignancy, on chemotherapy, on drugs that may impair uric acid level such as allopurinol/ feboxostat/ diuretics, known infection, recent surgery/trauma from the study. History, clinical examination & laboratory investigations were noted in a semi structured data sheet. Alanine transaminase(ALT), aspartate aminotransferase (AST), endoscopy upper git, ultrasonography was done in all patients. The results were noted on the data sheet. Etiology of cirrhosis was ascertained by appropriate investigations, if not known previously, i, e HbsAg, anti Hbc total, Anti HCV, serum caeruloplasmin Urinary copper was done and noted in data sheet. Serum uric acid level was measured for single time for all patients, and send to biochemistry department, the result was noted in the data sheet. CTP score was done for each patient. This study was approved by Institutional Review Board of BSMMU, Dhaka.

Statistical analysis: All the data were checked and edited after collection. The statistical analysis of the results being obtained by using windows based computer software devised with Statistical Packages for Social Sciences (SPSS-22) (SPSS Inc., Chicago, IL, USA). The results were presented in tables and figures. Statistical significance was set at $p<0.05$ and confidence interval set at 95% level. Continuous variables were expressed as mean with standard deviation and categorical variables as count with percentage. Categorical data were assessed by Chi-square test. Association between uric acid and different etiology and CTP class were assessed by Analysis of Variances (ANOVA) test. The correlation between variables were be evaluated by means of Pearson's correlation test.

Operational definitions: Cirrhosis of liver: Cirrhosis, a final pathway for a wide variety of chronic liver diseases, is a pathologic entity defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture by

nodules. Cirrhosis is strictly speaking a histological diagnosis, a combination of clinical, laboratory, and imaging features can help confirm a diagnosis of cirrhosis.[11] Physical findings suggestive of cirrhosis of liver are, palmer erythema, gynecomastia, spider telangiectasia's or angioma, caput medusa, parotid enlargement, enlarge left lobe of liver with splenomegaly suggests cirrhosis of liver especially in setting of thrombocytopenia and impaired hepatic function (e.g., hypoalbuminemia, prolongation of prothrombin time). Clinical history of chronic liver disease with gastroesophageal varices, ascites, or hepatic encephalopathy is likely to have cirrhosis, and liver biopsy is not essential for confirming cirrhosis. Fibroelastography or Magnetic resonance elastography can help confirm a diagnosis of cirrhosis. Liver biopsy has long been the gold standard for diagnosing cirrhosis but may be associated with costs and procedure related risks, albeit infrequently. The ideal combination of clinical findings and routine laboratory tests to determine whether a patient has cirrhosis without need for liver biopsy has been addressed in systematic fashion [12].

Child-Turcotte-Pugh (CTP) classification of the severity of cirrhosis

CTP score is obtained by adding the score for each parameter.

CTP class: A =5-6 points, B = 7-9 points, C = 10-15 points.

RESULTS

This cross sectional study was carried out in the Department of Gastroenterology, BSMMU, Dhaka, Bangladesh during the period of September 2015 to October 2016 involving 220 diagnosed patients of cirrhosis of liver due to any etiology to investigate serum uric acid level in cirrhosis of liver patients and its relation with cirrhosis of different etiology, disease severity. Mean age was 47.8 ± 14.6 years. Male (65.5%) were and female (34.5%), and female male ratio was 1:1.9

	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant -induced)	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3 5	2 8-3 5	<2 8
PT (sec prolonged)	<4	4-6	>6
orlNR	<1.7	1.7-2.3	>2.3

Table-I Shows tha among 220 cirrhotic patients, maximum 63 (28.6%) patients were in the age group of 51–60 years followed by 43 (19.5%), 41 (18.6%), 37 (16.8%) and 36 (16.4%) patients were in the age group of 41-50 years, 31-40 years, >60 years and ≤30 years respectively.

Table -I: Distribution of patients according to age and sex

Parameters	Frequency (n)	Percentage (%)
Age		
≤30	36	16.4
31 – 40	41	18.6
41 – 50	43	19.5
51 – 60	63	28.6
>60	37	16.8
	Mean ± SD: 47.8 ± 14.6 (Min – Max): (18 - 75)	
Sex		
Male	144	65.5
Female	76	34.5
Total	220	100.0

Table-II Shows the distribution of hyperuricemia patients according to CTP class among the 220 patients 48(21.8%), 57(25.9%) and 115 (52.3%) patients were in CTP class A, B and C respectively. Hyperuricemia were followed in 2(3.3%) in A cases and 13 (21.3%), 46 (75.4%) in B and C class respectively.

Table-II: Distribution of Uric acid level in patients according to CTP class

CTP class	Patients n (%)	Hyperuricemia (Serum Uric Acid >7 mg/dl) n (%)	Mean±SD	Range (Min-Max)
A	48 (21.8)	2 (3.3)	4.30±1.64	2.30-9.80
B	57 (25.9)	13 (21.3)	5.60±1.83	3.10-9.80
C	115 (52.3)	46 (75.4)	6.98±3.80	1.70-21.00
Total	220 (100.0)	61 (100.0)	6.19±3.25	1.70-21.00

Statistical analysis

Groups	p value
A vs B vs C	<0.001
A vs B	0.210
A vs C	<0.001

B vs C   0.027One way ANOVA followed by Bonferroni test was performed to compare between groups.

Table-III: Shows the distribution of Serum uric acid concentrations in different etiology of liver cirrhosis patients. Among the 220 patients of cirrhosis of different etiology, the mean serum uric acid level was found NAFLD patients (19.54 mg/dl), followed by cirrhosis of liver due to CHC, WD, CHB where the mean of serum uric acid level was 6.74,5.91,5.61 mg/dl respectively.

Table - III: Distribution of Serum uric acid concentrations in different etiology of patients

Diagnosis	n(%)	Hyperuricemia n (%)	Mean SD	Range (Min-Max)
CHB	119 (54.1)	28 (23.5)	5.61±2.19	1.70-11.20
CHC	49 (22.3)	16 (32.7)	6.74±2.75	3.30-14.10
Wilson's disease	18 (8.2)	5 (27.8)	5.91±2.76	2.30-10.00
NAFLD	5 (2.3)	5 (100.0)	19.54±2.20	15.70-21.00
Non B/ non C	29 (13.2)	7 (24.1)	4.96±2.20	2.30 - 8.00
Total	220 (100.0)	61 (27.7)	6.19 ± 3.25	1.70 - 21.00

Table –IV Shows the patients of cirrhosis indifferent etiology, non-NAFLD patients was 97.7% and rest 2.3% was NAFLD. The mean serum uric acid level was found among NAFLD patients 19.54±2.20 mg/dl and non-NAFLD Patients 5.83±2.42

Table -IV: Serum uric acid concentrations in NAFLD and other causes of liver cirrhosis patients.

Diagnosis	Patients n (%)	Mean±SD	Range (Min-Max)	P value
Non NAFLD	215 (97.7)	5.83 ± 2.42	1.70 - 14.10	0.001
NAFLD	5 (2.3)	19.54 ± 2.20	15.70 - 21.00	
Total	220 (100.0)	6.19 ± 3.25	1.70 - 21.00	

Unpaired t test was done to measure the level of significance.

Table-V: Association of serum uric acid level (normal and hyperuricemia) with severity of liver cirrhosis according to CTP class. It shows that among 61 patients of hyper-uricemia 46 patients were in CTP class C followed by 13 and 2 cases in CTP class B and A respectively. The association of serum uric acid (normal and Hyperuricemia) with severity of liver cirrhosis according to CTP Class was Statistically significant.

Table -V: Association of serum uric acid level with severity of liver cirrhosis

CTP class	Hyperuricemia n (%)	Normal n (%)	P value
A	2 (3.3)	46 (28.9)	<0.001
B	13 (21.3)	44 (27.7)	0.334
C	46 (75.4)	69 (43.4)	<0.001
Total	61 (100.0)	159 (100.0)	

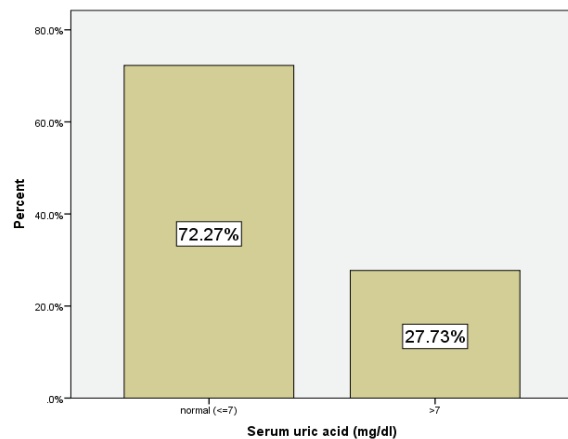Chi-square test was done to measure the level of significance

Figure-1: Bar Diagram on serum uric acid distribution in 220 cirrhotic patients

Figure-1 Shows tha among 220 patients, 159 (72.27%) patients had normal level of serum uric acid (≤ 7 mg/dl) and the rest 61(27.73%) patients had hyperuricemia (>7 mg/dl).

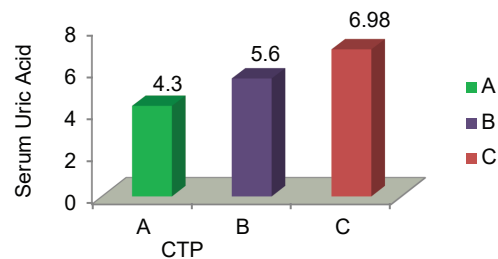**Figure-2:** Bar diagram of relation of Serum Uric Acid with severity of liver cirrhosis according to CTP class.

DISCUSSION

In this study a total of 220 cirrhotic patients of any etiology were investigated for serum uric acid level and its relationship with different etiology of cirrhosis, severity of cirrhosis and liver enzymes were assessed. According to patient's age, mean age was 47.8± 14.6 years with an age

range of 18-75 years. Maximum 63 (28.6%) patients were in the age group of 51-60 years followed by 43 (19.5%), 41 (18.6%), 37 (16.8%) and 36 (16.4%) were in the age group of 41-50 years, 31-40 years, >60 years and ≤30 years respectively.

A recent survey Shih et al. (2015) determined the association between nonalcoholic fatty liver disease (NAFLD) and serum uric acid (SUA) levels. The mean age of his study subjects was 40.8 years. Another prospective study by Xu et al. (2010) on NAFLD & serum uric acid involving 7412 participants found the mean age to be 44.4 years. These were nearer to our study in both the instances. Considering gender distribution, male (65.5%) was predominant than female (34.5%) and the ratio was 1.9:1. In a recent study revealing the association of serum uric acid and liver diseases by Shih et al. (2015), reported 47.6 % study population were male. Another study by Paul et al. (2013) found that 31% were female among their study population while carrying out study on serum uric acid level in chronic liver disease. These were also consistent with this study result.

In our study, the focus of our laboratory variable was serum uric acid. The mean serum uric acid was 6.19 (±3.25) mg/dl. The range was found between 1.70 to 21.00 mg/dl. Among 220 patients, 159 patients had normal level of uric acid (≤ 7 mg/dl) which represents about 72.27% and the rest 61 of patients i.e. 27.73% had hyperuricemia (>7 mg/dl). A national survey on association between serum uric acid and nonalcoholic fatty liver disease in the US population reported that overall 16.4% had hyperuricemia [13]. A study in India by Benerji, et al.(2013) found the mean level of serum uric acid was 10.6 (±2.0) mg/dl among 55 cirrhotic patients. Antony et al. (2012) measured the serum uric acid to be 5.63 (±0.08) mg/dl in liver disease patients. The most common cause of cirrhosis of liver in this study was chronic HBV infection followed by chronic HCV, Wilson disease, Non B/Non C and NAFLD. Among the 220 patients of liver cirrhosis, the frequency of CHB was 54.1% followed by chronic HCV in 22.3%, Wilson disease in 8.2%, NAFLD in 2.3% and Non B/ non C in 13.2% patients. Alcoholic was found to be the commonest (36.5%; n=19) commonest cause followed by NAFLD (28.8%), Wilsons disease, autoimmune hepatitis and cryptogenic cirrhosis in a study by Paul et al. (2013), titled as 'Study of serum uric acid in chronic liver disease and its relation with other parameters.

Considering the relation of uric acid with etiology of liver cirrhosis, mean serum uric acid was found maximum in

NAFLD patients followed by Cirrhosis liver disease due to CHC, Wilson disease and CHB patients. The mean (SD) level of serum uric acid in NAFLD was found 19.54 (±2.20) mg/dl. Shih et al. (2015), found a significant association between serum uric acid levels and NAFLD among the US population. Moreover, Afzali et al. (2010), have showed that serum uric acid levels were associated with the progression of chronic liver diseases such as NAFLD and NASH; and hyperuricemia was found independently associated with the severity of liver damage among NAFLD patients. In a cohort study in China which followed 6890 men and women without NAFLD for 3 years and found a higher incidence of NAFLD in those with higher baseline serum uric acid levels [14]. Another cross-sectional study showed that NAFLD patients had higher serum uric acid levels than healthy controls and that the prevalence of NAFLD was increased at higher serum uric acid levels, suggesting significant association between serum uric acid and NAFLD [16]. Severity of Cirrhosis of liver was assessed by CTP score in this study and among 220 cirrhotic patients 21.8% belonged to CTP Class A, 25.9% to CTP Class B and the majority i.e. 52.3% belonged to CTP Class C. Paul et al. (2013) reported in a similar study that 55.76% of his patients belonged to CTP Class B & 69.2% fell into combined CTP Class B and C. Regarding the relationship of uric acid with severity of liver cirrhosis according to CTP class, mean serum uric acid level increased gradually as the patients progressed to higher CTP class. Mean serum uric acid level (mg/dl) was maximum in CTP class C patients (6.98 ± 3.80) followed by class B (5.60 ± 1.83) and class A (4.30 ± 1.64). This increase of serum uric acid was statistically significant. Paul et al.(2013) reported serum uric acid levels were significantly higher in CTP classes B and C as compared to CTP class A (p<0.0001) & serum uric acid levels were higher with higher CTP scores (r=0.44). These findings were consistent with our findings. On observing the liver enzymes level, the mean level of ALT and AST was found to be 48.61 ± 45.48 U/L and 61.33 ± 53.35 U/L respectively. In this study, the correlation of uric acid with AST & ALT, there was significant positive correlation of serum uric acid with AST (r value=0.236; p=0.003). Uric acid had positive correlation with ALT also but the relationship was not statistically significant. Shih et al. (2015) also found that patients with hyperuricemia were more likely to have elevated liver enzymes. Findings of liver enzymes by Benerji, et al (2013) in liver cirrhosis patients correlate with our study findings. They found the ALT level as 67±31.4 U/L and AST as 65±27.5U/L. Paul et al.

(2013) also found that serum uric acid levels showed significant correlation with AST (r=0.464) in patients with cirrhosis which is consistent with our study findings.

The study was done in limited time of span; cases were collected from only one center hence may not represent the whole population of the country.The sample size was small and there was no control group in this study.

Further multi centered prospective cohort study with large sample size with follow-up for prolong period is recommended.

CONCLUSION

Among all etiological causes of liver cirrhosis, serum uric acid was higher among NAFLD patients. Significant positive correlation of serum uric acid level has been found with serum AST. Mean serum uric acid level increased gradually as the patients progressed to higher CTP classes. Based on this observation, serum uric acid could be considered as a marker of severity of CLD but it requires further large scale multicenter studies with increased sample size & prolong follow-up to establish it as a surrogate marker.

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

| Sl.No.	Name & Address	Date of Death
1	Dr. BM Faruk Ex. Lecturer, Department of Physiology Rangpur Medical College Life Member, BMA Bogura Branch Ex. Student of Sylhet MAG Osmani Medical College (10th Batch)	2/9/2020
2	Dr. Shamsun Nahar Bala Ex. Associate Professor of Gynaecology & Obstetrics Ibrahim Medical College, Dhaka Ex Student of Dhaka Medical College (K-27 Batch)	3/9/2020
3	Professor. Dr. A.F.M Siddiqur Rahman Ex. Head, Department of Medicine Community Based Medical College, Mymensingh Ex Student of Dhaka Medical College (K-16 Batch)	7/9/2020
4	Professor. Dr. Humayun Kabir Retd. Professor, Department of Ortho Surgery Sir Salimullah Medical College Ex Student of Sylhet MAG Osmani Medical College (6 Batch)	7/9/2020
5	Professor Dr. Suraiya Rowshan Ara Begum (Rasna) Ex Professor of Community Medicine, NIPSOM Life Member, BMA Ex Student of Mymensingh Medical College (15 Batch)	8/9/2020
6	Dr. Nirmalendu Chowdhury Ex. Director, Institute of Public Health (IPH), Mohakhli, Dhaka Life Member, BMA Ex Student of Rangpur Medical College (7 Batch)	8/9/2020
7	Dr. Md. Obaidur Rahman Assistant Professor of Nephrology, Cumilla Medical College Ex Student of Sylhet MAG Osmani Medical College (21th Batch)	17/9/2020
8	Dr. Hedayetul Islam Ex. Registrar, Department of Orthopaedic Surgery Mymensingh Medical College Ex Student of Rangpur Medical College (6th Batch)	28/9/2020
9	Dr. Muhammad Hossain Associate Professor of Urology, BSMMU Ex Student of Chattogram Medical College (25th Batch)	1/10/2020
10	Professor Dr. Mirja Mazharul Islam Chief Consultant, Department of Surgery BIRDEM General Hospital, Ex. Head, Department of Surgery and Principal, DMCH Ex Student, Dhaka Medical College (K-1 Batch)	11/10/2020

Sl.No.	Name & Address	Date of Death
11	Dr. Kawser Ahmed Mazumder Sub Chief Officer (Medical Treatment) Chattogram Port Hospital Ex Student of Sylhet MAG Osmani Medical College (23th Batch)	13/10/2020
12	Dr. Ramash Chandra Nath Ex. Director, Sher E Bangla Medical college Hospita, Barishal President, BMA Meherpur Branch Ex Student of Chattogram Medical college (4 Batch)	14/10/2020
13	Dr. Md. Khalil Uddin Medical Officer, Diabetic Association Hospital, Moulvibazar Ex Student, of Rangpur Medical College (16th Batch)	14/10/2020
14	Dr. A K M Masud Rahaman Professor and Head, Department of Medicine TMSS Medical College, Bogura Ex. Student of Chattogram Medical College(20th Batch)	25/10/2020
15	Freedom Fighter Dr. Salim Ahmed Life Member and Ex. Executive Committee Member, BMA Ex. Student of Dhaka Medical College (K 29 Batch)	29/10/2020
16	Professor Dr. M A Jalil Ex. Principal and Head Department of Biochemistry Mymensingh Medical College and Kumudini Womens Medical College Ex. Student of Dhaka Medical College	30/10/2020
17	Dr. Sazzad Kamal Heru Senior Consultant, Radiology and Imaging 250 Bed General Hospital, Jashore Ex. Student of Rangpur Medical College (13th Batch)	1/11/2020
18	Dr. Nasir Uddin Ahmed Assistant Professor of Medicine Monno Medical College, Manikganj Ex Student of Mymensingh Medical College (16th Batch)	3/11/2020
19	Professor Dr. A B M Ali Akbar Biswas Ex. Head, Department of Surgery Shahabuddin Medical College, Dhaka Life Member, BMA Ex. Student of Chattogram Medical College	8/11/2020
20	Dr. A B M Maksudus Salahi Life Member, BMA Eye Specailist, Mymensingh City Ex Student of Mymensingh Medical College (15th Batch)	14/11/2020

Sl.No.	Name & Address	Date of Death
21	Dr. Razaur Rahman Prodhan Senior lecturer, Department of Anatomy Prime Medical College, Rangpur Life Member, BMA Ex. Student of Rangpur Medical College (6 Batch)	15/11/2020
22	Dr. Nurul Islam Dermatologist Ex. Director, Agrabad Skin Hospital (American Hospital) Chattogram Ex. Student of Chattogram Medical College (11th Batch)	18/11/2020
23	Dr. AJM Shafiul alam Shah (Babu) Assistant Professor, Department of Anesthesiology Ma O Shishu Hospital, Matuail, Dhaka Life Member, BMA Ex Student of Rangpur Medical College (22th Batch)	19/11/2020
24	Dr. Bushra Sarwar Sonologist, Islami Bank Hospital, Rajshahi Ex Student of Islami Bank Hospital Rajshahi (5th Batch)	29/11/2020
25	Dr. Mujibur Rahman Khan Hira Ex. Associat Professor, Department of Gynaecology Mymensingh Medical College Ex Student of Mymensingh Medical College (10th Batch)	29/11/2020
26	Dr. A K M Shamsul Haque Senior Consultant of Pediatric Impulse Hospital, Dhaka Ex Student of Mymensingh Medical College (7th Batch)	3/12/2020
27	Dr. Irin Parvin Consultant of Gynaecologist Eastern Medical College Hospital, Cumilla Ex Student of Cumilla Medical College (4th Batch)	6/12/2020
28	Dr. Saidul Islam Sonologist Ex Student of Rajshahi Medical College (14th Batch)	9/12/2020
29	Dr. Rashed Sarwar Alam Rani Medical Officer Bangladesh Public Administration Training Centre, Saver Ex Student of Dhaka Medical College (K-49th Batch)	13/12/2020
30	Professor Dr. Abdul Kader Khan Department of Biochemistry Bikrampur Bhuiyan Medical College Ex. Principal of Dhaka Medical College Ex. Director of Central for Medical Education, DGSH Ex Student of Dhaka Medical College (K-22th Batch)	13/12/2020

Sl.No.	Name & Address	Date of Death
31	Dr. Gazi Shafique Alam Choudhury Chairman, Gazi Real Assets, Bogura Ex Student of Dhaka Medical College (K-20th Batch)	19/12/2020
32	Professor Dr. Abdul Mukit Sarkar Ex. Professor and Head, Department of Community Medicine Rajshahi Medical College and Islami Bank Medical College, Rajshahi Ex Student of Rajshahi Medical College (13th Batch)	20/12/2020
33	Dr. Mohammad Hasan Murad Medical Officer, RTPCR lab, Department of Microbiology Chattogram Medical College Hospital Ex. Student of Chattogram Medical College (35th Batch)	21/12/2020
34	Dr. Nizam Uddin Bhuiyan Copyrighter, Dhaka Clinic, Mitford Ex. Consultant, Chest Diseases Clinic, Dhaka Life Member, BMA, Ex Student of Sir Salimullah Medical College (2 Batch)	21/12/2020
35	Dr. Anwarul Karim Babul Pediatrician Director of Nibedita Shisu Hospital, Dhaka Life Member BMA Ex Student of Sir Salimullah Medical College (6 Batch)	25/12/2020
36	Dr. Shakh Sayem Ex. Lecturer, Institute of Health Technology, Sylhet Ex Student of Sylhet MAG Osmani Medical College (43th Batch)	28/12/2020
37	Professor Dr. A K M Shamsul Haque Chest Diseases Specialist Ex. Director, National Institute of Chest Disease and Hospital Ex Student of Dhaka Medical College (K-12th Batch)	28/12/2020
38	Professor Dr. Lutfor Kader Lenin Joint Director, Sheikh Hasina National Institute of Burn and Plastic Surgery Life Member, BMA Ex Student of Dhaka Medical College (K-48th Batch)	30/12/2020

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.
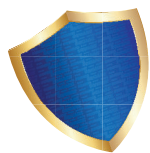
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