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## Present Situation of Thalassaemia in Bangladesh

Jhulan Das Sharma<sup>1\*</sup>

Thalassaemia was first described in 1925 by a Detroit physician who studied Italian children with severe anemia poor growth, huge abdominal organs and early childhood death.

Thalassaemia name is derived from the Greek word "thalassa" meaning "the sea" because the condition was first described in populations living near the Mediterranean Sea. So, Thalassaemia also called Mediterranean Anemia.

### What is Thalassaemia?

Thalassaemia is a blood disorder passed down through families (Inherited) in which the body makes an abnormal form or inadequate amount of hemoglobin. Hemoglobin is the protein in red blood cells that carries oxygen. The disorder results in large numbers of red blood cells being destroyed, which leads to anemia.

### Causes of Thalassaemia

Thalassaemia is caused by mutations in the DNA of cells that make haemoglobin – the substance in red blood cells that carries oxygen throughout the body. The mutation associated with thalassaemia are passed from parents to children.

### Hemoglobin is made of two proteins:

- Alpha globin.
- Beta globin.

Thalassaemia occurs when there is a defect in a gene that helps control production of one of these proteins.

There are two main types of thalassaemia:

- Alpha thalassaemia occurs when a gene or genes related to the alpha globin protein are missing or changed (Mutated).
- Beta thalassaemia occurs when similar gene defects affect production of the beta globin protein.

Alpha thalassaemias occur most often in people from Southeast Asia, the Middle East, China, and in those of African descent.

Beta thalassaemias occur most often in people of Mediterranean origin. To a lesser extent, Chinese, other Asians, and African Americans can be affected.

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There are many forms of thalassaemia. Each type has many different subtypes. Both alpha and beta thalassaemia include the following two forms:

- Thalassaemia major.
- Thalassaemia minor.

You must inherit the gene defect from both parents to develop thalassaemia major.

Thalassaemia minor occurs if you receive the faulty gene from only one parent. People with this form of the disorder are carriers of the disease. Most of the time, they do not have symptoms.

Beta thalassaemia major is also called Cooley anemia.

Risk factors for thalassaemia include:

- Asian, Chinese, Mediterranean, or African American ethnicity.
- Family history of the disorder.

### Treatment of Thalassaemia

- Treatment for thalassaemia major often involves regular blood transfusions and folate supplements.
- If you receive blood transfusions, you should not take iron supplements. Doing so can cause a high amount of iron to build up in the body, which can be harmful.
- People who receive a lot of blood transfusions need a treatment called chelation therapy. This is done to remove excess iron from the body.
- A bone marrow transplant may help treat the disease in some people, especially children.

Thalassaemia is the most common inherited hemoglobin disorder emerging as a global public health concern. As estimated, 320,000 babies are born each year with a clinically significant haemoglobin disorder. Nearly 80% of these births occur in developing countries. Although in global map Bangladesh lies in the Thalassaemia hot spot, no nationwide study has yet been conducted regarding the prevalence of Thalassaemia. According to World Health Organization (WHO) Report 3.0% of population of Bangladesh are carriers of Beta Thalassaemia and 4.0% are carriers of Hb-E. Using the demographic data of Bangladesh and gene frequency, Hardy-Weinberg equation estimated the annual births of haemoglobin variants and found that at least 9250-10.000 [7503 HbE/Beta Thalassaemia (EBT) and 1725 Beta Thalassaemia Major (BTM)] children are born annually in Bangladesh with pathological haemoglobin disorders. Unfortunately, majority of them are not receiving adequate treatment. From WHO

Report and the analysis of existing literature, it can be said that prevalence of both beta Thalassaemia trait and HbE trait is significantly high in Bangladesh. Although no national registry of Thalassaemia is available, analysis of data from registry book of different Thalassaemia care-giving-centre shows that majority patients of symptomatic haemoglobin disorder belong to E/Beta Thalassaemia (Comprising 75 to 80% of total patients). This high prevalence of HbE/beta Thalassaemia in Bangladesh is also a feature of Thalassaemia epidemiology in South and Southeast Asian countries like India, Sri Lanka and Thailand.

E/Beta Thalassaemia displays wide clinical heterogeneity and is variable in clinical severity, about 20-30% require regular transfusions from early childhood (Phenotypically Thalassaemia major) and 50% are moderate to severe Thalassaemia intermedia: symptomatic, but requiring only occasional transfusion in childhood. The remaining 25% are mild.

Thalassaemia intermedia and Thalassaemia minor may not be diagnosed at all during childhood. They are now labeled as Non- Transfusion Dependent Thalassaemia (NTDT). Non-transfusion-dependent Thalassaemia (NTDT) is a term used to label patients who do not require lifelong regular transfusions for survival, although they may require occasional or even frequent transfusions in certain clinical settings and for defined periods of time.

So, management protocol should be formulated according to the severity of the disease. All published guidelines and standards in text books and other national organizations, have so far addressed the management of Thalassaemia as one clinical entity, and mainly the management of homozygous beta Thalassaemia major and its complications are described. Particularly, management protocols are not formulated considering the severity of the disease. Now, it is recommended that these E/Beta Thalassaemia patients who are mainly non transfusion dependent, require separate attention, early identification and unique need-based clinical care. In fact, many patients with NTDT develop serious complications over time and require careful monitoring and unique management which is sometimes different from the clinical care for Thalassaemia major. So, now is the time that our hematologist and Thalassaemia care-givers should be aware and sensitized to the special monitoring and management requirements of the NTDT E/Beta Thalassaemia.

Although blood transfusion is the cornerstone of the management of Thalassaemia, arrangement of safe blood is one of the biggest challenges being faced by transfusion-dependent families in Bangladesh like other developing countries. In Bangladesh, 85% of collected blood is contributed by patient's relatives and friends, while the rest (15%) is donated by voluntary blood donors. Regarding transfusion facilities, there are 201 government and 145 private registered blood banks. Only few centers have refrigerated centrifuge machine so component blood are

available only in big cities. Option for pre-storage leucodepletion which is universal in developed countries is not available in our country. Facilities for genotype matched blood transfusion are also very limited; available in two centers only. Although during blood collection, screening for infectious diseases (HBV, HCV, HIV, Malaria and Syphilis) are routinely being done, ICT methods are mainly used, ELISA is practiced in only few centers and NAT is virtually nonexistent except in 2 highly expensive corporate hospitals. In view of the above, it may be concluded that there is a scarcity of safe blood in our country. Due to lack of availability of safe blood, Thalassaemia patients are at risk of developing post-transfusion hepatitis. Among these infections, hepatitis B and C are the most common in our country. Specially HCV infection poses significant threat as no vaccine is available for prevention of this viral infection. A number of studies have reported the higher prevalence of HCV among multi-transfused Thalassaemia patients, ranging from 3 to 67.3% in our country. In view of the above, before starting regular blood transfusion therapy accurate diagnosis on the basis of transfusion requirement should be a mandatory part of the Thalassaemia management practice in Bangladesh and alternative to transfusion should be sought.

Over the last decades there has been phenomenal progress regarding use of Fetal haemoglobin (HbF) inducing agents that has been found to be effective in reducing transfusion requirement. In this regard name of Hydroxyurea, Thalidomide and Luspatercept should be mentioned. Hydroxyurea is the most commonly used HbF inducer but the effect is relatively modest. Thalidomide recently has demonstrated outstanding achievement as haemoglobin F inducer. Several published studies in international journals confirmed the efficacy and safety of thalidomide in Thalassaemia. It could be a promising therapeutic strategy for patients with Thalassaemia in low income country like Bangladesh. There may be a role for new non-transfusion therapies such as costly novel drug Luspatercept (Recently got FDA approval) yet to be available in our country. Although allogenic haemopoietic stem cell transplantation is the only curative approach in Thalassaemia and although this facility is now available in our country it is not affordable for most of our patients due to its high cost. So, we need an evidence based, effective and feasible management protocol for EBT distinct from beta Thalassaemia major.

Previously, Thalassaemia was a lethal disorder and majority of patient would die before second decade of life. It can now be treated as chronic disease and with optimum care patient may live long with good quality of life. But in our country access to quality health care services is inadequate due to lack of awareness and low income of patients. Quality of Thalassaemia care is mostly poor, attributed partly to the lack of safe and adequate blood, an inadequate supply of iron chelating drugs and insufficient monitoring of complications by specialists.

Thalassaemia-disorder places a huge burden on the suffering families as majority of them are self-funded, facilities of health insurance and that of free/subsidized treatment are very insignificant. So, it is the high time to shift from treatment to prevention i.e. prevention of birth of such children in future through carrier screening at the premarital stage or to pregnant women.

Finally, it is to be noted that the Government of Bangladesh has recognized Thalassaemia as a significant public health concern. A subsidized thalassaemia-treatment program and awareness cum prevention program have been developed by DGHS and the Ministry of Health is committed to mobilizing the required funds to implement these programs. So, it is expected that the Thalassaemia situation in Bangladesh will improve soon by implementing these programs through a public-private partnership and concerted efforts of the Ministry-DGHS-academic and research organizations.

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# An Observational Study of Pattern of Abdominal Injuries Encountered at Combined Military Hospital Dhaka

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## ABSTRACT

**Background:** Abdominal trauma is a common scenario found in day to day practice of surgery. But identification of intra-abdominal derangement due to trauma in emergency setup, along with other associated extra abdominal injuries in a polytrauma patient is challenging. Increasing number of various accidents has led to a surge in the number of patients presenting to health care centers including Combined Military Hospital (CMH) Dhaka with abdominal trauma. Currently, there are no published data on pattern of abdominal injury. So a study aiming to determine the Pattern of Abdominal Injuries encountered was conducted at CMH- Dhaka.

**Materials and methods:** A descriptive, prospective, hospital-based study was carried out. Consecutive admissions of all patients with abdominal and associated injuries attending the Department of Surgery CMH- Dhaka was enrolled in the study. The study was conducted from July 2013 to December 2014. Total 92 patients have been included in this study.

**Results:** The male to female ratio in this study was 7.4:1. 67.4% were in the age group of 21-40 years. 55.4% sustained abdominal injuries due to road traffic accidents, the commonest among the causes. Sixty (60) patients had blunt pattern of abdominal injury, 32 patients had penetrating variety of abdominal injury. Associated injuries of other body regions were found in 36.9% of patients. The spleen was found to be the most commonly injured solid organ in blunt pattern of abdominal injuries constituting 22.2%, while bowel was found to be the commonest injured intra-abdominal organs affecting in 33.3% of all cases of penetrating variety of abdominal injuries.

**Conclusion:** Study of such patterns will help clinicians to assess and evaluate the patients presenting in the hospital and will also help to postulate a protocol for better management of such patients.

**Key words:** Abdominal injuries; Blunt abdominal trauma; Pattern of trauma.

## Introduction

It was estimated that by the year 2020, 8.4 million people will die every year from injury, and injuries from road traffic accidents will be the third most common cause of disability worldwide and the second most common cause in the developing world.<sup>1</sup> There are characteristic injury patterns, with multisystem injury being the rule rather than the exception. In 1990, about 5 million people died worldwide as a result of injury.<sup>2</sup> Although sophisticated pre-hospital and trauma center systems have been shown to reduce the number of preventable deaths after trauma, maximum impact in reducing the burden of trauma must come from injury prevention strategies.<sup>3</sup>

Abdominal trauma is among the leading causes of morbidity and mortality in all age groups worldwide.<sup>4</sup> Men tend to be affected slightly more than women.<sup>5</sup> However, identifying serious intra-abdominal pathology due to trauma can be a challenge. Many injuries may not be manifested during the initial assessment and treatment period. Mechanisms of injury often result in other associated injuries that may divert the physician's attention from potentially life-threatening intra-abdominal pathology.<sup>4</sup>

## Materials and methods

A descriptive, prospective, hospital-based study involving observation of patients from the day of admission to final outcome of management at discharge or death, was conducted in the Department of Surgery of Combined Military Hospital (CMH) Dhaka. All consecutive admissions (Total 92) of patients with either blunt or penetrating abdominal injuries with or without associated other system injuries attending the Department of Surgery from July 2013 to December 2014 were included.

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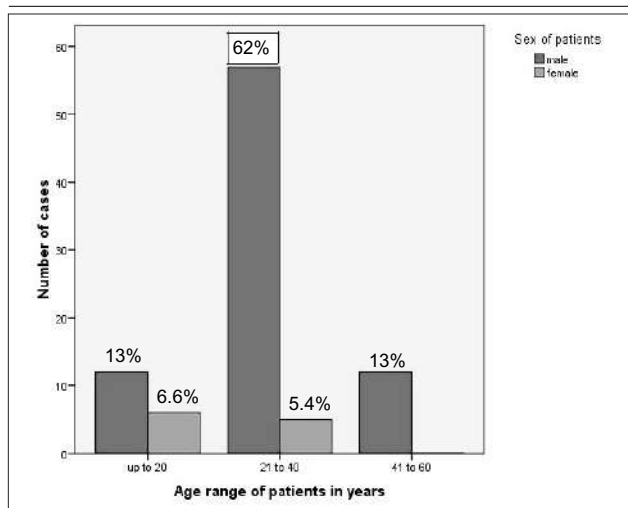
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## Results

**Table I** Demographic characteristics of the study population (n=92)

Characteristics	Frequency	Percentage (%)
<b>Age range (Years)</b>		
>0-20	18	19.5
21-40	62	67.4
41-60	12	13.1
<b>Sex</b>		
Male	81	88.0
Female	11	12.0
<b>Occupation</b>		
Soldiers	39	42.3
Nonprofessionals	23	25.0
Pupils /students	13	14.1
Driver	8	8.7
Farmer	7	7.6
Other Professionals	7	7.6
<b>Residence</b>		
Dhaka proper	28	30.4
Savar	24	26.1
Other parts of Dhaka	22	23.9
Other district	18	19.6
Total	92	100.0



**Figure 1** Bar diagram showing age and sex distribution of the 92 studied patients

**Table II** Mechanism of injury in relation to the type of abdominal injury

Cause of injury	Type of abdominal injury		Total (Percentage)
	Blunt	Penetrating	
RTA	44	7	51(55.4%)
Physical Assaults	2	22	24(26.1%)
Sports	10	0	10(10.9%)
Bomb blast	2	0	2(2.2%)
Falls from height	4	0	4(4.3%)
Gunshot	0	1	1(1.1%)
Total	60(65.3%)	32(34.7%)	92(100.0%)

Two cases of bomb blast (Granade) injury were referred from BGB Hospital, Pilkhana, Dhaka. In this study there was only one case of gunshot injury, a soldier, suffered accidentally.

**Table III** Per-operative findings in relation to the type of abdominal injury (n=18)

Injured organ	Type of abdominal injury			Percentage (%)
	Blunt	Penetrating	Total	
Bowel (Stomach, small intestine, colon, rectum)	2	4	6	33.3
Spleen	4	0	4	22.2
Urinary bladder	2	1	3	16.6
Liver	3	0	3	16.6
Mesentery	1	2	3	16.6
Retroperitoneal haematoma	2	0	2	11.1
Normal intra-abdominal organ	0	1	1	5.5
Omentum	0	2	2	11.1
Diaphragm	2	0	2	11.1
Pancreas	1	0	1	5.5

Total 18 (19.56%) out of 92 patient underwent laparotomy. Rests were managed conservatively after thorough clinical and radiological (USG and CT scan) evaluation. One patient (5.5%) of penetrating abdominal injury was found to have normal intra-abdominal organs.

**Table IV** Distribution of the studied subjects in relation to associated extra-abdominal injuries (n=34)

Extra abdominal injury	Frequency	Percentage (%)
Skeletal injury (limbs, pelvis and spine)	25	73.5
Chest injury	10	29.4
Soft tissue injury	7	20.6
Traumatic Brain Injury (TBI) (Head Injury)	6	18.0

Among 92 patients, 34 were found to have associated extra abdominal injuries. Total frequency of associated injuries is more than 34 because many patients had associated injuries of more than one organ or tissue.

## Discussion

In this study 67.4% of patients were in 21-40 year age group (Table I). The age range of patients was 7 to 55 years and the Mean age was 29.43 years. Musau P et al observed mean age of 28.2 years.<sup>6</sup> In a study by Smith J et al, Mean age for abdominal trauma was 35.0 years (n = 1224).<sup>7</sup> This study supports the findings of others that the young, economically active segment of the population is more vulnerable to injuries.

Males were more involved compared to females in a ratio of 7.4:1 (Table I). In most sub continental countries, males represent the active group in any society that takes part in high risk activities. Smith J et al observed similar pattern with 865 (70.66%) male and 359 (29.33%) females with a ratio of 2.4:1.<sup>7</sup> In another study of Hemang A there were 44 (88%) male and 06 (12%) female with a ratio of 7.3:1.<sup>8</sup>

Blunt trauma was the commonest pattern of abdominal injury encountered, occurring in 65.3% of the studied cases (Table II). RTA was found to be the commonest cause of blunt abdominal trauma as found elsewhere worldwide. In this study, 44 out of 60 patients with blunt abdominal injury sustained their injuries from RTA as passengers, drivers or pedestrians. Penetrating abdominal injury was found in 34.6% of cases. Most of the patients with penetrating injury were involved in assaults. Out of 24 patients who were involved in assaults, 22 (91.7%) had penetrating injury. J Smith et al observed similar pattern with 969 (79.16%) blunt trauma and 255 (20.83%) penetrating trauma.<sup>7</sup> Study of Hemang A observed 74% patients suffered blunt abdominal trauma while 26% patients suffered penetrating abdominal trauma.<sup>8</sup> In all patients, there was only one gunshot injury, accidental, of a soldier during training activity. The incident of bomb blast injury can be explained by its common usage in military training and the study place being a Military hospital. Our country is also at peace, hence there is a low rate of warfare injuries and armed banditry that is more common in certain other countries.

Among all patients with abdominal trauma in this study, 18 underwent laparotomy (Table III). The spleen was found to be the most commonly injured intra-abdominal organ in blunt injuries while bowel was the commonest organ injured when all types of injuries are combined. In their study, Hemang A found that commonly involved organs are liver (32%), followed by spleen (30%), small bowel (24%) and retro-peritoneum (28%).<sup>8</sup> In study of Smith J et al liver (17.15%) and spleen (15.93%) were commonly affected organs followed by vascular injury 13.72% and small bowel 13.07%.<sup>7</sup> This is probably due to the fact that, most of the patient in this study underwent advanced radiological evaluation with repeated USG and early CT scan, and clinically stable patients were managed conservatively.

In this study, 34 patients (37%) had associated injuries. Skeletal injuries (Pelvic, Lower and upper limbs fracture) were the most common associated injuries, i.e 73.5% (Table IV). Seven patients (20.6%) had multiple associated injuries. Isolated abdominal injuries constituted 63% of all cases. In a study by Davis J et al thoracic injury was associated with 27% (n = 120) abdominal trauma while orthopedic injuries were associated with 14.68% (n = 69) cases of abdominal trauma.<sup>9</sup>

In their study, Ntundu, S.H et al concluded that, the most common cause of abdominal injury was road traffic accidents and commonly injured organs in blunt and penetrating injuries were, respectively, the spleen and small bowel. Associated extra-abdominal injury was significantly associated with mortality.<sup>10</sup>

Ramachandra M. L., Krishna S. R, published their work on 2018, stating, majority of their patients belonged to male sex and of the age group of 21-40 years. Road traffic accident was the most common mode of injury. Splenic injury was commonest, followed by liver injury and all were managed conservatively.<sup>11</sup>

The burden of road traffic accidents and trauma in low-resource settings in a underdeveloped country like us, was studied by de Costa et al.<sup>12</sup> RTA patients were 2.3 times more likely to have a peripheral injury in their study. These patients were found to have been occupying emergency department, Operation Theater and internal patient department for significantly more time than other patients as they concluded in their study.

In other recently published studies in our region i.e Indian subcontinent and international arena, many researchers have found similar pattern of abdominal injuries in their setup.<sup>13-17</sup>

Our study is not free of limitations. The study place is a military hospital in the capital city of Bangladesh. It may not reflect the actual overall scenario of the whole country. Our patient with entitlement to get free treatment in this hospital, may not reflect the actual population of this country too.

### Conclusion

From our study we can conclude that abdominal trauma can present differently and may injure organ depending upon pattern of injury and require clinical assessment expedited investigations to set goal for prompt primary resuscitation and timely, definitive treatment.

### Disclosure

Both the authors declared no competing interests.

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# Comparison of Mechanical Complications between Internal Jugular and Subclavian Central Venous Access in Intensive Care Unit

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## ABSTRACT

**Background:** Central Venous Catheters (CVCs) play an important role in treating critically ill patients in an adult ICU. The most frequently used anatomical sites for CVC insertion are the internal jugular and subclavian vein. An improved understanding of CVC related risks might help clinicians to choose one approach over the other in specific clinical settings. The purpose of the study to detect the occurrence of CVC related mechanical complications in different insertion site.

**Materials and methods:** This observational cross sectional study was carried out prospectively in the Department of Critical Care Medicine BIRDEM General Hospital, Dhaka and Critical Care Centre, Combined Military Hospital (CMH) Dhaka. The Catheters were inserted using Seldinger technique.

**Results:** Mechanical complications included bleeding (56 patients), catheter related complications (40 patients) and pneumothorax (10 patients). It was found that complications were higher with IJV insertion attempts and in patients who had two or more insertion attempts during the procedure. Catheter related complications included guidewire kinking (15 patients), and catheter tip malposition (25 patients). The overall rate of mechanical complications between the two groups were not statistically significant but there were significantly more overall mechanical complications associated with 2 or more insertion attempts.

**Conclusion:** We found that Subclavian access was associated with a low rate of mechanical complications in the Intensive Care Unit as compared with Internal Jugular access. As the study included only two centres and the sample size was small, a multicentre large sample study is needed to make conclusive comment.

**Key words:** Central venous access; Intensive care unit; Mechanical complications.

## Introduction

Complications associated with Central Venous Catheters (CVCs) have a major impact on the hospital course of patients admitted to the Intensive Care Unit (ICU) due to the morbidity, mortality and increased health care costs associated with them.<sup>1</sup> In critically ill patients, barotrauma and puncture of an incompressible artery are probably the most common mechanical complications and can be life threatening.<sup>2</sup> Mechanical complications include arterial puncture, pneumothorax, mediastinal haematoma, haemothorax and injury to adjacent nerves.<sup>3,4</sup>

Despite the advent of ultrasound guided vascular cannulation, which has reduced the incidence of insertion complications drastically, many hospitals in Bangladesh and other developing countries still rely on the landmark-based technique for cannulation. The most frequently used

anatomical sites for CVC insertion are the internal jugular and subclavian vein.<sup>5,6,7</sup> However, in an individual patient, criteria for choosing one approach over the other often remain unclear. This choice could depend on the complication rate with each approach and individual skill.<sup>8</sup> Thus, this study was conducted with the objective to have an improved understanding of CVC related mechanical complications between the two approaches that might help clinicians to choose one approach over the other in specific clinical settings.

## Materials and methods

This observational cross sectional study was carried out prospectively in the Department of Critical Care Medicine BIRDEM General Hospital, Dhaka and Critical Care Centre, Combined Military Hospital (CMH) Dhaka, between September 2018 to October 2019. The catheters used were multilumen radiopaque polyurethane catheters (Arrow, Reading, PA, USA). The catheters were inserted by physicians with sterile barrier precautions. The catheters were percutaneously inserted using landmark and Seldinger technique and fixed to the skin with 2-0 silk suture. After the line insertion, the area surrounding the catheter was cleaned with a sterile gauze soaked with povidone iodine and a occlusive gauze dressing applied over the site. No topical antimicrobial ointment was applied to insertion sites. If the patient had any Intravenous (IV) line at other site, that was removed after insertion of CVC

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line. All cannulations were performed either by an ICU consultant or by a 2<sup>nd</sup> or 3<sup>rd</sup> year registrar. The choice of the CVC insertion sites (Either IJV or SCV) was left to the discretion of the performing doctor. The date, site and side of cannulation and the number of punctures required for successful cannulation as well as complications, if any, were noted for each insertion procedure. Chest radiograph was performed on all patients to verify the position of the tip of the CVC and to detect delayed complications like pneumothorax or haemothorax. CVCs were changed if required for more than 14 days or removed when no longer required or when suspected to be infected. The outcomes of all patients included in the study were noted at the end of ICU stay, i.e died or transferred to ward.

The SPSS software for Windows, Version SPSS 16.0 (SPSS Inc, Chicago, IL, USA) and the EPI Info software (3.5.1) were used to process the data and generate the statistics. Mean and standard deviation (SD) was calculated as required for numerical variables. Univariate analysis was performed to compare the survivor with the non-survivor groups. Unpaired 't' test and Chi-square ( $\chi^2$ ) tests were performed where appropriate.  $p < 0.05$  was considered statistically significant.

#### Inclusion criteria

- i) Age >18 years.
  - ii) Multi-lumen 16 cm polyurethane CVCs (Arrow, USA) inserted using Seldinger approach under maximum sterile barrier precautions.
- #### Exclusion criteria
- i) CVCs inserted in other hospitals.
  - ii) Patients having IV cannulation at more than one anatomical sites.
  - iii) Total Platelet Count <50,000/ $\mu$ l and INR >1.5.

Ethical approval was obtained from appropriate authority prior to the commencement of the study.

#### Results

During the study period, a total of 324 catheters fulfilled our inclusion and exclusion criteria. 156 catheters were inserted through IJV and 168 catheters were inserted through SCV (Table I). There were no difference between the two groups in terms of age, gender distribution, presence of co-morbid illness, (Table II). Number of insertion attempts were significantly more in SCV route than IJV route ( $p=0.02$ , Table III). Number of failed attempts was also more in SCV access than IJV access but that was not statistically significant ( $p=0.46$ , Table III). Mechanical complications included bleeding (56 patients), catheter related complications (40 patients), and pneumothorax (10 patients). It was found that bleeding complications (arterial puncture and haematoma formation) were significantly higher with IJV insertion attempts ( $p=0.01$  and  $p=0.006$  respectively, Table IV) and in patients who had two or more insertion attempts during the procedure ( $p < 0.001$ , Table V).

Catheter related complications included guidewire kinking (15 patients) and catheter tip malposition (25 patients). Catheter tip malposition occurred significantly more with SCV insertion ( $p=0.03$ , Table IV) and in two or more insertion attempts ( $p=0.001$ , Table V). Catheter related guidewire kinking also occurred significantly more in two or more insertion attempts ( $p=0.01$ , Table V). A total of 10 pneumothorax developed during the study period. Although more pneumothorax developed with SCV route but there was no statistically significant difference between the two groups (Table IV).

**Table I** Distribution of CVCs in study subjects

	Number	Percentage
IVJ	156	48.15
SCV	168	51.85
Total CVCs	324	100.0

CVC : Central Venous Catheter  
 IJV : Internal Jugular Vein  
 SCV : Subclavian Vein

**Table II** Univariate analysis comparing the demographic profile between the patients in IJV and SCV groups

	IVJ n=156	SCV n=168	Total	p value
Mean age (Mean SD)	61.59 ( $\pm 17.52$ )	59.63 ( $\pm 15.87$ )		0.56
Sex				
● Male	82(52.56)	108(64.28)	190	0.06
● Female	74(47.43)	60(35.71)	134	
Co-morbid illnesses:				
Diabetes mellitus	142(91.02)	157(93.45)	299	0.41
Hypertension	80(51.28)	92(54.76)	172	0.53
Coronary artery disease	66(42.30)	77(45.83)	143	0.52
Chronic Kidney Disease	74(47.43)	82(48.80)	156	0.77
Others	24(15.38)	31(18.45)	55	0.46
Medical cases	146(93.59)	152(90.48)	298	0.21
Surgical cases	10(6.41)	16(9.52)	26	0.30

Unpaired 't' test and  $\chi^2$  test were done.

Values are number (percentage) unless otherwise indicated.

n : Number of patients

**Table III** Comparison of insertion characteristics between the patients in IJV and SCV groups

Insertion characteristics	IVJ n=156	SCV n=168	Total	p value
Right side	143	152	295	$\chi^2-0.04$
Left side	13	16	29	$p=0.70$
$\geq 2$ insertion	54	79	133	$\chi^2-5.15$
$< 2$ insertion	102	89	191	$p=0.02$
Success attempts	143	150	293	$\chi^2-0.53$
Failed attempts	13	18	31	$p=0.46$

Values are number (Percentage) unless otherwise indicated.

**Table IV** Mechanical complications associated with CVC insertions

Complication	IJV n=156	SCV n=168	Total	p value
Bleeding Haematoma	18(11.54)	06(3.57)	24	0.006
Arterial trauma	22(14.10)	10(5.95)	32	0.01
Catheter-related Guidewire kinking	4(2.56)	11(6.55)	15	0.09
Catheter tip malposition	7(4.49)	18(10.71)	25	0.03
Pneumothorax	3(1.92)	7(4.17)	10	0.34

$\chi^2$  test was done.

Values are number (Percentage) unless otherwise indicated.

**Table V** Mechanical complications associated with CVC insertion attempts

Complication	1 puncture	$\geq 2$ punctures	Total	p value
Bleeding Haematoma	05	19	24	<0.001
Arterial trauma	05	27	32	<0.001
Catheter-related Guidewire kinking	04	11	15	0.01
Catheter tip malposition	07	18	25	0.001
Pneumothorax	03	07	10	0.07

$\chi^2$  test was done.

Values are number (Percentage) unless otherwise indicated.

## Discussion

Central Venous Catheters (CVCs) are essential for the clinical management of many patients. Indications for a CVC are the intravenous administration of specific drugs (e.g. Catecholamine), parenteral nutrition, haemodialysis, and haemodynamic monitoring.<sup>10,11,12</sup> In many institutions, patients undergoing major surgery and patients with critical illness or cancer routinely receive a CVC. Thus, percutaneous placement of a catheter into a central vein is a frequent procedure in many clinical settings.<sup>13</sup>

Unsuccessful insertion attempts are reported to be the strongest predictor of mechanical complications, and are reported to occur in up to 28% of failed insertions.<sup>9,13,14</sup> Kaur et al found that CVCs inserted via the IJV route had a significantly higher proportion of failed cannulations, possibly contributing to the greater number of mechanical complications via this route.<sup>2</sup> Ruesch et al, Memon et al also had similar findings.<sup>3,4</sup> In our study, we found that the incidence of 2 or more insertion attempts was significantly more with SCV cannulation ( $p=0.02$ ) but although the incidence of failed attempts was more with SCV access, it was not statistically significant ( $p=0.46$ ).

In the meta-analysis by Ruesch et al, arterial punctures were significantly more common with the jugular than with the subclavian approach (Six trials, 2010 CVCs, 3% vs 0.5%, Relative Risk (RR) 4.7, 95% Confidence Interval (CI) 2.05-10.77).<sup>3</sup> There may be a possibility that the increased risk with the jugular access was the result of an under reporting of arterial punctures with the subclavian approach as puncture of a carotid artery is usually easier to detect

than puncture of a subclavian artery. Marik et al, Chittick et al, Tan et al found that increased incidence of arterial puncture is associated with increased risk of local infection.<sup>5,6,7</sup> In our study, bleeding complications like haematoma formation and arterial puncture were significantly more in IJV route than SCV route ( $p=0.006$  and  $p=0.01$  respectively). Moreover, it was observed that these complications were associated more significantly with more than 2 insertion attempts ( $p<0.001$ ).

Catheter malpositions may result in vascular perforations and dangerous arrhythmias. Malpositioning have been reported in 14% of CVCs even when they were inserted by experienced clinicians.<sup>8,9,11</sup> The positioning of catheter tip within the cardiac silhouette is associated with an increased risk of cardiac tamponade.<sup>13</sup> Also, positioning of a catheter tip in a subclavian vein is associated with a high risk of thrombus formation and vessel occlusion.<sup>14</sup> In the meta-analysis done by Ruesch et al, only four trials reported on vessel occlusion (Vessel stenosis or thrombosis), and there was no evidence of any difference between the two CVC approaches.<sup>3</sup> Catheter tip malpositions were significantly more with SCV approach than IJV approach in our study ( $p=0.03$ ). Although the incidence of guidewire kinking was more with SCV route, it was not statistically significant ( $p=0.09$ ). Moreover, these complications occurred more significantly when more than 2 insertion attempts were made ( $p=0.001$  and  $p=0.01$  respectively). It is reported in some literatures that pneumothorax, one of the most feared complications of CVC insertions, occurs in up to 0.1% to 3.1% patients undergoing the procedure, with increasing risk with larger needle size and number of passes made, use of the SCV route and in emergency situations.<sup>1,15</sup> Kaur et al found that this complication occurred equally with the IJV and SCV insertion routes, however, 2 or more attempts at needle passes were associated with a significantly higher risk of pneumothorax ( $p=0.0052$ ).<sup>2,8</sup> In the meta-analysis by Ruesch et al, there was no evidence of any difference in the incidence of haemo and pneumothorax with the two approaches.<sup>3</sup> In our study, although the incidence of pneumothorax happened more with SCV route than IJV route, it was not statistically significant.

## Conclusion

Interest in catheter-related complications lies in the mortality, morbidity and the costs it represents. We found that Subclavian access was associated with a low rate of severe mechanical complications in the intensive care unit as compared with internal jugular access. CVCs need proper precaution during insertion and aftercare. Standard hand hygiene, proper technique and sterile precautions can lower the rate of CVC related mechanical complications significantly. It is concluded that although CVCs play an important role in treating critically ill patients in an adult ICU this may cause serious multiple mechanical complications if proper precautions are not taken.

**Disclosure**

All the authors declared no competing interests.

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# Molecular Subtyping of Nodal Diffuse Large B-cell Lymphoma, NOS on the Basis of Hans Algorithm along with Double and Triple Hit Expression

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## ABSTRACT

**Background:** Diffuse large B cell lymphoma, NOS is the most common type of non Hodgkin lymphoma. Like other Asian countries, in Bangladesh very little is known about the exact incidence and prevalence of molecular subtypes of nodal diffuse large B cell lymphoma, NOS. So, to reduce the morbidity and mortality of the patients, it is the high time to work on proper diagnosis of the entities. Good outcome of treatment depends on effective and correct diagnosis. The aim of the study is to determine the frequency of activated B cell subtype and germinal center B cell subtypes of diffuse large B cell lymphoma, NOS and double hit and triple hit lymphomas after molecular subtyping.

**Materials and methods:** The study is a prospective study, performed in Department of Histopathology, Armed Forces Institute of Pathology, Dhaka from 01 July 2020 to 30 December 2020 by convenient sampling. Cases diagnosed with diffuse large B cell lymphoma, NOS by morphology and primary panel of immunohistochemistry were selected for subsequent immunohistochemistry panel. The subtyping is done by Hans' algorithm.

**Results:** Among the 50 cases in the study, 37 (74%) are activated B cell subtype and 13 are (26%) are germinal center B cell subtype. Among 13 cases of double hit diffuse large B cell lymphoma, NOS; 12 (92.31%) are activated B cell subtype and 01 is (7.69%) germinal center B cell subtype. Among the study population, in 36 cases the hit expression is inconclusive. In these 36 cases of non expressed diffuse large B cell lymphoma, 25 (69.45%) are activated B cell subtype and 11 (30.56%) are germinal center B cell subtype.

**Conclusion:** As the current precise treatment is more dependent on immunohistochemical analysis so, hit expression is recommended to be reported along with molecular subtyping.

**Key words:** Double hit; Triple hit; Immunohistochemistry; Diffuse large B cell lymphoma.

## Introduction

Lymphoma is the tumors of lymphoid system and specifically of lymphocytes and their precursor cells, whether of T, B or null phenotypes. The lymphomas are divided into two major categories: Hodgkin-lymphoma and non-Hodgkin lymphoma.<sup>1</sup> The non-Hodgkin lymphomas are a heterogeneous group of lympho-proliferative malignancies, with distinct causes and showing distinctive patterns of behavior and responses to treatment. It consists of many subtypes, diffuse large B cell lymphoma, NOS being the most prevalent, each with distinct epidemiology, etiology, morphologic, immunophenotypic, and clinical

features.<sup>2</sup> Several Mature B cell neoplasms have characteristic genetic abnormalities that are important in determining their biological features and can be useful in differential diagnosis. These genetic abnormalities include t(11;14)(q13;q32) in mantle cell lymphoma, t(14;18)(q32;q21) in follicular lymphoma, t(8;14)(q13;q32) and variants in Burkitt lymphoma and t(11;18)(q21;q21) in MALT lymphoma. The (11;14) translocation is seen in both mantle cell lymphoma and some cases of plasma cell myeloma.<sup>3</sup> It is essential to distinguish each one by its morphological and immunophenotypic features, as the treatment and prognosis of these neoplasms involve different principles.<sup>4</sup> The most common cancers in male patients are lung followed by non-Hodgkin lymphoma.<sup>5</sup> Immunohistochemistry is generally performed on formalin-fixed, paraffin embedded tissues (Hans' algorithm) using three antibodies CD10, multiple myeloma oncogene 1 (MUM1) and polyclonal B-cell lymphoma 6 (BCL6) to classify diffuse large B cell lymphoma, NOS.<sup>6</sup> A double-hit lymphoma has the cytogenetic abnormalities of chromosomal rearrangements consistent with Bcl2/Bcl6 and c-MYC genes. Triple-hit lymphoma has cytogenetic abnormalities consistent with chromosomal rearrangements of BCL-6, BCL-2 and c-MYC genes. Triple-hit lymphomas have a poorer prognosis than double-hit lymphomas and either diffuse large B cell lymphoma, NOS or Burkitt lymphoma.<sup>6</sup>

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### Materials and methods

This prospective study is done on 50 cases of diffuse large B cell lymphoma, NOS over a period of six months (Between 01 July 2020 and 31 December 2020) who were diagnosed in the Department of Histopathology, Armed Forces Institute of Pathology, according to the inclusion criteria of study. Initially the cases were diagnosed as diffuse large B cell lymphoma on the bases of morphology and initial immunohistochemistry panel of CD3 and CD20. Then antibodies were employed for molecular subtyping and hit expression. Primary nodal diffuse large B cell lymphoma diagnosed by morphology and immunohistochemistry in Armed Forces Institute of Pathology, Dhaka during the study period are included in the study. Total 50 cases were selected. Exclusion criteria were unwilling patients, patients who already received chemotherapy and patients admitted in ICU.

After obtaining informed written consent, the biopsied lymph nodes specimen or paraffin embedded blocks of lymph nodes with proper patient identification were received in the department. After taking sections from the specimens, tissue were processed and paraffin blocks were prepared. Haematoxylin & eosin stained slide were prepared and evaluated under microscope. Some blocks of lymph nodes were received for review and/or immunohistochemistry. The initial panel of IHC antibodies included CD20 and CD3. During morphological assessment certain histologic characteristics were taken into account. Panel of antibodies were decided based on the morphological pattern.

The initial panel of IHC antibodies included CD20 and CD3. During morphological assessment certain histologic characteristics were taken into account. Panel of antibodies was decided based on morphological pattern. Morphologic features evaluated were effacement of nodal architecture (Monomorphous or polymorphous cell population), pattern of growth (Nodular or diffuse), size of the cells (Small, intermediate or large), size and shape of nucleus, nature of chromatin (Fine, coarse or vesicular), amount of cytoplasm (Scant, moderate or abundant). CD20 positive non-Hodgkin Lymphoma, B cell phenotype having intermediate to large neoplastic cells arranged or infiltrating diffusely, were categorized as diffuse large B cell lymphomas, NOS. The IHC panels used are CD10, Bcl-2, Bcl-6, MUM-1 and c-MYC.

### Results

Among the 50 patients, 37 (74%) are activated B cell subtype and 13 are (26%) are germinal center B cell subtype of diffuse large B cell lymphoma, NOS. Among the study population, in 36 cases, the hit expression is inconclusive. In these 36 cases of non-expressed diffuse large B cell lymphoma, NOS; 25 (69.45%) are activated B cell subtype and 11 (30.56%) are germinal center B cell subtype.

Among 13 patients of double hit diffuse large B cell lymphoma, NOS, 12 (34.28%) are activated B cell subtype and 01 is (7.69%) germinal center B cell subtype.

Among the 13 double hit lymphomas, 08 are male and 05 are female. Only triple hit lymphoma case is male.

**Table I** Sex wise distribution of study population among the molecular subtypes (n=50)

Sex	Activated B cell subtype		Germinal center B cell subtype		
	Number	%	Sex	Number	%
Male	26	70.27%	Male	11	84.62%
Female	11	29.72%	Female	02	15.38%

**Table II** Distributions of study population among the molecular subtypes according to age groups

Subtypes	0-9	10-19	20-29	30-39	40-49	50-59	60-69	>70
	years	years	years	years	years	years	years	years
Activated B Cell subtype (37)	-	02	02	08	03	13	05	04
Germinal Center B cell subtype (13)	-	01	02	03	01	03	02	01

**Table III** Expressions of double hit lymphomas in activated B cell and germinal center B cell subtype

Type of diffuse Large B cell lymphomas, NOS	Double hit lymphomas (13)
Activated B cell subtype	12 (92.31%)
Germinal Center B cell subtype	01 (7.69%)

Among 13 patients of double hit lymphomas, 12 (92.31%) are activated B cell subtype and 01 is (7.69%) germinal center B cell subtype.

**Table IV** Expressions of triple hit lymphoma in activated B cell and germinal center B cell subtype

Type of diffuse large B cell lymphoma, NOS	Triple hit diffuse large B cell lymphoma, NOS (01)
Activated B cell subtype	Nil
Germinal Center B cell subtype	01 (100%)

**Table V** Undetermined hit expressions in activated B cell and germinal center B cell subtypes.

Type of diffuse large B cell lymphoma, NOS	Non expressed diffuse large B cell lymphoma (36)
Activated B cell subtype	25 (69.45%)
Germinal Center B cell subtype	11 (30.56%)

Among the study population, in 36 cases, the hit expression is inconclusive. In these 36 cases of non expressed diffuse large B cell lymphoma, NOS, 25 (69.45%) are activated B cell and 11 (30.56%) are germinal center B cell subtype.

### Discussion

Cell of origin distinction underlie fundamentally different biology based on gene expression, chromosomal aberration and recurrent mutation. They are also associated with reproducible survival difference in patients

treated with the CHOP chemotherapy regimen plus rituximab (R-CHOP). So the accurate distinction of the molecular subtype is an important predictive factor in diffuse large B cell lymphoma, NOS.

Immunohistochemical technologies are considered an acceptable alternative where gene expression technologies are not available. Numerous immunohistochemical algorithms exist for molecular subtyping, among them WHO recommends Hans' algorithm where diffuse large B cell lymphoma, NOS is classified into germinal center B cell subtype and activated B cell subtype and thus does not recognize the unclassified cases.

Age is a risk factor for any malignancy. In our study, most number of diffuse large B cell lymphoma, NOS cases are found in 50-59 years. Total 16 cases of diffuse large B cell lymphoma, NOS are found in this age group. Among those, 13 cases are activated B cell subtype and 3 are germinal center B cell subtype. Most of the studies have reported, age >60 years is a risk of developing diffuse large B cell lymphoma, NOS. The finding regarding age group of Akhter A, Rahman MR, Majid N et al and Akifumilchiki et al closely coincides with our present study.<sup>7,10</sup>

EBV related diffuse large B cell lymphoma, NOS are typically of activated B cell subtype, which gives a clue about the more number of activated B cell subtypes in Asian population. The study conducted by Rebekka Rebera et al reported 51 cases of germinal center B cell subtype and 49 cases of diffuse large B cell lymphoma, NOS subtype, which is almost equal.<sup>8</sup>

Male predominance is an exclusive feature of this study. About 74% of the study population are male. Other studies conducted by Lucka Boltezar et al and Akifumilchiki et al also reported male predominance.<sup>9,10</sup>

In our study, activated B cell subtype (74%) is remarkably more than germinal center B cell subtype (26%). Although most studies have found more number of germinal center B cell subtype than activated B cell subtype. But studies conducted by William W.L. Choi et al has also found more activated B cell subtype than germinal center B cell subtype.<sup>11</sup> Majority of the cases in the study did not show any hit expression. Arianna Di Napoli et al showed that even if there is c-MYC rearrangement in diffuse large B cell lymphoma, a good percentage (20%) does not express MYC protein.<sup>12</sup>

More activated B cell subtypes than germinal center B cell subtypes, is a clear contrast from many other studies, like the studies conducted by Lucka Boltzar et al and Grzegorz S. Nowakowski et al.<sup>13,9</sup>

Among the double-hit lymphomas of the study, all are c-MYC and Bcl-2 positive. None of the double hit lymphoma is c-MYC and Bcl-6 positive. This statistics coincides with the study conducted by Yang Xia et al.<sup>14</sup>

Study conducted by Cristiano Claudino Oliveira et al also found more activated B cell subtype than germinal center B cell subtype among Brazilian population.<sup>15</sup>

### Conclusion

A rapid and rational approach for diagnosing Double/Triple hit lymphoma can be established based on IHC result. Cytogenetic study would add further value and consolidate the report of IHC. Molecular subtyping and hit expressions along with proliferation index (Ki67) provide a good prognostic marker. According to the result, treatment may be intensified as patients' outcome varies a great deal with the expression of different immunohistochemical markers. New entities with clinical relevance are emerging. In the near future this will have a major impact on defining appropriate treatment to propose to patients.

### Recommendations

- The study recommends to Follow Hans algorithm for molecular subtyping or determining Cell of Origin (COO) of diffuse large B cell lymphoma, NOS.
- Cell of origin and hit expression should be reported in all diffuse large B cell lymphoma, NOS cases.
- Standard tissue processing manual/protocol should be ensured to avoid aberrant expressions, questionable positivity and inconclusive expressions of immunohistochemistry markers.
- Core biopsy of accessible lymph node at times create dilemma in determining the cell of origin. Hence, total intact lymph node excision is preferred and suggested.

### Disclosure

All of the authors declared no competing interest.

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## Baseline Biochemical Characteristics of Hospitalized COVID-19 Patients

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### ABSTRACT

**Background:** Coronavirus disease 2019 (COVID-19) alters various biochemical parameters of blood. Some of these biomarkers have been suggested to indicate disease severity and have prognostic values. So, this study aimed to investigate the changes in four such parameters and their possible relations with imaging findings (Extent of lung involvement), length of hospital stays and presence of comorbid conditions.

**Materials and methods:** This was a hospital-based cross-sectional comparative study conducted at dedicated COVID-19 unit of Parkview Hospital Ltd. of Chattogram during the period of December 2020 to April 2021. Two hundred twenty-seven (227) RT-PCR test positive hospitalized COVID patients of 18 to 90 years were purposively recruited. Along with patients' general and imaging characteristics (e.g., percentage of lung infiltration in CT scan) four inflammatory markers- plasma D-dimer, serum LDH, CRP and ferritin were analysed on or shortly after admission.

**Results:** Levels of all four biomarkers increased significantly in high proportion of COVID patients (Plasma D-dimer increased in 60.66%, serum LDH in 60%, CRP in 88.67% and ferritin in 41.72%). Mean concentrations of plasma D-dimer, serum LDH, CRP and ferritin were also significantly higher ( $0.97 \pm 0.10$  microgram/mL FEU,  $291.81 \pm 13.72$  U/L,  $50.30 \pm 3.75$  mg/L and  $505.44 \pm 50.56$  ng/mL respectively) than their corresponding reference values. Duration of hospital stay (Mean =  $7.64 \pm 0.25$ ) increased with increase in age, percentage of lung involvement, serum LDH and serum ferritin concentrations. However, levels of plasma D-dimer and serum CRP did not correlate significantly with duration of hospital stay. Also, percentage of lung involvement (An index of severity of COVID-19 in imaging) correlated significantly with biochemical parameters of severity (LDH, CRP, ferritin levels) except for D-dimer levels.

**Conclusion:** This study reveals that on admission, measurement plasma D-dimer, serum LDH, CRP and ferritin levels in hospitalized COVID patients complement with comorbid and imaging information for better prediction of severity and patient outcome.

**Key words:** Coronavirus; COVID-19; CRP; CT scan; D-dimer; Ferritin; LDH; RT-PCR.

### Introduction

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic. Since its first outbreak in Wuhan City, China, more than 560 million cases have been reported worldwide with nearly 6.4 million deaths.<sup>1</sup> In Bangladesh,

total cases reached around 2 million marks with close to 30,000 deaths.<sup>2</sup> Management and outcome of COVID-19 patients largely depend on severity of disease. Current scientific evidence suggests that disease severity is determined by clinical features and by presence of clinical, laboratory and imaging risk factors. Clinical risk factors are pre-existing comorbid medical conditions such as hypertension, diabetes, heart conditions, asthma, chronic lung disease etc.<sup>3-5</sup> Proposed laboratory risk factors include low lymphocyte count, high levels of D-dimer, lactate dehydrogenase (LDH), CRP, ferritin, troponin, CPK etc.<sup>6-14</sup> Main imaging risk factors involve type and extent of lung involvement.<sup>10, 15-16</sup> So, in this study of hospitalized COVID-19 patients, all three types of disease severity determinants and their interrelations were further investigated in a community context.

### Materials and methods

This hospital-based cross-sectional comparative study was conducted at dedicated COVID-19 unit of Parkview Hospital Ltd. of Chattogram during the period of December 2020 to April 2021. Among the hospitalized COVID-19 patients, two hundred twenty-seven (227) RT-PCR test positive subjects of 18 to 90 years were purposively recruited following the undermentioned inclusion and exclusion criteria.

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*Inclusion criteria:*

- Hospitalized COVID-19 patients.
- Aged from 18-90 years.
- Tested positive for COVID-19 RT-PCR Test (Initially or subsequently).
- Had undergone high-resolution chest CT scan and pre-set biochemical tests (Plasma D-dimer, serum LDH, CRP & ferritin) on admission day.

*Exclusion criteria:*

- COVID-19 RT-PCR Test negative suspected COVID patients.
- Patients lacking required imaging and biochemical data.
- Patients leaving hospitals (Early) without advice.

The patients had underwent high-resolution chest CT scan and expert radiologists interpreted the results with percentage of lung involvement. Serum CRP was estimated by turbidimetric immunoassay and serum LDH by enzymatic method on Siemens Dimension system. Serum ferritin was estimated on ADVIA Centaur CP using direct Chemiluminescence Immunoassay (CLIA) technology. Plasma D-dimer was measured by CLIA on Snibe MAGLUMI 2000 Plus system.

Statistical analyses were performed using Statistical Package for Social Science (SPSS) for Windows version 22.0. p values < 0.05 were considered statistically significant. Quantitative data were expressed as mean  $\pm$  SEM (Standard error of the mean) and qualitative data were expressed in frequency and percentage. Relevant statistical tests of significance were done as needed.

**Results**

**Table I** General, CT and Biochemical Characteristics of hospitalized COVID-19 patients. Values in parentheses indicate range

Characteristics	Result
Mean Age in years	55.51 $\pm$ 0.97 (18-90)
Patients of 18 to 34 years	7.93% (n = 18)
Male	56.83%, n = 129
Female	43.17%, n = 98
Comorbidity present in	81.06%, n = 184
Mean number of comorbidities	2.19, n = 184
Mean Hospital Stay in days	7.64 $\pm$ 0.25 (1-31)
Mean % Lung Involvement	31.02 $\pm$ 1.42 (2-77.5)
Mean D-dimer	0.97 $\pm$ 0.10 (0.01-9.97)
D-dimer increased in	60.66%
Mean LDH	291.81 $\pm$ 13.72 (125-800)
LDH increased in	60%
Mean CRP	50.30 $\pm$ 3.75 (0.59-305.30)
CRP increased in	88.67%
Mean Ferritin	505.44 $\pm$ 50.56 (8.01-3000)
Ferritin increased in	41.72%

The above table shows that a significant portion (81.06%) of studied cases had comorbid medical conditions. On high-resolution chest CT scan, mean percentage of lung involvement was 31.02%. As expected, concentrations of all the four studied biochemical parameters (Plasma D-dimer, serum LDH, CRP & ferritin) increased significantly from their reference values. Levels of plasma D-dimer, serum LDH, CRP & ferritin were increased in 60.66%, 60%, 88.67% & 41.72% of patients respectively in their initial check on or shortly after admission.

**Table II** Correlations of Length of Hospital Stay (In days) with Age, Percentage of Lung Involvement and studied Biochemical Parameters

Correlation with	Correlation Coefficient (r)	p-value
Age	0.16	< 0.05, significant
% Lung involvement	0.26	< 0.05, significant
D-dimer	0.08	> 0.05
LDH	0.24	< 0.05, significant
CRP	0.10	> 0.05
Ferritin	0.18	< 0.05, significant

In this table correlation test shows that duration of hospital stays increased with increase in age, percentage of lung involvement, serum LDH and serum ferritin concentrations. However, levels of plasma D-dimer and serum CRP did not significantly correlate with duration of hospital stay.

**Table III** Correlations of Percentage of Lung Involvement with studied Biochemical Parameters

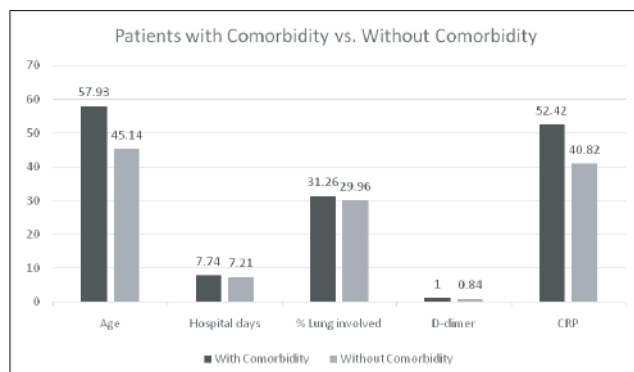
Correlation with	Correlation Coefficient (r)	p-value
D-dimer	0.10	> 0.05
LDH	0.44	< 0.05, significant
CRP	0.43	< 0.05, significant
Ferritin	0.19	< 0.05, significant

Table shows that percentage of lung involvement (a definite index of severity of COVID-19 in imaging) correlated significantly with biochemical parameters of severity (LDH, CRP, ferritin levels) except for D-dimer levels.

**Table IV** Frequency of Comorbid Medical Conditions

Comorbid Conditions	Number (n)	Percentage (%)
Hypertension	145	63.88%
Diabetes	132	58.15%
Heart Conditions	49	21.59%
Asthma	20	8.81%
Chronic Lung Disease	13	5.72%
Chronic Kidney Disease	15	6.61%
Neurologic Conditions	10	4.41%
Cerebrovascular Disease	8	3.52%

Table showing hypertension, diabetes and heart conditions as the three most common comorbidities among hospitalized COVID-19 patients in this study.



**Figure 1** Comparison between Patients with Comorbidity and Patients without Comorbidity

Above figure illustrates that patients with pre-existing comorbid medical conditions were comparatively of higher age and were also more severely affected in terms of duration of hospital stay, imaging and biochemical abnormalities.

### Discussion

In the present study, two hundred twenty-seven (227) RT-PCR test positive, hospitalized COVID-19 patients of 18 to 90 years were studied for imaging and biochemical abnormalities on or shortly after admission. Pre-existing comorbid medical conditions were also analysed for their potential effects.

Here, mean age of the cases was  $55.51 \pm 0.97$  years. 18 to 34 years individuals comprised of only 7.93% of patients (Table I). Similar trend was also observed in previous studies of hospitalized COVID-19 patients where the median age ranged from 49 to 56 years<sup>7, 9, 17</sup> Likewise, in another large study, subjects of 18 to 34 years accounted for only 5% of adult, hospitalized COVID patients.<sup>18</sup> In COVID-19, age and sex are important because increased age and male sex were associated with higher morbidity and mortality in a number of studies.<sup>19-27</sup> Increased age was related to increased hospital stay in our study as well (Table II).

81.06% (n = 184) of our patients had pre-existing comorbid medical conditions. The mean number of comorbidities was 2.19 (Table I). Hypertension, diabetes and heart conditions were the three most common comorbidities with frequency of 63.88%, 58.15% and 21.59% respectively (Table IV). In a multicentre cohort study of adult, hospitalized COVID patients by Zhou and his colleagues, 48% patients had comorbidities. Hypertension (30%), diabetes (19%) and coronary heart disease (8%) were the most common comorbid conditions in that study also.<sup>8</sup>

As shown in Figure 1, patients with pre-existing comorbid medical conditions were comparatively of higher age and were also more severely affected in terms of length of hospital stay and of imaging or biochemical abnormalities. These are in line with results of numerous studies where comorbidities are associated with more severe illness or death.<sup>3-5, 8, 10, 18, 22-23</sup> Although severe disease can affect

anyone, most of the severely affected patients in similar studies had at least one risk factor. For comparison, in a study of 355 Italian patients dying with COVID-19, the mean number of comorbidities was 2.7 where only 3 patients were without comorbid medical conditions.<sup>24</sup>

In this study, levels of plasma D-dimer, serum LDH, CRP and ferritin increased significantly in large proportion of COVID patients (plasma D-dimer was increased in 60.66%, serum LDH in 60%, CRP in 88.67% and ferritin in 41.72%). Mean concentrations of these inflammatory biomarkers were also significantly higher than their corresponding reference values (Table I). Similar results were also found in previous studies.<sup>6-11</sup> Data of 1099 patients with COVID-19 from 552 hospitals in China show that most of the patients (60.7%) had elevated levels of CRP (reference range: < 10 mg/L). Elevated levels of D-dimer (46.4%) and LDH (41%, reference range: <250 U/L) were less common.<sup>6</sup> In separate study of 191 COVID patients in China, LDH was increased in 67% (Reference value: <245 U/L), D-dimer in 68%, and ferritin in 80% (reference value: < 300 ng/mL).<sup>8</sup>

Elevations in plasma D-dimer, serum LDH, CRP and ferritin have been associated with severe disease and demonstrated to have prognostic value.<sup>6-14</sup> This phenomenon is well-illustrated in our study by positive correlations of these parameters with duration of hospital stay or with percentage of lung involvement (Table II & III). In Table II, duration of hospital stays increased with increase in serum LDH and serum ferritin concentrations whereas in Table III, percentage of lung involvement (A definite index of severity of COVID-19 in imaging) correlated significantly with serum LDH, CRP & ferritin levels.

### Conclusion

In conclusion, the present study demonstrates that on admission, measurement plasma D-dimer, serum LDH, CRP and ferritin levels in hospitalized COVID patients provides useful additional laboratory information to complement with clinical and radiological data in better understanding of disease severity which may contribute positively to patient management and patient outcome.

### Disclosure

All the authors declared no competing interests.

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# Prostate Volume Measured by Using Ultrasonography and Post-Operative Histopathological Evaluation of Benign Prostatic Hyperplasia Patients

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## ABSTRACT

**Background:** Benign Prostatic Hyperplasia (BPH) or benign prostatic hypertrophy, is a histologic diagnosis status characterized by proliferation of the 'cellular elements' of the prostate, which may lead to an enlarged prostate gland. Ultrasonography is a prominent method to determine prostate volume or size. The aim of the study was to evaluate the prostate volume of benign prostatic hyperplasia patients by ultrasonography.

**Materials and methods:** This prospective, observational study was conducted in the Department of Anatomy, Chittagong Medical College Hospital, Chattogram, Bangladesh during the period from January 2018 to December 2019. A total 47 patients with benign prostatic hyperplasia confirmed by histopathological evaluation were selected as the study population. Abdominal ultrasonography was performed for all the patients. Prostate enucleations were done via the Transvesical approach and the enucleated tissue was weighed. The results of both the measurements were compared finally. Captured data were processed, analyzed, and disseminated by MS-word and SPSS programs as per need.

**Results:** In this study, according to the abdominal ultrasonographic reports the prostate volumes were >100 ccs of one-fourth participants (25.53%). Besides these, prostate volume was <20, 20-40, 40-60, 60-80 and 80-100 cc in 6.38%, 23.40%, 17.02%, 12.77% and 14.89% participants respectively. The mean volume was  $69.02 \pm 34.93$  cc,  $r=0.083$  and  $p$  value=0.579. On the other hand, among 25.53% of participants, the weight of the prostate was found >100 gm which was determined after enucleation. Besides these, the weights of prostates were found <20, 20-40, 40-60, 60-80 and 80-100 gm in 8.51%, 21.28%, 19.15%, 14.89% and 10.64% participants respectively. The mean weight was  $61.96 \pm 32.62$  gm,  $r=0.082$  and  $p$  value=0.585.

**Conclusion:** The findings of this study support the applications of abdominal ultrasonographic evaluation of BPH to know about the exact volumes of the prostates of the patients for selecting the appropriate surgical approach.

**Key words :** Benign prostatic hyperplasia; Prostate gland; Ultrasonography; Volume.

## Introduction

Characterized by the proliferation of the 'cellular elements' of the prostate, Benign Prostatic Hyperplasia (BPH) is a histologic diagnosis status that may lead to an enlarged prostate gland. Ultrasonography is a very widely used method to determine prostate volume or size. Benign Prostatic Hyperplasia (BPH), also known as prostate gland

enlargement is a very common surgical problem accounting for 20% of elective admissions in the surgical wards.<sup>1</sup> Although BPH is diagnosable by clinical examinations, 'information about gland volume/size', presence of nodules, and 'calcification' is important for selecting the proper management.<sup>1</sup> The decision on whether the patient requires surgery as well as the selection of the best surgical method is dependent upon the size of the prostate.<sup>2</sup> Ultrasonography is considered the most prominent method to determine prostate volume or size. Ultrasonography, specifically Transrectal Ultrasonography (TRUS) is the most commonly applied tool to estimate prostate volume.

Measuring the height, length, and width of the gland and multiplying the product by a coefficient of  $\pi/6$  (0.52), which is also known as the prolate ellipsoid formula, the ultrasonography computes the total volume of the prostate.<sup>3</sup> The same formula can also be used in MRI (Magnetic Resonance Imaging) modalities to estimate the prostate volume.<sup>3</sup> Besides these, as a potentially superior formula for estimating prostatic volume, another geometrical model is known as bullet formula ( $L \times H \times W \times 5\pi/24$ ) or ( $L \times H \times W \times 0.65$ ) was introduced in 2009.<sup>4</sup> In this

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study, our focus was on ultrasonographic findings. To evaluate the prostate volume of benign prostatic hyperplasia patients by ultrasonography.

**Materials and methods**

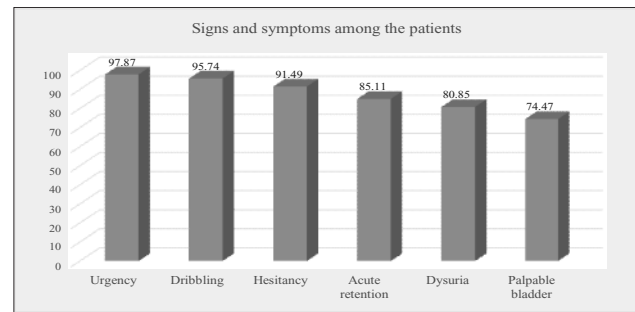
This prospective, observational study was conducted in the Department of Anatomy, Chittagong Medical College Hospital, Chattogram, Bangladesh during the period from January 2018 to December 2019. A total 47 patients with benign prostatic hyperplasia confirmed by histopathological evaluation were selected as the study population. For all the patients, abdominal ultrasonography was performed. Prostate enucleations were done via the Transvesical approach and the enucleated tissue was weighed. The results of both the measurements were compared finally. All patients were clinically diagnosed for BPH based on the present prostate symptoms and digital rectal examination. By using the transducer in a 45° caudally angulated position, preoperative abdominal ultrasound examinations were performed with a full bladder (200-300 ml urine).<sup>5</sup> To measure the width, height, and length of the prostate a 3.5 MHz transducer was applied. On the other hand, the volume was calculated by using the formula for a prolate ellipsoid as, maximum width x height x length x  $\pi/6$ . Before starting data collection, properly written consent was taken from all the participants. Collected data were processed, analyzed, and disseminated by MS-word and SPSS programs as per need.

**Results**

In this study, total 47 patients with BPH were finally enrolled as the study population. The mean age of the participants was 62.57±11.81 years. In analyzing the signs and symptoms among the patients we found urgency, dribbling, hesitancy, acute retention, dysuria, and palpable bladder in 97.87%, 95.74%, 91.49%, 85.11%, 80.85%, and 74.47% participants respectively. In this study, according to the abdominal ultrasonographic reports of the participants, in one-fourth participants (25.53%), the prostate volumes were >100 ccs. Besides these, prostate sizes were < 20, 20-40, 40-60, 60-80 and 80-100 cc in 6.38% 23.4%, 17.02%, 12.77% and 14.89% participants respectively. The mean volume was 69.02 ± 34.93 cc, r=0.083 and p value=0.579. On the other hand, among 25.53% of participants, the weight of the prostate was found >100 gm, determined after enucleation. Besides these, the weights of prostates were found <20, 20-40, 40-60, 60-80 and 80-100 gm in 8.51%, 21.28%, 19.15%, 14.89% and 10.64% participants respectively. The mean weight was 61.96 ± 32.62 gm, r=0.082 and p value=0.585.

**Table I** Signs and symptoms among the patients (n=47)

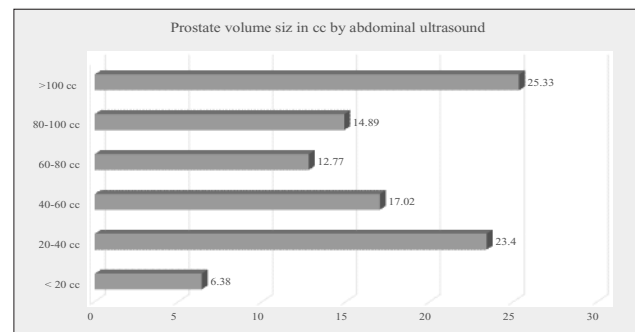
Symptoms	n	%
Urgency	46	97.87
Dribbling	45	95.74
Hesitancy	43	91.49
Acute retention	40	85.11
Dysuria	38	80.85
Palpable bladder	35	74.47



**Figure 1** Signs and symptoms among the patients

**Table II** Volume of prostate measured by abdominal ultrasound among the patients (n=47)

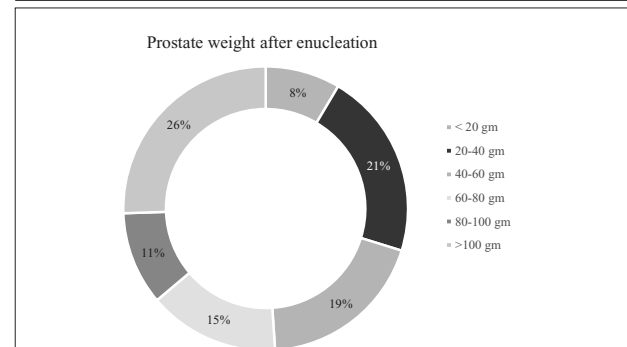
Size (cc)	n	%	Mean ± SD	r	p-Value
< 20	3	6.38	69.02 ± 34.93	0.083	0.579
20-40	11	23.4			
40-60	8	17.02			
60-80	6	12.77			
80-100	7	14.89			
>100	12	25.53			



**Figure 2** Prostate volume size by abdominal ultrasound

**Table III** Weight of prostate determined after enucleation (n=47)

Weight (gm)	n	%	Mean ± SD	r	p-Value
< 20	4	8.51	61.96 ± 32.62	0.082	0.585
20-40	10	21.28			
40-60	9	19.15			
60-80	7	14.89			
80-100	5	10.64			
>100	12	25.53			



**Figure 3** Prostate weight after enucleation

### Discussion

In our study, in analyzing the signs and symptoms among the patients, we found urgency, dribbling, hesitancy, acute retention, dysuria, and palpable bladder in 97.87%, 95.74%, 91.49%, 85.11%, 80.85%, and 74.47% of participants respectively. Assessment of the size of the prostate is an important factor in the management of Benign Prostatic Hyperplasia (BPH).<sup>6</sup> In such cases abdominal ultrasonography is needed. Intravenous urography or IVU and cystoscopy are not useful at all for determining the exact prostatic size or selecting the proper surgical approach.<sup>7</sup> As per the recommendation of Roehrborn et al, the best predictor of prostatic weight is abdominal ultrasound ( $r=0.975$ ).<sup>8</sup> The reliability of abdominal ultrasonography in the measurement of the volumes of the prostate was also confirmed by many other studies.<sup>9,10</sup> In our study, according to the abdominal ultrasonographic reports of the participants, among one-fourth of participants (25.53%), the prostate volumes were >100 ccs. Besides these, prostate volume was < 20, 20-40, 40-60, 60-80 and 80-100 cc in 6.38% 23.40%, 17.02%, 12.77% and 14.89% participants respectively. The mean volume was  $69.02 \pm 34.93$  cc,  $r=0.083$  and  $p$  value= $0.579$ . On the other hand, among 25.53% of participants, the weight of the prostate was found >100 gm which was determined after enucleation. Besides these, the weights of prostates were found < 20, 20-40, 40-60, 60-80 and 80-100 gm in 8.51%, 21.28%, 19.15%, 14.89% and 10.64% participants respectively. The mean weight was  $61.96 \pm 32.62$  gm,  $r=0.082$  and  $p$  value= $0.585$ . The fact is, the majority of the enucleated glands weighed less than 60 gm (71.7%) suggests the procedure of choice would have been Transurethral Resection of the Prostate (TURP) stated in a study.<sup>11</sup> Surgeons can depend upon the findings of ultrasonography in selecting the appropriate treatment method for BPH patients. The correlation coefficient in several series generally shows a statistically significant correlation between prostatic volume measured on abdominal ultrasonography and the weight of the prostate removed at surgery, indicating that it is a useful tool for selecting the appropriate surgical approach. Some studies have shown a similar correlation. Styles et al. found that abdominal estimation of prostatic volume, correlated well with the 'transrectal method' and good inter-observer agreement was found with the use of both modalities.<sup>12</sup> Ishida et al. demonstrated that abdominal measurement of prostatic volume correlated well with the resected weight ( $r=0.956$ ).<sup>13,14</sup>

### Limitation

As a single-centered study with small sample size, the findings of this study might not reflect the exact scenario of the whole country.

### Conclusion

The findings of this study support the applications of abdominal ultrasonographic evaluation of BPH to know about the exact volumes of the prostates of the patients for selecting the appropriate surgical approach. In this study, we found a similarity in the ranges of volumes and weights prostates of the patients.

### Recommendation

For getting more specific information regarding this issue we would like to recommend conducting more studies in several places with large sample sizes.

### Disclosure

All the authors declared no competing interests.

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# Ethnic-Nonethnic Differences in the Associated Factors of Nutritional Status and Disease Pattern among the Under-Five Children in Hill District of Bangladesh

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## ABSTRACT

**Background:** Childhood malnutrition is a leading public health issue in Bangladesh. The geographic and demographic factors affect nutritional status and morbidity patterns. This study aimed to determine the nutritional status and morbidity pattern of under-five ethnic children living in a Hill District of Bangladesh compared to the nonethnic children.

**Materials and methods:** This comparative cross-sectional study included 105 under five ethnic children from some selected rural areas of Bandarban Hill District of Bangladesh. An equal number of nonethnic under-five children from Rangamati Sadar was included as a comparison group. Demographic, anthropometric (Involving stunting, wasting and underweight) and other information related to nutritional status and morbidity patterns were collected using a structured case record form.

**Results:** The prevalence of severe stunting, severe wasting and severe underweight were, respectively, 8.6%, 3.8% and 6.7% among ethnic children. Among nonethnic children, severe stunting, severe wasting and severe underweight prevalence were 11.4%, 10.5%, and 7.6% respectively. Though the prevalence was higher in nonethnic, the differences were insignificant statistically. Statistically, significant associations were found between child malnutrition and the mother's education, monthly family income, place of delivery, toilet facilities, source of drinking water, distance from health facilities and morbidity history among the ethnic group. Among the nonethnic group, the mother's education and delivery place were the factors significantly associated with malnutrition. Upper Respiratory Tract Infection (URTI) was the most frequent morbidity reported by both groups, followed by febrile illness.

**Conclusion:** The prevalence of malnourished children in hilly communities in this study was very high. Of them, stunted children were higher than wasted and under weight children.

**Key words:** Chattogram Hill Tracts; Malnutrition; Stunted; Under-5 children; Underweight; Wasted.

## Introduction

Malnutrition, which encompasses undernutrition, micronutrient deficiencies and overweight/obesity, affects millions globally, impacting women, children and other vulnerable populations.<sup>1</sup> About half of all fatalities in under-5 children are attributable to undernutrition.<sup>2</sup> Asia is the home to over 70% of the world's malnourished children, with India, Pakistan and Bangladesh having the highest prevalence in this region.<sup>3</sup> Among the other South Asian countries, though Bangladesh made a significant achievement in declining the prevalence rate of stunting children from 60% (1997) to 31% (2018) it is still inadequate to attain the target of ending all forms of undernutrition by 2030 (Sustainable Development

Goal- 2, Target 2.2).<sup>4,5</sup> There are considerable geographic disparities in terms of stunting in Bangladesh, with a higher prevalence among rural than urban children.<sup>4</sup>

Malnutrition is a complicated issue that depends on multiple factors and presumably varies over time and thus needs to be studied constantly. Along with the geographic disparities, other associated factors for undernutrition are the families' socioeconomic and health service utilization patterns.<sup>6-10</sup> The subjects gain more importance in ethnic and settler children due to certain adverse realities like insufficient food intake, frequent infections, unsafe drinking water, lack of sanitary toilet facilities, lack of access to health services, illiteracy and damaging cultural practice.<sup>11</sup> Under-five ethnic children get less attention and are considered an under privileged part of Bangladesh. Many setbacks cannot be well-perceived due to a lack of necessary and sufficient information. This study aimed to investigate the prevalence of under-5 child undernutrition in hill districts of Bangladesh and its associated socioeconomic factors in the ethnic-nonethnic context.

## Materials and methods

This comparative cross-sectional study was conducted in Bangladesh's Bandarban and Rangamati Hill districts from January to March 2022. Informed consent was obtained from the mother or caregiver of the participating children.

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The Ethical Review Committee of Rangamati Medical College approved the study protocol.

One hundred and five ethnic children were selected from 11 paras or villages of Bandarban Hill District. A similar number of nonethnic settlers under-5 children were included from Sadar Upazila of Rangamati Hill District. Under-5 children (Age two months to 5 years) with a mother or caregiver present that signed the informed consent and children of both sexes were included. Those who refused to participate in the interview and were physically disabled were excluded.

Data regarding maternal education, occupation, father occupation, family income, age and sex of the children, birth order, young and infant feeding practice, immunization, deworming practice, toilet facilities, source of drinking water, distance from health facilities and type and frequency of self-reported morbidity of the children were collected using a structured case record form. Anthropometric measurements [Height/length, weight and Mid-upper Arm Circumference (MUAC)] were taken following standard techniques with standardized tools.

Weight for age (Underweight) weight for height (Wasting) and height for age (Stunting) will be used as indicators for assessing the nutritional status of under-five children. WHO criteria and Gomez classification classified nutritional status. WHO criteria were used for wasting and stunting. Z score  $<-3.00$  is Severe Acute Malnutrition (SAM),  $-3.00$  to  $<-2.00$  is Moderate Acute Malnutrition (MAM) and  $-2.00$  to  $+2.00$  is normal nutritional status.<sup>12,13</sup> MUAC was used for overall nutritional status ( $\geq 12.5$ cm normal nutrition,  $11.5-12.4$  cm MAM and  $\leq 11.4$  cm : SAM).<sup>12,13</sup>

All statistical analyses were performed in SPSS version 23.0. Data were analyzed through descriptive statistics (Frequency, percentage) and inferential statistics (Chi-square). A p-value less than 0.05 was considered of statistical significance.

## Results

Around 40% of the children were less than 24 months, regardless of ethnicity. In the ethnic group, females (59%) were higher than males and in the nonethnic group, opposite trends were observed (Male 54.3%). The absence of formal education was more in ethnic mothers (57.1%) than nonethnic (30.5%). Also were increased use of unsafe drinking water from river (49.5%) and absence of sanitary toilet facilities (65%) in ethnic. More than half of the families had a monthly income of less than 5000/- in both groups. Place of delivery was home in most cases (75.2%) for ethnic children and 63.8% for nonethnic. A comparatively higher proportion of nonethnic children (94.3%) had suffered from morbid conditions than the ethnic group (76.2%) (Table I).

**Table I** Background characteristics of the children

Characteristics	Ethnic		Nonethnic		p value
	n	%	n	%	
Children age					
2-11 months	21	20.0	23	21.9	0.649
12-23 months	20	19.0	27	25.7	
24-35 months	18	17.1	13	12.4	
36-47 months	19	18.1	20	19.0	
48-59 months	27	25.7	22	21.0	
Sex					
Male	43	41.0	57	54.3	0.053
Female	62	59.0	48	45.7	
Locality					
Rural	73	69.5	18	17.1	<0.001
Urban	32	30.5	87	82.9	
Mother's education					
No schooling	60	57.1	32	30.5	<0.001
Primary	19	18.1	29	27.6	
Secondary	15	14.3	37	35.2	
Higher secondary	11	10.5	7	6.7	
Mother's occupation					
Housemaker	31	29.5	94	89.5	<0.001
Farmer	64	61.0	6	5.7	
Job	10	9.5	5	4.8	
Fathers occupation					
Farmer	53	50.5	13	12.4	<0.001
Job	40	38.1	89	84.8	
Unemployed	12	11.4	3	2.9	
Monthly income					
<5000 tk	66	62.9	57	54.3	0.108
5000-10,000 tk	25	23.8	22	21.0	
>10,000 tk	14	13.3	26	24.8	
Place of delivery					
Home	79	75.2	67	63.8	0.072
Hospital	26	24.8	38	36.2	
Birth order					
First	47	44.8	40	38.1	0.405
Second	36	34.3	35	33.3	
Three and above	22	21.0	30	28.6	
EBF					
Yes	102	97.1	102	97.1	1.0
No	3	2.9	3	2.9	
Complimentary					
Not started	14	13.3	14	13.3	0.331
Appropriate	47	44.8	37	35.2	
Inappropriate	44	41.9	54	51.4	
Vaccination					
Incomplete	58	55.3	44	41.9	0.053
Complete	47	44.8	61	58.1	
Toilet facility					
Partial sanitary	36	34.3	98	93.5	<0.001
Non-sanitary	58	55.2	7	6.7	
Open	11	10.5	0	0	
Drinking water					
Supply water	31	29.5	95	90.5	<0.001
River	52	49.5	10	9.5	
Fall	22	21.0	0	0	
Distance from HF					
<2 km	32	30.5	81	77.1	<0.001
2-10 km	36	34.3	24	22.9	
>10km	37	35.2	0	0	
Deworming					
No	81	77.1	82	78.1	0.858
Yes	24	22.9	23	21.9	
Morbidity					
No	25	23.8	6	5.7	<0.001
yes	80	76.2	99	94.3	

HF: Health Facilities.

Table II shows severe stunting, severe wasting and severe underweight prevalence were 8.6%, 3.8%, and 6.7%, respectively, among ethnic children. Among nonethnic children, severe stunting, severe wasting, and severe underweight prevalence were 11.4%, 10.5%, and 7.6% respectively. Though the prevalence was higher in nonethnic, the differences were insignificant statistically.

**Table II** Nutritional status of the children

Nutritional status	Ethnic (n=105)	Nonethnic (n=105)	p value
Stunting			
Normal	71 (67.6)	77 (73.3)	0.266
Moderate	25 (23.8)	16 (15.2)	
Severe	9 (8.6)	12 (11.4)	
Wasting			
Normal	90 (85.7)	78 (74.3)	0.080
Moderate	11 (10.5)	16 (15.2)	
Severe	4 (3.8)	11 (10.5)	
Underweight			
Normal	68 (64.8)	62 (59.1)	0.695
Moderate	30 (28.6)	35 (33.3)	
Severe	7 (6.7)	8 (7.6)	

The overall prevalence of malnutrition (Stunting, wasting or underweight) was 49.5% in the ethnic group and 52.4% in the nonethnic group (Figure 1).



**Figure 1** Comparison of overall nutritional status between ethnic and nonethnic children

The key associated factors for under-5 child malnutrition among the ethnic group were: the mother’s education, monthly family income, place of delivery, source of drinking water, toilet facilities and morbidity history. Among the nonethnic group, the mother’s education and delivery place were the factors significantly associated with malnutrition. The proportion of malnutrition was higher among illiterate mothers, in a family with the lowest income, in children delivered at home, and in children who had morbidity in the last year (Table III).

**Table III** Proportion of under-5 child malnutrition in ethnic-nonethnic context for different demographic and socioeconomic characteristics

Variables	Ethnic			Nonethnic		
	n	%	p value	n	%	p-value
Children age						
2-11 months	9	42.9	0.394	6	26.1	0.033
12-23 months	13	65.0		13	48.1	
24-35 months	8	44.4		8	61.5	
36-47 months	7	36.8		13	65.0	
48-59 months	15	55.6		15	68.2	
Sex						
Male	22	51.2	0.780	26	45.6	0.130
Female	30	48.4		29	60.4	
Locality						
Rural	37	50.7	0.719	10	55.6	0.767
Urban	15	46.9		45	51.7	
Mother’s education						
No schooling	37	61.7	0.019	26	81.3	0.001
Primary	8	42.1		14	48.3	
Secondary	3	20.0		12	32.4	
HSC	4	36.4		3	42.9	
Monthly income						
<5000 tk	42	63.6	0.001	35	61.4	0.074
5000-10,000 tk	7	28.0		11	50.0	
>10,000 tk	3	21.4		9	34.6	
Mothers occupation						
Housemaker	18	58.1	0.333	49	52.1	0.670
Farmer	28	43.8		4	66.7	
Job	6	60.0		2	40.0	
Father’s occupation						
Farmer	24	45.3	0.407	9	69.2	0.362
Job	20	50.0		45	50.6	
Unemployed	8	66.7		1	33.3	
Place of delivery						
Home	44	55.7	0.027	40	59.7	0.046
Hospital	8	30.8		15	39.5	
Birth order						
First	22	46.8	0.323	20	50.0	0.926
Second	16	44.4		19	54.3	
Three & above	14	63.6		16	53.3	
Toilet facilities						
Partial sanitary	18	50.0	0.062	50	51.0	0.296
Non-sanitary	25	43.1		5	71.4	
Open	9	81.8		0	0	
Drinking water						
Supply water	13	41.9	0.590	49	51.6	0.612
River	27	51.9		6	60.0	
Fall	12	54.5		0	0	
Distance from HF						
<2 km	15	46.9	0.791	42	51.9	0.842
2-10 km	17	47.2		13	54.2	
>10km	20	54.1		0	0	
Morbidity						
No	7	28.0	0.014	1	46.7	0.071
yes	45	56.3		54	54.5	

Morbidity pattern in the past year was compared between ethnic and non-ethnic children in Table IV. The table depicted that Upper Respiratory Tract Infection (URTI) was the most frequent morbidity reported by both groups, followed by febrile illness. However, a significantly higher proportion of nonethnic children suffered from cough than ethnic children. An opposite trend was observed regarding diarrhoea.

**Table IV** Comparison of past year morbidity between ethnic nonethnic under-5 children

Morbidity	Ethnic		Nonethnic		p value
	n	%	n	%	
Febrile illness	72	68.6	79	75.2	0.283
URTI	79	75.2	92	87.6	0.021
Pneumonia	14	13.3	11	10.5	0.523
Diarrhoea	40	38.1	23	21.9	0.010

### Discussion

Severe stunting, underweight or child undernutrition in Bangladesh were investigated in different studies.<sup>10,11,14,15</sup> To the best of our knowledge, this is one of the few studies in Bangladesh that investigated under-5 undernutrition and its associated socioeconomic factors in the ethnic and non-ethnic context in Hill districts.<sup>11,14</sup> The overall prevalence of malnutrition (Stunting, wasting or underweight) was 49.5% in the ethnic group and 52.4% in the nonethnic group. The prevalence of stunting, wasting and underweight was 32.4%, 14.3% and 35.2% in ethnic children. The corresponding figures were 26.7%, 25.7%, and 40.9% in nonethnic children. In a press release of UNICEF (2020) the prevalence of moderate to severe underweight and stunting in Bangladeshi under-5 children was about 23 and 28% in 2019, respectively.<sup>15</sup> Another survey report in 2018 found the prevalence of stunted, wasted, and underweight was 37.20%, 8.60%, and 15.20% in preschool ethnic children in the Bandarban district of Bangladesh.<sup>14</sup> Despite the outstanding achievements of Bangladesh in consistently reducing the malnutrition rates among children over the last few decades through various intervention programs taken by the Government and the development partners, the findings of this study and other similar studies state the scope of further improvement of the child nutritional status in Bangladesh.

Though the prevalence of overall malnutrition, severe stunting, wasting and underweight was higher in the nonethnic group than in the ethnic children in the current study, the differences were not significant statistically. Maternal education and morbidity history were significantly different between the two groups. A higher proportion of ethnic mothers had no formal education, but the history of morbidity in the under-5 children was more among the nonethnic. The key associated factors for under-5 child malnutrition among the ethnic group were: the mother's education, monthly family income, place of delivery, and morbidity history. Among the non-ethnic group, the mother's

education and delivery place were the factors significantly associated with malnutrition. The proportion of malnutrition was higher among illiterate mothers, families with the lowest income, children delivered at home, and children who had morbidity in the last year. Age of children, place of residence, division, religion, education of parents, occupation of parents, nutritional status of mothers, wealth index and toilet facilities used by the household had significant association with child nutritional status in other studies conducted in Bangladesh.<sup>16,17</sup>

Other than the nutritional status, the present study identified some crucial gaps in the health status of ethnic and nonethnic under-5 children in Hill Districts of Bangladesh. Many children, irrespective of ethnicity, did not get antihelminthic drugs routinely, with incomplete vaccination and inappropriate complementary feeding. Though these factors are essential for good nutritional status, future studies should address the root causes for these gaps.

### Limitations

The study has certain limitations. First of all, since this study was based on cross-sectional data and as a result, exploring the association between selected factors and the prevalence of malnutrition cannot establish a causal association between the two. Secondly, due to the unavailability of the data on potential confounders, including diet, physical exercise and smoking behaviour of the parents, these were not included in the analysis. Third, the sample size was small and conveniently collected by following a random sampling.

### Conclusion

Based on the findings of this study, it was revealed that stunting, wasting and being underweight is highly prevalent in Hill Districts of Bangladesh, both in ethnic and nonethnic under-5 children. This study confirms that there are quiet rooms to perk up the child's nutritional status in Bangladesh.

### Recommendations

More research should be conducted using quantitative and qualitative approaches to depict the comprehensive scenario of severe undernutrition among the under-5 children of hill districts and address multi-sectoral intervening programs for eradicating severe child undernutrition.

### Disclosure

All the authors declared no competing interests.

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# Comparative Study on Single Posterior Field versus Two Opposed Anterior Posterior Fields Radiotherapy in Patients with Vertebral Metastases to See Treatment Outcome and Toxicities

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## ABSTRACT

**Background:** Painful vertebral metastases are a frequent manifestation of malignancies in their advanced stages and represent a challenging problem in oncology practice. Radiation therapy has been reported to be effective in palliating painful bone metastases. For patients with longer life expectancy, bone-only metastases and good performance status, a longer course of treatment (30Gy in 10 fractions) is more appropriate for effective treatment. Single posterior field and two opposed anterior-posterior fields in conventional radiotherapy is widely used worldwide in treating bone metastases patients. The aim of the study is to emphasize dose distribution variation between AP/PA and single direct plan, compare treatment outcome and toxicities, ascertain relief of symptoms, performance status, motor function and neurological deficit improvement in short term treatment. Also, to compare treatment response and toxicities between single posterior field versus two opposed anterior posterior fields radiotherapy in patients with vertebral metastases.

**Materials and methods:** This Quasi-Experimental study was done in National Institute of Cancer Research and Hospital, Dhaka, from November 2016 to November 2017. Total 60 patients were enrolled according to selection criteria, each received 30 Gy in 10 fractions. In Arm A, each of total 30 patients received 300 cGy per fraction in single posterior field. In Arm B, each of total 30 patients received 150 cGy in anterior -posterior field and 150 cGy in posterior anterior field per fraction. Every patient was evaluated routinely to see the treatment outcome and toxicities.

**Results:** The mean age of Arm-A was  $54.4 \pm 6.2$  years and that of Arm-B was  $54 \pm 7.3$  years. Slight male dominance was found in Arm-B. In both arms leading cancers were carcinoma breast (33.3% in Arm-A and 36.3% in Arm-B) and carcinoma prostate (23.3% in Arm-A and 26.3% in Arm-B). At last follow up overall symptomatic improvement was noticed in both groups which was significant. Decrease in pain was observed in both groups but was statistically significant in Arm-B. Analgesic requirement was significantly less in Arm-B patients at the end of treatment. Motor function status significantly improved in Arm-B patients. Patients of Arm-B had more nausea/vomiting and diarrhea but no other significant toxicities observed between the two arms.

**Conclusion:** It could be said from this study that though gastrointestinal toxicities were slightly high, two opposed anterior posterior fields are more effective than single posterior field radiotherapy as means of pain relief, better motor function outcome and reduced need for analgesics.

**Key words:** Motor function; Opposed anterior posterior fields; Vertebral metastases.

## Introduction

Bone metastases constitute a growing oncologic problem due to increasing life expectancy among cancer patients.<sup>1</sup> The presence of tumour in the bone can lead to local symptoms such as pain, spinal cord compression,

pathologic fracture as well as systemic effects caused by hypercalcemia.<sup>2</sup> Radiation therapy (RT) can represent an effective palliative intervention in metastatic diseases to maintain and improve patient's quality of life.<sup>3</sup> Either a single posterior field or opposed anterior posterior fields are used to encompass the involved segment plus one or two levels above and below this involved region.<sup>4</sup> Depending on the depth of the spinal cord according to CT scans or MRI, irradiation was delivered through PA or AP-PA fields.<sup>5</sup> The dose was prescribed to the midplane (Parallel opposed fields) or to the spinal cord (Single posterior field).<sup>5</sup> These techniques are widely used for palliative spinal bone irradiation using the International Commission on Radiation Units and measurements reference points (ICRU<sub>rps</sub>) and the International Bone Metastasis Consensus Working party reference points (IBMC<sub>rps</sub>).<sup>6</sup> Direct Single field is commonly used in RT for spinal bone metastases and it is crucial to define the point for which the dose is prescribed.<sup>7</sup> This variation may lead

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to misunderstanding the tolerance dosage of the spinal cord, especially in cases of re-radiation.<sup>7</sup> Dose heterogeneity may become vitally important in patients with long life expectancies.<sup>6</sup> Single posterior field is a long time practised technique in our country but we are not fully satisfied with the effective control, quality of life improvement and survival benefit. Two opposed AP-PA fields' treatment plans did achieve the intended dose ranges with a homogenous dose distribution to the medulla spinalis, oesophagus and intestines.<sup>6</sup> But a disadvantage is the higher dose in anterior organs, possibly leading to more abdominal side effects.<sup>8</sup> This difference was temporary, abdominal complaints were comparable five weeks after treatment.<sup>8</sup> This study will provide us excellent field to compare treatment response and toxicities between two therapeutic arms both having 30 Gy RT in 10 fractions. The results of this study would provide us the information regarding relief of symptoms, increased local control of diseases, and maintenance of adequate physiological function, provide best functional outcome and proper palliation of the patient by improving quality of life.

**Materials and methods**

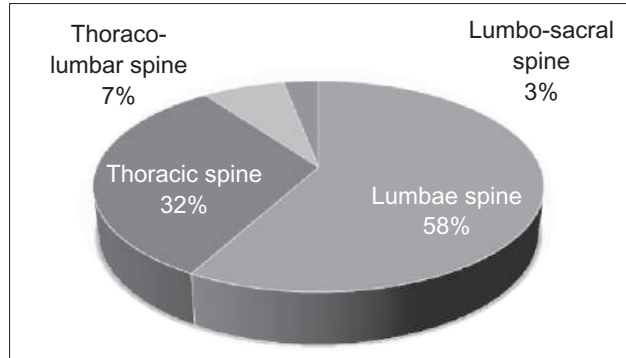
This Quasi-Experimental study was done in National Institute of Cancer Research and Hospital in twelve months (8<sup>th</sup> November 2016 to 7<sup>th</sup> November 2017) period. Study Population were patients with solitary or multiple vertebral metastases and radiological proven bone metastases. Total sample size was 60. There were two arms (arm A, arm B). Each arm included 30 cases. Samples were selected by purposive sampling technique. Dependent variables were loco-regional control and overall toxicities and independent variables were socio-demographic variables, histopathology, stage of the disease, treatment modalities, VAS, KPS, haematological toxicities. Ethical approval was obtained before commencing the study (Memo-NICRH/Ethics/ 2016/ 253 dt-20.10.2016).

**Treatment Plan:** All of the 60 patients received RT to planned fields one fraction per day, total 30 Gy in 10 fractions for 5 days a week. Treatment MUs were calculated in 2D planning system with the help of field size at standard practicing depth (Depending upon area of the spine involved, thoracic 4-5 cm, lumber 5-7 cm) in SSD technique, 300 cGy/# in PA field. And at isocenter/midplane dose in SAD technique; 150cGy/# in PA and 150 cGy/# in AP field. Comparative virtual 3D plans were generated for some patients with the help of their CT scan images. Among those patients two virtual plans were generated; one for single direct and another for AP/PA field. Dose coverage, hot spot etc were observed, DVH generated and noted. Treatment was delivered mostly with Cobalt-60 although 6-10 MV photons from a Linac was perhaps ideal.

**Results**

At last follow up overall symptomatic improvement noticed in both groups which was significant. Decrease in pain was

observed in both groups but was statistically significant in Arm-B. Analgesic requirement was significantly less in Arm-B patients at the end of treatment. Motor function status significantly improved in Arm-B patients. Patients of Arm-B had more nausea/vomiting and diarrhea but no other significant toxicities observed between the two arms.



**Figure 1** Radiological findings and sites of metastases (n=60)

**Table I** Assessment of common symptomatic improvement or deterioration at different follow-up schedule (n=60)

Follow up schedule	Clinical symptoms	Arm A (n = 30)		Arm B (n = 30)		p value
		No. (%)		No. (%)		
		No	%	No	%	
End of RT	Nausea/vomiting	15	50.0	18	60.0	0.646
	Anorexia	17	56.6	13	43.3	
	Generalized weakness	26	86.7	28	93.3	
After 1 week	Nausea/vomiting	12	40.0	15	50.0	0.511
	Anorexia	14	46.6	9	30.0	
	Generalized weakness	12	40.0	11	36.6	
After 4 week	Nausea/vomiting	8	26.6	11	36.6	0.468
	Anorexia	10	33.3	7	23.3	
	Generalized weakness	8	26.6	5	16.6	
After 3 month	Nausea/vomiting	6	20.0	12	40.0	0.017
	Anorexia	7	23.3	1	3.3	
	Generalized weakness	4	13.3	1	3.3	

**Table II** Evaluation of motor function status at different follow up

Muscle weakness and power	Arm A (n = 30)		Arm B (n = 30)		p value
	No. (%)		No. (%)		
	No	%	No	%	
Baseline	21	70.0	23	76.6	0.04
End of RT	19	63.3	19	63.3	
After 1 week	16	53.3	7	23.3	
After 4 week	15	50.0	5	16.6	
After 3 month	10	33.3	2	6.6	

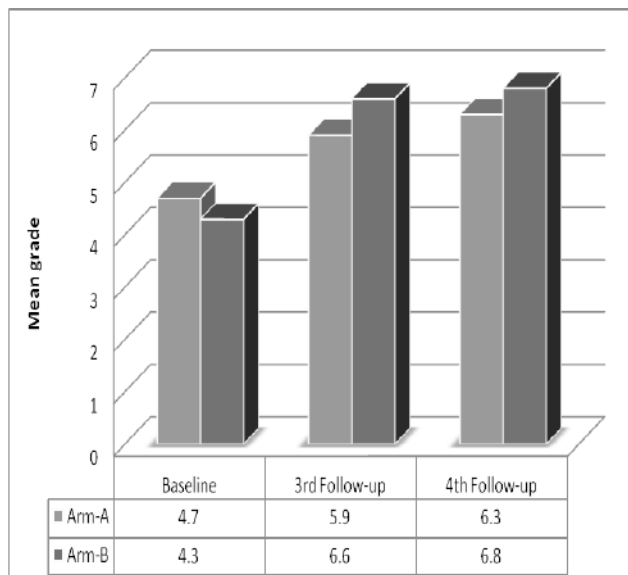
Difference between two groups were statistically significant, chi square statistics was 9.70 and p-value is <0.05.



**Table III** Evaluation of pain sensation using VAS score at different follow up schedules in Arm-A and Arm-B patients (n=60)

Arm A	VAS score	Before RT No (%)		After 3 months No (%)		p-value
	0-2	5	16.6	12	40	0.12
	3-7	10	33.3	12	40	
	8-10	15	50	6	20	
Arm B	0-2	4	13.3	18	60	0.002
	3-7	12	40	8	26.6	
	8-10	14	46.6	4	13.3	

Chi square value 16.09 and p-value was statistically significant (p<0.05) in Arm-B.



**Figure 2** Comparison of motor function grade by bar diagram

**Table IV** Assessment of pain responses by analgesic use (n=60)

Status at last Follow up	Arm A (no=30)		Arm B (no=30)		p-value
	No	%	No	%	
Complete Response	15	50.0	25	83.3	0.12
Partial Response	13	43.3	3	10.0	
No Response/ Progression	2	6.6	2	6.6	

Statistically significant difference was observed between two arms (p=0.12)

**Table V** Assessment of post treatment toxicities

Toxicity	Grade	Arm A (n = 30)		Arm B (n = 30)		p value
		No	%	No	%	
Respiratory Complaints	Grade I	10	33.3	8	26.3	0.753
	Grade II	03	10.0	4	13.3	
	Grade III	02	06.6	3	10.0	
Vomiting	Grade I	1	3.3	5	16.6	0.0001
	Grade II	8	26.6	9	30.0	
	Grade III	6	20.0	12	40.0	
Diarrhoea	Grade I	6	20.0	11	36.6	0.0001
	Grade II	0	0	2	6.6	
Urinary Complaints	Grade I	5	16.6	7	23.3	0.724
	Grade II	5	16.6	4	13.3	
	Grade III	3	10.0	2	6.6	
Rectal Complaints	Grade I	5	16.6	4	13.3	0.587
	Grade II	2	6.6	3	10.0	
	Grade III	2	6.6	1	3.3	
Neutropenia	Grade I	7	23.3	6	20.0	0.013
	Grade II	11	36.6	10	33.3	
	Grade III	03	10.0	7	23.3	

**Discussion**

Approximately one third of all patients with cancer will develop bone metastases and of these patients, approximately 70% will have metastases involving the vertebral column; most commonly the thoracic and lumbar spine.<sup>9</sup> The study was carried out with an aim to compare the outcome and toxicity of single posterior field versus two opposed AP-PA fields in vertebral metastases patients. The present study findings were discussed and compared with the previously published relevant studies. EBRT provides significant palliation of painful bone metastases in 50% to 80% of patients, with up to one third of patients achieving complete pain relief at the treated site.<sup>10</sup>

Metastatic bone cancer is a common and severe complication in advanced diseases.<sup>11</sup> Palliative RT for spine metastases has long been performed with 2D technique. Conventional 2D RT technique for spine metastases utilize a single posterior field or AP-PA opposed fields for thoracic-lumbar-sacral spines or parallel opposed lateral fields for cervical spines.<sup>12</sup>

In this study, mean age was 54.4±6.2 years and 54.8±7.3 years in Arm-A & Arm-B respectively. Most common malignancies were lung carcinoma (56.6% vs. 46.6%) and breast cancer (20.0% vs. 26.6%) in both arms. Most of the tumors were poorly and moderately differentiated. This is evident that to achieve the good response with RT there should be at least > 90% dose distribution in the target volume and can be achieved in conformal planning.<sup>13</sup> Whereas, in most of the developing countries 60% -70% of RT treatment

centers still depends on conventional 2D planning.<sup>13</sup> Hence common practice to use standard depths (Empirical) in manual planning to calculate the treatment planning units depending upon area of spine involved. Due to immediate proximity of vertebral metastases to spinal cord, the treatment dose delivered is limited by the tolerance of the spinal cord.<sup>9</sup>

To avoid a maximum dose in the spinal cord of more than 115%, a single field technique is recommended if the distance between skin and posterior part of the vertebral body is 5 cm or less. If it is more than 5 cm, a technique with two opposed fields is more appropriate<sup>11</sup>.

At the beginning most of the patients in both groups had KPS score 70 (53.3% & 60.0% in Arm-A and Arm-B respectively). 11 (18.3%) patients had KPS score 80, 15(25.0%) had KPS score 60 and none of patients had KPS score 90. KPS score gradually improved in both arms. After 3 months (Fourth follow up), in Arm-A patients, 20.0% had nausea, 23.3% had anorexia and 13.3% still had general weakness. In Arm-B patients, 40% had nausea, 23.3% had anorexia. Difference of overall symptomatic improvement between two groups was statistically significant. After 3 months, much decrease in pain sensation was observed in both groups. In Arm-A 12(40.0%) had mild pain, 12(40%) still had moderate pain and 6(20%) had severe pain. In Arm-B, 18(73.3%) had mild, 8(60%) had moderate and only 4(6.6%) still had severe pain. Decrease in pain was significant in Arm-B patients ( $p=0.002$ ). Muscle weakness was evaluated by motor function test. Baseline motor function grade was 4.7 and 4.3 in Arm-A and Arm-B respectively. A clear increase in muscle power was observed in both arms, 6.3 and 6.8 in Arm-A and Arm-B respectively. The end result of motor function improvement in Arm-B was statistically significant ( $p=0.04$ ). In IAEA criteria for palliation of bone metastases, it was stated that improvement of motor function was significantly associated with a favorable histology of the primary tumour, with a longer interval between tumour diagnosis and metastatic spinal cord compression, with involvement of only 1-2 vertebrae, with a slower development of motor deficits before RT, with being ambulatory before RT and with a good performance status.<sup>11</sup>

Several important hematological tests were measured in both arms after end of RT. All patients of both arms took analgesics for pain during the whole period of RT. It was found that patients of Arm-B needed less analgesic and the result was statistically significant. Statistical analysis revealed there was no significant difference but arithmetically this is proven that patients had better improvement in KPS score in Arm-B. Toxicities were comparable between two arms but nausea/vomiting and diarrhea were significant in Arm B. No significant difference was observed between the two arms regarding other toxicities. The advantage of a PA field is the sparing of anterior organs like the bowel, although the coverage of the vertebrae might be suboptimal.<sup>14</sup>

The advantage of the AP-PA technique is a better coverage of the vertebrae while sparing the posterior skin and paraspinal musculature.<sup>8</sup> A disadvantage is the higher dose in the anterior organs, possibly leading to more abdominal side effects. An AP-PA technique gives a better dose coverage, due to the deep location of the target volume.<sup>8</sup> In general, side effects from this treatment are mild and depend on factors like dose, field size, and the anatomic area being irradiated. An efficient and easy technique is a single PA field using 10MV, with the addition of a second AP field, contributing less than 50% of the dose, to increase the dose ventrally to at least 85% of the prescribed dose. In this way, side effects to the bowel can be minimized and a homogenous dose distribution could be achieved.<sup>8</sup>

### Conclusions

Conventional radiotherapy for painful spinal metastases can be delivered with a single PA or two opposed AP-PA fields to relieve pain from metastases, to prevent or relieve spinal cord compression and pathologic fractures. Good dose distribution is the prerequisite to achieve required optimum response in RT. AP-PA fields give a more homogenous dose distribution which can avoid overdosing the spinal cord or under dosing the tumour than PA field alone. From present study it may be said that two opposed AP-PA fields RT is more effective treatment than single PA field in the means of pain relief, better motor function outcome and reduced need for analgesics, though patients treated with AP-PA fields experienced more nausea/vomiting and diarrhea and treatment is much costly and time consuming.

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### Disclosure

All the authors declared no competing interest.

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# Experimental Study on Chronic Urticaria and Dyspepsia : Association and Treatment

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## ABSTRACT

**Background :** Urticaria is a common skin problem. Itchy wheals of various sizes, location and flare type cutaneous responses are the hallmark of urticaria. The purpose of the study was to estimate the prevalence of *Helicobacter pylori* infection among chronic idiopathic urticaria patients and to assess their urticarial response after the eradication of *H. pylori*.

**Materials and methods:** This study was a non-controlled, interventional study that was carried during the period from June 2021 to June 2022 at Dermatology Department, Combined Military Hospital, Chattogram. A total of 50 patients were included in our study. The patients who were positive for *H. pylori* were started on the eradication therapy. The effectiveness of the eradication therapy was assessed by repeating the *H. pylori* Urea Breath Test (UBT) after 4 weeks. Urticarial response was assessed 12 weeks after the eradication.

**Results:** The prevalence of Chronic Idiopathic Urticaria (CIU) at our dermatology department was 7%. The patients were predominantly females (60%) and the highest number (78%) belonged to the age group '20-50 years'. Of the study subjects 42.85% had positive *H. pylori*, 66.66% achieved eradication of *H. Pylori* while 33.33% did not.

**Conclusion:** *H. pylori* should be specifically investigated for all chronic urticaria patients and the eradication therapy should be advised for those who have are positive for *H. pylori*.

**Key words :** Chronic urticaria; Dyspepsia; *Helicobacter pylori*.

## Introduction

Urticaria is marked by itchy wheals that varies in flare-type dermal reactions, distribution, number and size.<sup>1</sup> Urticaria can be an acute (Less than 6 weeks) or a chronic urticaria (More than 6 weeks).<sup>2</sup> Chronic Urticaria (CU) is either idiopathic chronic (55%) and autoimmune chronic (45%) without urticarial vasculitis and physical urticaria.

CU is a case marked by almost daily spontaneous appearance of hives and/or angioedema.<sup>3</sup> The causes of CU may be unknown or known causes.<sup>4</sup> However, a patient may have more than one subtype of urticaria at the same time. Detailed history, a ruling out of severe systemic disease and physical workup are all necessary for accurate diagnosis of chronic urticaria.<sup>5</sup>

The term Chronic Idiopathic Urticaria (CIU) refers to the condition in which the underlying etiology remains unidentified in approximately 75% of cases. It also refers to the case where wheals develop without any external stimuli

that can be identified. The cause of CIU is functionally active circulating Immunoglobulin G (IgG) autoantibodies specific for the Immunoglobulin E receptor (FcRI) present on basophils and mast cells or for IgE itself.<sup>3</sup>

The etiological and pathogenic causes of CIU remain unknown. In the 1980s, *Helicobacter pylori* was found in patients with CIU. Some researchers have found out a relationship between CU and the infection of *H. pylori*. However, it is still controversial whether *H. pylori* is an etiological agent for CU or not.<sup>6</sup>

*H. pylori* is a gram-negative bacterium. It is among the most frequently detected bacterium in the human intestinal flora and still among the most common chronic bacterial infections that affect humans.<sup>7</sup> It induces acute gastritis, which becomes chronic active gastritis later on.<sup>8</sup>

There is no standard test for diagnosing *H. pylori* infection. There are two categories of them: invasive and non-invasive tests. The sensitivity of histopathology tests and Rapid Urease Test (RUT) which are two direct diagnostic tests, is decreasing. However, the sensitivity of serology (An antibody-based test) is quite high, despite its low specificity. Even though serological test is an effective screening tool for determining the infection of *H. pylori*, it does not differentiate between past exposure to *H. pylori* and the active infection. That is why other tests are needed before *H. pylori* eradication therapy for further confirmation.<sup>9</sup>

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Stool Antigen Test (SAT) and Urea Breath Test (UBT) among the indirect tests, are noninvasive, rapid, highly sensitive and specific.<sup>10</sup> and considered the best and more effective methods than serological or antibody based tests to detect the active infection and monitor the treatment response.<sup>11</sup>

Proton Pump Inhibitors (PPI) administration may give false-negative results, so, it should be discontinued at least 2 weeks before repeating the test.<sup>12</sup>

*H. pylori* infection can be treated with triple therapy, each taken twice a day for 14 days: clarithromycin 500 mg, amoxicillin 1000 mg and PPI (e.g. Omeprazole 20 mg).<sup>13</sup>

After the treatment, many patients were recovered from both the infection and the urticaria. So, the eradication therapy of *H. pylori* is considered very effective in CU patients. Therefore, detecting *H. pylori* is considered an essential test for all CU patients<sup>7</sup>.

Although *H. pylori* is frequently seen in patients who suffer from CIU, the correlation between *H. pylori* eradication and urticarial improvement is not confirmed.<sup>14</sup> This study was aimed to assess the prevalence of *H. Pylori* infection among CIU in our population and to assess the response of the urticaria after the eradication of *H. pylori*.

#### Materials and methods

The study was a non-controlled interventional prospective study that was conducted at the Dermatology Department, Combined Military Hospital, Chattogram over the period from June 2021 till April 2022. By consecutive sampling, 50 patients with history of urticarial lesions of > 6 weeks were included in this study. Exclusion criteria were patients less than 12 or greater than 60 years old, patients being treated with PPIs or other antibiotics within previous four weeks, pregnant females, patients of physical urticaria and patients suffering from other concomitant serious surgical and medical diseases. Fifty patients who met the study criteria were enrolled in the study (Table I).

**Table I** Classification of cases according to age group and gender (n=50)

Age (Years)	CIU		CU		Total
	Male	Female	Male	Female	
12-20	1	2	-	1	3
21-35	8	10	2	3	23
36-50	4	5	2	5	16
51-60	2	3	1	1	7
Total	35		15		50

Formal consent was obtained from all participants and local authorities. Each patient's preliminary screening panel comprised complete history and physical examination, complete laboratory tests (Complete blood count, routine urine and stool examination, renal and liver function, fasting blood glucose, erythrocyte sedimentation rate, antinuclear antibody, complement assays and thyroid function test) as baseline and to exclude other causes except *H. pylori*. The

*H. pylori* Urea Breath Test (UBT) was performed in all study subjects. Patients with a known cause received treatment accordingly, whereas patients with CIU got enrolled in the study and each patient with chronic urticaria was provided with an evaluation sheet for follow-up.

Immediately after taking all investigations from the participant, the *H. pylori* positive patients were started on the first course therapy which was consisted of clarithromycin 500 mg BID, omeprazole 20 mg, amoxicillin 1000 mg BID for a period of 14 days. Urea Breath Test (UBT) was used to assess *H. pylori* eradication 4 weeks after the treatment. If the infection of *H. pylori* persisted, patients received the second course of same treatment for an extra week. All infected patients were given prescription of antihistamines to use as 'rescue medicine'. Patients who became non-infected were given antihistamines when necessary. After completing the treatment, all patients were observed in follow-up visits for a period of six months. Moreover, we judged each patient's objective response after 12 weeks from the eradication treatment [on the basis of improvement of urticarial symptoms (Frequency, severity and duration) and the need for rescue medication] as follows: significant response: improvement of urticarial symptoms and no need or infrequent need for antihistamines, while not significant response as: little improvement of urticarial symptoms or frequent need for antihistamines.

Pearson  $\chi^2$  test and Fisher's exact test were used to explore the significant association of selected characteristics among the study patients.

#### Results

50 out of 500 patients who were seen in the clinic during the study period were suffering from chronic urticaria. The patients were predominantly females 30 (60%). The female participants were 30 patients, 20 cases were CIU and 10 cases were CU. Male participants were only 20 patients, 15 of them suffered from CIU and the other 5 suffered from CU. 35 (70%) patients were diagnosed with chronic idiopathic urticaria, (20 females, 15 males, male to female ratio was 3:4). The mean age was  $34.5 \pm 5.8$  years, and the highest number (78%) belonged to the age group '20-50 years'.

15 (42.85%) patients of CIU showed positive *H. pylori* infection i.e. 5 (33.33%) males and 10 (66.66%) females, while 20 (57.14%) patients showed negative *H. pylori*; 5 (25%) males and 15 (75%) females. 10 of 15 *H. pylori*-positive patients i.e. (66.66%) presented with G.I.T symptoms like dyspepsia and heartburn. Male and female percentages were approximately the same in *H. pylori*-positive patients (70% and 60%, respectively) but the female had more frequent GIT symptoms than males (72% vs. 60%) (Table II).

**Table II** Prevalence of H. pylori-positive patients and G.I.T symptoms among different age group

Age (Years)	GIT Symptoms		No GIT Symptoms	
	Male	Female	Male	Female
12-20	0	0	1	0
21-35	1	3	2	1
36-50	2	4	1	0
51-60	0	0	0	0
Total	3	7	4	1

**Table III** Objective response to treatment

H. Pylori eradications treatment	H. Pylori response to treatment		Urticarial improvement of cured Subjects	
	No of subjects	Cured	Significant	Not Significant
1 <sup>st</sup> Course	15	10	8	2
2 <sup>nd</sup> Course	5	3	2	1
Persistent H. Pylori	2	0	0	2
		13	10	5
Total	15		15	

The patients' response to the eradication therapy of H. pylori was as the following: 10 (66.66%) patients cured with the first course, 3 (20%) patients cured with the second course of eradication therapy and 2 (13.33%) patients had persistent H. pylori even after two courses of eradication therapy.

The urticarial symptoms response after the eradication therapy was significant in 10 (66.66%) patients in whom H. pylori was eradicated whereas not significant in 5 (33.33%) patients; 3 (20%) patients with eradicated H. pylori and 2 (13.33%) patients with persistent H. pylori infection as illustrated in Table III.

### Discussion

The current study aimed to investigate the association of H. pylori and chronic urticaria and to assess the impact of eradication therapy of H. pylori on chronic idiopathic urticaria. The study came to the conclusion that H. pylori needs to be included in investigation of chronic idiopathic urticaria patients for proper management. In this study, we used the experimental approach to assess the efficacy of H. pylori treatment in CIU patients. There are conflicting reports of the relationship between the infection of H. pylori and CIU based on several Western studies. The present study is medically valuable as it proves that there is a high level of prevalence of infection of H. pylori among the target population. There is high prevalence of the infection of H. pylori (42.85%) among CIU patients. Studies from African countries, reported a prevalence of H. pylori infection of 65.7% and 75.5% in Ethiopia and Morocco, respectively. The prevalence of the H. pylori infection was 93.6%, when tested with serology and 80% when histology tests were applied. In Brazil, a high prevalence of 41.1% was reported in patients from 2 to 19 years of age.<sup>14</sup>

The present study proves that there is high prevalence of H. pylori in CIU patients in accordance with previous studies and stresses the effectiveness of eradication therapy in treating H. pylori infection.<sup>15-20</sup> In CIU patients infected with H. pylori, urticarial symptoms were resolved after H. pylori eradication therapy was applied. This result agrees with recent studies, such as the study of Tareen et al carried out in 2016, which affirms that the eradicating therapy of H. pylori is effective in CU patients and that detecting H. pylori is essential for the diagnosis of all CU patients.<sup>7</sup> Another recent study conducted in 2015, by Gu et al found out a relationship between CU and the infection of H. pylori.<sup>6</sup> Some researchers showed no relationship between allergic diseases and infection of H. pylori in men in particular, like the Japanese study carried out in 2007.<sup>21</sup> However, other researchers, like Bruscky et al suggested that H. pylori and the occurrence of CU are correlated as H. pylori is considered an etiological agent of CU.<sup>22</sup> Researchers have confirmed the correlation between CU and the infection of H. pylori. However, it is still controversial whether H. pylori is an etiological agent for CU or not.<sup>11</sup> The therapy of eradicating H. pylori is effective in CU patients. Therefore, detecting H. pylori is essential for the diagnosis of all CU patients.<sup>7</sup>

In a recent study conducted in 2015, the researchers recommended the inclusion of the infection of H. pylori in the diagnosis of patients showing no response to treatment.<sup>23</sup> Another 2007 study proved that eradicating the infection of H. pylori, using triple therapy, effectively minimizes the score of urticarial activity in patients suffering from CU and showing negative and positive autologous serum test.<sup>24</sup>

The difference in the results of the above studies is probably because of the various methods that were used for detecting and establishing infection of H. pylori or the recurrences shortly after successful therapy or H. pylori resistance to therapy. The pathogenic mechanism between CIU and the infection of H. pylori, remains unknown. H. pylori is likely to reveal the existing antigens or facilitate the absorption of antigens, by inducing inflammation in the gastrointestinal tract. If this happens, IgE antibodies responsible for the symptoms of urticaria may continue to be produced even after H. pylori eradication. Hence, the infection of H. pylori is likely to perpetuate the tendency of an infected person for contracting urticaria. The infection of H. pylori is frequent. However, it just provokes urticaria in some patients infected with H. pylori. Therefore, long-duration studies are required to establish natural history of the infection of H. pylori, taking into consideration the symptoms of urticaria, reinfection, as well as retreatment. Only then, studies would be able to implement the Koch's postulate and H. pylori can be labeled a cause of CU.

### Conclusion

The study concludes that H. pylori needs to be investigated in all patients with chronic urticaria, and the infected patient should receive H. pylori eradication therapy.

Moreover, the current study proved that eradication therapy of *H. pylori* is effective in the management of chronic urticaria.

#### Recommendation

*H. pylori* should be among the diagnostic work-up of all chronic urticaria patients and considering the costs and accessibility for the diagnosis and monitoring of *H. pylori* infection.

#### Disclosure

All the authors declared no competing interests.

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# Study of Vitamin D during 10 to 14 Weeks of Pregnancy in Dhaka City

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## ABSTRACT

**Background:** Pregnancy outcome is very important for every family. Early detection of vitamin D deficiency in pregnant women and appropriate measures can reduce many fetal complications. Vitamin D deficiency now a days is quite common in 1st trimester of pregnancy which affect both fetal and maternal outcome. To assess the vitamin 25(OH)D level and state of its deficiency in the Dhaka City dwellers during 10 to 14 weeks of pregnancy in relation with non-pregnant state.

**Materials and methods:** The cross-sectional study has been conducted in Nostrum Hospital from 1st November 2021 to 31st March 2022. A total of 50 women were included in the study. Among them, 25 primigravid women in 10 to 14 weeks of pregnancy and aged between 19 to 35 years were considered as study group (Group A). Another 25 apparently healthy non-pregnant women (Age and BMI matched, having minor illness) from medicine out-patient department were considered as control group (Group B). In all cases, following aseptic precaution blood samples were collected from antecubital vein. Serum concentrations of 25(OH)D were estimated by Chemiluminescent Micro Particle Immunoassay (CMIA).

**Results:** The mean value of serum 25(OH)D concentration was 18.068 ng/mL in pregnant women and 60% of them had low vitamin D concentrations of <20 ng/mL. Covered-exposed part dressing style, no or less multivitamin replacement by oral route, time of sampling (November–March) and increased physiological demand maybe important factors associated with 25(OH)D deficiency. In this study, serum vitamin 25(OH)D level was significantly lower during 10 to 14 weeks of pregnancy in comparison to non-pregnant women ( $p < 0.0001$ ). Among the pregnant women only 40% had normal vitamin 25(OH)D level.

**Conclusion:** A significantly lower level of vitamin 25(OH)D and higher percentage of low vitamin D status was observed during 10 to 14 weeks of pregnancy in contrast to the non-pregnant women of Dhaka city. However, low 25(OH)D levels were not related with adverse pregnancy outcomes.

**Key words:** Early pregnancy vitamin D state; Vitamin 25(OH)D; 10-14 weeks of gestation.

## Introduction

The state of vitamin 25(OH)D deficiency has increased and day by day becoming a major public health hazard in many countries.<sup>1</sup> Vitamin D is a fat-soluble vitamin. Fortified milk, sea fish oils and dietary supplements are usual sources of Vitamin D apart from endogenous source in the skin which is related with exposure to sunlight.<sup>2</sup> It has to undergo hydroxylation in the liver to convert to 25-hydroxy vitamin D (25(OH)D), then further hydroxylation in the kidneys producing physiologically active 1,25-dihydroxy vitamin D. This active form is required to enhance absorption of calcium from the GI tract and mineralization of bone and its growth<sup>3</sup>.

During early pregnancy, marked maternal vitamin D deficiency has been associated with bone disorders, hemostasis of skeletal system, congenital rickets, and bony

fractures in the newborn<sup>4</sup>. Assessment of vitamin D status during 10 to 14 weeks of pregnancy provides an early chance for detection and appropriate management of vitamin D deficiency state which may decrease the number of unexpected pregnancy outcomes.

The aim of this study was to find out difference in the serum levels of vitamin 25(OH)D during 10 to 14 weeks of pregnancy in comparison to non-pregnant state.

## Materials and methods

A total of 25 cases at early pregnancy (10–14 weeks of pregnancy) attending for their first antenatal visit at the outdoor patient department of the Gynae and Obstetrics Wing of Nostrum Hospital, Uttara, Dhaka who fulfilled the inclusion criteria were included in Group A. 25 consecutive non-pregnant women having minor medical problems reporting to the Medicine Department of same Hospital from November 2021 to May 2022 and fulfilled the inclusion criteria were included for this study in Group B.

This study was begun after approval by the qualified Ethics Committee of Nostrum Hospital. All women were properly informed about the aim of the study and then self-motivated consent was taken. They were clearly advised to complete a questionnaire that included the basic information of their pregnancy profile and information about the probable factors with plausible association with vitamin D status.

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Random blood samples were taken and 25(OH)D levels were estimated. All the pregnancies were properly cared up till the delivery and the pregnancy related events were recorded in our database. At the terminal part of the study, the data of pregnancy and neonatal outcomes were obtained from medical records and reviewed methodically.

**Inclusion criteria:** Confirmed pregnant women (During 10 to 14 weeks of gestation) and non-pregnant women with low to middle socioeconomic status, aged 20 to 36 years, not covering usual exposed parts of the body in their daily life and not having any disease mentioned in exclusion criteria.

**Exclusion criteria:** Women having history of thyroid disease, parathyroid or adrenal insufficiency, liver disease or kidney failure, metabolic bone diseases and those taking drugs that might affect vitamin D level were excluded from the study.

Blood samples were taken from the antecubital vein during 10 to 14 weeks of pregnancy of 25 cases and of 25 non-pregnant women who fulfilled the inclusion criteria of the study. The serum was separated by centrifugation at 3500 rpm at 4°C for 10 minutes, then stored in aliquots at -80°C. The serum 25(OH)D was estimated by using Chemiluminescent Microparticle Immunoassay (CMIA) from AFIP, Dhaka Cantonment, Dhaka.

Although there is no WHO published optimal 25(OH)D level, serum 25(OH)D levels <10 ng/mL, between 10–19 ng/mL and >20 ng/mL were mentioned as deficiency, insufficiency and normal / desirable vitamin D concentrations respectively as per previous consensus.

All the estimated values were presented as mean ± SD (Range) for continuous variables, and as numbers and percentages for the binary and categorical variables. The unit of measurement of vitamin D concentrations was standardized to ng/mL for 25-hydroxy vitamin D. The categorical data were analyzed by the student's t test to compare the serum vitamin D levels between the two groups. All the data were managed and analyzed by using SPSS, version 20.0 and presented as tables and figures. A significance level of a p value of less than 0.05 and 95% CI was used to find the relationship.

## Results

A total of 50 women participated in this study. The 25 cases were selected out of 47 cases as per inclusion criteria and marked as Study group (Group A). Another 25 were selected as Control group (Group B) from a total of 59 non-pregnant women having minor medical problems. Both groups were age and BMI matched. Pulse, BP, FBS were almost similar and within normal ranges in both groups and the differences between the groups were statistically non-significant.

**Table I** Age and BMI in both groups (n=50)

Parameter	Group A (n=25)	Group B (n=25)	p value
Age (Years)	25.6 ± 3.78 (20-35)	25.8 ± 1.62 (20-36)	0.849
BMI (kg/m <sup>2</sup> )	22.93 ± 1.66 (19.78-26.04)	23.16 ± 2.37 (18.06-27.11)	0.737

Data were expressed as mean ± SD (Range). For statistical analysis, unpaired "t" test was performed to compare between groups. Group A findings were almost similar to that of Group B.

**Table II** Pulse rate and blood pressure in both groups (n=50)

Parameter	Group A (n=25)	Group B (n=25)	p value
Pulse Rate (Beats/min)	74.32 ± 5.19 (65-84)	74.4 ± 3.94 (68-82)	0.95
Mean Pressure (mm Hg)	92.6 ± 6.87 (82-106)	90.16 ± 18.35 (85-108)	0.536

Data were expressed as mean ± SD (Range). For statistical analysis, unpaired "t" test was performed to compare between groups. Group A findings were almost similar to that of Group B.

**Table III** Serum vitamin D levels in both groups (n=50)

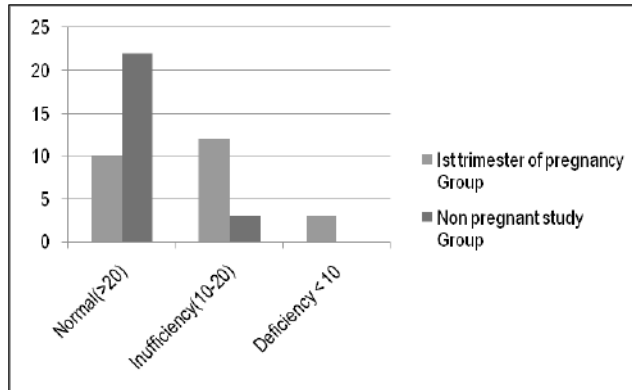
Parameter	Group A (n=25)	Group B (n=25)	p value
Vitamin D (ng/mL)	18.068 ± 6.362 (9.99-29)	28.92 ± 8.52 (16-42)	< 0.0001

Data were expressed as mean ± SD (Range). For statistical analysis, unpaired "t" test was performed to compare between groups. Mean Vitamin D in Group A is clearly lower than in Group B and the difference is statistically highly significant (p < 0.0001).

**Table IV** Distribution of vitamin D levels in pregnant (During 1st trimester) and non-pregnant women (n=50)

Vitamin D level (ng/mL)	Number of subjects (10-14 weeks of pregnancy)	Number of subjects (Non-pregnant state)
Normal (>20)	10	22
Insufficiency (10-20)	12	3
Deficiency (<10)	3	0

In pregnant cases, 15 (60%) women had low vitamin D levels (Insufficiency or deficiency). On the other hand, only 3 (12%) women in non-pregnant group showed low vitamin D levels.



**Figure 1** Comparative distribution of Vitamin D status in pregnant women during 1<sup>st</sup> trimester and non-pregnant women.

### Discussion

The present study has reflected the prevalence of low maternal vitamin D status in early pregnancy (During 10 to 14 weeks). The majority of our Group A subjects were either vitamin D deficient or insufficient (60%) compared to those who in Group B (12% only) according to the criteria published by the Institute of Medicine.<sup>5</sup>

Recent studies among the North Sumatra population have shown that 70% of women of childbearing age ( $n = 100$ ) had deficient status, 29% insufficient and only 1% had sufficient status.<sup>6</sup> There are several possible reasons for decreasing 25(OH)D serum levels; not only low consumption of vitamin D-rich food, but also certain external factors that contribute to preventing bodies from being exposed to sunlight.

Bukhary et al reported that in their study, 90% of first trimester pregnant women were suffering from hypovitaminosis D. Same study also suggested that dietary source of vitamin D was a significant predictive factor for hypovitaminosis D together with some other environmental factors including ethnic group, educational status and sunprotection.<sup>7</sup> This factor can be minimized by enhancing alternative sources i.e., the prevalence of Vitamin D Deficiency (VDD) during pregnancy can be reduced by appropriate dietary intake and supplied multivitamins during pregnancy.<sup>8</sup>

However, some other studies found that sources of vitamin D from food are lower and only contributes 10% of total needs. The main source of vitamin D is exposure to ultraviolet ray of sunlight, which contributes to 90% of vitamin D requirements.<sup>9</sup> Therefore, the principal reason of VDD is inadequate sunlight exposure.<sup>10</sup>

Apart from above mentioned factors, many other factors influence the vitamin D status of individuals, including latitude, season, time spent outdoors, clothing habitually worn, sunscreen use, weight status, skin colour, and some medications and medical conditions.<sup>11</sup>

Vitamin D deficiency continues throughout the pregnancy, but regarding the fetal effect, different studies reveal different opinions. Data regarding the indirect effect of hypovitaminosis D on the mode of delivery are controversial. In one study, Vitamin D lacking is associated with almost fourfold increased chance of cesarean section.<sup>12</sup> In contrast, other observational studies failed to show any correlation between hypovitaminosis D and delivery mode.<sup>13</sup>

Seda et al found no significant association between low 25(OH)D levels in the first trimester and adverse pregnancy outcomes such as pre-eclampsia, gestational diabetes, preterm birth, small for gestational age, delivery mode and bacterial vaginosis which is in agreement with our report.<sup>14</sup>

### Conclusions

A significantly lower level of vitamin 25(OH)D and higher frequency of low vitamin D status was observed during 10 to 14 weeks of pregnancy in contrast to the non-pregnant women of Dhaka city which may be related to dress style, lack of multi-vitamins, time of sampling (November to March) and increased physiologic demand. However, low 25(OH)D levels were not associated with adverse pregnancy outcomes.

### Disclosure

Both the authors declared no competing interest.

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## Recurrent Pancreatitis in Pregnancy : A Case Report

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### ABSTRACT

**Background :** Acute pancreatitis is a rare but dangerous surgical event that adversely affect pregnancy and worsen the both maternal and fetal outcome. The estimated incidence is 1 in 10,000 pregnancy. The diverse outcome are the formation of abscess, pseudocysts and multiorgan dysfunction. The dual challenging problem peculiar to gravid state is that clinicians have to decide a balance between risk and benefit for pregnancy continuation near term along with subsidence of acute abdomen. Among the aetiological background, cholelithiasis is of prime importance as the physiological, biochemical and endocrine changes during pregnancy affect gastrointestinal and hepatobiliary system favourable for bile stasis, hyperlipidemia and calculus formation. The purpose of the study was to disseminate knowledge and experience of clinical Characteristics and treatment about this issue for the readers as future references.

**Case Presentation :** MS. 'SN' 30 years old para : 1+2 visited to Emergency Department of MAX Hospital Ltd. Mehidibagh Chattogram on 30 September 2021 due to intense upper abdominal pain at 34 weeks gestation radiating to back associated with vomiting after taking food. She was advised for in-patient admission with conservative treatment eg. nil per oral, parenteral hydration, broad spectrum I/V antibiotic along with antiulcerant and antispasmodic.

**Conclusion :** Conservative management in early stages of mild pancreatitis prevents progression to severe pancreatitis and results in good maternal and fetal outcome.

**Key words :** Fetal outcome; Pancreatitis; Pregnancy.

### Introduction

Recurrent acute pancreatitis is defined as more than two attacks of acute pancreatitis without any evidence of chronic pancreatitis.

Underlying aetiologies are :

- \* Sludge or bile crystals of CBD.
- \* Dysfunction of Sphincter Of Oddi (SOD).
- \* Anatomic variation of ductal system that interfere with outflow of pancreatic juice.
- \* Obstruction of the main pancreatic duct or pancreatico biliary junction.
- \* Alcoholism
- \* Occult choletithiasis
- \* Idiopathic
- \* Pregnancy

The physiological and biochemical changes during pregnancy such as cholesterol secretion in the hepatic bile increase during 2nd and 3rd trimester compared to bile acid and phospholipids so that bile become supersaturated.<sup>1</sup>

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Endocrine changes during pregnancy i.e. hyperestrogenism and triglyceridemia with familial tendency in certain gravida triggers the pathology, that provide a sensitizer for the particular individual.<sup>2</sup>

Triglyceride (TG) level over 1000 mg/dl are necessary to initiate pancreatitis but reported incidence is reducing with bowel rest including total parenteral nutrition.<sup>3</sup>

When Triglyceride (TG) level become too high; oxygen cannot adequately travel to the pancreas via the bloodstream followed by initiation and propagation of inflammatory impulse of pancreatitis.

Metabolic changes during pregnancy such as increase or rise in lipid and lipoprotein including triglyceride specially in the 3rd trimester that may peak upto three fold which act as inducer of inflammation when serum biochemistry level remain between 750-1000mg/dl.<sup>4</sup>

The another biochemical event in pregnancy pancreatitis is the reduction of serum calcium level leading to secondary hypocalcemia that can be overcome by slow I/V administration of calcium gluconate.<sup>5</sup>

Pregnancy itself is a stressful state and stress is also considered to be a risk factor for pancreatitis specially chronic one, probably by sensitizing the exocrine portion of pancreas by exerting detrimental effect through activating distinct Heat Shock Protein (HSP) including HSP 27, HSP 60, TNF $\alpha$  also having mediator power to provide synergistic detrimental effect.

Stress is also considered as "threatened homeostasis" that can include physical or psychological force or both. Activation of hypothalamo pituitary adrenal axis and central sympathetic outflow that results in visceral hypersensitivity through release of different substance e.g. substance P and calcitonin gene related peptide from afferent nerve pathway.

Recent study revealed a link between pancreatitis and transmembrane conductance regulator gene mutation.<sup>6</sup>

### Case Report

Mrs. 'S N' 30 years old Para : 1+2 visited to emergency due to intense upper abdominal pain at 34 weeks gestation radiating to back associated with vomiting after taking meal.

This was her planned pregnancy. She was on regular ANC and duly immunized. Pregnancy was uneventful till 34 weeks, then she noticed acute attack of severe upper abdominal pain and vomiting following meal.

She also gave the history of similar attack during previous pregnancy 4 years back followed by spontaneous onset of preterm labour and delivery of a male baby with good Apgar score.

During puerperium she noticed subsequent similar attack of acute upper abdominal pain, vomiting and diagnosed as a case of calculus cholecystitis and treated by laparoscopic cholecystectomy with good post operative recovery.

With these clinical features and biochemical parameter (Amylase 500 IU/L and TG > 1000mg/dl) she was diagnosed as a case 4th gravida with 34 weeks gestation with history of recurrent pancreatitis and laparoscopic cholecystectomy.

She was advised for inpatient admission with conservative approach e.g nil per oral, parenteral hydration, broad spectrum I/V antibiotic along with antiulcerant and antispasmodic.

After 24 hours of hospital stay gradual subsidence of acuteness, she was eager to return home. As she has no complaint regarding perception of fetal movement, decided for discharge on request with advice and subsequent follow up accordingly as per schedule.

With the dietary fat restriction and plenty of fluid intake pregnancy continued till 38 weeks. There after spontaneous labour pain was initiated and delivered a healthy male baby of 2.5kg with good Apgar score, both the mother and baby remain healthy. Puerperium was uneventful and baby was on breast feeding.

### Discussion

Acute Pancreatitis in Pregnancy (APIP) is a challenging clinical problem though relatively limited but expanding clinical based issues.

The condition raises with gestational age i.e. 52% during 3rd trimester and 12% during 1st and 2nd trimester though the relationship between pregnancy and pancreatitis remain obscure and unclear. Observation revealed that 3rd trimester Acute Pancreatitis In Pregnancy (APIP) is associated with PE and HELLP syndrome.<sup>7</sup>

High level of estrogen is an inducer of increase cholesterol secretion in the hepatic bile and become supersaturated, associated progesterone secretion resulting in increase gall bladder volume, delayed emptying of bile responsible for bile stasis which offer a favourable media for calculus formation preferably in later period of gestation.<sup>8</sup>

Altered fluid and electrolyte balance during pregnancy resulting in weight gain that also predispose to biliary sludge and cholelithiasis.

Raised intraabdominal pressure of gravid uterus during 3rd trimester produce mechanical pressure on the biliary duct that increase the risk of Acute Pancreatitis (AP) which may aggravate even during early puerperium. The incidence is increased in this case during previous puerperium; so after that laparoscopic cholecystectomy was performed.

Reduced activity of lipoprotein lipase resulting in at least 2.5 fold increase in triglyceride level which may persist a span of six weeks predispose to women at risk of developing acute pancreatitis after pregnancy reported incidence is that, condition may decrease with bowel rest including total parenteral nutrition. In this case this was evident during her hospital stay even after returning home with the advices.<sup>9</sup>

Other aetiological background e.g. alcohol abuse responsible for 10% cases. Significant alcohol intake means more than 3.5 drink daily for more than 5 years.<sup>10</sup>

This case report probably belongs to the idiopathic or genetic causes aggravated by pregnancy as no other risk factor is observed or noticed.

Trauma, ischaemia, smoking and hereditary also may operate.

The rare instances that may contribute such as : hyperparathyroidism, connective tissue disorder, abdominal surgery, infections, iatrogenic sources (e.g. tetracycline) diuretics, antibiotic and antihypertensive drugs also reported. But drug history was not evident in this case.<sup>11</sup>

The main event is the inflammatory response whatever may be the underlying factor. It was also observed in this case as parenteral antibiotic administration plays a good role for the subsidence of acute abdomen.

Inflammation results from upregulation of a multitude of proinflammatory signalling molecules including TNF $\alpha$ , IL-6, IL-8 and others.

Activation of inflammatory pathway in the pancreas, is thought to damage pancreatic tissue and accelerate the disease progression.

So the prime pathological event include : initiation and propagation of inflammatory mediators which are responsible for inhibition of secretion and activation of intracellular protease, these are co-related with the morphological changes in the acini, such as : \* retention of enzyme content \* formation of large vacuoles having both digestive enzymes and lysosomal hydrolases that lead to necrosis.

Chemokine is released from the damaged pancreatic tissue which attracts inflammatory cells and call for systemic upset response which is the determinant of the severity of the disease.<sup>12</sup>

Poor digestion and absorption of food specially fatty diet due to pancreatic damage resulting in weight loss and steatorrhea (Bulky and smelly bowel movement).

The ultimate progression to the development of IDDM, stenosis or vascular obstruction of CBD, duodenum and pancreatic main duct; the ultimate development of pancreatic carcinoma.<sup>13</sup>

The final mirror image of Systemic Inflammatory Response Syndrome (SIRS) multiorgan dysfunction objectified by physiologic failure of interdependence organ system.<sup>14</sup>

The incidence of Fetal Distress (FD) and fetal loss increase with the worsening of the disease.

Once upon a time Acute Pancreatitis In Pregnancy (APIP) reported maternal and fetal mortality as high as 20% and 50% respectively.<sup>15</sup>

But recent advancement including modern diagnostic aid and available management options even endoscopy performed during conception provide better prognostic outcome. This treatment protocol offer improved result in this case as pregnancy was continued till 38 weeks, thereafter she started spontaneous labour pain.

The rate of maternal mortality is less than 1% and the incidence of Preterm Labour (PTL) is about 20% specially pancreatitis is associated with cholelithiasis. Sometimes fetal mortality is observed in the form of miscarriage or Stillbirth (SB).<sup>16</sup>

#### Conclusion

- Diagnosis of exclusion is mandatory to decide for management schedule as till date no protocol is recommended though conservative approach is followed.
- Being a small organ pancreas is often ignored but regarding digestive and endocrinology provide vital function.
- Life style and dietary modification can provide better option to reduce severity and prevent recurrence.
- Health care professional should be familiar with the pregnancy physiology and due consideration with the pathology accordingly.

#### Disclosure

The author declared no competing interests.

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