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BGS

Bangladesh Journal of Gastrointestinal and Liver Diseases

BANGLADESH GASTROENTEROLOGY SOCIETY

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An Official Publication of the Bangladesh Gastroenterology Society

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Bangladesh Journal of Gastrointestinal and Liver Diseases

The Bangladesh Journal of Gastrointestinal and Liver diseases (BJGL) is a biannually published journal dedicated to advancing knowledge and promoting research in the field of gastroenterology and liver diseases. BJGL welcomes submissions of high-quality original articles, review articles, case reports, special articles, case reports, different gastrointestinal images (radiological and endoscopic), letter to the editor and short communications related to various topics of gastrointestinal and liver diseases. Please read these instructions carefully to ensure your submission adheres to our guidelines. Manuscripts that do not comply with these instructions may be returned to the authors without review.

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Editorial

New liver, New life: Overcoming Barriers to Liver Transplantation in Bangladesh

Liver transplantation is a life-saving treatment for patients with liver failure, both acute and chronic, complications of cirrhosis, and early-stage (T2) hepatocellular carcinoma. Globally, liver-related diseases contribute to over two million deaths annually, accounting for one in every 25 deaths, making liver transplantation a necessity.[1] In Bangladesh, the 8th most common cause of death is liver diseases, and the age-adjusted death rate is 19.26 per 100,000.[2] The endemic prevalence of chronic Hepatitis B and Hepatitis C infections combined with the rising incidence of metabolic dysfunction-associated fatty liver disease (MAFLD), has led to a growing number of cirrhotic patients and end-stage liver disease cases. This poses a serious public health challenge, making the establishment of regular liver transplant facilities an urgent necessity.

The first successful liver transplantation (LT) in Bangladesh was performed in June 2010 at BIRDEM General Hospital, followed by another successful procedure in August 2011 at the same institute. Bangabandhu Sheikh Mujib Medical University (BSMMU) became the first public hospital to conduct a successful liver transplant in 2019. Despite these milestones, the growth of liver transplant programs in Bangladesh has been slow. This is primarily due to challenges such as inadequate infrastructure, a shortage of skilled personnel, and low public awareness. Thousands of Bangladeshi patients still travel abroad for liver transplants, which not only imposes significant financial burdens on families but also results in substantial outflows of foreign currency. By establishing comprehensive liver transplant services domestically, Bangladesh could save millions in medical expenses, reduce medical tourism, retain foreign currency, create jobs, enhance medical training, and improve healthcare equity by making lifesaving procedures accessible to all socioeconomic groups.

Bangladesh's healthcare system has evolved rapidly, yet a sustainable liver transplant program remains elusive. Key obstacles include a lack of public awareness, social and religious barriers, inadequate infrastructure, and insufficient government policies and regulations. The Bangladesh Organ Transplant and Donation Act of 1999, amended in 2018, permits two types of organ donation: living donor (from close relatives) and deceased (cadaveric) donation. However, deceased donation—where organs are surgically removed from consented donors after death or during brain death in ICUs—has yet to be implemented. To address this, Bangladesh must establish a robust deceased organ donation system, which would involve educating the public about organ donation, overcoming cultural and religious barriers, and improving the infrastructure to facilitate cadaveric liver transplantation. A national organ registry and improved coordination between hospitals could help in the equitable distribution of organs across the country. To remove social and cultural barriers to liver transplantation, public awareness campaigns on TV, radio, and social media can help normalize organ donation and dispel misconceptions. Gaining support from religious leaders through fatwas and community endorsements can address faith-based concerns.

The infrastructure for liver transplantation in Bangladesh remains inadequate, with a shortage of specialized centers, modern ICUs, surgical facilities, and skilled professionals. To overcome these challenges, the government and private sector must invest in hospital upgrades and expand training programs for transplant surgeons, gastroenterologists, nurses, and coordinators. To ensure that liver transplantation is affordable to individuals from all socioeconomic backgrounds, a comprehensive approach is essential. Strengthening government funding, introducing insurance schemes, and collaborating with international transplant centers for advanced technologies and best practices can reduce costs and improve care quality. Establishing a dedicated Liver Transplant Fund under the Ministry of Health, with transparent oversight, would ensure equitable resource distribution.

Liver transplantation in Bangladesh is still in its early stages but holds immense promise for saving lives. While challenges like organ availability, ethical concerns, socioeconomic barriers, and infrastructure gaps persist, collective efforts from the government, healthcare providers, and society can make this life-saving procedure more accessible and equitable. With sustained commitment, Bangladesh can transform its liver transplant landscape and offer hope to countless patients in need.

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Referencess:

1. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. *J Hepatol*. 2023;79(2):516–537.

2. Alam S, Azam G, Fahim SM, Chowdhury MAB, Ahmad N, Khan M. Prevalence and risk factors of hepatitis B and hepatitis C virus infections in Bangladesh: a nationwide population-based survey [Internet]. Dhaka (BD): Hepatology Society of Bangladesh; [cited 2025 May 1]. Available from: https://www.hepatolsocietybd.org/uploads/2/6/7/8/26786438/current_status_of_hbv_and_hcv_in_Bangladesh.pdf

Original Article

Clinical Outcomes and Complications of Endoscopic Retrograde Cholangiopancreatography: A Retrospective Study from a Tertiary Care Center in Bangladesh

MA Faisal[1], EU Ahmed[2], B Paul[3], M Rana[4], MN Mohsin[5], SMA Haider[6], SH Hasan[7]

Abstract

Background: Endoscopic retrograde cholangiopancreatography (ERCP) is a crucial interventional procedure for diagnosing and treating pancreatobiliary disorders. This study aimed to evaluate the indications, outcomes, and complications of ERCP in a tertiary care center in Bangladesh.

Materials and Methods: This was an observational, cross-sectional, retrospective study conducted in the Chittagong Medical College, Cottogram, Bangladesh. A total of 86 patients who underwent ERCP between January 2024 to January 2025 were included in this study.

Results: The study included 86 patients who underwent ERCP between January 2024 and January 2025. The median age was 45.5 years, with an equal gender distribution. Most patients were from rural areas (72.1%) and belonged to the lower socioeconomic class (67.4%). The most common indications for ERCP were choledocholithiasis (39.5%) and obstructive jaundice secondary to choledocholithiasis (27.9%). Complications were observed in 26.7% of patients, with post-ERCP pancreatitis being the most frequent (11.6%). Complete stone extraction was achieved in 36.6% of cases, while partial extraction and failure occurred in 31.7% each. The wire-guided technique was the most commonly used cannulation maneuver (66.3%). Cannulation was achieved within 10 minutes in 84.9% of cases. The balloon sweep was the most frequently employed extraction method (61.6%).

Conclusion: The study highlights the importance of ERCP in managing biliary and pancreatic diseases, particularly in resource-limited settings. While the procedure remains effective and safe, efforts to improve complete stone extraction rates and minimize complications are warranted. Further training, better equipment, and enhanced peri-procedural care may improve patient outcomes.

Keywords: Endoscopic Retrograde Cholangiopancreatography (ERCP), Post-ERCP Pancreatitis (PEP), Biliary Obstruction, Choledocholithiasis, Biliary Strictures.

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Introduction:

Endoscopic retrograde cholangiopancreatography (ERCP) is a highly specialized endoscopic procedure that combines endoscopy and fluoroscopy to diagnose and treat conditions affecting the biliary and pancreatic ductal system. The first ERCP was performed in 1968 by McCune et al. in Japan, which marked the beginning of a transformative era in gastrointestinal endoscopy.[1] Initially, ERCP served both diagnostic and therapeutic purposes, providing endoscopists with an unprecedented view of the biliary tree and pancreatic duct. In 1973, a landmark advancement occurred when Dr. Meinhard Classen in Germany and Dr. Keiichi Kawai in Japan independently performed the first endoscopic biliary sphincterotomy.[2] This therapeutic application significantly broadened the scope of ERCP, allowing for the minimally invasive management of previous surgical conditions.

Over the past few decades, the role of ERCP has evolved dramatically owing to the development of advanced noninvasive imaging modalities. Magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and high-resolution computed tomography (CT) offer detailed visualization of the biliary and pancreatic ducts without risks associated with invasive procedures. These technological advancements have led to a paradigm shift, relegating ERCP to a predominantly therapeutic role.[3,4] It is now reserved for interventions such as biliary and pancreatic duct stenting, sphincterotomy, stone extraction, dilatation of strictures, and drainage of the obstructed ducts.

Despite its clinical utility, ERCP is associated with several potential complications. These include post-ERCP pancreatitis (PEP), hemorrhage, perforation, cholangitis, and infections. The incidence of post-ERCP pancreatitis alone ranges from 3% to 15%, depending on patient risk factors and procedural complexity.[5] Because of these risks, ERCP is no longer recommended as the first-line diagnostic modality. Safer and more effective diagnostic options, particularly MRCP and EUS, should be utilized before ERCP, ensuring that ERCPs are reserved for therapeutic indications.[6]

ERCP remains the cornerstone in the management of various pancreatobiliary disorders, including choledocholithiasis, malignant biliary obstruction, benign biliary strictures, postoperative bile leaks, and acute cholangitis. In the context of acute cholangitis, early ERCP with biliary decompression has been shown to significantly reduce the

30-day mortality. Delays of more than 48 hours in performing ERCP in such cases are associated with prolonged hospital stays and an increased risk of adverse outcomes, including sepsis and hypotension. Therefore, timely intervention is critical in emergencies.ERCP requires a high level of technical expertise and is generally performed in tertiary care centers by trained endoscopists.[7]

From an epidemiological perspective, gallstone disease is a major contributor to biliary disorders that require ERCP. The incidence varies regionally. In Bangladesh, the prevalence of gallstone disease is notably higher, resulting in increased demand for ERCP services and regional differences in their utilization. Chattogram, a prominent city in southeastern Bangladesh, reports relatively fewer ERCP procedures. This may be due to a lower regional incidence of gallstone-related complications or the limited availability of specialized medical services.[8,9]

Considering the clinical significance of ERCP and the regional variability in its use, it is crucial to assess its outcomes, challenges, and patient characteristics within specific populations. This study was carried out at a tertiary care and teaching hospital in Bangladesh, with the main objective of analyzing the indications, results, complications, and limitations associated with ERCP procedures in this context. The findings aim to enhance the existing regional data on ERCP and support the development of evidence-based practices and healthcare policies in resource-constrained environments.

Materials and Methods:

We conducted a retrospective analysis of patients who underwent ERCP between January 2024 to January 2025 in the endoscopy suite of the Gastroenterology Department at Chittagong Medical College, Chattogram, Bangladesh. The study included individuals aged over 18 who gave written informed consent before the procedure. All ERCPs were performed either by or under the supervision of five skilled endoscopists, using a side-viewing endoscope (TJF Q180V,150 Olympus, Tokyo, Japan).

Selective cannulation of the common bile duct (CBD) was carried out with a triple lumen sphincterotome (ULTRATOME, Boston Scientific, USA and Clever Cut, Olympus, Tokyo, Japan) and guide wires measuring 0.025 and 0.035 inches (Visi Glide, Olympus, Japan). An ERCP procedure was deemed successful in cases of biliary sepsis if biliary drainage was achieved. If drainage was not possible, the procedure was considered a failure. In other clinical contexts, success or failure was determined based on the indication and outcome of the procedure.

Patient data from these 13 months were gathered using a structured case record form and analyzed with SPSS software (IBM Corp., Armonk, NY). The study included all adult patients who underwent ERCP during the specified time frame. Exclusion criteria were patients under 18 years of age, pregnant women, and individuals with significant cardiac or pulmonary risks.

Results:

A total of 86 patients underwent Endoscopic Retrograde Cholangiopancreatography (ERCP) during the study period. The median age was 45.5 years (interquartile range: 35–58.5 years). The study population had an equal gender distribution, with 43 males (50%) and 43 females (50%). In terms of occupation, the majority were homemakers (45.3%), followed by students (22.1%), service holders (15.1%), businessmen (11.6%), and retired individuals (5.8%). Most patients resided in rural areas (72.1%), while the remaining 27.9% lived in urban settings. Regarding socio-economic status, 67.4% of patients were from the lower class, 30.2% from the middle class, and 2.3% from the upper class (Table 1).

Table 1: Distribution of patients according to demographic profile of patients (n=86).

Variable	Number (Percentage)
Age	45.5 years (Median) (interquartile range: 35-58.5 years).
Gender	
Male	43 (50%)
Female	43 (50%)
Occupation	
Homemaker	39 (45.3%)
Student	19 (22.1%)
Service holder	13 (15.1%)
Business	10 (11.6%)
Retired	5 (5.8%)
Residence	
Rural	62 (72.1%)
Urban	24(27.9%)
Socio-economic Status	
Lower	58 (67.4%)
Middle	26 (30.2%)
Upper	2 (2.3%)

The most common indication for ERCP was choledocholithiasis (39.5%), followed by obstructive jaundice secondary to choledocholithiasis (27.9%), and post-ERCP stent replacement or removal (11.6%). Less frequent indications included benign biliary stricture (7.0%), cholangiocarcinoma (5.8%), biliary ascariasis (4.7%), chronic pancreatitis (4.7%), carcinoma of the head of the pancreas (3.5%), and bile leak (2.3%). These findings highlight that stone-related diseases and biliary obstructions were the predominant reasons for ERCP (Figure 1).

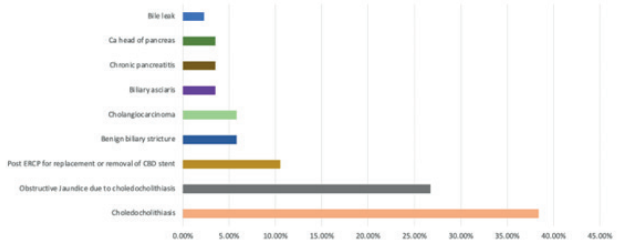

Figure 1: Distribution of patients according to indication of ERCP (n=86).

Complications were observed in 23 patients (26.7%). The most frequent complication was post-ERCP pancreatitis (11.6%), followed by cholangitis (8.1%), bleeding (5.8%), and perforation (1.2%). The remaining 63 patients (73.3%) experienced no complications (Figure 2).

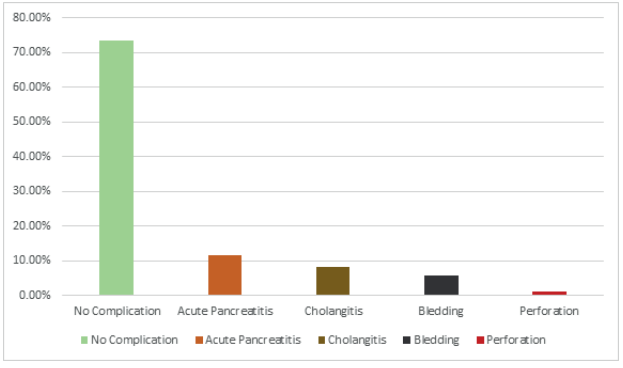

Figure 2: Distribution of patients according to complications of ERCP (n=86).

With regard to stone extraction outcomes, complete extraction was achieved in 23 patients (36.6%), partial extraction in 20 patients (31.7%), and failure occurred in 20 patients (31.7%) (Table 2).

Table 2: Distribution of patients according to success of stone extraction (n=86).

Stone Extraction	Frequency (Percent age)
Complete	23 (36.6)
Partial	20 (31.7)
Failed	20 (31.7)

On endoscopic evaluation, the papilla appeared normal in 73.3% of cases, short in 8.1%, swollen in 7%, long in 5.8%, and showed growth in 5.8%. The endoscope position was short in 95.3% of patients and long in 4.7%. Cannulation was achieved within 5 minutes in 38.4% of cases, between 5 and 10 minutes in 46.5%, and took more than 10 minutes in 15.1%. The wire-guided technique was the most commonly used cannulation maneuver (66.3%), followed by precut (24.4%), double-wire technique (4.7%), over-the-pancreatic stent approach (2.3%), and fistulotomy (2.3%). In terms of stone size, 27.9% measured less than 1 cm, 18.6% were 2 cm, 15.1% were greater than 1.5 cm, and 11.6% exceeded 2 cm. The balloon sweep was the most frequently employed extraction method (61.6%), followed by Dormia basket (14%) and mechanical lithotripsy (2.4%). Cannulation of the pancreatic duct occurred in 31.4% of patients (Table 3).

Table 3: Distribution of patients according to profiles of ERCP (n=86).

Variable	Number (Percentage)
Papilla	
Normal	63 (73.3)
Swollen	6 (7)
Short	7 (8.1)
Long	5 (5.8)
Growth	5 (5.8)
Scope position	
Short	82 (95.3%)
Long	4 (4.7%)
Cannulation time	
<5 minutes	33 (38.4%)
5-10 minutes	40 (46.5%)
>10 minutes	13 (15.1%)
Manuevre	
Wire guided	57 (66.3%)
Precut	21 (24.4%)
Fistulotomy	2 (2.3%)
Over pancreatic stenting	2 (2.3%)
Double wire	4 (4.7%)
Stone size	
<1 cm	24 (27.9%)
>1.5 cm	13 (15.1%)
2 cm	16 (18.6%)
>2 cm	10 (11.6%)
Stone extraction	
Balloon sweep	53 (61.6%)
Dormia basket	12 (14%)
Mechanical lithotripsy	2 (2.4%)
Cannulation of the pancreatic duct	27 (31.4%)

Discussion:

This study highlights a comprehensive analysis of patients undergoing Endoscopic Retrograde Cholangiopancreatography (ERCP), focusing on demographic profiles, indications, procedural outcomes, and associated complications. The median age of 45.5 years indicates that ERCP is commonly performed in middle-aged individuals, while the equal distribution between males and females suggests no gender predominance in the need for these procedures-findings that are consistent with previous studies.[10]

The socio-demographic profile of the study population reveals that a significant majority resided in rural areas (72.1%) and belonged to the lower socio-economic class (67.4%).

This emphasizes the importance of addressing access to specialized healthcare services like ERCP in rural settings, where late presentations and limited diagnostic facilities may contribute to the need for such interventions.

Choledocholithiasis accounted for the majority of ERCP indications (39.5%), followed by obstructive jaundice due to choledocholithiasis (27.9%), totaling 67.4% overall. Most of the other studies support the findings.[11,12] Especially in developing countries, these findings align with previous literature that cites biliary stone disease as the leading cause of ERCP.[13-16] Other notable indications in our study included post-ERCP stent management, benign biliary strictures, and malignancies such as cholangiocarcinoma and carcinoma of the pancreas. These results underscore the broad utility of ERCP in both diagnostic and therapeutic contexts. Ascaris lumbricoides is a widespread parasitic worm, with a higher prevalence in developing nations. It can migrate into the bile duct, leading to obstruction and presenting clinically as cholangitis or obstructive jaundice.[17] The standard treatment involves ERCP with removal of the worm(s) from the bile duct.[18] In our study, biliary ascariasis was also observed in 4.7% of patients, and we successfully managed the case using sphincterotomy followed by worm extraction with a basket.

Research has indicated that ERCP carries a higher risk of complications, which may reach as high as 15.7%, with a mortality rate of 0.7% in the general population.[19] The overall complication rate in this study was 26.7%. A meta-analysis study conducted by Kochar et al.[20] On 108 randomized controlled trials (RCT) involving 13296 patients reported an overall incidence of 9.7% for PEP (95% CI = 8.6–10.7%), with an increased incidence of 14.7% (95% CI = 11.8–17.7%) in the high-risk patients. In our study post-ERCP pancreatitis was the most frequent (11.6%), which is consistent with findings reported in most other studies,[21] followed by cholangitis, bleeding, and perforation. While this rate is slightly higher than some global averages, it may reflect the complexity of cases or the learning curve in resource-limited settings. The slightly elevated incidence of pancreatitis in our study may be explained by the fact that ERCP procedures were conducted in a teaching center involving trainees. Nonetheless, the majority (73.3%) of patients experienced no complications, indicating that ERCP remains a relatively safe procedure when performed under appropriate conditions. Although many risk factors related to the patient, endoscopist, and procedure have been identified concerning adverse events, there remains significant potential to discover additional ones.[22] Early recognition and prompt, timely management are crucial to improve outcomes and decrease the morbidity of ERCP complications.[5]

Hossain et al. studied at Dhaka Medical College and showed that stone extraction was successful during the initial ERCP in 65.06%.[8] In our study, complete stone extraction was achieved only in 36.6% of cases, while partial or failed extractions accounted for a combined 63.4%. This relatively modest complete success rate suggests potential areas for improvement in technique, equipment availability, or patient selection.

A study in Sri Lanka focusing on CBD stone extraction using ERCP reported an 82.7% success rate in CBD stone removal, with the majority of patients undergoing balloon extraction (98.1%),[15] Similar to that study, balloon sweep was the most commonly used extraction method, followed by Dormia basket and mechanical lithotripsy, reflecting standard practice for managing biliary stones.

Cannulation techniques varied, with wire-guided cannulation being the predominant method (66.3%). Precut techniques like others[23] and other advanced methods were employed in more challenging cases. Cannulation was successfully achieved within 10 minutes in 84.9% of cases, suggesting generally efficient endoscopic access.

The endoscopic appearance of the papilla and endoscope positioning was mostly unremarkable, though a small proportion showed abnormal or variant anatomy, which may have contributed to the complexity of the procedure. Interestingly, pancreatic duct cannulation occurred in about a third of patients, which may be an unintended consequence during biliary cannulation and could be associated with the incidence of post-ERCP pancreatitis. Although we did not use temporary pancreatic stenting to prevent ERCP-related pancreatitis.

In summary, the findings of this study reinforce the role of ERCP as a vital intervention for managing biliary and pancreatic diseases. While the procedure remains largely effective and safe, efforts to improve complete stone extraction rates and minimize complications are warranted. Further training, better equipment, and enhanced peri-procedural care, particularly in resource-limited and rural settings, may improve patient outcomes.

Conclusion:

Despite the limitation of being a single-center, retrospective study where a prospective design would have provided stronger evidence, our findings indicate that ERCP can be performed successfully with a high technical success rate. The overall complication rates were in line with those reported in existing literature. Therefore, ERCP appears to be an effective and viable procedure in our setting, demonstrating both satisfactory success rates and a manageable complication profile.

Conflicts of Interest: There is no conflict of interest.
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Referencess:

1. Kozarek RA. The past, present, and future of endoscopic retrograde cholangiopancreatography. *Gastroenterol Hepatol* (N Y). 2017 Oct;13(10):620–622.

2. Classen M, Safrany L. Endoscopic papillotomy and removal of gallstones. *Br Med J.* 1975 Nov 15;4(5993):371–374.

3. Hollerbach S. EUS and ERCP: brothers in arms. *Gastrointest Endosc.* 2008 Sep;68(3):467–469.

4. Dumot JA. ERCP: current uses and less-invasive options. *Cleve Clin J Med.* 2006 May;73(5):418, 421, 424-425.

5. Pal P, Ramchandani M. Management of ERCP complications. *Best Pract Res Clin Gastroenterol.* 2024 Mar 1;69:101897.

6. Jagtap N, Kumar JK, Chavan R, Basha J, Tandan M, Lakhtakia S, et al. EUS versus MRCP to perform ERCP in patients with an intermediate likelihood of choledocholithiasis: a randomized controlled trial. *Gut.* 2022 Feb 10;gutjnl-2021-325080.

7. Schwed AC, Boggs MM, Pham XBD, Watanabe DM, Bermudez MC, Kaji AH, et al. Association of Admission Laboratory Values and the Timing of Endoscopic Retrograde Cholangiopancreatography With Clinical Outcomes in Acute Cholangitis. *JAMA Surg.* 2016 Nov 1;151(11):1039–1045.

8. Hossain MI, Salimullah ASM, Hasan R, Podder S, Alam J, Datta R, et al. Outcome of the endoscopic biliary stenting for irretrievable common bile duct stones in an academic hospital – a prospective study. *Eur J Med Health Sci.* 2023 Sep 12;5(5):7–12.

9. Ahmed EU, Paul B, Datta B, Mohsin MN, Ali Haider SM. ERCP in a tertiary care hospital of south-eastern Bangladesh: a clinical audit. *JCMCTA.* 2020;31(2):14–18

10. Anwar M, Hayat MK, Ahmad Z, Iftikhar M, Khan MAA. Endoscopic retrograde cholangiopancreatography (ERCP) profile of a tertiary care hospital in Peshawar: indications, procedures, and complications. *J Rehman Med Inst.* 2020 Jun 10;6.

11. Qureshi LA, Alzanbagi A, Tashkandi A, Khan MS, Malik ZM, Hefny ME, et al. Retrospective analysis of characteristics, indications and outcomes of endoscopic retrograde cholangiopancreatography (ERCP) in a tertiary referral center in Saudi Arabia. *Cureus* [Internet]. 2023 Mar 28 [cited 2025 Apr 5]; Available from: https://www.cureus.com/articles/85472-retrospective-analysis-of-characteristics-indications-and-outcomes-of-endoscopic-retrograde-cholangiopancreatography-ercp-in-a-tertiary-referral-center-in-saudi-arabia

12. Polat YH, Yozgat A. A retrospective analysis of 500 ERCP procedures: outcomes, adverse events, and risk factors over two years. *J Med Palliat Care.* 2024 Jul 12;5(6):309–313.

13. Panda CR, Das HS, Behera SK, Nath P. Retrospective analysis of endoscopic retrograde cholangiopancreatography (ERCP) procedures in a tertiary care centre in coastal Odisha. *Int J Res Med Sci.* 2017 Sep 28;5(10):4281–4284

14. Shah D, Mahey R, Dharap S, Chilbule P, Deka H. A retrospective analysis of the outcome of endoscopic management in choledocholithiasis in a tertiary care centre. *Int Surg J.* 2022 Apr 26;9(5):1006–1011.

15. Gobishangar S, Charles JC, Shathana P. Endoscopic retrograde cholangiopancreatography: a single tertiary care centre experience from northern Sri Lanka. *Jaffna Med J.* 2024 Jul 26;36(1):38–44.

16. Muslim OT, Dakhil AS, Abdlmajed MA. Endoscopic retrograde cholangiopancreatography in central Iraq: a retrospective single-center study. *Res J Pharm Technol.* 2020 Jun 23;13(6):2681–2684.

17. Bosunia ZH, Foez SA, Akter A, Khanum MJA, Sutradhar P, Mobin AQM. Endoscopic retrograde cholangiopancreatography (ERCP) experience in a tertiary level hospital in the northern division of Bangladesh. *J Med Sci.* 2019 Jul 29;5(4):122–125.

18. Dal NA, Memon MA, Memon SK, Brohi S, Jabeen H, Saim M. Limitations and success ratio of ERCP in the treatment of obstructive jaundice. *Pak J Med Health Sci.* 2023 Apr 19;17(02):790–790.

19. Salama HZ, Alnajjar YA, Owais TA, Jobran AWM, Safi R, Bahar M, et al. Endoscopic retrograde cholangiopancreatography utilization and outcomes in the first advanced endoscopy centre in Palestine at Al-Ahli Hospital: a retrospective cohort study. *BMJ Open* [Internet]. 2023 Dec 1 [cited 2025 Apr 13];13(12):e077806. Available from: https://bmjopen.bmj.com/content/13/12/e077806

20. Kochar B, Akshintala VS, Afghani E, Elmunzer BJ, Kim KJ, Lennon AM, et al. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. *Gastrointest Endosc.* 2015 Jan 1;81(1):143-9.e9.

21. Joseph D, Muraleedharanpillai R, Kolassery S, Sebastian S, MR, Joseph D, et al. Clinical profiles and outcomes of patients undergoing endoscopic retrograde cholangiopancreatography in a tertiary care center. *Cureus* [Internet]. 2024 Feb 27 [cited 2025 Apr 6];16(2):e44275. Available from:https://www.cureus.com/articles/225262-clinical-profiles-and-outcomes-of-patients-undergoing-endoscopic-retrograde-cholangiopancreatography-in-a-tertiary-care-center

22. Forbes N, Koury HF, Bass S, Cole M, Mohamed R, Turbide C, et al. Characteristics and outcomes of ERCP at a Canadian tertiary centre: initial results from a prospective high-fidelity biliary endoscopy registry. *J Can Assoc Gastroenterol.* 2021 Apr 1;4(2):78–83.

23. Siiki A, Tamminen A, Tomminen T, Kuusanmäki P. ERCP procedures in a Finnish community hospital: a retrospective analysis of 1207 cases. *Scand J Surg.* 2012 Mar 1;101(1):45–50.

Original Article

Spleen Stiffness as A Predictor of Esophageal Varices in Patients with Cirrhosis of Liver

H Sultana[1], H Aftab[2], MU Rahman[3], W Mahbub[4]

Abstract

Background: Current guidelines recommend upper GI endoscopy for detection of esophageal varices (EV) in patients with cirrhosis. Upper GI endoscopy is invasive, so several non-invasive methods for detecting varices were proposed. This study evaluates if spleen stiffness measurement (SSM) by vibration controlled transient elastography (VCTE) using FibroScan can be used as a viable predictor of EV.

Materials and Methods: This study was carried out to evaluate the utility of spleen stiffness measurement in detecting the presence of esophageal varices. Study included 100 patients with cirrhosis attending the inpatient and outpatient department of Gastroenterology of Dhaka Medical College Hospital. All patients underwent liver stiffness and spleen stiffness measurements by VCTE and upper GI endoscopy. According to the endoscopic findings, they were divided into no varix, low-risk varices, and high-risk varices groups. Diagnostic performance of the spleen stiffness cutoff for the cirrhotic population obtained from the ROC curve was evaluated in terms of sensitivity, specificity, positive predictive value, negative predictive value and accuracy in detecting high-risk EV.

Results: Of the 100 cirrhosis patients, 76 (76%) had EV (low risk varices=34, high risk varices=42). There was a significant difference ($p < 0.05$) in mean spleen diameter, spleen stiffness measurement, and liver stiffness measurement among the no varix, low-risk varices, and high-risk varices groups. A tendency towards increasing spleen stiffness levels was observed with increasing severity of varices (25.87±10.48 kPa in no varix, 46.58±14.03 kPa in low-risk varices, and 77.29±17.59 kPa in high-risk varices). Spleen stiffness cutoff 46.7 kPa has 95.2% sentivety, Sp 81% specificty, 87% accuracy, 78.4% PPV and 95.91% NPV in predicting high-risk varices.

Conclusion: The study result suggests that spleen stiffness is significantly correlated with the presence and severity of esophageal varices. Spleen stiffness measured using VCTE can be useful in diagnosing high-risk varices in patients with cirrhosis.

Keywords: Vibration-controlled transient elastography, Cirrhosis of the liver, Esophageal varices, Spleen stiffness, Liver stiffness.

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Introduction:

Liver cirrhosis, the advanced stage of most chronic liver diseases, affects nearly a billion people worldwide and results in approximately 2 million deaths annually, accounting for 3.5% of all global deaths.[1] Portal hypertension and esophageal varices, which occur in about 40–60% of cases, are two major consequences of the disease course of cirrhosis.[2] Once esophageal varices have developed, the incidence of variceal bleeding is 35%, and mortality is as high as 10-20%.[3]

According to current guidelines, screening endoscopy should be performed on all cirrhotic patients at the time of diagnosis in order to identify those who have varices.[3] After that, patients should have screening endoscopies every two to three years if they have compensated disease and no varices, every 1-2 years if they have small varices, and every year if they have decompensated disease, with or without varices. Upper GI endoscopy is considered the gold standard against which all other tests are compared.[4] Studies have shown that the annual incidence of EV is only 7%, EV incidence is 21% over a 5-year period, and 50% of patients do not acquire esophageal varices 10 years following diagnosis of cirrhosis.[5,6] So, repetitive negative endoscopies would increase the costs of care of newly diagnosed cirrhotic patients. Though endoscopy is generally a safe procedure, it can be unpleasant for patients; there are risks related to conscious sedation, and it is relatively resource-intensive. It might not be economical or convenient to have screening endoscopies on every cirrhosis patient. Instead, identifying high-risk individuals using easily obtainable clinical factors could allow for more cost-effective screening.

Splenomegaly is 60–65% prevalent in patients with liver cirrhosis and portal hypertension.[7] It is typically caused by blood congestion, elevated portal pressure, increased resistance to splenic vein outflow, and increased angiogenesis and fibrogenesis.[8] Using transient elastography (TE), these alterations in fibrogenesis or spleen stiffness can be measured. Non-invasive methods that quantify SSM to detect EVs and their risk of bleeding are gaining more interest lately.[9] Fibroscan evaluates tissue stiffness using the vibration-controlled transient elastography

(VBTE) principle. According to several studies, TE was also connected with the severity of PH and the existence of esophageal varices.[10] It was utilized in chronic liver disorders and demonstrated to accurately predict liver fibrosis in a range of clinical circumstances.[11] Recently, FibroScan started to be used for the assessment of spleen stiffness in cirrhotic patients. Because spleen stiffness better represents splanchnic flow than liver stiffness, previous investigations using transient elastography have revealed that spleen stiffness has good diagnostic accuracy in predicting portal hypertension and esophageal varices. This study was designed to investigate the efficacy of spleen stiffness, as determined by TE, in predicting the presence and size of esophageal varices in patients with cirrhosis of the liver.

Materials and Methods:

This descriptive cross-sectional study included a total of 150 patients (aged >18 years) with cirrhosis from the Gastroenterology department of Dhaka Medical College Hospital between November 2022 to March 2024. The diagnosis of cirrhosis was made based on clinical, biochemical, and imaging (ultrasound) evidence. Patients were excluded from the study if they have moderate to severe ascites, history of treatments for portal hypertension (β-blocker therapy, or endoscopic therapies, splenectomy, partial splenic embolization, trans-jugular intrahepatic portosystemic shunt, balloon-occluded retrograde transvenous obliteration), acute/ chronic liver failure, HCC/SOL in liver, active gastrointestinal bleeding, portal vein thrombosis, biliary obstruction and acute cholangitis, other end organ failure i.e., renal, cardiac or respiratory failure or not willing to be included in the study. Among the 150 patients, 50 were excluded. All patients underwent TE for measurement of liver stiffness and spleen stiffness, and upper GI endoscopy for evaluation of esophageal varices. Routine biochemical parameters were also recorded for every patient, which included hemoglobin, platelet count, INR, ALT, albumin, bilirubin, serum creatinine, and relevant workup for evaluation of the cause of CLD. All patients also underwent an ultrasonogram, and spleen and liver sizes were recorded. Informed written consent was taken from all patients. The study was approved by the ethical review committee of Dhaka Medical College.

Vibration-controlled transient elastography (VCTE) was performed on each patient, after at least 3 hours of fasting, using FibroScan 630 Xpert. After the liver was localized in each patient and the probe positioned correctly, at least 10 valid measurements on the same spot were taken. LSM>12.5 kPa was marked as cirrhosis. After the spleen was localized in each patient and the probe positioned correctly, at least 10 valid measurements on the same spot were taken for spleen stiffness measurement.

Esophageal varices were evaluated for each patient, using upper gastrointestinal endoscopy, and were classified into three groups, according to the expanded Baveno VI criteria.[12] Group 1 included patients with no esophageal varices, Group 2 patients with low risk esophageal varices (varices that had a thickness of less than 5 mm) and Group 3 patients with high risk varices needing treatment (VNT- either large esophageal varices that had a thickness of more than 5 mm or varices displaying any signs of a high risk of bleeding: red wales, cherry red spots).

All the data collected were analyzed and correlated. Statistical analysis was performed by using the Statistical Package for Social Sciences (SPSS, version 25). Descriptive analysis was performed on participants' socio-demographic characteristics. The Kruskal-Wallis test was used to analyze the clinical characteristics of the study population with cirrhosis. The correlation between endoscopic findings and SSM values were obtained using Kruskal Wallis test. Variables were considered statistically significant if $p < 0.05$. To evaluate the diagnostic efficiency SSM for the detection of EV, an analysis of the area under the ROC curve (AUROC) was performed. The value of the highest point of the Youden index was taken as the cut-off point. The diagnostic efficiency of this cut-off value of SSM for the detection of large EV was calculated using the comparative analysis and ROC curve.

Results:

This study included a total of 100 patients, out of which 67 were male and 33 were female. Mean BMI was 20.55 ±3.34 kg/m2. Most of the people (n=46) are middle-aged (40- 59 years) (Table 1).

Table 1. Distribution of patients according to socio-demographic characteristics (n=100)

Variables	Number of Patients (Percentage)
Sex	
Male	67 (67)
Female	33 (33)
Age (years) Mean±SD:	48.22±12.23
18-39	32 (32)
40-59	46 (46)
>60	22 (22)
BMI (kg/m ^{2}) Mean±SD:	**20.55±3.34**
<18.1	4 (4)
18.5 -23	54 (54)
23-27.5	38 (38)
>27.5	4 (4)
Place of living	
Rural	54 (54)
Urban	46 (46)

The etiologies of cirrhosis were hepatitis B (59 patients), NAFLD (11patients), hepatitis C (10 patients), autoimmune (1 patient), alcohol (1 patient) and cryptogenic (18 patients) (Figure 1).

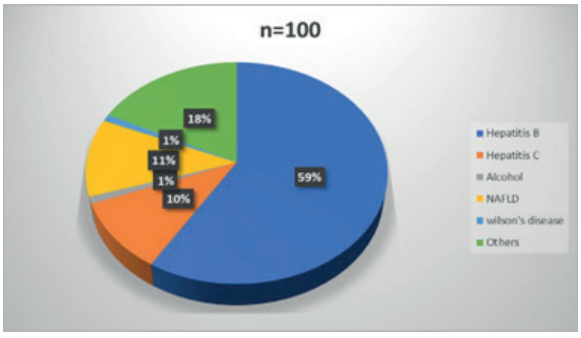

Figure 1: Distribution of patients according to etiology of cirrhosis (n=100)

Univariate analysis identified several factors that were associated with the size of varices, including hemoglobin, platelet count, SGPT, serum albumin, INR, Spleen size, liver stiffness, and spleen stiffness ($p<0.05$). Higher values of spleen stiffness, spleen size, and lower values of serum albumin and platelet counts were observed in the high-risk varices group, as listed in Table 2.

Table 2: Distribution of patients according to clinical and biochemical characteristics (n=100)

Variable	Esophageal varices			*p* value
	No varix (n=24)	Low risk varices (n=34)	High risk varices (n=42)	
Hemoglobin (g/dl)	11.75±2.07	11.37±1.99	10.23±1.86	.008[s]
Platelet($\times10^3$/mm^3)	207.71±87.96	151.03±75.12	109.51±65.52	.000[s]
SGPT(IU/ml)	73.11±46.20	57.63±36.55	50.57±36.22	.048[s]
Bilirubin (mg/dl)	1.35±1.36	1.28±0.93	1.93±3.41	.392
Albumin (g/dl)	3.68±0.78	3.20±0.64	3.10±0.56	.003[s]
INR	1.09±0.13	1.34±0.31	1.31±0.31	.000[s]
Creatinine (mg/dl)	1.00±0.26	1.07±0.35	0.95±0.21	.611
Spleen size (cm)	10.37±2.26	12.52±2.13	13.54±2.41	.000[s]
Liver Stiffness	26.23±18.20	44.93±20.34	41.362±21.17	.001[s]
Spleen Stiffness	25.87±10.48	46.58±14.03	77.29±17.59	.000[s]

There was a stepwise increase in spleen stiffness values with increased risk of varices among the study population with cirrhosis. The population with low-risk varices had higher SSM than those with no varices (46.58±14.034 vs 25.87±10.48), while those with high-risk varices had an even higher SSM than those with low-risk varices (77.29±17.59 vs 46.58±14.034) (Figure 2). This difference of SSM among the no varices, low risk varices, and high risk varices groups was significant ($p<.05$) (Table 2).

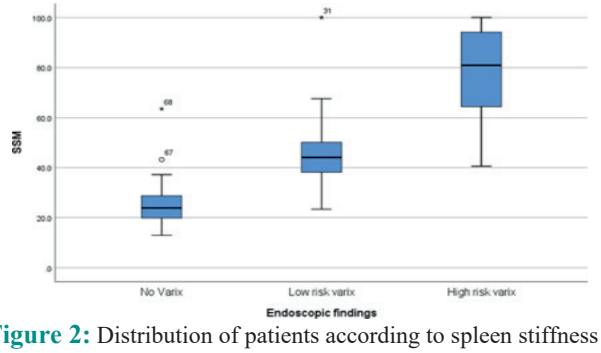

Figure 2: Distribution of patients according to spleen stiffness esophageal variceal status (n=100).

Our study showed that SS measured using VCTE is a good method of predicting high-risk esophageal varices (AUROC = 0.942, CI 95%:.898-.987). A spleen stiffness cut-off value of 46.7 kPa using the highest Youden index could exclude EV with 95.2% sensitivity and 81% specificity. Positive predictive value was 78.4% and negative predictive value was 95.91% with an accuracy of 81% (Figure 3 and Table 3).

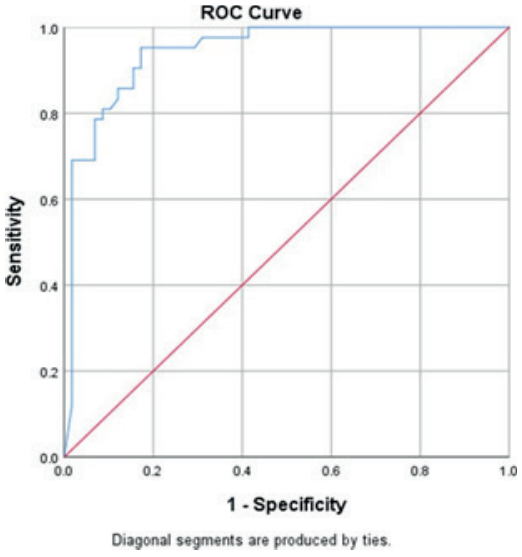

Figure 3: Area under the receiver operating curve (AUROC) analyses spleen stiffness in predicting the presence of high-risk esophageal varices.

Table 3: Cut of value, Sensitivity, specificity, and AUC from ROC curve by spleen stiffness for predicting high-risk varices in the study population with cirrhosis

	AUC	Cutoff value (kPa)	Sensitivity (%)	Specificity (%)	*p* value	95% CI
Spleen stiffness	.942	46.7	95.2	82.8	.000[s]	.898-.987

Discussion:

Multiple observations of our study were significant, and many of them matched with the previous studies published in the literature. One hundred patients with cirrhosis of the liver underwent transient elastography for measurement of liver and spleen stiffness. The study populations with cirrhosis were further divided into three groups according to their upper GI endoscopy findings: No varix group (n=24), low risk varix group (n=34), and high risk varix (n=42) group. Among the study population, 67 (67%) were male and 33 (33%) were female. Most of the people (n=46) were middle-aged (40-59 years). Most of the patient (54%) had a BMI within 18.5-23 kg/m2. Mean BMI was 20.55 ±3.34 kg/m2. Gomes and Ali., conducted a study on the Bangladeshi population where 100 patients with cirrhosis were included.[13] Socio-demographical characteristics of cirrhotic patients were consistent with this study. Most of the study population in this study suffered from Hepatitis B (59%), 11% of participants suffered from NAFLD, and 10% suffered from Hepatitis C. Total 18% of participants did not have hepatitis B, hepatitis C, NAFLD, or alcoholic related liver cirrhosis. Al Mahtab et al., also found that Hepatitis B virus was the most common cause (53.2%) of cirrhosis, followed by NASH in 18.8% and cryptogenic (16.7%) patients in their study.[14] Most of the study population with cirrhosis were CTP class A (80%), and 20% were CTP class B, and none were CTP class C. This was due to the exclusion criteria of our study, which excluded all patients with

moderate to severe ascites. Regarding the clinical characteristics of the study population with cirrhosis, significant differences were observed in spleen size, liver stiffness, and spleen stiffness measurement values among the no varix, low-risk varices, and high-risk varices groups ($p< .05$). These findings align with a study conducted by Fierbinteanu-Braticevici in 2019.[15] Similarly, in a study by Wang et al., in LSM and SSM values differed significantly between the no varices, moderate esophageal varices, severe esophageal varices, and esophageal variceal bleeding groups.[16] Furthermore, Sharma et al., also found significant differences in spleen diameter, LSM, and SSM values between the no esophageal varices and esophageal varices groups.[17]

There was a stepwise increase in spleen stiffness values with increased risk of varices among the study population with cirrhosis. The population with low-risk varices had higher SSM than those with no varices (46.58±14.034 kPa vs 25.87±10.48 kPa), while those with high-risk varices had an even higher SSM than those with low-risk varices (77.29±17.59 kPa vs 46.58±14.034 kPa). This pattern of increasing SSM with increased risk of varices is also observed in studies conducted by Wang et al[16], Fierbinteanu-Braticevici et al[15] and Sharma et al[17] This difference of SSM among the no varices, low risk varices and high-risk varices group was significant ($p<.05$).

Several studies have evaluated SSM measured by transient elastography as a non-invasive method of predicting esophageal varices. Like our study, Sharma et al., 2013 found that a SSM cutoff of 40.8 kPa with AUROC 0.898 had 94% sensitivity and 76% specificity.[17] The study of Anta et al., 2018 had an AUROC curve of 0.8 for a cut-off value of 48 kPa, with 87% sensitivity and 69% specificity.[18]

Our study showed that SS measured using VCTE is a good method of predicting high-risk esophageal varices (AUROC = 0.942, CI 95%:.898-.987). A spleen stiffness cut-off value of 46.7 kPa using the highest Youden index could exclude EV with 95.2% sensitivity and 81% specificity. In this study, the diagnostic performance of SSM was evaluated, revealing a sensitivity of 95.2%, specificity of 81%, and accuracy of 87%. These findings suggest that SSM has high sensitivity (95.2%) in correctly identifying positive cases of high-risk varices. The specificity of 81% indicates that the SSM has a moderately high ability to correctly identify individuals without the high-risk varices. The overall accuracy of 87% suggests that SSM has a high level of accuracy in diagnosing high-risk varices. In this study, positive predictive value was 78.4% and negative predictive value was 95.91%. Overall, these results indicate that SSM has shown satisfactory results in diagnosing high-risk varices, with reasonably good sensitivity and negative predictive value. Our result was almost similar to previous studies conducted to find the diagnostic efficacy of SSM in detecting varices. Rizzo et al. reported sensitivity of SSM in detecting high-risk varices to be 96.4%, specificity 88.5%, positive predictive value 90%, and negative predictive value to be 96%.[19]

Conclusion:

In conclusion, this study evaluated the role of SSM in predicting esophageal varices in cirrhotic patients. Here SSM has shown satisfactory result in predicting presence of esophageal varices, demonstrating reasonably acceptable sensitivity (95.2%), negative predictive value (95.91%) and accuracy (87%), along with moderate specificity (81%) and positive predictive value (78.4%) in detecting high risk varices. However, this study was a single-center study with a small sample size, which may limit the generalizability of the findings to other populations or different healthcare settings. Further study with a large sample size from multiple centers is recommended.

Conflicts of Interest: There is no conflict of interest.

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Referencess:

1. Marcellin P, Kutala BK. Liver diseases: A major, neglected global public health problem requiring urgent actions and large-scale screening. *Liver Int.* 2018;38(2):2-6.
2. Bosch J, Abraldes JG, Groszmann R. Current management of portal hypertension. *J Hepatol.* 2003;38(1):54-68.
3. De Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop. *J Hepatol.* 2010;53(4):762-8.
4. Rye K, Scott R, Mortimore G, Lawson A, Austin A, Freeman J. Towards noninvasive detection of oesophageal varices. *Int J Hepatol.* 2012;2012:343591.
5. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol.* 2006;44(1):217-2131.
6. D'Amico G, Pasta L, Madonia S, Tarantino IG, Mancuso A, Malizia G, Giannuoli GC, Pagliaro L. The incidence of esophageal varices in cirrhosis. *Gastroenterology.* 2001;120(5 Suppl 1):A2.
7. Gibson PR, Gibson RN, Ditchfield MR, Donlan JD. Splenomegaly—an insensitive sign of portal hypertension. *Aust NZ J Med.* 1990;20(6):771- 774.
8. Bolognesi M, Merkel C, Sacerdoti D, Nava V, Gatta A. Role of spleen enlargement in cirrhosis with portal hypertension. *Dig Liver Dis.* 2002;34(2):144-150.
9. Kim HY, Jin EH, Kim W, Lee JY, Woo H, Oh S, Seo JY, Oh HS, Chung KH, Jung YJ, Kim D. The role of spleen stiffness in determining the severity and bleeding risk of esophageal varices in cirrhotic patients. *Medicine (Baltimore).* 2015;94(24):e1031.
10. Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, Petrarca A, Moscarella S, Belli G, Zignego AL, Marra F. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology.* 2007;45(5):1290-1297.
11. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, Christidis C, Ziol M, Poulet B, Kazemi F, Beaugrand M. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol.* 2003;29(12):1705- 1713.
12. Augustin S, Pons M, Maurice JB, Bureau C, Stefanescu H, Ney M, Blasco H, Procopet B, Tsochatzis E, Westbrook RH, Bosch J. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. *Hepatology.* 2017;66(6):1980-1988.
13. Gomes RR, Ali MA. Evaluation of association of demographic profiles and sero prevalence of HBV and HCV among the patients presenting with chronic liver disease and its complications: A Tertiary Care Hospital Based Study. *Open J Hepatol.* 2020;2(1):1-5.
14. Al Mahtab M, Alam SM, Rahim MA, Alam MA, Khondaker FA, Moben AL, Mohsena M, Akbar SM. Hepatic venous pressure gradient measurement in Bangladeshi Cirrhotic patients: A correlation with Child's status, variceal size, and bleeding. *Euroasian J Hepato-Gastroenterol.* 2017;7(2):142-145.
15. Fierbinteanu-Braticevici C, Tribus L, Peagu R, Petrisor A, Baicus C, Cretoiu D, Pasternak A, Oprea G, Purcareanu A, Moldoveanu AC. Spleen stiffness as predictor of esophageal varices in cirrhosis of different etiologies. *Sci Rep.* 2019;9(1):16190.
16. Wang H, Wen B, Chang X, Wu Q, Wen W, Zhou F, Guo Y, Ji Y, Gu Y, Lai Q, He Q. Baveno VI criteria and spleen stiffness measurement rule out high-risk varices in virally suppressed HBV-related cirrhosis. *J Hepatol.* 2021;74(3):584-592.
17. Sharma P, Kirnake V, Tyagi P, Bansal N, Singla V, Kumar A, Arora A. Spleen stiffness in patients with cirrhosis in predicting esophageal varices. Am *J Gastroenterol.* 2013;108(7):1101-1107.
18. Anta JA, González MG, Guerrero MT, Gómez EG, de Santiago ER, Durán SL, de la Fuente CZ, León VB, Gismero FM, de Argila CM, Martínez AA. Prediction of the presence of esophageal varices using spleen stiffness measurement by transient elastography in cirrhotic patients. *Acta Gastroenterol Belg.* 2018;81(4):496-502.
19. Rizzo L, Attanasio M, Pinzone MR, Berretta M, Malaguarnera M, Morra A, L′ Abbate L, Balestreri L, Nunnari G, and Cacopardo B. 2014. A new sampling method for spleen stiffness measurement based on quantitative acoustic radiation force impulse elastography for noninvasive assessment of esophageal varices in newly diagnosed HCV- related cirrhosis. *Biomed Res Int.* 2014;2014:365982.

Original Article

Gastrointestinal and Other Atypical Presentations of Dengue Fever: A Multicenter Study in the Northern Region of Bangladesh

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Abstract

Background: Dengue is a global problem, but has a greater impact on developing and tropical countries. Dengue is surging due to increasing Aedes mosquitoes in overcrowded areas. Atypical presentations of dengue are a challenge during management. That's why we intended to determine the pattern, prevalence, and outcome of gastrointestinal and other atypical presentations of dengue fever during the 2023 epidemic in Bangladesh.

Materials and Methods: This was a multicenter hospital-based cross-sectional study held in two tertiary medical college hospitals in the northern part of Bangladesh: Rangpur Medical College Hospital and Dinajpur Medical College Hospital. All the patients who were admitted with laboratory-confirmed dengue cases from June 2023 to October 2023 were included in this study.

Results: Out of a total of 160 patients, majority were between 21-40 years of age (57%), and the predominant study subjects were male, 120 (75%). We found that 73 (45.6%) patients presented with gastrointestinal and atypical manifestations, while rest 87 (54.4%) patients had only classical presentation. The atypical manifestations are acute watery diarrhea (17.5%), acute acalculus cholecystitis (8.1%), ascites (4.4%), acute hepatitis (3.1%), pleural effusion (2.5%), pneumonia (2.5%), acute pancreatitis (1.3%), GIT bleeding (1.3%), Encephalitis (1.3%), meningitis and myocarditis.

Conclusions: Looking for these atypical features of dengue fever at least during the outbreak season of dengue may save health resources and many valuable lives.

Key words: Dengue fever, Outbreak, Gastrointestinal manifestations

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Introduction:

Dengue fever (DF) is a vector-borne disease, transmitted by various species of female Aedes mosquitoes. Amazingly, Bangladesh has achieved tremendous success in controlling communicable diseases at present. But, it is also true that we are passing a decade of up surging dengue and other vector-borne diseases like Chikungunya and Zika virus. In South East Asia, particularly in Bangladesh, this emerging disease causes a huge social and financial burden, as well as cuts the ongoing health budget.[1] Earlier this year, WHO mentioned dengue fever as a potential threat among ten diseases for 2019, and recent outbreaks in many countries confirm this observation. The WHO on 2008 proposed a new classification of DF. This revised classification divides dengue into three types: 1) Dengue without warning signs (D-W), 2) Dengue with warning signs (D+W), and 3) Severe dengue fever.[2,3] Classically, dengue cases presented as either asymptomatic or fever, body aches, and malaise, like other viral illnesses. But about one-third of cases may develop severe complications such as dengue hemorrhagic fever and dengue shock syndrome. However, it may present with the involvement of other systems such as gastrointestinal, neurological, renal, respiratory, cardiac, or other systems. [4,5] Dengue clinical features vary in presentation and extension of disease according to age, geography, the season of an epidemic, and host factors. In the few recent outbreaks, it was observed that new and atypical features are increasing.[6] So, global awareness regarding the atypical manifestation of dengue fever is a burning issue for early diagnosis and adequate management, as well as to prevent unwanted death. This study aimed to determine the pattern, prevalence, and outcome of gastrointestinal (GI) and other atypical presentations of dengue fever during the 2023 epidemic in Bangladesh to enrich our current management strategy.

Materials and Methods:

This was a descriptive type of cross-sectional study held in two tertiary-level Medical College Hospitals, Rangpur Medical College Hospital and Dinajpur Medical College Hospital, located in the northern part of Bangladesh.

All the patients who were admitted with laboratory-confirmed dengue cases from June 2023 to October 2023 were included in this study. Dengue patients with pregnancy, bleeding disorders, viral hepatitis, malaria, and leptospirosis were excluded from the study to maintain uniformity. After taking a detailed history and clinical examination by a respective physician or focal persons few investigations were given to patients. Complete blood count, RBS, Serum creatinine, Liver function test- serum bilirubin, ALT, AST, alkaline phosphatase were done for all patients. Ultrasound of the Abdomen was done for patients who presented with abdominal pain. Chest X-Ray and ECG were done for patients who complained of chest pain or dyspnea. CSF examination, CT scan/MRI of the brain was done for patients who presented with altered consciousness or focal neurological deficits.

All patients were reviewed and assessed daily for any new changes till discharge from the hospital. Data were collected using a self-structured and pretested questionnaire containing demographic variables, investigations, clinical manifestations, complications, and mortality. We included symptoms of DF as follows: 1) General symptoms; 2) Gastrointestinal symptoms; 3) Respiratory; 4) Cardiovascular; 5) Neurological; 6) Renal symptoms; and 7) Severe features. Data were analyzed by statistical software SPSS Version 15.0 (IBM Corp., Armonk, NY, USA). Statistical analyses were performed to determine: 1) the Frequency of different typical, gastrointestinal, and other atypical features of Dengue fever; 2) the Association of age and sex with atypical features; and 3) the Association of atypical features and hospital outcomes of admitted patients. All continuous variables were analyzed using Student's t-test, and categorical variables using the Chi-square test. P-values of < 0.05 were considered as significant. Ethical permission was taken from the respective authority of both Medical College hospitals.

Results:

In this multicenter study, 97 patients were from Rangpur Medical College Hospital, and the remaining 63 were from Dinajpur Medical College Hospital (Figure 1). Out of a total of 160 patients, majority of the patients were between 21-40 years of age (57%), and the predominant study subjects were male, 120 (75%).

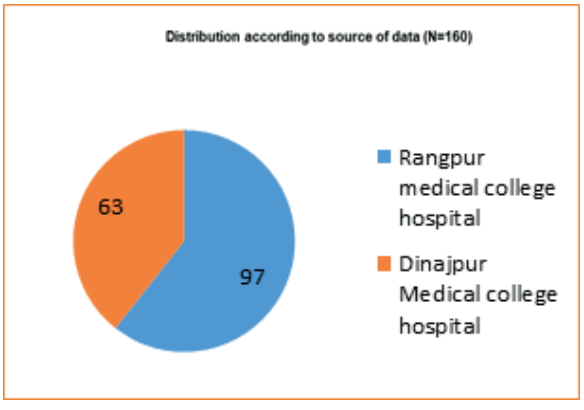

Figure 1: Distribution of the study subjects according to source of data (N=160)

Almost all patients had fever, and the majority of them experienced general symptoms. However, a good number of people also suffered from less common and easily overlooked symptoms that are not usual in dengue. Among GI symptoms, 33.1% had abdominal pain, 23.8% had diarrhea, and 08% from GIT bleeding. Moreover, 14.4% and 13.1 % had chest pain and cough, respectively. Only 04 % suffered from renal symptoms, and 20% of patients had severe features like spontaneous bleeding and shock. Figure 2 depicts the frequency of symptoms of the study subjects.

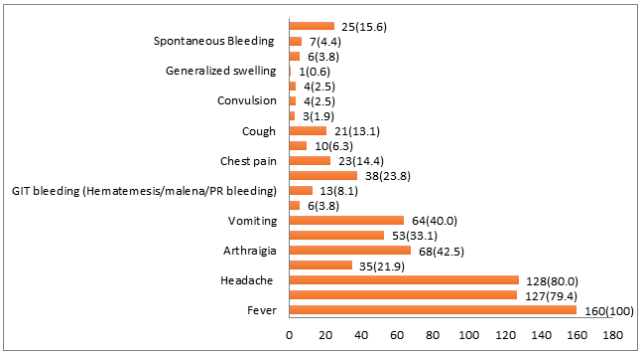

Figure 2: Distribution of patients according to clinical features (n=160)

In this epidemic, we noticed that more than half of the patients, 84 (52.5%) patients, have leucopenia, and 130 (81 %) patients have low platelet count. Among abnormal ultrasound reports of 21 patients (13.13%), 13 (8.12%) had acalculous cholecystitis, 07(4.37%) had ascites, and 01 patient (0.62%) had hepatomegaly. Only 04 (2.5%) patients showed pleural effusion on chest X-Ray reports. (Table-1)

Table 1: Distribution of patients according to investigation reports (n=160)

Investigation reports	Frequency (%)
Biochemical Reports	
ALT (elevated)	38 (23.8)
AST (elevated)	12 (7.5)
Blood urea (elevated)	8 (5.0)
S. Creatinine (elevated)	15 (9.4)
Electrolyte imbalance	15 (9.4)
Ultrasonogram of abdomen	
Normal	139 (86.87)
Acalculous cholecystitis	13 (8.1)
Hepatomegaly	1 (0.62)
Ascites	7 (4.37)
Chest X-Ray findings	
Normal	154 (96.3)
Pleural effusion	4 (2.5)
Not done	2 (1.3)

So, finally out of 160 dengue cases 73(45.60%) patients were presented with atypical manifestation and among them 45(61.64%) patients had severe dengue features. Figure-3 shows the frequency of typical and all atypical manifestations among the study subjects. Table 2 depicts the details of gastrointestinal and atypical manifestations of study populations.

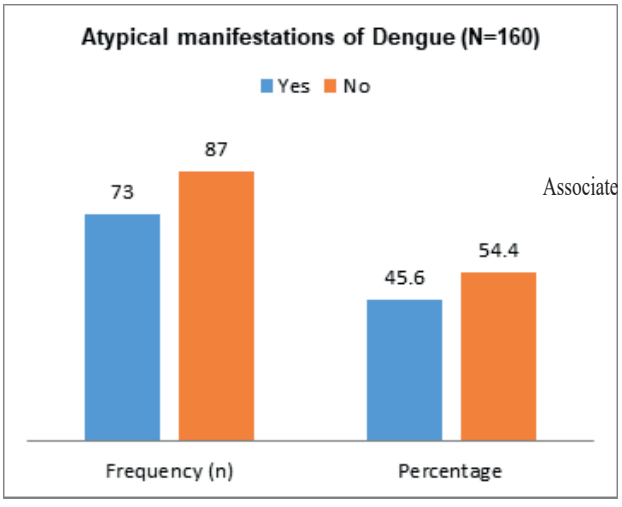

Figure 3: Distribution of patients according to frequency of typical and atypical manifestations (n=160).

Table 2: Distribution of patients according to gastrointestinal and other atypical manifestations (n=160)

Manifestations	Frequency (%)
Gastrointestinal	
Acute acalculous cholecystitis	13(8.1)
Acute diarrhea	28(17.5)
Acute hepatitis	5(3.1)
Ascites	7(4.4)
Acute pancreatitis	2(1.3)
GIT bleeding	2(1.3)
Respiratory	
Pleural effusion	4(2.5)
Pneumonitis	4(2.5)
Neurological	
Encephalitis	2(1.3)
Meningitis	1(0.6)
Transverse myelitis	1(0.6)
Myocarditis	1(0.6)
Severe manifestations	
DHF	20(12.5)
DSS	21(13.1)
DIC	3(1.9)
Sepsis	1(0.6)

Associate Professor,

In this study, 152 (95%) of those admitted patients were managed conservatively and 04 (2.5%) patients needed ICU support, and 04 patients needed medical intervention like dialysis. While 158 (98.8%) patients were cured completely and only 02 (1.2%) of them died during hospital admission.

Table 3: Association of Gastrointestinal and other atypical manifestations of Dengue with age and Gender (n=160)

Age	GI and other atypical manifestations		Total(160)	*p-value
	Yes	No		
<20	22 (51.1)	21 (49.1)	43 (26.9)	0.297
20 - 40	45 (47.36)	50 (53.64)	95 (59.4)	
41 - 60	5 (26.8)	14 (73.2)	19 (11.9)	
60 - 80	1 (33.33)	2 (66.66)	3 (1.9)	
Gender	**GI and other atypical manifestations**		**Total(160)**	**p-value**
	Yes	**No**		
Male	58 (48.33)	62 (52.66)	120 (75.0)	0.234
Female	15 (37.5)	25 (53.5)	40 (25.0)	

***Chi-square test was done to see the level of significance (p≤0.05).**

There was no significant association found between atypical manifestations with age and gender in our study (Table. 3). The same results were also depicted regarding the association with the outcome of dengue patients in both places (Table 4).

Table 4: Association of Gastrointestinal and other atypical manifestations of Dengue with outcome (n=160)

Outcome	GI and other Atypical manifestations		Total(160)	*p-value
	Yes	No		
Cured	71 (44.3)	87 (55.7)	158 (98.8)	0.207
Died	2 (100)	0 (0.0)	2 (1.2)	

***Chi- square test was done to see the level of significance (p≤0.05).**

Discussions:

Dengue fever has been reported from all regions of the world, including Africa, Southeast Asia, the Eastern Mediterranean, the Western Pacific, and the Americas.7 Dengue is a communicable disease like tuberculosis and malaria that is also increasing day by day, especially in developing countries. Its endemic area and epidemic seasons are also changing. The pattern of presentation and age group is also different from previous reports.8 All these changes made the diagnosis of dengue a notorious challenge, especially in the early periods of the disease. Delayed diagnosis is the cause of delayed lifesaving interventions and more loss of life. In this multicenter hospital-based study, we studied 160 dengue-infected patients admitted to both medical college hospitals within our study period. In this study, males were predominantly affected (75%), and nearly half (48.33%) of them presented with GI and other atypical manifestations. This study is very similar to a study conducted by Antony et al. conducted in India in 2014.8 Another study by Perez R et al. also shows that in Manila, Philippines, male were more affected by dengue fever than

female in 2011.9 Related study in Bangladesh by Azad AK et al. also found male predominance in 2006.10 However, A South American study conducted by Kaplan et al. showed in their study that females were more infected than males.[11]

Our main focus was to identify the prevalence of gastrointestinal and atypical manifestations of dengue fever in Bangladesh. We found that 73 (45.6%) patients presented with atypical manifestations, while the rest 87(54.4%) patients had only a classical presentation of dengue fever. This proves that nearly half of them had atypical presentations. Ahlawat et al. in India found 39.3% of their patients had atypical manifestations.12 Acute watery diarrhea was the most common atypical feature in our study (17.5%). Others were acute acalculous cholecystitis (8.1%), ascites (4.4%), acute hepatitis (3.1%), pleural effusion (2.5%), pneumonia (2.5%), acute pancreatitis (1.3%), GIT bleeding (1.3%), Encephalitis (1.3%), meningitis and myocarditis. Natarajan et al. found 85.5% of patients have febrile diarrhea, 28.3% of patients have acalculous cholecystitis, and acute pancreatitis was observed in 1.8% of dengue patients.13 Diarrhea and acalculous cholecystitis were also common atypical features in a study by Azad et al. in Bangladesh.10 However, some other researchers found acalculous cholecystitis as the most common atypical presentation, such as Ahlawat et al.12 32.7%, Bhatty et al. 16.36% 14, and Sai PMV et al. 85%.15 Acute diarrhea and pancreatitis in dengue fever may be due to widespread cytokine release in the body due to inflammatory response. Acalculous cholecystitis may be due to cholestasis and cystic duct spasm.[16]

Neurological manifestations are also not uncommon in dengue fever. Altered consciousness, subdural hematoma, and signs of raised intracranial pressure have been reported in many studies. The other rare presentations are the weakness of limbs and cranial nerve palsies.[17,18] Ahlawat et al. found 8.1% neurological presentation in their study.[12]

In our study, 1.2% of patients died, and all of them presented with atypical features of dengue. If we analyze dengue patients with only atypical features, 2.7% died and 97.3% recovered. A study by Antony et al. showed a case fatality rate of 1.2%, with 0.97% in males and 1.49% in females,8 which is very similar to ours.

Conclusions:

Dengue is a disease that has no drugs or vaccines yet to be invented. So, prevention of spread and early diagnosis is the mainstay of successful management. As it is a tropical disease, every year we face a surge of dengue at the beginning of the rainy season. This is our small effort to identify the rate of atypical manifestations of dengue infection, which are less common but easily overlooked by physicians. So, keeping in mind these atypical features of dengue fever at least during the peak season of dengue we may detect dungue fever early, save many lives and health resources.

Conflicts of interest: There is no conflict of interest.

Acknowledgments: We are grateful to our beloved Intern doctors and attending doctors of the dengue treatment unit while conducting this study

Referencess:

1. Amin MMM, Hussain AMZ, Nahar K, Chowdhury IA, Murshed M, Chowdhury MA. Sero-diagnosis of dengue infections in four metropolitan cities of Bangladesh. *Dengue Bull.* 2000;24:29–33. Available from: https://policycommons.net/artifacts/486926/searo-diagnosis-of-dengue-infections-in-four-metropolitan-cities-of-bangladesh/1461730/

2. World Health Organization. Dengue: guidelines for diagnosis, treatment, prevention and control. New ed. Geneva: WHO; 2009. Available from: https://apps.who.int/iris/handle/10665/44188

3. Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare (MOHFW), Bangladesh. National guideline for clinical management of dengue syndrome. 4th ed. Dhaka: Communicable Disease Control, DGHS; 2018. Available from: https://drive.google.com/-file/d/1Xzz6XsnBzAd8nyskk2EWX0kv7BwQ6ymL/view

4. Khanna S, Vij JC, Kumar A, Singal D, Tandon R. Dengue fever is a differential diagnosis in patients with fever and abdominal pain in an endemic area. *Ann Trop Med Parasitol.* 2004 Oct;98(7):757–760. doi:10.1179/000349804X3153

5. Kyle JL, Harris E. Global spread and persistence of dengue. *Annu Rev Microbiol.* 2008;62:71–92. doi:10.1146/annurev.micro.62.081307.163005

6. Karim MN, Munshi SU, Anwar N, Alam MS. Climatic factors influencing dengue cases in Dhaka city: a model for dengue prediction. *Indian J Med Res.* 2012 Jul;136(1):32–39.

7. World Health Organization. Global strategy for dengue prevention and control 2012–2020 [Internet]. Geneva: WHO; 2012. p. 16–17 [cited 2023 Jan 26]. Available from: https://apps.who.int/iris/handle/10665/75303

8. Antony J, Celine TM. A descriptive study on dengue fever reported in a Medical College Hospital. *Sahel Med J.* 2014;17:83–6. doi:10.4103/1118-8561.140285.

9. Perez R. Males more prone to dengue than females – DOH. *Inquirer.net* [Internet]. 2011 Sep 6 [cited 2023 Jan 26]. Available from: https://newsinfo.inquirer.net

10. Azad AK, Mohammad H, Billal A, Saha AK, Ahmed T. Clinical presentation of dengue in 150 admitted cases in Dhaka Medical College Hospital. *J Med.* 2006;7(1):3–9. doi:10.3329/jom.v7i1.1355

11. Kaplan JE, Eliason DA, Moore M, Sather GE, Schonberger LB, Cabrera-Coello L, et al. Epidemiologic investigations of dengue infection in Mexico, 1980. *Am J Epidemiol.* 1983 Mar;117(3):335–43. doi:10.1093/oxfordjournals.aje.a113546

12. Ahlawat RS, Kalra T. Atypical manifestations of dengue fever in a recent dengue outbreak. *Ann Trop Med Public Health.* 2017;10:1448–1452. doi:10.4103/ATMPH.ATMPH_18_17.

13. Natarajan N, Cugati S, Tirupathi RP, Padmapriya N. Patterns and trends in atypical manifestations of dengue among inpatient adults in tertiary care teaching institute of South India. *Int J Contemp Med Res.* 2017;4(10):2152–2156. Available from: https://www.ijcmr.com

14. Bhatty S, Shaikh NA, Fatima M, Sumbhuani AK. Acute acalculous cholecystitis in dengue fever. *J Pak Med Assoc.* 2009 Aug;59(8):519-521.

15. Venkata Sai PM, Dev B, Krishnan R. Role of ultrasound in dengue fever. *Br J Radiol.* 2005 May;78(929):416-418. doi:10.1259/bjr/54704044

16. Premaratna R, Bailey MS, Ratnasena BG, de Silva HJ. Dengue fever mimicking acute appendicitis. *Trans R Soc Trop Med Hyg.* 2007 Jul;101(7):683-685. doi:10.1016/j.trstmh.2007.02.006

17. Gupta N, Srivastava S, Jain A, Chaturvedi UC. Dengue in India. *Indian J Med Res.* 2012 Sep;136(3):373-390.

18. Neeraja M, Lakshmi V, Dash PK, Parida MM, Rao PV. The clinical, serological and molecular diagnosis of emerging dengue infection at a tertiary care institute in southern India. *J Clin Diagn Res.* 2013 Mar;7(3):457-461. doi: 10.7860/JCDR/2013/4786.2798

Original Article

Impact of COVID-19 Outbreak on Gastrointestinal Practices in Bangladesh

MN Hasan[1], SC Das[2], MAM Sakar[3], MA Hoque[4], MNE Azam[5]

Abstract

Background: The COVID-19 pandemic has had a major global impact on most of the fields of medical practice including gastroenterology practice and endoscopy service. This study was conducted among gastroenterologists in Bangladesh to assess the impact of the COVID-19 pandemic on gastrointestinal practices in the country.

Materials and Methods: The survey questionnaire, containing 24 questions, was circulated through emails of the gastroenterologists between July 2nd to August 1st, 2020. Filled forms were automatically received into the Survey Monkey system and retrieved in Excel sheet and analyzed.

Results: A total of 53 gastroenterologists (male 90.57%) responded to the survey. Weekly outpatient appointments were reduced by 75.8%. Only 26.4% of the gastroenterologists continued regular face-to-face consultations. The weekly number of gastroscopies and colonoscopies performed by the participants were reduced by 89.3% and 83.3% respectively. Three fourths of the gastroenterologist stopped doing endoscopy. Only 50.93 % of the endoscopists used N95 or similar masks.

Conclusion: As with the rest of the world, the COVID-19 pandemic has significantly impacted gastroenterology practice and endoscopy service in Bangladesh. Further study may be required to identify the impact of this significantly altered workflow on gastrointestinal disease detection and treatment.

Keywords: COVID-19, Gastrointestinal endoscopy, Colonoscopy.

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Introduction:

Since the coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China, in early December 2019, it has become a global pandemic posing a significant impact on the lives of people around the world.[1] As of 2nd August 2021, there have been 198,778,175 confirmed cases of COVID-19, including 4,235,559 deaths have been reported worldwide by the WHO.[2] COVID-19 virus mainly spreads from person to person via respiratory droplet transmission, which occurs when a person is in close contact with an infected person who is actively coughing or sneezing.[3] Excretion of the viruses in feces and fecal transmission of the viruses have also been reported in previous studies.[4] Though the virus mainly involves the respiratory tract, several gastrointestinal symptoms, including diarrhea, vomiting, nausea, abdominal pain, and gastrointestinal bleeding have been reported among a wide range of affected people (3–79%).[5] Endoscopy is an important tool that has a great diagnostic and therapeutic role in gastroenterology.[6] As endoscopy is an aerosol-generating procedure, healthcare professionals working in the endoscopy units are at risk of COVID-19 infection from airborne droplets, nasal discharges, conjunctival secretions, contact, and potential for fecal-oral transmission.[7] Therefore, all major gastrointestinal (GI) or GI endoscopy societies have recommended rescheduling or canceling non-urgent procedures except for emergent cases with adequate protection although some variations are noticeable among the different guidelines.[8-12] However, the risk of transmission of the virus could be reduced significantly by the appropriate use of Personal Protective equipment. Recent data show that there is a low risk of SARS-CoV-2 transmission during gastrointestinal endoscopy when adequate protective measures are taken and contact and workload are reduced.[7] The American Society for Gastrointestinal Endoscopy (ASGE) also recommends carrying out endoscopic procedures in negative-pressure rooms.[13] In the above scenario, the number of general endoscopies was dramatically decreased worldwide.[14] In addition, restrictions in endoscopic volumes have led to a reduction in young gastroenterologist trainees' opportunities to participate in GI endoscopy, which ultimately causes a reduction of performance in procedural skills and competency development.[15]

The COVID-19 pandemic has had a major global impact on most of the fields of medical practice including gastroenterology practice and endoscopy service. Like all other parts of the world, Bangladesh is also affected greatly by the COVID-19 pandemic. Reports regarding the impact of the COVID-19 pandemic on gastroenterology practice and

endoscopy service are lacking. Thus, this study was conducted to observe the impact of COVID-19 on gastroenterology practice and endoscopy service in Bangladesh.

Materials and Methods:

Email addresses of gastroenterologists across Bangladesh were collected from the Bangladesh Gastroenterology Society office database. The survey questionnaire, containing 24 questions assessing the participant's current position, workplace, Knowledge about COVID-19 and gastrointestinal endoscopy, and the impact of the COVID-19 outbreak on gastrointestinal practices, including outdoor patient services and gastrointestinal endoscopy, was circulated through emails between July 2nd to August 1st, 2020. The purpose of the study was explained in a message before starting the survey, which was attached with the email. Responding to the survey questions was considered consent to participate. All participants were allowed to participate in the survey only once and the results were kept anonymous. A reminder was given twice weekly who were not submitting the form. The filled forms were automatically received into the Survey Monkey system retrieved in an Excel sheet and analyzed. Most questions were closed-ended, and participants were allowed to select one appropriate option. A few questions had the provision of choosing multiple options. No personal data or identifiers linked to any endoscopist or unit were obtained. The study was approved by the Institutional Review Board of Shaheed Ziaur Rahman Medical College, Bogura.

Results:

A total of 53 gastroenterologists (male 90.57%) responded to the survey. Most (35.7 %) were aged 40 to 49 years. A total 75% of the gastroenterologists worked at government hospitals mostly situated in metropolitan cities (75.47%), 5(9.43%) of the participants were infected with Covid-19 before the study period and were managed at home. Characteristics of the gastroenterologists are given in Table 1.

Table 1: Distribution of Gastroenterologists according to demographic characteristics (n=53).

Characteristics	Number (Percentage)
Age	
<30	1 (1.89)
30-39	10 (18.87)
40-49	27 (50.94)
>50	15 (28.3)
Sex	
Male	48 (90.57)
Female	5 (9.43)
Place of work	
Government hospital	44 (83)
Private multi-specialty hospital	5 (9.4)
Private chamber	4 (7.5)
Location of workplace	
Metropolitan city	40 (75.47)
Urban area	11(20.75)
Rural area	2 (3.77)
Infected with Covid-19	**5 (9.43)**

Weekly outpatient appointments were reduced by 75.8%. Only 26.4% of the gastroenterologists continued regular face-to-face consultations. A total of 26.41% of the gastroenterologists canceled more than 50% of their appointments and 47.16% of the gastroenterologists closed their outpatient practice. All participating gastroenterologists in this study could perform gastroscopy and colonoscopy. The weekly number of gastroscopies and colonoscopies performed by the participants was reduced by 89.3% and 83.3%, respectively (Table 2).

Table 2: Weekly number of patient appointments and procedures by time period and changes over time.

	Time period	
	Pre-COVID	COVID impacted
OPD appointments		
The average number of OPD appointments per week	186	45
% reduction in activity compared with pre-COVID	75.8%	
Gastroscopy		
Average number of procedures per week	66	7
% reduction in activity compared with pre-COVID	89.3%	
Colonoscopy		
Average number of procedures per week	18	3
% reduction in activity compared with pre-COVID	83.3%	

Of the study participants 11% and 4% followed the British Society of Gastroenterology (BSG) guideline and the American Society of Gastrointestinal Endoscopy (ASGE) guideline for endoscopy, respectively whereas 26.1% of the participants followed local guidelines for endoscopy. Only 5.66% of the participants reported that they did not follow any guidelines for endoscopy (Figure 1).

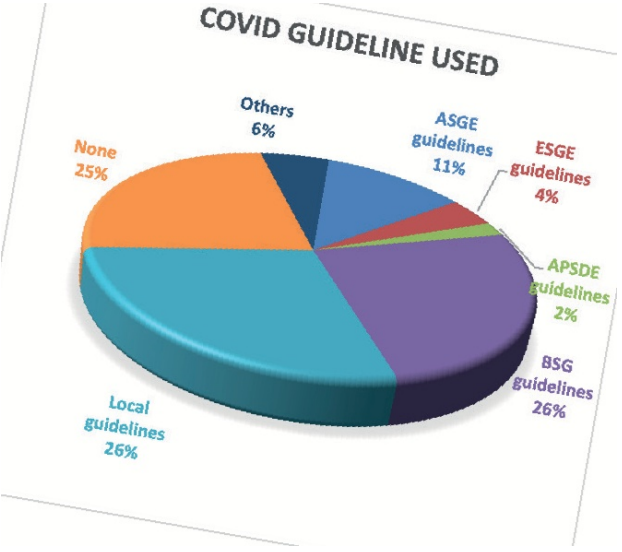

Figure 1: Guidelines followed by the gastroenterologists during endoscopy practice (American Society of Gastrointestinal Endoscopy, ESGE-European Society of Gastrointestinal Endoscopy, APSED- Asia Pacific Society for Digestive Endoscopy, BSG- British Society of Gastroenterology)

Seventy-four percent of the gastroenterologists stopped doing endoscopy, while 22.64% of the gastroenterologists reduced the number of procedures. 13.2% of the gastroenterologists performed only emergency endoscopies. In addition, 5.66% and 15.95% of gastroenterologists increased the time between endoscopies and reduced the number of staff respectively to reduce the spread of infection. While performing endoscopy procedures, 50.93 % of the endoscopists used N95 or similar masks, 37.72% used simple surgical masks, and surprisingly 11.32% used no masks during endoscopy procedures. During the study period, no negative pressure room was available in any Gastroenterology unit. 68.6% of the participants used the manual method for scope disinfection.

Discussion:

In Bangladesh, the first case of COVID-19 was reported on 7th March 2020. Thereafter, the country adopted several measures including a national lockdown to control the spread of COVID-19. In this study, we presented data on the impact of the COVID-19 pandemic on the Gastroenterology practice in Bangladesh.[16] This study revealed a substantial and drastic impact of the pandemic on Gastroenterology activities throughout the country. More than 40% of gastroenterologists stopped their private practice and more than 11% of gastroenterologists canceled 80% of their appointments. The unpredictable nature of COVID-19 has instilled fears among doctors leading to workplace avoidance. A recent study revealed that doctors were afraid of getting infections themselves and transmitting them to their families.[17,18]

In this current study gastroscopies and colonoscopies were reduced by 93% and 92% respectively per week. Similar findings were also reported in the UK, where the number of gastroscopies and colonoscopies was reduced by 90% and 86% respectively.[19] Significant reductions in gastroscopies, colonoscopies, and other endoscopic procedures were also reported in other studies in Italy, the Netherlands, Brazil, and India.[20-23] One of the reasons for performing fewer endoscopy procedures during COVID-19 might be due to decreased patient volume in the hospital due to the nationwide lockdown. Another important reason for the lower number of endoscopies is due to the latest guidelines recommending avoidance of routine endoscopies regarding it a high-risk procedure. In a recent study in India, 34% of endoscopists limited the number of patients and 29 % of endoscopists were advised by the administrators of their centers to limit the number of endoscopies to avoid exposure to healthcare personnel and to conserve resources.[23]

COVID-19 is thought to be highly contagious and as many as 44 % of transmissions were reported to occur through asymptomatic carriers in China.[24] So, even the COVID-19-infected asymptomatic persons coming for endoscopies could also transmit the disease, which justifies labeling endoscopies as a high-risk procedure. In the current study, 5(9.43%) of the participants were infected with COVID-19 before the study period. In a recent study in Brazil, 1.7 % of participants had serologic or swab confirmation of COVID-19 and 1 % stated that the infection was secondary to endoscopic procedures performed in infected patients.[21]
In our survey, we observed that 50.93% of respondents used N95 or equivalent masks but a large portion of endoscopists used simple surgical masks (37.72%) while performing endoscopic procedures. 11.32% used no masks at all during endoscopy procedures. In an international survey of endoscopists, 57.1% of the endoscopists used N95 respiratory masks during endoscopy procedures which is comparable to our survey results.[14] In other surveys conducted in different countries 65%, 74.7%, and 86% of participants used N95 masks for endoscopy in their centers in the USA, India, and Africa, respectively. The main reason for this might be due to the limited availability of N95 or equivalent masks in country.

Several International guidelines are available for practicing endoscopy to reduce viral transmission. However, recommendations of those guidelines are hard to follow in a developing country like Bangladesh with limited resources, including limited PPE including N95 masks, lack of negative pressure endoscopy rooms, overcrowding of government centers, and limited resources in privately owned smaller endoscopy units. In our study, 43% of the endoscopists followed one or both of the international guidelines whereas 26% of the endoscopists followed the local endoscopy guideline. One-fourth (25%) of the endoscopists did not follow any guidelines during endoscopy practice.

The study had a few limitations- i) the sample size was relatively small and may not be representative of gastroenterologists of the entire country (ii) The study only covered the impact of Covid-19 on the outpatient department, impact on the inpatient department were not considered (iii) Impact of reduced number of endoscopy procedure on gastrointestinal disease detection and treatment were not observed.

Conclusion:

As with the rest of the world, the COVID-19 pandemic has significantly impacted gastroenterology practice and endoscopy service in Bangladesh. Only half of the endoscopists used N95 or similar masks during endoscopy procedure due to lack of availability making them more vulnerable to exposure to the virus. Further study may be done to identify the impact of this significantly altered workflow of the endoscopy unit on gastrointestinal disease detection and treatment.

Conflicts of Interest: There is no conflict of interest.

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References:

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; 382: 727–733. doi:10.1056/nejmoa2001017

2. Khalil MM, Mahbub-Uz-Zaman K, Hossain AS, Ahmed F, Chowdhury MFK, Khan ST, Miah MSA, Khaleque N, Kibria MG, Ahmed F, Khan AM. Adverse Events Following COVISHIELD Vaccination Among Adult Population in Bangladesh. *SN Compr Clin Med.* 2021;3(11):2207-2213. doi: 10.1007/s42399-021-01021-z. Epub 2021 Jul 31. PMID: 34368624; PMCID: PMC8324453.

3. Parasher A. COVID-19: Current understanding of its Pathophysiology, *Clinical presentation and Treatment.* Postgrad Med J 2021; 97: 312–320. doi:10.1136/postgradmedj-2020-138577

4. Guo M, Tao W, Flavell RA, et al. Potential intestinal infection and fecal-oral transmission of SARS-CoV-2. Nat Rev *Gastroenterol Hepatol* 2021; 18: 269–283. doi:10.1038/s41575-021-00416-6

5. Tian Y, Rong L, Nian W, et al. Review article: gastrointestinal features in COVID-19 and the possibility of fecal transmission. *Aliment Pharmacol Ther* 2020; 51: 843–851. doi:10.1111/apt.15731

6. Nguyen VX, li Nguyen VT, Nguyen CC. Appropriate use of endoscopy in the diagnosis and treatment of gastrointestinal diseases: Up-to-date indications for primary care providers. *Am J Clin Hypn* 2011; 53: 345–357. doi:10.2147/IJGM.S14555

7. Repici A, Aragona G, Cengia G, et al. Low risk of COVID-19 transmission in GI endoscopy. *Gut* 2020; 69: 1925–1927. doi:10.1136/gutjnl-2020-321341

8. Guda NM, Emura F, Reddy DN, et al. Recommendations for the Operation of Endoscopy Centers in the setting of the COVID-19 pandemic – World Endoscopy Organization guidance document. *Dig Endosc* 2020; 32: 844–850. doi:10.1111/den.13777

9. Repici A, Maselli R, Colombo M, et al. Coronavirus (COVID-19) outbreak: what the Department of Endoscopy should know. *Gastrointest Endosc* 2020; 92: 192–197. doi:10.1016/j.gie.2020.03.019

10. Gralnek IM, Hassan C, Beilenhoff U, et al. ESGE and ESGENA Position Statement on Gastrointestinal Endoscopy and the COVID-19 pandemic. *Endoscopy* 2020; 52: 483–490. doi:10.1055/a-1155-6229

11. Chiu PWY, Ng SC, Inoue H, et al. Practice of endoscopy during COVID-19 pandemic: Position statements of the Asian Pacific Society for Digestive Endoscopy (APSDE-COVID statements). *Gut* 2020; 69: 991–996. doi:10.1136/gutjnl-2020-321185

12. Sultan S, Lim JK, Altayar O, et al. AGA Rapid Recommendations for Gastrointestinal Procedures During the COVID-19 Pandemic. *Gastroenterology* 2020; 159: 739-758.e4. doi:10.1053/j.gastro.2020.03.072

13. Calderwood AH, Day LW, Muthusamy VR, et al. ASGE guideline for infection control during GI endoscopy. *Gastrointest Endosc* 2018; 87: 1167–1179. doi:10.1016/-j.gie.2017.12.009

14. Alboraie M, Piscoya A, Trung Q, et al. The global impact of COVID-19 on gastrointestinal endoscopy units: An international survey of endoscopists. *Arab J Gastroenterol.* 2020;21:156-161. doi: 10.1016/j.ajg.2020.08.008.

15. Pawlak KM, Kral J, Khan R, et al. Impact of COVID-19 on endoscopy trainees: an international survey. *Gastrointest Endosc.* 2020;92:925-935. doi: 10.1016/j.gie.2020.06.010.

16. Anwar S, Nasrullah M, Hosen MJ. COVID-19 and Bangladesh: Challenges and How to Address Them. *Front Public Heal* 2020; 8: 1–8. doi:10.3389/fpubh.2020.00154

17. Malik S, Ullah I, Irfan M, et al. Fear of COVID-19 and workplace phobia among Pakistani doctors: A survey study. *BMC Public Health* 2021; 21: 1–9. doi:10.1186/s12889-021-10873-y

18. Kumar J, Katto MS, Siddiqui AA, et al. Predictive Factors Associated With Fear Faced by Healthcare Workers During COVID-19 Pandemic: A Questionnaire-Based Study. *Cureus* 2020; 12: 8–12. doi:10.7759/cureus.9741

19. Rutter MD, Brookes M, Lee TJ, et al. Impact of the COVID-19 pandemic on UK endoscopic activity and cancer detection: A National Endoscopy Database Analysis. *Gut* 2021; 70: 537–543. doi:10.1136/gutjnl-2020-322179

20. Maida M, Sferrazza S, Savarino E, et al. Impact of the COVID-19 pandemic on Gastroenterology Divisions in Italy: A national survey. *Dig Liver Dis* 2020; 52: 808–815. doi:10.1016/j.dld.2020.05.017

21. Arantes VN, Martins BC, Seqatto R, et al. Impact of coronavirus pandemic crisis in endoscopic clinical practice: Results from a national survey in Brazil. *Endosc Int Open* 2020; 08: E822–E829. doi:10.1055/a-1183-3324

22. Lantinga MA, Theunissen F, Ter Borg PCJ, et al. Impact of the COVID-19 pandemic on gastrointestinal endoscopy in the Netherlands: Analysis of a prospective endoscopy database. *Endoscopy* 2021; 53: 166–170. doi:10.1055/a-1272-3788

23. Goenka MK, Afzalpurkar S, Ghoshal UC, et al. Impact of COVID-19 on gastrointestinal endoscopy practice in India: a cross-sectional study. *Endosc Int Open* 2020; 08: E974–E979. doi:10.1055/a-1181-8391

24. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020; 26: 672–675. doi:10.1038/s41591-020-0869-5

Original Article

Perception of Gastric Acid-Related Symptoms and Reasons for Use of Proton Pump Inhibitors: A Population-Based Study

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Abstract

Background: Retrosternal burning and upper abdominal pain or burning are well-established symptoms related to gastric hydrochloric acid. In our day-to-day practice, population perception of gastric acid-related symptoms is variable and interesting, like incomplete bowel evacuation, belching, headache, vertigo, in addition to typical acid peptic symptoms.

Materials and Methods: This observational study was done at the field level to find out the population perception of symptoms related to gastric acid, which is popularly known as "Problems of Gastric", their demographic profile, reasons for using PPIs, and to determine the prescribing authorities.

Results: Among 367 participants, 55.22% were between 21-40 years of age group with mean age of 36.19 ± 12.07 years, and the majority were male (77.4%). A total of 64% of participants think that they have got "Problems of gastric." Among this group, 67.66% had gastric acid-related symptoms (Retrosternal burning 48.51% and upper abdominal pain/burning 28.51%), and the remaining 32.34% had falsely interpreted their symptoms as "Problems of gastric". Even 42% of lawyers, 32% of medical promotion officers, and 18% of doctors falsely interpreted their symptoms as originating from gastric acid. The prevalence of acid peptic-related symptoms among study participants was 43.32%. In this study, more than 50% participants were taking medicine by themselves and 39.57% were prescribed by the physician. A total of 31.53% of participants were taking proton pump inhibitors for inappropriate indications.

Conclusion: Misinterpretation of gastric acid related symptoms are noticed among all studied communities including the well-educated population. Inappropriate use of PPIs for various disorders not related to gastric acid is also very common. Health education and awareness development regarding gastric acid related symptoms is very important, and PPIs should be available only with prescription.

Keywords: Problems of gastric, Gastric acid-related symptoms, Falsely interpreted symptoms, Inappropriate use of PPIs, Prescribing authority.

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Introduction:

Dyspepsia is often broadly defined as pain or discomfort centered in the upper abdomen.[1,2] Patients with dyspepsia commonly report several other symptoms like postprandial fullness, early satiety, anorexia, belching, nausea and vomiting, upper abdominal bloating, and even heartburn and regurgitation.[3]

In contrast, GERD is a spectrum of disease that usually produces symptoms of heartburn and acid regurgitation.[4]

However, in the majority of subjects with dyspeptic symptoms, no organic abnormality is identified by a routine clinical evaluation (including Upper GIT Endoscopy), and these patients are said to have functional dyspepsia.[5]

The term Peptic Ulcer Disease (PUD) is used to include ulcerations and erosions in the stomach and duodenum from a number of causes. These lesions are called "peptic" because the enzyme pepsin, proteolytic at an acidic pH, plays a major role in causing the mucosal breaks, regardless of the inciting agent.[6] The predominant symptom of patients with uncomplicated PUD is epigastric pain; some patients complain of heartburn.[7]

Of the above symptoms, retrosternal burning and upper abdominal pain or burning are truly related to gastric hydrochloric acid. Medications commonly found at market to neutralize or counteract this gastric acid are various antacid preparations, H_2 receptor blockers (H_2RA) and Proton Pump Inhibitors (PPI). In our country, population perception of gastric acid-related symptoms is interesting, like incomplete bowel evacuation, belching, headache, vertigo, etc, in addition to typical acid peptic symptoms. And for these various types of symptoms, people are taking different types of medicines (Antacids, H_2RA and PPI) by themselves as well as prescribed by doctors.

This observational study was done to find out the population perception of symptoms related to gastric acid, which is popularly known as "Problems of Gastric", their demographic profile, reasons for using PPIs, and to determine the prescribing authority.

Materials and Methods:

This observational study was carried out at Faridpur, Bangladesh, among populations from different occupations during January 2019 to December 2020. The purpose of the study was clearly described to participants, and those who agreed to participate were included in the study. Participants' names were not recorded to maintain the privacy of the data. Face-to-face interviews were conducted by several investigators, and data were recorded in predesigned data collection sheets. After data collection, all the sheets were compiled by the principal investigator. Data consistencies were checked manually, and incomplete and inconsistent data sheets were discarded. Finally, data from 367 participants were entered into computer-based software SPSS for Windows, Version 15.0 (IBM Corp., Armonk, NY, USA) for analysis. Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as frequencies and percentages, and results were presented by different tables and charts.

Results:

Among 367 participants, the majority lies between 21-30 years and 31-40 years age groups (109, 29.7% and 101, 27.5% respectively with a mean age of 36.19 ± 12.07 years (Table 1).

Table 1: Distribution of participants according to age (n=367).

Age group (In years)	Frequency (%)
≤ 20	30 (8.2)
21 -30	109 (29.7)
31 -40	101 (27.5)
41 -50	81 (22.1)
51 -60	34 (9.3)
61 -70	10 (2.7)
≥ 71	2 (0.5)
Total	**367 (100.0)**

The majority of participants were male (284, 77.4%) with a male-to-female ratio of 3.4:1 (Figure 1).

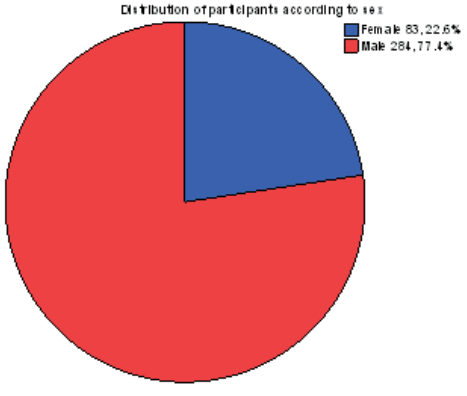

Figure 1: Distribution of participants according to sex (n=167).

Regarding occupation of our participants, 100 patients (27.2%) were lawyers, followed by medical promotion officers and students (Both were 61, 16.6%) (Table 2).

Table 2: Distribution of participants according to occupation (n=367).

Occupation	Frequency (%)
Business	24 (6.5)
Doctor	28 (7.6)
Farmer	4 (1.1)
Housewife	22 (6.0)
Other job holder	22 (6.0)
Lawyer	100 (27.2)
Medical promotion officer	61 (16.6)
Student	61 (16.6)
Teacher	45 (12.3)
Total	**367 (100.0)**

Participants of this study were mainly educated group, as doctors, lawyers, teachers, students and medical promotion officers. So, they have collected data mainly from their colleagues. More than 50% have completed post-graduation (185, 50.4%), and another 113 (30.8%) have completed their graduation level (Table 3).

Table 3: Distribution of participants according to educational status (n=367).

Educational Status	Frequency (%)
Graduation	113 (30.8)
Illiterate	2 (0.5)
Post -graduation	185 (50.4)
Primary	6 (1.6)
Secondary	61 (16.6)
Total	**367 (100.0)**

"Problem of Gastric" or "Problem of Gas" is a very commonly uttered term among our population, they use to describe different problems as Gastric. One of the key questions of this study was "Are you suffering from 'Problem of Gastric"? A total of 235 (64%) participants have said "Yes, I have" (Figure 2).

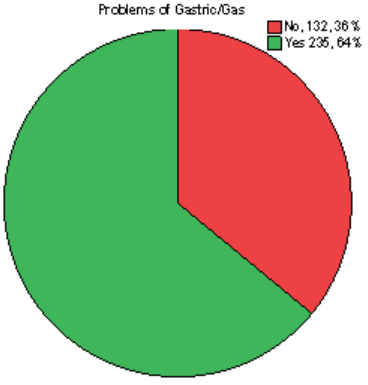

Figure 2: Distribution of patients according to the presence or absence of "Problem of Gastric" (n=367).

People's perception regarding symptoms of acid peptic disorder was assessed, out of 367 participants, 235 answered that they have "Problem of Gastric" (Figure 2). Among them, 114 (48.51%) participants had retrosternal burning; of them, 56 (23.83%) had isolated retrosternal burning, but the remaining 58 (24.68%) had a combination of other symptoms like incomplete bowel evacuation, upper abdominal pain/burning and others.

Another 67 (28.51%) participants described upper abdominal pain/burning as their symptoms; of them, 35 (14.89%) had solely upper abdominal pain/burning, and the remaining 32 (13.61%) had other symptoms with pain like retrosternal burning, incomplete bowel evacuation and others.

A total of 159 (67.66%) had acid peptic related symptoms like upper abdominal pain/burning and retrosternal burning alone or in combination with other symptoms.

Interestingly, 86 (36.59%) participants thought that incomplete bowel evacuation is a "problem related to gastric"; of them, 31 (13.19%) had solely this symptom. Another 51 (21.70%) participants described abdominal fullness as their gastric problem; of them, 19 (8.08%) had isolated abdominal fullness.

Remaining 7 (2.98%) participants with belching, 3 (1.28%) with headache, 2 (0.85%) with chest pain, 2 (0.85%) with nausea, 2 (0.85%) with loose stool, 2 (0.85%) with milk intolerance, 1 (0.43%) with anorexia and 1 (0.43%) participant with raised blood pressure thought that these symptoms are due to "Problem of Gastric".

So, a total of 157 (66.81%) participants thought that incomplete bowel evacuation, abdominal fullness, belching, headache, chest pain, loose stool are due to "Problem of Gastric". Among them, 76 (32.34%) had only these symptoms without having upper abdominal pain/burning or retrosternal burning (Table 4).

Table 4: Distribution of participants according to symptoms thought to be "Problem of Gastric" (n=235)

Symptoms described for "Problem of Gastric"*	Frequency (%)
Anorexia	1 (0.43)
Belching	2 (0.85)
Chest pain	2 (0.85)
Abdominal Fullness	19 (8.09)
Abdominal Fullness, ICE	11 (4.68)
Headache	1 (0.43)
ICE	31 (13.2)
ICE, Belching	2 (0.85)
ICE, Headache	2 (0.85)
ICE, Milk Intolerance	1 (0.43)
Loose Stool	1 (0.43)
Milk Intolerance	1 (0.43)
Nausea	1 (0.43)
Raised Blood Pressure	1 (0.43)
RSB	56 (23.83)
RSB, Belching	3 (1.28)
RSB, Abdominal Fullness	7 (2.98)
RSB, Abdominal Fullness, ICE	3 (1.28)
RSB, Abdominal Fullness, Loose Stool	1 (0.43)
RSB, ICE	21 (8.94)
RSB, Nausea	1 (0.43)
UAP	35 (14.89)
UAP, Abdominal Fullness	2 (0.85)
UAP, Abdominal Fullness, ICE	3 (1.28)
UAP, ICE	5 (2.13)
UAP, RSB	14 (5.96)
UAP, RSB, Abdominal Fullness	1 (0.43)
UAP, RSB, Abdominal Fullness, ICE	4 (1.70)
UAP, RSB, ICE	3 (1.28)
Total	**235 (100.0)**

*NB: ICE-Incomplete Bowel Evacuation, RSB-Retrosternal Burning, UAP-Upper Abdominal Pain/Burning.

Symptoms attributable to gastric acid and the profession of study participants were also assessed. Among 235 respondents who thought that they were suffering from "Problems of Gastric", actually only 159 (67.66%) had acid peptic-related symptoms like upper abdominal pain/burning and retrosternal burning alone or in combination with other symptoms, remaining 76 (32.34%) were falsely interpreted their symptoms (Mentioned previously). About 42% of lawyers, 32% of medical promotion officers, and even 18% of doctors falsely interpreted their symptoms as originating from gastric acid (Table 5).

Table 5: Distribution of symptomatic participants according to their profession and perception of symptoms attributable to gastric acid (n=235)

Occupation	Symptoms attributable to Gastric Acid		Total
	Yes, Frequency (%)	No, Frequency (%)	
Lawyer	42 (58.33)	30 (41.67)	72
MPO	32 (68.09)	15 (31.91)	47
Students	22 (70.97)	9 (29.03)	31
Teacher	23 (82.14)	5 (17.86)	28
Business	10 (58.82)	7 (41.17)	17
Housewife	11 (75.57)	3 (21.43)	14
Doctor	9 (81.82)	2 (18.18)	11
Farmer	2 (100)	0 (0)	2
Other Job	8 (61.54)	5 (38.46)	13
Total	**159 (67.66)**	**76 (32.34)**	**235**

Among these 235 participants, 222 (94.47%) are taking some sort of treatment like different Antacid preparations, H_2 receptor blockers, and proton pump inhibitors. More than 50 % (118) of participants are taking medicine by themselves and 39.57% (93) were prescribed by a physician (Table 6).

Table 6: Distribution of participants according to medicine prescriber (n=222)

Prescriber	Frequency (%)
Salesman of medicine shop	5 (2.13)
MBBS doctor	37 (15.74)
Postgraduate doctor	56 (23.83)
Rural medical practitioner	6 (2.55)
Self	118 (50.21)
Total	**222 (100)**

Participants had typical acid peptic-related symptoms (Retrosternal burning and Upper abdominal pain/burning) and their prescribing authorities were compared. A total of 31.53% of participants had no such symptoms but were receiving medications. Among them about 38.57% (27) were prescribed by registered doctors and among them 25.7% (18) were postgraduate doctors (Table 7).

Table 7: Distribution of participants according to typical acid peptic symptoms and prescribing authorities (n=222).

		Prescribed by Doctor		Total
		Yes	No	
Typical dyspeptic symptoms	Yes	66 (43.42%)	86 (56.58%)	152 (68.47%)
	No	27 (38.57%	43 (61.43)	70 (31.53%)
Total		**93**	**129**	**222***

*A total of 13 patients having typical or atypical dyspeptic symptoms are not taking any form of medicine.

Discussion:

This study was conducted to see the population perception of gastric acid-related symptoms, their demographic profile, reasons for using PPIs, and to determine their prescribing authority.

Among 367 participants, 210 (55.22%) were between 21-40 years of age, group mean age of 36.19 ± 12.07 years, and the majority were male (284, 77.4%).

Data were collected by investigators mainly from professions they belong to, so this was confined to a limited number of professions. Among them, the main bulk were lawyers (27.2%), medical promotion officers (16.6%) and students (16.6%). As study investigators belong to an educated group and they have collected data mainly from their peer group; so, 298 (81.2%) participants were graduate or postgraduate.

A total of 235 (64%) participants claimed that they have got "Problems of gastric", among them 159 (67.66%) had acid peptic related symptoms, like retrosternal burning (48.51%) and upper abdominal pain/burning (28.51%) alone or in combination with other symptoms. Accordingly prevalence of acid peptic-related symptoms among study participants is 43.32%. The majority of patients have a combination of different symptoms. In a similar study Hasan et al. described that most of the patients had multiple presenting complaints, among them 54% of patients had heartburn, 38% had upper abdominal pain and discomfort, 33% had abdominal bloating, 23% had anorexia, 19% had nausea, 10% had vomiting, and 10% had early satiety.8 Another study by Sony et al. described that about 47% of patients used PPIs inappropriately, among them 29.59% for reduced appetite and nausea, 20% for gastric discomfort, 13.57% for asthma, 8.57% for infections and 15% had no clear indication.[9]

Though the majority of participants in this study group were highly educated, 157 (66.81%) participants falsely perceived that incomplete bowel evacuation, abdominal fullness, belching, headache, chest pain, loose stool, chest pain high blood pressure are due to "Problem of Gastric". Even 42% of lawyers, 32% of medical promotion officers, and 18% of doctors falsely interpreted their symptoms as originating from gastric acid.

In this study, more than 50 % participants were taking medicine by themselves without consulting any physician and only 39.57% were taking medicine prescribed by the physician. Akter et al. showed 41.7% of patients were taking PPI as per the advice of physicians and 12.6% by patients themselves.[10] In the study by Hasan et al. 67% of patients had taken PPI prescribed by doctors and 33% by non-doctors.[8] Sheikh et al. also reported that 31% of patients received prescriptions from gastroenterologists, 37% from primary care physicians, and 32% purchased OTC PPIs.[11]

Another finding of this study revealed that, 70 (31.53%) patients were taking different types of Antacid preparations, H_2 receptor blockers and proton pump inhibitors inappropriately (without having typical acid-related symptoms); of them, 27 (38.57%) were prescribed by doctors. Inappropriate use of PPI was also described in many other studies at home and abroad. In a Malaysian study by Elnaem et al. showed that about 31% of the prescriptions did not have a clear indication of PPI.[12] Spanish study by Ramirez et al. showed that inappropriate indications of PPI were 74.47% at admission, 61.25% during hospitalization, and 80.24% at discharge.[13] Study by Narido et al. described that PPIs were not indicated in 65% of prescriptions.[14] According to Haroon et al., 45% of patients have no valid indication for PPI.[15] Chia et al. have also found that 54.1% of patients have no indication of PPI.[16] A study at Dhaka Medical College found that discharge certificates of 87% of patients had PPI, and only about 28% of them actually needed it.[17] Study by Ahmed et al. showed that 54.2% of patients were inappropriately prescribed PPIs, of them 24.1% were prescribed for infections, 15.5% for cardiovascular disease and 10.3% for CKDand 18.9% were prescribed for no apparent reason.[18] Similarly, Ali et al. found that 54.7% of patients were prescribed PPI without any documented indication.[19] Nousheen et al. also found PPIs were prescribed irrationally in 58 % of patients without any valid indication.[20] According to Sandozi et al., the indication for prescription was present in only 45% of the patients.[21]

Conclusion:

False perception of symptoms originating from gastric acid is prevalent among the well-educated population, even among doctors. Availability of PPIs without prescription is another issue. These factors lead to inappropriate uses of PPIs for various disorders not actually related to gastric acid causing economic burden as well as health hazards. Proper health education and awareness, mainly regarding "Every problem is not originating from Gastric/Gas," is very important; availability of PPIs without prescription should also be prohibited.

Conflicts of Interest: There is no conflict of interest.

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Referencess:

1. Tack J, Talley NJ. Functional dyspepsia-symptoms, definitions and validity of the Rome III criteria. *Nat Rev Gastroenterol Hepatol.* 2013; 10:134-141.

2. Talley NJ, Stanghellini V, Heading RC, et al. Functional gastro-duodenal disorders. *Gut.* 1999;45(Suppl 2):37-42.

3. Tack J, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology.* 2004;127:1239-1255.

4. Richter JE, Vaezi MF. Gastroesophageal Reflux Disease. In: Feldman M, Friedman LS, Brandt LJ, editors. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease.* 11th ed. Philadelphia: Elsevier; 2021. p.670.

5. Tack J. Dyspepsia. In: Feldman M, Friedman LS, Lawrence, Brandt J, editors. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease.* 11th ed. Philadelphia: Elsevier; 2021. p. 177.

6. Chan FKL, Lau JYW. Peptic Ulcer Disease. In: Feldman M, Friedman LS, Lawrence, Brandt J, editors. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease.* 11th ed. Philadelphia: Elsevier; 2021. p.806.

7. Chan FKL, Lau JYW. Peptic Ulcer Disease. In: Feldman M, Friedman LS, Lawrence, Brandt J, editors. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease.* 11th ed. Philadelphia: Elsevier; 2021. p. 808.

8. Hasan MQ, Mondal NT, Parvin R, Perveen I. Uses of proton pump inhibitors and their prescribing pattern among the patients attending the outpatient department at a tertiary care hospital in Bangladesh. *J Enam Med Col Bull.* 2020;10(1):10–16. doi:10.3329/jemc.v10i1.45060.

9. Sony TA, Alam MN, Hoque MM. An investigation performed in a Bangladeshi general hospital on the use of proton pump inhibitors by patients. *Hosp Pharm Multidiscip j.* 2024;11(3):1476-1482. doi:10.5937/hpimj2403476S

10. Akter H, Khan MZI, Islam MA, Mali B, Arafat SMY. Consumer attitude and awareness regarding use of anti-ulcerant drugs in Bangladesh. *South Asian Res J Bus Manag.* 2019;1(1):5–9.

11. Sheikh I, Waghray A, Waghray N, Dong C, Wolfe MM. Consumer use of over-the-counter proton pump inhibitors in patients with gastroesophageal reflux disease. *Am J Gastroenterol.* 2014;109(6):789-794. doi:10.1038/ajg.2013.421

12. Elnaem MH, Mohamed MHN, bin Nazar AH, binti Ibrahim RNK. Evaluation of proton pump inhibitors prescribing among non-critically ill hospitalized patients in a Malaysian tertiary hospital. *J Appl Pharm Sci.* 2017;7(12):77–83. doi:10.7324/JAPS.2017.71210

13. Ramirez E, Lei SH, Borobia AM, Piñana E, Fudio S, Muñoz R, et al. Overuse of PPIs in patients at admission, during treatment, and at discharge in a tertiary Spanish hospital. *Curr Clin Pharmacol.* 2010;5(4):288-297. doi:10.2174/157488410793352067.

14. Nardino RJ, Vender RJ, Herbert PN. Overuse of acid-suppressive therapy in hospitalized patients. *Am J Gastroenterol.* 2000;95(11):3118-3122. doi:10.1111/j.1572-0241.2000.03259.x

15. Haroon M, Yasin F, Gardezi SK, Adeeb F, Walker F. Inappropriate use of proton pump inhibitors among medical inpatients: a questionnaire-based observational study. *JRSM Short Rep.* 2013;4(8):2042533313497183. doi:10.1177/2042533313497183

16. Chia CT, Lim WP, Vu CK. Inappropriate use of proton pump inhibitors in a local setting. *Singapore Med J.* 2014;55(7):363-366. doi:10.11622/smedj.2014087

17. Imtiaz DMC. Over use of gastric medication; are we safe? *The Financial Express.* 1 June 2022. Available from: https://thefinancialexpress.com.bd/health/overuse-of-gastric-medications-are-we-safe-1654075544 [Accessed 4 April 2025]

18. Ahmed A, Akter B, Naby MM, Rahman MR, Hossain SZ.Proton pump inhibitors usage among discharged patients in a tertiary care hospital- an observational study. *J Medicine.* 2023;24:125-130. doi: https://doi.org/10.3329/jom.v24i2.67275

19. Ali O, Poole R, Okon M, Maunick S, Troy E. Irrational use of proton pump inhibitors in general practice. *Ir J Med Sci.* 2019;188(2):541-544. doi:10.1007/s11845-018-1891-1

20. Nousheen S, Tadvi NA, Shareef SM. Use of proton pump inhibitors in general practice: is it rationale? *Int J Med Res Health Sci.* 2014;3(1):37-42. Available from: https://www.ijmrhs.com/medical-research/use-of-proton-pump-inhibitors-in-general-practice-is-it-rationale.pdf

21. Sandozi T. A comparative study of cost analysis of H2 antagonists and proton pump inhibitors in a tertiary care hospital. *Res J Pharm Biol Chem Sci.* 2013;4(1):888-897.

Original Article

The Role of Neutrophil-Lymphocyte Ratio (NLR), Red Blood Cell Distribution Width (RDW) and Red Blood Cell Distribution Width-Platelet Ratio (RPR) in Assessment of Severity of Liver Damage in Cirrhotic Patients

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Abstract

Background: Liver cirrhosis is a major worldwide health issue, marked by ongoing liver damage that leads to the development of fibrosis and regenerative nodules. The conversion of compensated to decompensated cirrhosis indicates an unwanted outcome. This necessitates tools to assess severity and guide clinical management. This study evaluates the utility of hematological indices Neutrophil-Lymphocyte Ratio (NLR), Red Cell Distribution Width (RDW), and RDW-to-Platelet Ratio (RPR) as non-invasive markers of cirrhosis severity, compared to established scoring systems like Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver disease (MELD).

Materials and Methods: A cross-sectional type of observational study was conducted on 100 cirrhotic patients at Khulna Medical College, Khulna (KMCH), Khulna. Data was collected on selected age group, their clinical history, and laboratory values. Hematological indices (NLR, RDW, RPR) were compared against CTP scores to evaluate diagnostic accuracy. Statistical analyses were done using SPSS-26, and a p-value < 0.05 is considered significant.

Results: Among the patients, RPR demonstrated the highest diagnostic accuracy (AUC=0.805, sensitivity=76.5%, specificity=53.3%) for cirrhosis severity, followed by RDW (AUC=0.780). NLR showed limited diagnostic value (AUC=0.541). Elevated RDW and RPR correlated significantly with advanced cirrhosis ($p<0.001$). Patients predominantly presented with ascites (57%), and hepatitis B was the leading etiology (55%).

Conclusion: RPR and RDW are promising non-invasive markers for assessing liver cirrhosis severity, with RPR being the most reliable. Incorporating these indices into traditional scoring systems could enhance diagnostic accuracy and risk stratification.

Keywords: Neutrophil to lymphocyte ratio, Red blood cell distribution width, Red blood cell distribution width platelet ratio, Cirrhosis of liver, Predictor.

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Introduction:

Liver cirrhosis is a major public concern responsible for significant morbidity and mortality. It is associated with 2.4% of global deaths in 2019. The 2017 Global Burden of Disease (GBD) Study found 112 million people globally were living with compensated cirrhosis, reflecting an age-standardized worldwide prevalence of 1,395 cases per 100,000 individuals.[1]

The primary reasons for liver cirrhosis include chronic hepatitis B, alcoholism, chronic hepatitis C, and metabolic dysfunction-associated steatotic liver disease.2,3 In Bangladesh, the prevalence of hepatitis B virus (HBV) averages 4%-7% in the communities and is the predominant aetiology of chronic liver disease in Bangladesh. 4-6

All chronic liver diseases have the potential to develop into cirrhosis. During this progression, the fibrotic process occurs in several stages, involving abnormal collagen build-up that alters both the composition and amount of the intercellular matrix. Cirrhosis represents a structural alteration of the liver, defined by the formation of regenerative nodules, and indicates a late stage of liver disease. Once cirrhosis reaches an advanced stage, treatment options become very limited.2 Each year, about 5–12% of patients transition from a compensated stage to a decompensated stage of liver disease, which may involve complications such as ascites, hepatic encephalopathy, or variceal bleeding.1 Decompensated cirrhosis is generally associated with a limited survival time of 3 to 5 years. In this scenario, a liver transplant is recommended in the absence of contraindications and needs to be evaluated. It is recommended that a different scoring system should be used to identify and predict the stage of liver failure. As an instance, Child-Turcotte Pugh is generally scored based on different variables, which include bilirubin level, albumin, INR, ascites, and hepatic encephalopathy. In addition to that, the Model for End-stage Liver Disease (MELD) can help us determine stages of liver failure. This can also help to prioritize the patient eligible for liver transplantation, and influence their health-related quality of life and the outcome.[7]

Recently, there has been a growing field to find simple, noninvasive, and cost-effective biomarkers that can reflect the extent of liver injury. Among the emerging biomarkers, hematological indices derived from complete blood counts have gained potential. Necroinflammation is frequently observed in individuals with advanced liver cirrhosis. The neutrophil-to-lymphocyte ratio (NLR) serves as a marker of systemic inflammation, illustrating the interaction between two key immune mechanisms.[8-10] On the other hand, in advanced cirrhotic patients, elevated RDW levels and decreased platelet counts reflect impaired erythropoiesis due to chronic disease and thrombocytopenia from splenic sequestration, respectively.[11] Thus, the neutrophil-lymphocyte ratio (NLR), red blood cell distribution width (RDW), and RDW-to-platelet ratio (RPR) are increasingly being studied for their association with systemic inflammation, disease severity, and clinical outcomes in various inflammatory diseases, malignancies, and hepatic conditions.[10, 12-16]

This study proposed to explore the significance of NLR, RDW, and RPR in the assessment of liver damage in patients with cirrhosis. By analyzing their correlation with established markers of liver injury, we aimed to evaluate their utility as adjuncts in the diagnostic workup and monitoring of cirrhotic patients.

Materials and Methods:

This cross-sectional type of observational study was conducted at Inpatient Department of Gastroenterology and the Department of Medicine, Khulna Medical College Hospital (KMCH), Khulna, Bangladesh, over twelve months, extending from November 2023 to October 2024.

The study included all adult patients (over 18 years old) diagnosed with liver cirrhosis who were admitted to the Department of Gastroenterology at KMCH. A purposive nonprobability sampling technique was performed. Patients with space-occupying lesions in the liver, liver transplant before admission, hematological disorders such as iron deficiency anemia, myeloproliferative disorders, myelodysplastic syndrome, and recent blood transfusion (within 3 months) were excluded. Informed written consent was taken from the patients before they participated in the study. A total of 100 patients were finally enrolled in this study.

Detailed clinical information was taken from each patient and documented on a pre-structured questionnaire. Liver cirrhosis was diagnosed based on clinical, laboratory, radiological, and endoscopic methods. Laboratory parameters were obtained, including complete blood count (CBC), S. albumin, S. bilirubin, prothrombin time (PT), international normalized ratio (INR), S. creatinine, and viral markers (Hepatitis B surface antigen and Anti Hepatitis C virus). The CBC was performed using an automated hematology analyzer. Hematological indices, such as NLR (Neutrophil count / Lymphocyte count), RDW (References range: 11.5-14.5%), and RPR [RDW% / platelet count (×109/ L)] were calculated from the CBC. The severity of cirrhosis was assessed using both the Child-Turcotte-Pugh (CTP) score and the MELD score. After collection, the overall data was carefully reviewed, coded, and revised to ensure accuracy and completeness.

Data analysis was carried out using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables, including age and laboratory results, were reported as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables were summarized as frequencies and percentages. Patients were grouped into Child-Turcotte-Pugh (CTP) classes A, B, and C to assess disease severity. Group comparisons were conducted using independent t-tests or Mann-Whitney U tests for continuous data, and Chi-square or Fisher's exact tests for categorical variables. The relationship between hematological markers (NLR, RDW, RPR) and the severity of cirrhosis was analyzed using Pearson or Spearman correlation coefficients. Receiver Operating Characteristic (ROC) curve analysis was employed to assess the diagnostic performance of these indices, calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the Area Under the Curve (AUC). A p-value less than 0.05 was considered statistically significant, reinforcing the validity of the results.

An ethical review committee of Khulna Medical College, Khulna, cleared the ethical issue, References no. KMC/ERC/106 dated: 16 April 2023 and conducted following the Declaration of Helsinki for human study.

Results:

Of the 100 patients enrolled in this cross-sectional study, 68% were male and 32% were female. The mean age was 50.2 ± 13.6 years, with the majority (44%) falling within the 40 to 60-year age group. Chronic hepatitis B was the most common cause of cirrhosis (55%), followed by Non-B Non-C causes (44%) and alcoholism (1%). About 85% of patients were in a decompensated state (CTP B and C). Ascites (57%) was the most common clinical presentation, followed by variceal bleeding (27%), jaundice (15%), and hepatic encephalopathy (6%) (Table 1).

Table 1: Distribution of study population according to demographic profile (N=100)

Characteristics	Number(%)
Age	
<40 years	29 (29%)
40-60 years	44 (44%)
> 60 years	27(27%)
Mean±SD	50.2±13.6
Gender	
Male	68 (68%)
Female	32 (32%)
Aetiology	
HBV	55 (55%)
Alcohol	1 (1%)
Non B, Non C	44 (44%)
Clinical Symptoms	
Ascites	57 (57%)
Variceal bleeding	27 (27%)
Jaundice	15 (15%)
Hepatic encephalopathy	6 (6%)
Child Turcotte Pugh (CTP) scores	
CTP A	15 (15%)
CTP B	53 (53%)
CTP C	32 (32%)

Table 2 demonstrates S. Bilirubin, ESR, RDW, RPR, and MELD score were significantly higher and S. Albumin and platelet count were significantly lower in class B and C in comparison to class A.

Table 2: Laboratory parameters of the studied population with compensated and decompensated cirrhosis (N=100)

	Class A (n=15) mean±SD	Class B and C (n=85) mean±SD	p-value
S. Bilirubin (mg/dL)	0.92 ± 0.11	4.66 ± 6.98	<0.001**
S. Albumin (g/dL)	20.04 ± 16.34	7.56 ± 8.85	<0.001**
Hemoglobin (g/dL)	10.93 ± 1.20	9.80 ± 2.24	0.061*
TC (cells/mm³)	7863.33 ± 2847.10	9453.18 ± 6291.29	0.340*
Neutrophil (%)	61.39 ± 8.21	63.85 ± 14.20	0.517*
Lymphocyte (%)	29.65 ± 5.98	24.93 ± 10.36	0.090*
NLR	3.13 ± 1.61	3.59 ± 3.39	0.610*
Platelet (cells × 10³/µL)	180.33 ± 43.79	141.35 ± 55.61	0.012*
S. Creatinine (mg/dL)	1.10 ±0.14	1.20 ± 0.43	0.391*
ESR (mm in 1st hour)	28.47 ± 21.52	50.08 ± 26.82	0.004*
PT (seconds)	13.93 ± 1.67	16.32 ± 7.44	0.221*
INR	5.23 ± 5.87	5.91 ± 6.36	0.695*
RDW (%)	14.87 ± 2.69	17.41 ± 3.29	0.006*
RPR	0.09 ± 0.02	0.15 ± 0.09	0.007*
MELDscore	7.79 ± 0.9	14.90 ± 4.81	<0.001*

p-value was determined by *Independent sample t test and **Mann-Whitney test.

[ESR, erythrocyte sedimentation rate; PT, prothrombin time; INR, international normalized ratio; NLR, neutrophil to lymphocyte ratio; RDW, red blood distribution width; RPR, red blood cell distribution width to platelet ratio; MELD, model for end-stage liver disease.]

RDW (%) and RPR level significantly increased with the increased severity of the disease. In Class C, RDW (%) was significantly higher in comparison to Class A and Class B.A significant difference was found between Class A and Class C CTP categories regarding RPR (Table 3).

Table 3: Comparison of NLR, RDW (%), and RPR among different severity of disease using CTP category (N=100)

	Class A	Class B	Class C	p-value*
	Mean±SD	Mean±SD	Mean±SD	
NLR	3.1±1.6	3.3±2.6	4.1±4.4	0.452
RDW (%)	14.9±2.7	16.6±3.2	$18.7\pm3.1^{\alpha\beta}$	<0.001
RPR	0.09±0.02	0.15±0.07	$0.16\pm0.11^{\alpha}$	0.018

*p-value was determined by Post Hoc analysis by Bonferroni test of One Way ANOVA test.

NLR, RDW (%), and RPR were all positively correlated with MELD score. But RDW (%) and MELD score showed significant correlation (Table 4, Figure 1).

Table 4: Correlation of NLR, RDW (%), and RPR with MELD score of the patients (N=100)

	MELD score	
	Correlation coefficient (r)	p-value*
NLR	0.103	0.153
RDW (%)	0.323	0.001
RPR	0.089	0.190

*p-value was determined by the Pearson correlation test.

[NLR, neutrophil to lymphocyte ratio; RDW, red blood distribution width; RPR, red blood cell distribution width to platelet ratio; MELD, model for end-stage liver disease.]

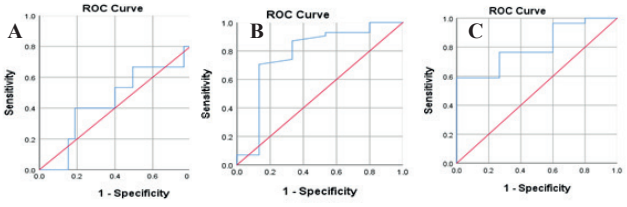

Figure 1: ROC curve analysis of NLR (A), RDW (%) (B), and RPR (C) in the prediction of cirrhosis severity based on CTP score.

In this study, RPR at a cut-off value of 0.10 showed a better marker, with the highest AUC (0.805), better sensitivity (76.5%), and strong PPV (90.3%). Although RDW at a cut-off value of 14.9 % also performs well and has slightly better specificity (74.1%), but a lower AUC (0.780) compared to RPR. NLR at a cut-off value of 2.5 with AUC (0.541) has the poorest performance as diagnostic accuracy (Table 5).

Table 5: Area under the curve, Diagnostic accuracy of NLR, RDW (%), and RPR in the prediction of severity of liver cirrhosis according to CTP score.

	Cut off value	AUC	95% CI	SN (%)	SP (%)	PPV (%)	NPV (%)	Accuracy	p-value
NLR	2.5	0.541	0.386-0.697	49.4	46.7	84	14	49	0.612
RDW (%)	14.9	0.780	0.625-0.934	74.1	66.7	92.6	31.3	73	0.001
RPR	0.10	0.805	0.705-9.04	76.5	53.3	90.3	28.6	73	<0.001

[AUC, area under curve; SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval]

Discussion:

Liver cirrhosis develops gradually over time from chronic liver injury and is often characterized by irreversible fibrosis of liver tissue. As the disease progresses, it disrupts liver function and increases systemic inflammation, making the assessment of disease severity crucial for management and prognosis. This study was tailored to assess the diagnostic accuracy of RDW, RPR, and NLR in evaluating the severity of liver cirrhosis based on Child-Turcotte-Pugh (CTP) scoring.

In this study, most of the patients (71%) were aged 40 years or older, with a mean age of 50.2 ± 13.6 years. This finding is consistent with the study by Hossain et al., which involved patients aged between 22 and 106 years and reported a mean age of 52.33 years.[17] In the previous study by Sungkar et al., the mean age of the patients was 52.76±12.57 years, which was similar to the current study [9]. Another study conducted in Bangladesh, where the mean age was 59.05 ± 12.05 years among cirrhosis patients, which was slightly higher than the current study.[18] A study conducted in China, where the mean age of the cirrhosis patients was 47.23 ± 12.78 years, which was lower than the current study.[19] These differences may reflect regional demographic differences or healthcare accessibility variations.

A male predominance was observed among the patients, with 68% being male, as reported in a previous study. Similarly, out of 78 cirrhosis patients, 62 were male.18 Hossain et al. also found that the majority of cases were male (69.7%), with a male-to-female ratio of 1:0.44, which aligns with the findings of the current study.[17] Another study was conducted by Hong Zhao et al. among the liver cirrhosis patients of China also found a male predominance of 72%.20 This gender disparity likely reflects higher exposure to risk factors like HBV infection and alcohol consumption among males. But a study by Rahut et al. found slightly higher female patients with 52.7%, which may reflect differences in healthcare-seeking behavior or underlying etiological factors like autoimmune or metabolic causes more common in females.[18]

Among all the patients, 55% had HBV, 1% had liver cirrhosis due to alcohol, and 44% showed a Non-B Non-C cause. A previous study reported hepatitis B virus (HBV) as the most common cause of infection, responsible for 53.7% of cases, while 46.3% had no identifiable cause. These results are consistent with findings from other studies in Bangladesh that also recognize HBV as the leading cause of liver disease.[6,17] The low prevalence of alcohol-related cirrhosis (3%) is notable, reflecting cultural or policy-driven low alcohol consumption in the region.

In the present study, ascites was the most frequent clinical manifestation, observed in 57% of patients, followed by variceal bleeding (27%), jaundice (15%), and hepatic encephalopathy (6%). Similarly, a study conducted in Faridpur, Bangladesh, reported ascites in 49.4% of cases, gastrointestinal bleeding in 27%, peripheral edema in 24.7%, and encephalopathy in 21.3% of patients.[17] Previous studies also revealed that ascites as the leading symptom in cirrhosis-related hospitalizations.[5,6]

Among all the patients, 15% had a Class A CTP score, 53% had a Class B, and 32% had a Class C CTP score. Besides, a significant association of S. Bilirubin, S. Albumin, and platelet count with CTP classes repeats their role as critical indicators of cirrhosis severity, and these findings were consistent with other studies.[21,22]

CBC is a simple, inexpensive, readily accessible, and reproducible tool in all resource settings, usually done during the initial evaluation of all patients. The NLR, calculated from CBC, is a marker of systemic inflammation. In liver cirrhosis, the NLR reflects the heightened inflammatory milieu and immune dysregulation characteristic of advanced liver disease. Elevated neutrophil counts indicate a pro-inflammatory state, while lymphopenia reflects immune suppression, both of which are hallmarks of cirrhosis.[23] RDW is the measuring tool to estimate the variation in red blood cell size or anisocytosis, and is a routine parameter in the complete blood count. In cirrhotic patients, elevated RDW levels reflect the interplay of several pathological processes, including systemic inflammation, malnutrition, and impaired erythropoiesis due to chronic disease. The pro-inflammatory cytokines associated with cirrhosis, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), disrupt erythropoiesis and iron metabolism, contributing to increased RDW.24 RPR is a novel composite index combining RDW and platelet count,[25] two parameters frequently altered in cirrhosis. Thrombocytopenia, a hallmark of cirrhosis, results from splenic sequestration, reduced thrombopoietin production, and bone marrow suppression.[26]

In the current study, RPR and RDW are the best markers for severity assesment, with RPR having the highest AUC of 0.805 at a cutoff value of 0.10, demonstrating 76.5% sensitivity, 53.3% specificity, 90.3% positive predictive value (PPV), and 28.6% negative predictive value, along with 73% accuracy and a significant p-value (<0.001). RDW also performs well, with an AUC of 0.780 at a cutoff value of 14.9%, 74.1% sensitivity, 66.7% specificity, 92.6% PPV, and 31.3% NPV, achieving 73% accuracy and a p-value of 0.001. In contrast, NLR shows a lower severity assesment value with an AUC of 0.541 at a cutoff value of 2.5, 49.4% sensitivity, 46.7% specificity, 84% PPV, 14% NPV, and 49% accuracy, making it less effective compared to RPR and RDW. Hashemi et al. demonstrated that the NLR, with an optimal cut-off value of > 1.95, showed a sensitivity of 84.75% and specificity of 93.91% in predicting complications during a 1-year follow-up (AUC = 0.905, P < 0.0001).8 A previous study found that RDW and RPR levels were significantly higher in decompensated cirrhosis patients compared to those with compensated cirrhosis (all P < 0.001). The area under the curve (AUC) for NLR was 0.801, with a cut-off value of 2.06, demonstrating 71.7% sensitivity and 78.1% specificity. The AUC values for RDW and RPR were 0.815 (cut-off value: 15.5%; sensitivity: 76.1%; specificity: 75.0%) and 0.876 (cut-off value: 0.166; sensitivity: 93.5%; specificity: 75.0%), respectively. Both NLR, RDW, and RPR were significantly elevated and correlated with disease severity in HBV-related cirrhosis patients, with RPR emerging as the most reliable marker for assessing disease severity, followed by RDW(%).[24] Another study by Li et al. also revealed that liver cirrhosis was significantly associated with an increased RPR and area under the curve (0.821) of RPR levels, indicating that it has high diagnostic performance for predicting disease severity.19 Another study suggested that RPR and RDW are strong biomarkers for assessing disease severity in liver cirrhosis. Among these, RPR is highlighted as the most effective, with a higher sensitivity and AUC value compared to other biomarkers. RPR showed a high sensitivity of 93.5% and specificity of 75%, making it the best non-invasive biomarker for predicting complications in cirrhosis patients.[11]

In this study, a comparison of NLR, RDW (%) and RPR among different classes of CTP scores showed that RDW (%) and RPR levels significantly increased with the increased severity of disease. Besides, correlation analysis of NLR, RDW (%), and RPR with the MELD score was found positive in this study. However, only RDW (%) and MELD score showed a correlation with a p-value equal to 0.001 (r = 0.323).

A positive correlation with a significant p value was also observed between NLR, RDW and RPR with MELD scores, respectively ($r = 0.340$, $r = 0.425$, and $r = 0.464$).[24] In a similar study by HeQ et al. Correlation between NLR and CTP score was also obtained significantly ($r = 0.326$, $p = 0.008$ and $p < 0.001$ respectively) by other studies.[9,23]

In this current study, NLR showed the least diagnostic accuracy. The value of NLR could be influenced by certain factors like timing of blood sampling, ongoing treatment of subjects, renal dysfunction, hematological alterations due to hypersplenism in an advanced cirrhotic stage, and point time of approach of the cross-sectional study might limit the findings of the study. Therefore, future studies of larger sample sizes that consider confounding variables are needed.

Conclusion:

This study emphasizes the value of hematological indices-Red Blood Cell Distribution Width (RDW), RDW-to-Platelet Ratio (RPR), and Neutrophil-to-Lymphocyte Ratio (NLR)-as non-invasive tools for evaluating liver damage severity in patients with cirrhosis. Among these, RPR exhibited the highest diagnostic accuracy, demonstrating notable sensitivity and specificity in identifying advanced cirrhosis (Child-Turcotte-Pugh Classes B and C). RDW also showed strong predictive capability, while NLR was comparatively less accurate. As these markers are cost-effective and readily available through routine blood tests, they can serve as useful adjuncts to conventional scoring systems like CTP and MELD. The findings support the integration of RPR and RDW into standard evaluation protocols to enhance early detection and management of liver cirrhosis.

Conflicts of Interest: There is no conflict of interest.

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Referencess:

1. Huang DQ, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E, et al. Global epidemiology of cirrhosis: aetiology, trends and predictions. *Nat Rev Gastroenterol Hepatol.* 2023;20(6):388–398.

2. Stasi C, Silvestri C, Voller F, Cipriani F. Epidemiology of liver cirrhosis. *J Clin Exp Hepatol* [Internet]. 2015 [cited 2025 May 2];5(3):272–280. Available from: http://dx.doi.org/10.1016/j.jceh.2015.06.002

3. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet.* 2008; 371 (9615):838–851.

4. Uz-Zaman MH, Rahman A, Yasmin M. Epidemiology of hepatitis B virus infection in Bangladesh: prevalence among general population, risk groups and genotype distribution. *Genes (Basel).* 2018;9(11):e548.

5. Das D, Mahtab MA, Rahim MA, Malakar DR, Kabir AKMH, Rahman S. Hepatitis B virus is the leading cause of cirrhosis of liver in Bangladesh. *Hepatol Int.* 2007;1(1):120–122.

6. Rahman S, Ahmed MF, Alam MJ, Hoque MI, Debnath CR. Distribution of liver disease in Bangladesh: a cross-country study. *Euroasian J Hepatogastroenterol.* 2014;4(1):25–30.

7. Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. *Gut.* 2017;66(3):541–553.

8. Hashemi SJ, Tosi MS, Hajiani E, Parsi A, Alavinejad P. The association between peripheral blood neutrophil-to-lymphocyte ratio and cirrhosis complications in adults with compensated liver cirrhosis in Ahvaz, Iran. *Shiraz E-Med J.* 2023;24(8):e139042.

9. Sungkar T, Rozi MF, Dairi LB, Zain LH. Neutrophil-to-lymphocyte ratio (NLR) and its correlation with severity of decompensated liver cirrhosis based on Child-Turcotte Pugh (CTP) score. *J Clin Diagn Res.* 2019;13(4):OC09-OC12.

10. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the immune system and diseases. *Int J Mol Sci.* 2022;23(7):3216.

11. Chen B, Ye B, Zhang J, Ying L, Chen Y. RDW to platelet ratio: a novel noninvasive index for predicting hepatic fibrosis and cirrhosis in chronic hepatitis *B. PLoS One.* 2013;8(7):e68780.

12. Kushwaha S, Kaushik R, Kakkar R, Kaushik RM. Red cell distribution width and neutrophil-lymphocyte ratio as inflammatory markers in patients with rheumatoid arthritis. *Reumatologia.* 2023;61(1):13–20.

13. Chen S, Zhang L, Yan G, Cheng S, Fathy AH, Yan N, et al. Neutrophil-to-lymphocyte ratio is a potential prognostic biomarker in patients with ovarian cancer: a meta-analysis. *Biomed Res Int.* 2017;2017:7943467.

14. Liu D, Huang Y, Li L, Song J, Zhang L, Li W. High neutrophil-to-lymphocyte ratios confer poor prognoses in patients with small cell lung cancer. *BMC Cancer.* 2017;17(1):882.

15. Lou YF, Wang MY, Mao WL. Clinical usefulness of measuring red blood cell distribution width in patients with hepatitis *B. PLoS One.* 2012;7(5):337644.

16. Li X, Xu H, Gao P. Red blood cell distribution width-to-platelet ratio and other laboratory indices associated with severity of histological hepatic fibrosis in patients with autoimmune hepatitis: A retrospective study at a single center. *Med Sci Monit.* 2020;26:e921465.

17. Hossain MI, Islam MA, Bodiuzzaman M, Talukder MSI, Ul Islam MS, Raha A. Mode of presentation of liver cirrhosis: a study in a tertiary level hospital. *Faridpur Med Coll J.* 2021;16(1):39–41.

18. Rahut A, Datta IK, Ullah P, Akhter R, Mia MR, Sarkar S. Role of serum ferritin as a marker of decompensated cirrhosis and its correlation with CTP, MELD and MELD-Na scores. *World J Biol Pharm Health Sci.* 2024;20(1):165–175. doi:10.30574/wjbphs.2024.20.1.0696

19. He Q, He Q, Qin X, Li S, Li T, Xie L, et al. The relationship between inflammatory marker levels and hepatitis C virus severity. *Gastroenterol Res Pract.* 2016;2016:5793718.

20. Zhao H, Gu X, Zhao R, Shi Y, Sheng J. Evaluation of prognostic scoring systems in liver cirrhosis patients with bloodstream infection. *Medicine* (Baltimore). 2017;96(50):e9256.

21. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. *J Hepatol.* 2005;42(Suppl 1):S100–107.

22. Garcia-Tsao G. The Child–Turcotte classification: from gestalt to sophisticated statistics and back. *Dig Dis Sci.* 2016;61(11):3102–3104.

23. Sarma PK, Roy P, Ahmed NU, Sarkar H, Rongpi L. Evaluation of neutrophil-to-lymphocyte ratio (NLR) and its correlation with severity of liver cirrhosis based on Child–Turcotte–Pugh score in a tertiary care hospital, Barpeta, Assam. *J Evid Based Med Healthc.* 2021;8(38):3395–3400.

24. He Q, He Q, Deng Y, He Y, Xie L, Li T, Qin X, Li S. The relationship between inflammatory marker levels and HBV-related cirrhosis severity. *Int J Clin Exp Med.* 2016;9(11):22200-22205.

25. Çetinkaya E, Şenol K, Saylam B, Tez M. Red cell distribution width to platelet ratio: new and promising prognostic marker in acute pancreatitis. *World J Gastroenterol.* 2014;20(39):14450–14454.

26. Hayashi H, Beppu T, Shirabe K, Maehara Y, Baba H. Management of thrombocytopenia due to liver cirrhosis: a review. *World J Gastroenterol.* 2014;20(10):2595–2605.

Original Article

Hepatitis B Virus Core Antibody and Anti-HBs Status of HBsAg Negative Persons Working in a Diagnostic Center in Sylhet, Bangladesh

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Abstract

Background: Hepatitis B virus (HBV) infection is a significant global health concern. Exploring the serological markers of HBV infection, particularly the core antibody (anti-HBc), in HBsAg-negative individuals is crucial for understanding their prior exposure to the virus and possible risk of transmissibility.

Materials and Methods: This cross-sectional study was conducted at the Department of Gastroenterology, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh, from July 2022 to December 2022 to assess the frequency of hepatitis B virus core antibody status among HBsAg-negative persons working in a diagnostic center in Sylhet, Bangladesh. In this study, 51 individuals who tested negative for HBsAg were included as the study subjects. The sample selection process utilized a purposive sampling technique, and data analysis was performed using MS Office tools.

Results: In this study, the prevalence of anti-HBc antibodies among participants was found to be 17.65%. Within the ≤30 years age group, 15% of cases exhibited reactivity, while in the >30 years age group, the reactivity was found in 27% of cases. Regarding the gender-specific distribution of anti-HBc status, among males, 12.5% had a reactive status, while among females, 36.4% exhibited reactivity.

Conclusion: In this study, among the HBsAg negative subjects, the frequency of Anti-HBc positivity was higher in the older age group and in females. Though these associations are not statistically significant, they might provide an insight into further research in this field.

Keywords: Hepatitis B virus, HBsAg negative, Anti-HBc antibodies

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Introduction:

Hepatitis B virus (HBV) is a highly prevalent viral infection.[1] Some countries have adopted anti-HB core (HBc) assays to detect chronic carriers with low-level viremia but lacking detectable HBsAg.[2] Despite the screening methods applied, it was observed that HBV infection can still occur even in the absence of HBsAg, which is known as occult HBV infection (OBI).[3]

This phenomenon is becoming increasingly recognized in several clinical settings worldwide. OBI may be an antibody positive-anti-HBc alone or together with anti-HBs (seropositive OBI) or antibody negative (seronegative OBI).[4] The Taormina Consensus Conference in 2008 further defined "OBI" as the "presence of HBV DNA in the liver of individuals testing HBsAg negative with currently available assays" and introduced a cutoff value for serum HBV DNA (< 200 IU/mL).[5]

OBI can cause fulminant hepatitis. It is associated with the development of hepatocellular carcinoma and cryptogenic liver disease. It can also affect the disease progression of chronic hepatitis C virus (HCV) patients.[6] Previously, detection of anti-HBc antibodies was rarely done as it was not mandatory.[7] But, patients with occult HBV infection, who lack detectable HBsAg with anti-HBc positivity and HBV DNA, are a potential source of HBV infection.[8] HBV can also be transmitted when the liver is transplanted from an HBsAg-negative, anti-HBc-positive patient, which proves that the liver harbors infectious HBV in some patients negative for HBsAg but positive for anti-HBc.[9] OBI carriers with high anti-HBs levels are unlikely to transmit the infection, whereas those with "anti-HBc only" might transmit the infection.[10]

The objective of this study was to assess the frequency of hepatitis B virus core antibody among HBsAg-negative persons working in a diagnostic center in Sylhet, Bangladesh.

Materials and Methods:

This cross-sectional study was conducted at the Department of Gastroenterology, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh, from July 2022 to December 2022. This study included 51 individuals with negative HBsAg results. The participants, of both genders and aged between 18-65

years, were selected using a purposive sampling technique. Before data collection, explicit and informed consent was obtained from each participant.

The participants underwent screening for HBsAg through both rapid diagnostic test (RDT) and enzyme-linked immunosorbent assay (ELISA), and anti-HBc was assessed using ELISA. Exclusion criteria for this study comprised individuals unwilling to participate, those below 18 years of age, and patients testing positive for HBsAg. Comprehensive demographic and clinical information of the participants was recorded. The data underwent processing, analysis, and dissemination using MS Office tools.

Results:

This study involved 51 individuals with negative HBsAg results who were employed at a diagnostic center in Sylhet, Bangladesh. In this study, an examination of the age distribution among the study subjects revealed that most of the participants (80%) belonged to the age group of <30 years, while the remaining 20% were from the >30 years age group (Table 1).

Table 1: Distribution of study subjects according to age (N=51)

Age (Years)	Number (Percentage)
≤30	41 (80)
>30	10 (20)

Upon analyzing the gender distribution of the study subjects, it was observed that the predominant majority of participants (78%) were male, while the remaining cases (22%) were female (Figure 1).

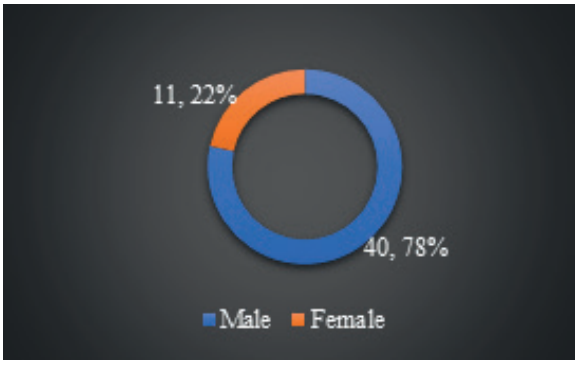

Figure 1: Distribution of study subjects according to gender (N=51)

During the assessment of the prevalence of anti-HBc antibodies among participants, it was noted that the frequency of cases with anti-HBc antibodies was 17.65% (Figure 2).

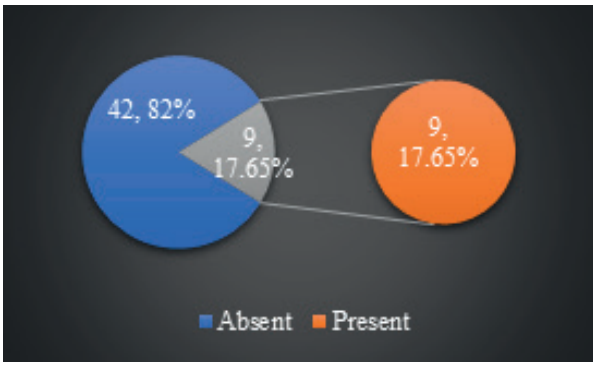

Figure 2: Prevalence of anti-HBc antibodies among participants

In examining the distribution of anti-HBc status, it was noted that within the ≤30 years age group, 15% of cases were reactive, while 85% tested negative. Conversely, in the >30 years age group, 27.3% were reactive, and 72.7% tested negative for anti-HBc (Table 2).

Table 2: Age-wise anti-HBc antibodies status distribution (N=51)

	Age ≤30 years	Age >30 years	p value*
HBsAg status	(n=40)	(n=11)	
	Number (Percentage)	Number (Percentage)	0.30
Reactive	6 (15.0)	3 (27.3)	
Negative	34 (85.0)	8 (72.7)	

*Chi-Square test was done to see the level of significance.

In terms of the gender-specific distribution of anti-HBc status, it was observed that among males, 12.5% had a reactive status, while 87.5% tested negative. In contrast, among females, 36.4% showed a reactive status, and 63.6% tested negative for anti-HBc (Table 3).

Table 3: Gender-wise anti-HBc status distribution

	Male	Female	p value*
HBsAg status	(n=40)	(n=11)	
	Number (Percentage)	Number (Percentage)	0.067
Reactive	5 (12.5)	4 (36.4)	
Negative	35 (87.5)	7 (63.6)	

*Chi-Square test was done to see the level of significance.

Discussion:

This study aimed to assess the frequency of hepatitis B virus core antibody among HBsAg-negative persons working in a diagnostic center in Sylhet, Bangladesh. In the present study, the analysis of the age distribution among the study subjects revealed that a substantial majority (80%) fell within the <30 years age group, with the remaining 20% belonging to the >30 years age group. In contrast, a different study demonstrated that 61.2% of their participants were from the <30 years age group and 38.8% were from the >30 years age group.[11]

Upon examining the gender distribution of our study subjects, it was noted that the significant majority (78%) were male, while the remaining cases (22%) were female. A study conducted by Fasola et al. reported a similar pattern where 86.5% of participants were male, and 13.5% were female.[12]

In our study, the assessment of the prevalence of anti-HBc antibodies among participants revealed that the frequency of cases with anti-HBc antibodies was 17.65%. A nearly similar finding of 14.6% was observed in another study.[13] Additionally, the prevalence of anti-HBc total antibodies among HIV-positive individuals in a study in eastern India, reported a prevalence of 17.8%, which finding is similar to our study.[14] Furthermore, in our study, an examination of the distribution of anti-HBc status showed that within the ≤ 30 years age group, 15% of cases were reactive, while, in the >30 years age group, 27.3% were reactive, for anti-HBc. A prior study reported that the proportion of participants aged 18–35 years with a positive anti-HBc was lower (42.2%) compared to participants above 36 years (61.8%), aligning with the findings in the current study.[12] Conversely, dissimilar observations were noted in another study conducted in Nepal.[15] In our study, regarding the gender-specific distribution of anti-HBc status, it was observed that among males, 12.5% had a reactive status while among females, 36.4% showed a reactive status. In a study conducted in India by Asim et al., no difference in the seroprevalence of the core antibody between male and female donors was reported (19.3% vs. 18%).[16] This finding does not align with the results of our study. Despite variations in results of our study when compared to other studies, both similarities and dissimilarities could contribute valuable insights for further similar studies.

This study was conducted at a single center and involved a relatively small sample size. Additionally, the study duration was limited to a short period. Consequently, it is important to acknowledge that the findings of this study may not accurately represent the broader scenario across the entire country.

Conclusions:

The analysis of findings from this study sheds light on the prevalence of anti-HBc antibodies in HBsAg-negative individuals employed in a diagnostic center in Sylhet, Bangladesh. The overall prevalence is notably not very high, indicating a potential level of resilience or low exposure within this specific occupational group. Nevertheless, the disparities in prevalence among age groups and genders are noteworthy. The higher prevalence among individuals aged over 30 years implies a potential cumulative risk over time, while the elevated prevalence among females compared to males warrants further exploration and consideration in public health strategies. These insights underscore the importance of targeted interventions and ongoing surveillance to effectively manage and mitigate the risk of hepatitis B in this specific population.

Conflicts of Interest: There is no conflict of interest.

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Referencess:

1. Calderon GM, González-Velázquez F, González-Bonilla CR, et al. Prevalence and risk factors of hepatitis C virus, hepatitis B virus, and human immunodeficiency virus in multiply transfused recipients in Mexico. *Transfusion.* 2009;49(10):2200–2207. https://doi.org/10.1111/-j.1537-2995.2009.02248.x

2. Busch MP. Should HBV DNA NAT replace HBsAg and/or anti-HBc screening of blood donors? *Transfus Clin Biol.* 2004;11(1):26–32.

3. Allain JP. Occult hepatitis B virus infection. *Hep B Annu.* 2005;2:14–30.

4. Said ZN. An overview of occult hepatitis B virus infection. World J *Gastroenterol.* 2011;17(15):1927–1938.

5. Raimondo G, Allain JP, Brunetto MR, et al. Statements from the Taormina expert meeting on occult hepatitis B virus infection. *J Hepatol.* 2008;49(4):652–657.

6. Giudice CL, Martinengo M, Pietrasanta P, et al. Occult hepatitis B virus infection: a case of reactivation in a patient receiving immunosuppressive treatment for allogeneic bone marrow transplantation. *Blood Transfus.* 2008;6(1):46–50.

7. Chattopadhyay S, Rao S, Das BC, Singh NP, Kar P. Prevalence of transfusion-transmitted virus infection in patients on maintenance hemodialysis from New Delhi, India. *Hemodial Int.* 2005;9(4):362–366.

8. Dreier J, Kröger M, Diekmann J, Götting C, Kleesiek K. Low-level viremia of hepatitis B virus in an anti-HBc- and anti-HBs-positive blood donor. Transfus Med. 2004;14(2):97–103.

9. Dickson RC, Everhart JE, Lake JR, et al; National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. *Gastroenterology.* 1997;113(5):1668–1674.

10. Allain JP, Mihaljevic I, Gonzalez-Fraile MI, et al. Infectivity of blood products from donors with occult hepatitis B virus infection. *Transfusion.* 2013;53(7):1405–1415.

11. Ghosh DK, Biswas A, Mondal RK, et al. Prevalence of anti-HBc total positivity in an impoverished urban community in *Bangladesh. Bangladesh Med Res Counc Bull.* 2017;43(2):63–70.

12. Fasola FA, Fowotade AA, Faneye AO, Adeleke A. Prevalence of hepatitis B virus core antibodies among blood donors in Nigeria: implications for blood safety. *Afr J Lab Med.* 2022; 11(1):a1434.

13. Madhavan A, Nair CB, Radhakrishnan N, et al. Prevalence of anti-HBc antibodies among HBsAg-negative individuals and its association with occult hepatitis *B. J Lab Physicians.* 2021;13(1):1–5.

14. Saha D, Pal A, Sarkar N, et al. Occult hepatitis B virus infection in HIV-positive patients at a tertiary healthcare unit in eastern India. *PLoS One.* 2017;12(6):e0179035.

15. Shrestha SM. Seroepidemiology of hepatitis B in *Nepal. J Commun Dis.* 1990;22:27–32

16. Asim M, Ali R, Khan LA, Husain SA, Singla R, Kar P. The significance of the anti-HBc screening of blood donors and its association with the occult hepatitis B virus infection: the implications for blood transfusion. *Indian J Med Res.* 2010;132:312-317.

17. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50:661-662.

18. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol.* 2012;57:167-185.

Original Article

Yields of Ultrasonogram, Upper GIT Endoscopy, and Stool Antigen Test for H. pylori in Dyspeptic Patients

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Abstract

Background: Dyspepsia is a common problem of diverse etiology. This study was done to see the sonographic and endoscopic findings and H. pylori infection status of dyspeptic patients.

Materials and Methods: A Total of 156 consecutive dyspeptic patients attending outpatient department consultations were included in this cross-sectional study following inclusion and exclusion criteria. Epidemiological information, anthropometric measurements, symptoms, results of clinical examinations, and reports of investigations, specifically ultrasonography, stool antigen for H. pylori, and upper GIT endoscopy, were recorded in a predesigned data sheet. Mean and standard deviation were calculated for qualitative data. The percentage was calculated for categorical data. The Chi-square test was done to compare variables of categorical data and a P value < 0.05 was taken as significant.

Results: NAFLD, Gastro-duodenal pathology, and stool antigen for H. pylori positivity were higher in patients of the 31-50 years age group. NAFLD was significantly higher among patients from rural communities with higher BMI and higher educational backgrounds. Stool antigen for H. pylori positivity significantly differed between sexes. Endoscopic findings differed significantly within educational groups.

Conclusion: Inflammatory gastroduodenal lesions, H. pylori infection, and gallstone disease are common findings in patients with dyspepsia.

Keywords: Dyspepsia, H. pylori, Ultrasonogram, Upper GIT Endoscopy, Stool Antigen Test.

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Introduction:

Dyspepsia is defined as symptoms – pain in the epigastrium, burning in the epigastrium, early satiety, and postprandial fullness singly or in combination and arising from the upper gastrointestinal tract.[1,2] It is very common and worldwide, about 25% of the general population are suffering from dyspepsia.[1,3-5] It leads to significant morbidity that interferes with quality of life and requires huge costs for consultation, investigations, medication, and extended time.[6,7] Causes of dyspepsia are variable. It includes peptic ulcer disease, gastro-oesophageal reflux disease, gastric cancer and other tumors, gallstone disease, medication, and functional dyspepsia or non-ulcer dyspepsia.[8] Functional dyspepsia constitutes about 70-80% of total dyspeptic patients, while about 11% of patients show peptic ulcer disease by endoscopy.[9] Helicobacter pylori infection plays a significant role in peptic ulcer and gastric neoplasm. However, only *H. pylori* infection with or without an ulcer can cause dyspepsia. Eradication of *H. pylori* leads to a 25% reduction in consultations for dyspeptic patients.[10]

Among noninvasive tests for H. pylori, the stool antigen test is one with sensitivity and specificity of 94% and 97%, respectively.11 Gallstone disease can also cause dyspeptic symptoms, and transabdominal ultrasonography can detect gallstone disease with a sensitivity and specificity of more than 95%.12 Previous studies show that the prevalence of dyspepsia ranges from 8-61% in the general population.13,14 But these are uninvestigated dyspepsia. As clinical features alone cannot always reliably differentiate organic from functional dyspepsia, abdominal ultrasonogram, stool for antigen for H. pylori test, and endoscopy of the upper GI tract are important tools for evaluation of dyspepsia. 15 With this view, we designed this study to see the outcome of USG, stool antigen test for H. pylori, and upper GI tract endoscopy among dyspeptic patients in Sylhet, Bangladesh.

Materials and Methods:

This study was conducted in Popular Medical Centre, Sylhet, Bangladesh, from January 2021 to June 2021. All the consecutive patients presenting with dyspepsia attending for consultation were included. Previously diagnosed cases of peptic ulcer disease, hepato-biliary and pancreatic disease, having a history of UGI bleeding, having a history of abdominal surgery, pregnant lady, suffering from chronic debilitating disease, history of taking chemotherapy, and patients not agreeing to take part in the study were excluded. Epidemiological information, symptoms, results of clinical examinations, and reports of relevant investigations, including ultrasonography, stool antigen for *H. pylori*, and upper GIT endoscopy, were recorded in a data sheet.

Data were analyzed using SPSS version 20 (IBM Corp., Armonk, NY, USA). For continuous data, mean, standard deviation, and categorical data percentages were calculated. The Chi-square test was done to compare variables, and a P value < 0.05 was taken as significant.

Results:

A total of 156 patients, male 106 (67.9%) and female 50 (32.1%), aged varying from 16 years to 76 years (mean 42.50±14.39), were included. Of them, 134 (85.9%) were from rural areas. In this series, most of the participants, 125 (80.1%), were married. Among them, 33 (21.2%) were illiterate, while 61 (30.1%), 41 (26.3%), and 21 (13.5%) had up to primary level, up to secondary, and higher secondary level, and above education, respectively. In this study, 100 (64.1%) and 53(34.0%) were from poor, middle-class economic groups, respectively. In this series, 30 (19.2%) and 24 (15.4%) were smokers and betel nut chewers, respectively. In this series, 148 (94.9%) were taking proton pump inhibitors (PPI) and 18 (11.5%) were taking non-steroidal anti-inflammatory drugs (NSAID) (Table 1).

Table 1: Distribution of study subjects according to epidemiological data, clinical, and laboratory data (N=156)

Variables	Number (Percentage)
Sex	
Male	106 (67.9)
Female	50 (32.1)
Age	
Up to 30 years	38 (24.4)
31-50 y	76 (48.7)
51 and above	42 (26.9)
Residence	
Rural	135 (86.5)
Urban	21(13.5)
Marital status	
Married	125 (80.1)
Single	21 (13.5)
Widow/widower	10 (6.4)
Education	
Illiterate	34 (21.8)
Primary	61 (39.1)
Secondary and higher secondary	42 (26.9)
Above	19 (12.2)
Economic group	
Poor	100 (64.1)
Middle class	53 (34.0)
Rich	3 (1.9)
Other	
Smoker	30 (19.2)
Betel nut chewer	24 (15.4)
Taking PPI	148 (94.9)
Taking NSAID	18 (11.5)

Presenting complaints were abdominal pain (77; 49.4%), fullness of abdomen (47; 30.1%), early satiety, vomiting, and others (37; 23.7%), burning abdomen (12; 7.7%), and abdominal discomfort (3; 1.9%).

Ultrasonogram (USG) of the abdomen revealed gallstones in 8 (5.1%), and nonalcoholic fatty liver disease (NAFLD) in 14 (9.0%). USG scan was normal in 102 (65.4%), and the remaining 32 (20.5%) had nonspecific findings not related to the hepato-biliary system or pancreas. In this study, stool antigen for *H. pylori* was positive in 59 (37.8%).

Table 2: Distribution of study subjects according to clinical and laboratory data (N=156)

Variables	Number (%)
Symptoms	
Pain abdomen	77 (49.4)
Burning abdomen	12 (7.7)
Fullness ofthe abdomen	47 (30.1)
A bdominal discomfort	3 (1.9)
Early satiety, vomiting, and others	37 (23.7)
Ultrasonogram	
Normal	102 (65.4)
Gall stone	8 (5.1)
Non Alcoholic Fatty Liver Disease	14 (9.0)
Others	32 (20.5)
Stool Antigen Test for *H. pylori*	
Positive	59 (37.8)
Negative	97 (62.2)
Endoscopy of UGIT	
Normal	29 (18.5)
gastritis (non-erosive, erosive, pangastritis)	69 (44.23)
gastric ulcer	10 (6.4)
Duodenal ulcer, duodenitis, DU in remission	31 (19.9)
O esophagitis	4 (2.6)
Gastric and duodenal lesions	13 (8.33)

Abdominal pain (41; 26.28%) and abdominal fullness (21; 13.46%) were more common in patients of the 31 to 50 years age group. Gastro-duodenal pathology and stool antigen for *H. pylori* positivity were also more common in patients of the 31-50 years age group. Symptoms of fullness of the abdomen significantly differed among patients within age groups (Table 3).

Table 3: Relation of symptoms and investigation reports with age groups (N=156)

Variables		Up to 30 y N (%)	31-50 y N (%)	>50 y N (%)	*p value
Abdominal pain	Yes (77)	20 (25.97)	41(53.25)	16(20.78)	0.23
	No (79)	18(22.78)	35(44.30)	26(32.91)	
Burning	Yes (12)	5(41.66)	6(50.00)	1(8.33)	0.19
	No (144)	33(22.91)	55(38.19	23(15.97)	
Fullness	Yes (47)	7(14.89)	21(44.68)	19(40.42)	0.027
	No (109)	31(28.44)	55(50.46)	23(21.10)	
Discomfort	Yes (3)	1(33.33)	2(66.66)	0	0.569
	No (153)	37(24.18)	74(48.66)	42(27.45)	
Early satiety, others	Yes (38)	7(18.42)	20(52.63)	11(28.95)	0.618
	No (118)	31(26.27)	56(47.46)	31(26.27)	
PPI use	Yes (148)	35(23.65)	72(48.65)	41(27.70)	0.535
	No (8)	3(37.5)	4(50.0)	1(12.5)	
NSAID	Yes (18)	3(16.66)	11(61.11)	4(22.22)	0.521
	No (138)	35(25.36)	65(47.10)	38(27.53)	
USG of the abdomen	Normal (102)	31(30.39)	49(48.03)	22(21.57)	0.194
		2 (25.0)	3(37.5)	3(37.5)	
	NAFLD (14)	1(7.14)	8(57.14)	5(35.71	
	Other (32)	4(12.5)	13(40.62)	15(46.87)	
Stool H. pylori	Positive (59)	13(22.03)	30(50.84)	16(27.12)	0.861
	Negative (97)	25(25.77)	46(47.42)	26(26.80)	
	Normal (29)	5(17.24)	20(68.96)	4(13.79)	0.420
	Gastritis(69)	18(26.07)	30(43.48)	21(30.43)	
	DU (31)	8(25.80)	12(38.71)	11(35.48)	
	GU (10)	2(20.0)	7(70.0)	1(10.0)	
	Oesophagitis(4)	0	3(75.0)	1(25.0)	
	Others (13)	5(38.46)	4(30.77)	4(30.77)	

*Chi-Square test was done to see the level of significance.

Patients from rural communities, patients with higher BMI, and higher education levels had significantly higher incidences of NAFLD. Stool antigen for *H. pylori* positivity significantly differed within sex. Endoscopic findings differed significantly within educational groups (Tables 4,5,6,7).

Table 4: Relation of clinical and laboratory reports with sexes and residence (N=156)

Variables		Male	Female	p	Rural	Urban	*p
PPI	Y (148)	100 (67.56)	48 (32.43)	0.398	127 (85.81)	21 (14.19)	0.306
	N (8)	6(75.0)	2(25.0)		8(100.0)	0	
NSAID	Y (18)	12 (66.66)	6(33.33)	0.547	18 (100.0)	0	0.063
	No (138)	94 (68.11)	44 (31.88)		117 (84.78)	21 (15.22)	
USG	Normal (102)	70 (68.63)	32 (31.37)	0.781	94 (92.16)	8)7.84)	0.015
	Stone (8)	5(62.5)	3(37.5)		6(75.0)	2(25.0)	
	NAFLD (14)	11 (78.57)	3(21.43)		9(64.28)	5(35.72)	
	Others (32)	20 (62.5)	12 (37.5)		26 (81.25)	6(18.75)	
Stool *H. pylori*	Positive (59)	49 (83.05	10 (16.95)	0.001	53 (89.83)	6(10.17)	0.246
	Negative (97)	57 (58.76)	40 (41.24)		82 (84.54)	15 (15.46)	
Endoscopy	Normal (29)	15 (51.72)	14 (48.28)	0.310	25 (86.21)	4(13.79)	0.692
	Gastritis (69)	48 (69.56)	21 (30.44)		65 (94.2)	4(5.80)	
	DU (31)	25 (80.64)	6(19.35)		25 (80.64)	6(19.35)	
	GU (10)	8(80.0)	2(20.00)		8(80.0)	2(20.0)	
	Oesophagitis (4)	3(75.0)	1(25.0)		4(100.0)	0	
	Others (13)	7(53.85)	6(46.15)		8(61.54)	5(38.46)	

*Chi-Square test was done to see the level of significance.

Table 5: Relation of laboratory data with smoking and marita status (N=156)

Variables		Smoking			Marital status			
		Yes	No	p	Single	Married	Others	*p
USG	Normal(102)	16(15.7)	86(84.3)	0.241	20(19.6)	76(74.5	6(5.9)	0.087
	Stone(8)	1(12.5)	7(87.5)		1(12.5)	6(75.0)	1(12.5)	
	NAFLD(14)	5(35.7)	9(64.3)		0	13(92.9)	1(7.1)	
	Others(32)	8(25.0)	24(75.0)		0	30(93.8)	2(6.3)	
Stool *H. pylori*	Positive(59)	17(28.8)	42(71.2)	0.016	7(11.9)	50(84.7)	2(3.4)	0.41
	Negative(97)	13(13.4)	84(86.6)		14(14.4)	75(77.3)	8(8.2)	
Endoscopy	Normal(29)	3(10.3)	26(89.7)	0.532	0	27(93.1)	2(6.9)	0.655
	Gastritis(69)	11(15.9)	58(84.1)		10(14.5)	55(79.7)	4(5.8)	
	DU(31)	6(19.4)	25(80.7)		7(22.6)	22(70.9)	2(6.5)	
	GU(10)	3(30.0)	7(70.0)		1(10.0)	9(90.0)	0	
	Oesophagitis(4)	2(50.0)	2(50.0)		0	4(100.0)	0	
	Others(13)	5(38.5)	8(61.5)		3(23.1)	8(61.5)	2(15.4)	

*Chi-Square test was done to see the level of significance.

Table 6: Relation of laboratory data with betel nut chewing and BMI (N=156)

Variables		Betel nut chewer			BMI				p
		Yes	No	P	U wt	N wt	Owt	Obese	
USG	Normal(102)	17(16.7)	85(83.3)	0.825	24(23.5)	50(49.0)	2(1.9)	6(5.9)	0.004
	Stone(8)	1(12.5)	7(8.8)		1(12.5)	4(50.0)	3(37.5)	0	
	NAFLD(14)	1(7.1)	13(929)		0	2(14.3)	10(71.4)	2(14.3)	
	Others(32)	5(15.6)	27(84.4)		2(6.2)	14(43.8)	13(40.6)	3(9.4)	
Stool *H. pylori*	Positive(59)	6(10.1)	53(89.8)	0.118	7(11.9)	28(47.5)	21(35.6)	3(5.1)	0.391
	Negative(97)	18(18.6)	79(81.4)		20(20.6)	42(43.3)	27(27.8)	8(8.3)	
Endoscopy	Normal(29)	8(27.6)	21(72.4)	0.386	5(17.2)	13(44.9)	7(24.1)	4(13.8)	0.37
	Gastritis(69)	7(10.1)	62(89.9)		9(13.0)	28(40.6)	29(42.0)	3(4.4)	
	DU(31)	5(16.1)	26(83.9)		6(19.3)	17(54.8)	5(16.1)	3(9.7)	
	GU(10)	0	10(100.0)		2(20.0)	5(50.0)	3(30.0)	0	
	Oesophagitis(4)	1(25.0)	3(75.0)		1(25.0)	2(50.0)	1(25.0)	0	
	Others(13)	3(23.1)	10(76.9)		4(30.8)	5(38.5)	3(23.1)	1(7.7)	

BMI <18.5 = underweight, 18.55-22.9= normal, 23-24.9= overweight; ≥25= Obese

*Chi-Square test was done to see the level of significance.

Table 7: Relation of laboratory data with education and economic status (N=156)

Variables		Education				Economic group			
		Up to 5	6-12	>12	p	Poor	M.class	Rich	*p
USG	Normal(102)	64(62.7)	30(29.4)	8(7.8)	0.004	72(70.6)	29(28.4)	1(0.9)	0.271
	Stone(8)	4(50.0)	4(50.0)	0		4(50.0)	4(50.0)	0	
	NAFLD(14)	5(35.7)	3(21.4)	6(42.9)		6	7	1(7.1)	
	Others(32	22(68.8)	5(15.6)	5(15.6)		19(59.4)	12(37.5)	1(3.1)	
Stool *H. pylori*	Positive(59)	32(54.2)	20(33.9)	7(11.9)	0.299	40(67.8)	19(32.2)	0	0.368
	Negative(97)	63(64.9)	22(22.7)	12(12.4)		61(62.9))	33(34.0)	3(3.1)	
Endoscopy	Normal(29)	17(58.6)	7(24.1)	5(17.2)		16(55.2)	13(44.8)	0	0.012
	Gastritis(69)	45(65.2)	19(27.5)	5(7.2)		44(63.8)	24(34.8)	1(1.5))	
	DU(31)	16(51.6)	10(32.3)	516.1)		22(70.9)	7(22.6)	2(6.5)	
	GU(10)	5(50.0)	2(20.0)	3(30.0)		7(70.0)	3(30.0)	0	
	Oesophagitis(4)	4(100.0)	0	0		3(75.0)	1(25.0)	0	
	Others(13)	8(61.54)	4(30.8)	1(7.7)		9(69.2)	4(30.8)	0	

*Chi-Square test was done to see the level of significance.

Discussion:

In our series, abdominal pain was the most common symptom, which is consistent with another report from our country[17] and a report from China.[18] In the past, *H. pylori* infection was very common, and peptic ulcer disease was mostly associated with *H. pylori* infection. But recently the prevalence of *H. pylori* infection in the community and ulcers related to *H. pylori* infection is decreasing.[19-21] Likewise, in our series, the rate of *H. pylori* infection was low. Abstinence from PPI for 14 days is difficult in our country, and the stool antigen tests were performed without stopping PPI in our study, which might have resulted in a few false negative results and have shown a lower *H. pylori* infection rate.

In this series, dyspepsia was more prevalent among patients in the 31 to 50 years age group, followed by the older age group. However, the prevalence of dyspepsia was found to be higher among patients aged more than 45 years in Poland.[22] Our smaller sample size and environmental differences may be the cause of this difference.

In our study, more than half of the patients were from lower economic groups, which is consistent with reports from Australia,[23] the USA,[24] and Canada.[25] Dyspepsia was also more prevalent among patients with lower levels of education in our series, which is also consistent with reports from Canada.[25] Lack of health-related knowledge might have influenced this result. In our group, dyspepsia was more common among patients with lower BMI (Asia-Pacific criteria), which contradicts with report from Sweden.[26] Small sample size may be an important factor in this regard. In our series the incidence of gallstone disease is higher than another report from our country[17], but lower than that of India[28]. In our study incidence of gastroduodenal pathology was 81.5%, which was higher than another report from our country[17] and reports from India[28] and the USA.[29] Functional dyspepsia was present in only 13.46% of our series, which is much lower than other reports[17,28] and this difference may be due to higher *H. Pylori* infection. In our series, gastritis was found in about half of the total patients, which is like other reports,[17, 28] but the incidence of duodenal ulcer disease and gastric ulcer disease was higher than other reports in our country[17] and a bit lower than that of India.[28]

Conclusion:

Inflammatory gastroduodenal lesions are common endoscopic findings in dyspeptic patients. *H. pylori* infection and gallstone disease are also common findings in patients with dyspepsia. NAFLD is also a common finding in dyspeptic patients. This is a single-center study with a relatively small sample size, which may limit the acceptance of the study findings to represent other populations of different ethnic groups. Studying with a large sample size and multiple centers is recommended to comment on nationwide findings.

Conflicts of Interest: There is no conflict of interest.

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Referencess:

1. Tack J, Talley NJ, Camilleri M, et al. Functional gastroduodenal disorders. *Gastroenterology.* 2006 Apr;130(5):1466-1479

2. Miwa H, Ghoshal UC, Fock KM, et al. Asian consensus report on functional dyspepsia. *J Gastroenterol Hepatol.* 2012;27(4):626-641. doi:10.1111/j.1440-1746.2011.07037.x

3. El-Serag HB, Talley NJ. Systemic review: the prevalence and clinical course of functional dyspepsia. *Aliment Pharmacol Ther.* 2004;19(6):643-654. doi:10.1111/j.1365-2036.2004.01897.x

4. Locke GR 3rd. Prevalence, incidence, and natural history of dyspepsia and functional dyspepsia. *Baillieres Clin Gastroenterol.* 1998;12(3):435-442. doi:10.1016/s0950-3528(98)90016-1

5. Ghoshal UC, Singh R, Chang FY, et al. Epidemiology of uninvestigated and functional dyspepsia in Asia: facts and fiction. *J Neurogastroenterol Motil.* 2011;17(3):235-244. doi:10.5056/jnm.2011.17.3.235

6. Buzas GM. Quality of life issues. In: M Duvnjak, editor, Dyspepsia in Clinical Practice. *Springer;* 2011. p161-73

7. Moayyedi P, Mason J. Clinical and economic consequences of dyspepsia in the community. *Gut.* 2002;50(Suppl 4):iv10-iv12. doi:10.1136/-gut.50.suppl_4.iv10

8. Lambert L. Dyspepsia: heartburn, hernia, gallstones, and ulcers. *S Afr Pharm Assist.* 2013;13:29–30

9. Ford AC, Marwaha A, Lim A, Moayyedi P. What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia? Systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2010;8(10):830–837.e2.

10. Harvey RF, Lane JA, Nair P, et al. Clinical trial: prolonged beneficial effect of Helicobacter pylori eradication on dyspepsia consultations-the Bristol Helicobacter Project. *Aliment Pharmacol Ther.*2010;32(3):394–400.doi:10.1111/j.1365-2036.2010.04363.x

11. Gisbert JP, de la Morena F, Abraira V. Accuracy of monoclonal stool antigen test for the diagnosis of H. pylori infection: a systematic review and meta-analysis. *Am J Gastroenterol.* 2006;101(8):1921–1930. doi:10.1111/j.1572-0241.2006.00668.x. [Correction in: Am J Gastroenterol. 2006;101(10):2445.]

12. Portincasa P, Moschetta A, Petruzzelli M, Palasciano G, Di Ciaula A, Pezzolla A. Gallstone disease: Symptoms and diagnosis of gallbladder stones. *Best Pract Res Clin Gastroenterol.* 2006;20(6):1017-1029. doi:10.1016/j.bpg.2006.05.005.

13. Chowdhury J, Islam MS, Miah AR, et al. Study of the prevalence of dyspepsia in the adult population in a rural community of Bangladesh. *Mymensingh Med J.* 2019;28(1):163-174.

14. Perveen I, Rahman MM, Saha M, Rahman MM, Hasan MQ, et al. Prevalence of irritable bowel syndrome and functional dyspepsia, overlapping symptoms, and associated factors in a general population of Bangladesh. *Indian J Gastroenterol.* 2014;33(3):265-273. doi:10.1007/s12664-014-0447-1

15. Moayyedi P, Talley NJ, Fennerty MB, Vakil N, et al. Can the clinical history distinguish between organic and functional dyspepsia? *JAMA.* 2006;295:1566-1576. DOI: 10.1001/jama.295.13.1566

16. Vakil N, Moayyedi P, Fennerty MB, Talley NJ, et al. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. Gastroenterology. 2006;131(2):390-660. doi:10.1053/j.gastro.2006.04.029

17. Nessa A, Hossain MR, Rahman MH, Rahman S, Mamun A, Khan J, et al. Evaluation of 105 cases of dyspepsia by upper gastrointestinal endoscopy and ultrasonography of hepatobiliary system in a rural setting. *J Armed Forces Med Coll Bangladesh.* 2019;11(2):25–29. doi:10.3329/-jafmc.v11i2.39819

18. Xiao YL, Peng S, Tao J, et al. Prevalence and symptom pattern of pathologic esophageal acid reflux in patients with functional dyspepsia based on the Rome III criteria. *Am J Gastroenterol.* 2010;105(12):2626-2631. doi:10.1038/ajg.2010.351

19. Sonnenberg A, Turner KO, Genta RM. Low prevalence of Helicobacter pylori–positive peptic ulcers in private outpatient endoscopy centers in the United States. *Am J Gastroenterol.* 2020;115(2):244–250. doi:10.14309/ajg.0000000000000517

20. Lee SY, Park HS, Yu SK, et al. Decreasing prevalence of Helicobacter pylori infection: a 9-year observational study. *Hepatogastroenterology.* 2007;54(74):630-633.

21. Aftab H, Yamaoka Y, Ahmed F, et al. Validation of diagnostic tests and epidemiology of Helicobacter pylori infection in Bangladesh. *J Infect Dev Ctries.* 2018;12(5):305-312. doi:10.3855/jidc.984

22. Piotrowicz G, Stępień B, Rydzewska G. Socio-demographic characteristics of patients with diagnosed functional dyspepsia. *Prz Gastroenterol.* 2013;8(6):354-365. doi:10.5114/pg.2013.39918

23. Bytzer P, Howell S, Leemon M, Young LJ, Jones MP, Talley NJ. Low socioeconomic class is a risk factor for upper and lower gastrointestinal symptoms: a population-based study in 15,000 Australian adults. *Gut.* 2001;49(1):66-72. doi:10.1136/gut.49.1.66

24. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci.* 1993;38(9):1569-1580-doi:10.1007/BF01303162

25. Tougas G, Chen Y, Hwang P, Liu MM, Eggleston A. Prevalence and impact of upper gastrointestinal symptoms in the Canadian population: findings from the DIGEST study. Domestic/International Gastroenterology Surveillance Study. *Am J Gastroenterol.* 1999;94(10):2845-2854. doi:10.1111/j.1572-0241.1999.01427.x

26. Wallander MA, Johansson S, Ruigómez A, García Rodríguez LA, Jones R. Dyspepsia in general practice: incidence, risk factors, comorbidity and mortality. *Fam Pract.* 2007;24(5):403-411. doi:10.1093/fam-pra/cmm050

27. Heikkinen M, Pikkarainen P, Takala J, Räsänen H, Julkunen R. Etiology of dyspepsia: four hundred unselected consecutive patients in general practice. *Scand J Gastroenterol.* 1995;30(6):519-523. doi:10.3109/00365529509089783

28. Mubarak M, Bhat FA, Malik GM, Ahmad F. Diagnostic Yield of Upper GI Endoscopy and Ultrasonography Patients of Dyspepsia. *JK-Practitioner.* 2012;17(4): 15-19

29. Zagari RM, Law GR, Fuccio L, Pozzato P, Forman D, Bazzoli F. Dyspeptic symptoms and endoscopic findings in the community: the Loiano-Monghidoro study. *Am J Gastroenterol.* 2010;105(3):565-571. doi:10.1038/ajg.2009.706

Case Report

Endoscopic Submucosal Dissection: A Newer Technique to Remove GI Epithelial Lesion

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Abstract

Background: Endoscopic submucosal dissection (ESD) is an established endoscopic method to resect early gastric neoplasm as well as large gastrointestinal epithelial lesions. It enables the removal of larger and potentially deeper lesions with curative intention.

Case Report: Here in this report, a 31-year-old female presented to us with dyspepsia. Gastroscopy revealed a large, wide-based, polypoid lesion at the antrum. We performed ESD, and follow-up gastroscopy after 3 months showed a healed scar with no residual lesion.

Conclusion: Only very few centers (1-2) are performing ESD in our country; extended practice of this relatively newer procedure can help our patients a lot.

Keywords: Endoscopic submucosal dissection.

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Introduction:

Tremendous advancement in medical science allows meticulous interventions of the specified issues. Upper GI endoscopy is widely accepted in determining the early neoplastic lesions commonly termed as gastrointestinal superficial lesions. Most superficial gastrointestinal (GI) lesions are usually treated by Endoscopic Mucosal Resection (EMR). EMR is less suitable for en bloc resection for lesions more than 2cm or of non-lifting lesions because it does not permit adequate histological information of early cancers.[1] To combat these limitations, here comes Endoscopic Submucosal Dissection (ESD), first invented in the late 80s in Japan.[2] It enables the operator to achieve an en bloc resection of superficial lesions irrespective of tumor size. It is now a widely accepted method for dealing with superficial GI lesions as it is an extremely effective and safe procedure. It is applicable to the esophagus, stomach as well as large bowel. Lesions in the duodenum and small bowel are not recommended for ESD.[1]

ESD is strongly recommended for superficial gastric lesions (low- or high-grade non-invasive neoplasm, adenocarcinoma with no evidence of deep submucosal invasions) as it ensures complete removal (R0) and en bloc curative resection with a good safety profile when compared to other therapies.[3-6] A large prospective study shows that en bloc and R0 resection rates are 99.2 and 91.6% respectively.2 For this reason, ESD is now included in the Japanese guideline for Gastric Cancer.[7] Here are a few indications of ESD, as these have a very low chance of nodal metastasis.[7-8]

- Non-invasive neoplasia independent of size.
- Intramucosal differentiated-type adenocarcinoma, without ulceration (size ≤ 2cm absolute indication, >2cm expanded indication).
- Intramucosal differentiated-type adenocarcinoma, with ulcer, size ≤3cm (expanded indication).
- Intramucosal undifferentiated-type adenocarcinoma, size ≤2cm (expanded indication).
- Differentiated-type adenocarcinoma with superficial submucosal invasion (sm1, ≤500μm), and size ≤3cm (expanded indication).

Recently, the European Society of Gastrointestinal Endoscopy (ESGE) panel opinionated that ESD may be considered for any lesion that has less chance of lymph node metastasis, whether it meets either the absolute or expanded indication criteria, even though surveillance may be difficult[1]. EMR was the first endoscopic treatment that was a real alternative to surgery for the treatment of early gastric cancer.[1] In the early stage, EMR cures cancer in 85% of cases, a value that approached gastrectomy outcomes at the time. In selected cases, long-term follow-up of this technique showed 99% disease-specific survival both at 5 and 10 years. However, EMR is associated with high rates of local recurrence (almost 30% in some studies), which must be treated either by another endoscopic treatment or surgery.[9-12] ESD has emerged as a technique that could allow higher en bloc resection rates for larger lesions, consequently with lower levels of recurrence. So it is undeniable that ESD is appreciated over EMR with higher en bloc resection, lower recurrence rate and complete histological resection. There are chances of a few procedural and post-procedural complications like bleeding and perforation.[13] Nevertheless, ESD is now a well-accepted technique to deal with larger gastric lesions. Here we are dicussing and ESD approach by our department.

Case report:

A 31-year-old female presented with dyspepsia for 6 months. Her dyspepsia was described as epigastric discomfort

aggravated by taking meals and associated with nausea. She gave no history of weight loss, any bleeding episodes, vomiting, dysphagia, abdominal lump, or positive family history of GI malignancy. She is a non-smoker and non-alcoholic. She took several courses of antibiotics by unregistered medical practitioners and Proton pump inhibitors for almost 3 months. General and systemic examination of this patient reveals no abnormalities. We advised a few routine investigations for this patient. Her investigations were normal. Then we approached for upper GI endoscopy. It revealed a large, wide-based polypoid lesion at the antrum. Then we planned for ESD.

Steps we followed during resection: The perimeter of the lesion was marked with cautery. Adrenaline mixed with Methylcellulose and normal saline was injected into the submucosa to elevate the lesion. The mucosa was then incised by using an electrosurgical knife (DualKnife J, Olympus) and cut circumferentially around the lesion by another electrosurgical knife (ITKnife, Olympus). The submucosa beneath the lesion was injected and then dissected in a free-hand manner by using an electrosurgical knife (Triangle Tip Knife J, Olympus) until the lesion had been completely resected.

No immediate complications occurred. Histopathology revealed adenomatous polyp. Follow up Endoscopy was done three months later, and a healed scar was seen. (Figure 1).

Figure 1: A. Image before ESD, B. Image during ESD and C. Image 3 months after ESD

Discussion:

ESD is a comparatively newer method for the treatment of mucosal and superficial submucosal lesions because of its unique characteristics of en bloc resection. Pre-procedural evaluation is an important part of a successful procedure. Multiple studies showed that endoscopic findings alone have high accuracy for predicting the depth of the lesion.[14-15] Findings associated with mucosal disease only included protrusion or depression of a smooth surface, slight marginal elevation and smooth tapering of converging folds where ESD is feasible. On the other hand, irregular surface, marked marginal elevation, clubbing, abrupt cutting or fusion of converging folds indicate the situation where ESD is not feasible. The necessity of EUS before ESD is controversial. Although EUS is considered to be the most reliable method for local staging, its global accuracy, particularly for gastric superficial lesions, is rather low.[16-17] A comparative study of EUS versus endoscopic evaluation for predicting endoscopic resectability favored endoscopy since EUS findings would indicate gastrectomy for many lesions that did not need surgery.[15] As EUS is not widely available nowadays in our country, we can strongly rely on endoscopic evaluation. CT abdomen is not generally necessary since the risk of metastatic disease is very low in a lesion where endoscopic resection is considered to be feasible.[17-20]

Though well accepted, ESD is a battle against intra-procedural bleeding, particularly in a lesion located in the upper and middle third of the stomach because large vessels penetrate the muscle layer horizontally, then go vertically and form a ramified network. Just above the muscularis mucosa, fewer vessel layers are found, so the safety depth for ESD is just above the muscle layer.[2] Bleeding is categorized as immediate or delayed. Some immediate bleeding is inevitable in almost all ESDs. If a large vessel is observed, it should be coagulated before proceeding with the dissection. The near-side approach combines the use of an insulated and needle-type knife strategy to reduce the risk of making the bleeding points difficult to recognize and does not impair the advantages of the IT knife as a safe and fast method.[2]

Perforation occurs in about 1% to 4% of the procedure. In such cases, visualization is the first step to be attempted. Then, sealing of the points with hemostatic clips should be tried.[21] Delayed perforation can also happen sometimes, but it is very rare. Concerning other possible complications of ESDs are stenosis, pneumonia, and mucosal lacerations, should be handled according to the clinician's experience and situation.[1]

The technical and histological outcome of ESD is an important discussion matter. After a lesion has been resected, the histopathological analysis will determine whether the resection was curative or whether further surgery is needed.[22] In a non-ulcerated, well-differentiated submucosal lesion, independent of size, R0 resection is thought to be curative. Small ulcerated lesions less than 30mm appear to be curative when treated through R0 resection.[1]

ESGE suggests that after an en bloc R0 resection of lesions meeting the expanded criteria (particularly ulcerated, minimally submucosally invasive, or undifferentiated/diffuse carcinomas), the option of gastrectomy should be discussed with the patient and a decision made on an individual basis considering patient pReferences, co-morbidities, and information from other procedures (for example CT in the case of suspicious lymph nodes).[1]

Long-term follow-up of patients after successful ESD for early gastric cancer has shown that these patients are at high risk, of around 10% to 20%, for developing synchronous or metachronous multiple gastric neoplastic lesions. In accordance with these results, Japanese guidelines also recommend annual or biannual endoscopy in all patients, as well as a CT abdominal scan in the subgroup of patients treated under extended indications.[7] It is recommended that the first endoscopy after ESD should be performed 3–6 months after ESD and then annually, similarly to the schedule in most series. If the resection was incomplete but there were no clear indications for surgery, it is recommended that a first endoscopy at 3 months be followed by another endoscopy in the first year, since some studies show that most of the recurrences after incomplete resection are identified in the first year.[23-27]

Conclusion:

Endoscopic submucosal dissection (ESD) has been developed to overcome the limitations of endoscopic mucosal resection (EMR).1 Our patient responded well and got relief symptomatically with ESD. With improvements in techniques and devices, excellent therapeutic results have been achieved despite the inherent technical difficulties of this procedure. Extended practice of ESD with expert gastroenterologists is recommended.

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References:

1. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline.*Endoscopy.*2015;47(9):829–854. doi:10.1055/s-0034-1392882

2. Saito Y, Abe S, Inoue H, Tajiri H. How to perform a high-quality endoscopic submucosal dissection. *Gastroenterology.* 2021;161(2):405–410. doi:10.1053/j.gastro.2021.05.051.

3. Chung IK, Lee JH, Lee SH, Kim SJ, Cho JY, Cho WY, et al. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD study group multicenter study. *Gastrointest Endosc.* 2009;69(7):1228-1235. doi:10.1016/j.gie.2008.09.027

4. Gotoda T, Jung HY. Endoscopic resection (endoscopic mucosal resection/endoscopic submucosal dissection) for early gastric cancer. *Dig Endosc.* 2013;25(Suppl 1):55-63. doi:10.1111/den.12003

5. Lian J, Chen S, Zhang Y, Qiu F. A meta-analysis of endoscopic submucosal dissection and EMR for early gastric cancer. *Gastrointest Endosc.* 2012;76(4):763-770. doi:10.1016/j.gie.2012.06.014

6. Park YM, Cho E, Kang HY, Kim JM. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and meta-analysis. *Surg Endosc.* 2011;25(8):2666-2677. doi:10.1007/s00464-011-1627-z

7. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer.* 2011;14(2):113-123. doi:10.1007/s10120-011-0042-4

8. Gotoda T, Iwasaki M, Kusano C, Seewald S, Oda I. Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria. *Br J Surg.* 2010;97(6):868-871. doi:10.1002/bjs.7033

9. Takekoshi T, Baba Y, Ota H, Kato Y, Yanagisawa A, Takagi K, et al. Endoscopic resection of early gastric carcinoma: results of a retrospective analysis of 308 cases. *Endoscopy.* 1994;26(4):352-358. doi:10.1055/s-2007-1008990

10. Hiki Y, Shimao H, Mieno H, Sakakibara Y, Kobayashi N, Saigenji K. Modified treatment of early gastric cancer: evaluation of endoscopic treatment of early gastric cancers with respect to treatment indication groups. *World J Surg.* 1995;19(4):517-522. doi:10.1007/BF00294712

11. Uedo N, Iishi H, Tatsuta M, Ishihara R, Higashino K, Takeuchi Y, et al. Long-term outcomes after endoscopic mucosal resection for early gastric cancer. *Gastric Cancer.* 2006;9(2):88-92. doi:10.1007/s10120-005-0357-0

12. Nagano H, Ohyama S, Fukunaga T, Seto Y, Fujisaki J, Yamaguchi T, et al. Indications for gastrectomy after incomplete EMR for early gastric cancer. *Gastric Cancer.* 2005;8(3):149-154. doi:10.1007/s10120-005-0328-5

13. Libânio D, Pimentel-Nunes P, Dinis-Ribeiro M. Complications of endoscopic resection techniques for upper GI tract lesions. *Best Pract Res Clin Gastroenterol.* 2016;30(5):735-748. doi:10.1016/j.bpg.2016.09.010.

14. Choi J, Kim SG, Im JP, Kim JS, Jung HC, Song IS. Endoscopic prediction of tumor invasion depth in early gastric cancer. *Gastrointest Endosc.* 2011;73(5):917-927. doi:10.1016/j.gie.2010.11.053

15. Choi J, Kim SG, Im JP, Kim JS, Jung HC, Song IS. Comparison of endoscopic ultrasonography and conventional endoscopy for prediction of depth of tumor invasion in early gastric cancer. *Endoscopy.* 2010;42(9):705-713. doi:10.1055/s-0030-1255617

16. Cardoso R, Coburn N, Seevaratnam R, Sutradhar R, Lourenco LG, Mahar A, et al. A systematic review and meta-analysis of the utility of EUS for preoperative staging for gastric cancer. *Gastric Cancer.* 2012;15(Suppl 1):S19-26. doi:10.1007/s10120-011-0115-4

17. Mocellin S, Marchet A, Nitti D. EUS for the staging of gastric cancer: a meta-analysis. *Gastrointest Endosc.* 201;73(6):1122-1134. doi:10.1016/-j.gie.2011.01.030

18. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer.* 2000;3(4):219-225. doi:10.1007/pl00011720

19. Folli S, Morgagni P, Roviello F, De Manzoni G, Marrelli D, Saragoni L, et al. Risk factors for lymph node metastases and their prognostic significance in early gastric cancer (EGC) for the Italian Research Group for Gastric Cancer (IRGGC). *Jpn J Clin Oncol.* 2001;31(10):495-499. doi:10.1093/jjco/hye107

20. Son SY, Park JY, Ryu KW, Eom BW, Yoon HM, Cho SJ, et al. The risk factors for lymph node metastasis in early gastric cancer patients who underwent endoscopic resection: is the minimal lymph node dissection applicable? A retrospective study. *Surg Endosc.* 2013;27(9):3247-3253. doi:10.1007/s00464-013-2901-z

21. Jeon SW, Jung MK, Kim SK, Cho KB, Park KS, Park CK, et al. Clinical outcomes for perforations during endoscopic submucosal dissection in patients with gastric lesions. *Surg Endosc.* 2010;24(4):911-916. doi:10.1007/s00464-009-0693-y

22. Fujita K, Nishide S, Takashima R, Wada T, Hashimoto A. Novel technique for double traction from inside and outside in endoscopic submucosal dissection. *Am J Gastroenterol.* 2022;117(11):1738. doi:10.14309/a-jg.0000000000001844

23. Pimentel-Nunes P, Mourão F, Veloso N, Afonso LP, Jácome M, Moreira-Dias L, et al. Long-term follow-up after endoscopic resection of gastric superficial neoplastic lesions in Portugal. *Endoscopy.* 2014;46(11):933-940. doi:10.1055/s-0034-1377348

24. Horiki N, Omata F, Uemura M, Suzuki S, Ishii N, Fukuda K, et al. Risk for local recurrence of early gastric cancer treated with piecemeal endoscopic mucosal resection during a 10-year follow-up period. *Surg Endosc.* 2012;26(1):72-78. doi:10.1007/s00464-011-1830-y

25. Ahn JY, Jung HY, Choi JY, Kim MY, Lee JH, Choi KS, et al. Natural course of noncurative endoscopic resection of differentiated early gastric cancer. *Endoscopy.* 2012;44(12):1114-1120. doi:10.1055/s-0032-1325676

26. Oda I, Gotoda T, Sasako M, Sano T, Katai H, Fukagawa T, Shimoda T, Emura F, Saito D. Treatment strategy after non-curative endoscopic resection of early gastric cancer. *Br J Surg.* 2008;95(12):1495-1500. doi:10.1002/b-js.6305

27. Yoon H, Kim SG, Choi J, Im JP, Kim JS, Kim WH, et al. Risk factors of residual or recurrent tumor in patients with a tumor-positive resection margin after endoscopic resection of early gastric cancer. *Surg Endosc.* 2013;27(5):1561-1568. doi:10.1007/s00464-012-2627-3

Case Report

Brunner's Gland Adenoma: An Unusual Cause of Abdominal Pain

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Abstract

Background: Brunner's gland adenoma is a rare entity. It can cause various symptoms like bleeding, abdominal pain, and obstruction.

Case Report: This is a case report of a 35-year-old shopkeeper who presented with a 2-month history of episodic upper abdominal pain, burning, and nausea. Upper gastrointestinal endoscopy revealed a pedunculated submucosal swelling with normal overlying mucosa at the first part of the duodenum. Endoscopic ultrasound revealed a mixed echogenic mass originating from the mucosa and submucosa. It was resected endoscopically. Histopathological evaluation of the resected polypoid mass revealed the proliferation of benign Brunner's gland cells in the submucosal region.

Conclusion: Most of the Brunner's gland adenomas are diagnosed by Endoscopy. Endoscopic or surgical intervention remains the mainstay of treatment.

Keywords: Brunner's gland adenoma

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Introduction:

Duodenal tumors are an extremely rare entity. It accounts for only 0.5 to 1.0% of the entire gastrointestinal tract tumors.[1,2] Brunner's gland adenoma is a benign tumor originating from the small bowel. It is scarce, with an estimated incidence of < 0.01%.[3] Curveilhier described the first benign duodenal Brunner's gland adenoma case in 1835.[4] It usually originates from the posterior wall of the first or second part of the duodenum as per the distribution of the alkaline mucin-secreting Brunner glands. The pathogenesis is yet unknown. However, primary dysembryoplasia or an exaggerated compensatory response to hyperchlorhydria, pancreatic insufficiency, or H pylori infection have been hypothesized to be the important mechanisms.[5] It is typically found incidentally on endoscopy. When symptomatic, the most common presentations are hemorrhage or gastric outlet obstruction. However, pancreatitis, intussusception, and diarrhea have also been reported.[6,7] Treatment is endoscopic or surgical removal.[8] Here we present a case of Brunner's gland adenoma presenting with upper abdominal pain, burning and nausea.

Case Report:

A 35-year-old male with no significant past medical history presented to the outpatient gastroenterology department with a history of occasional upper abdominal pain, burning, and nausea for 2 months. The pain was mild, burning, episodic, and non-radiating, located in the epigastric region. He had no history of significant weight loss, melena or hematemesis. The patient's medical history was non-contributory. The patient was well-appearing and cooperative during the physical examination. The abdominal examination revealed mild tenderness in the epigastric region. No organomegaly or ascites was found. The rest of the systemic examination was unremarkable. Initial laboratory investigations, including complete blood count (CBC), liver function tests (LFTs) and abdominal ultrasound were within normal limits. The patient underwent an upper gastrointestinal endoscopy and it revealed a smooth, non-ulcerated, submucosal polypoid lesion located in the first part of the duodenum (Figure 1). A biopsy was not performed due to the suspected submucosal nature of the lesion.

Figure 1: UGIT Endoscopic image

Due to the indeterminate nature of the lesion on endoscopy, the patient underwent an endoscopic ultrasound (EUS). The EUS shows a mixed echoic, pedunculated mass approximately 1.5 cm in diameter in the first part of the duodenum. Mass was located in the mucosa and submucosa with minimal vascularity within the mass. These findings were highly suggestive of a benign submucosal lesion, with Brunner's gland adenoma being the most likely diagnosis (Figure 2).

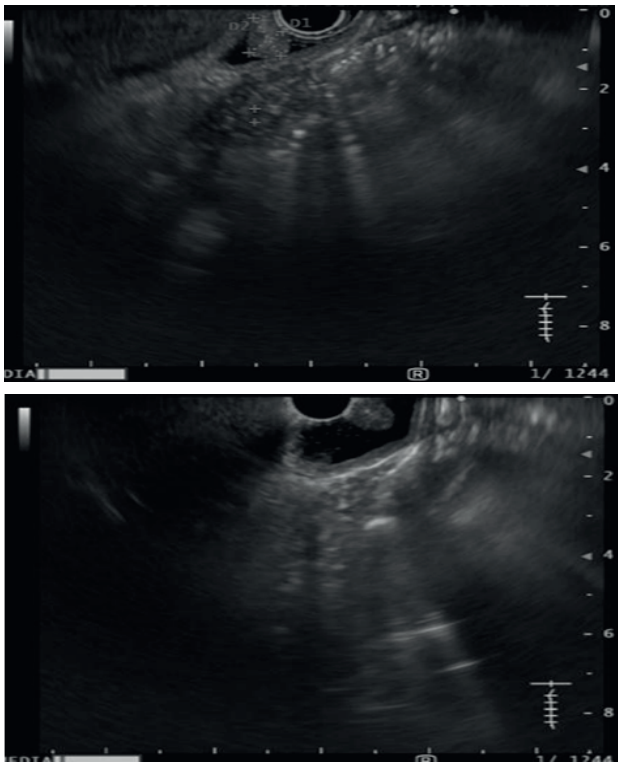

Figure 2: EUS image

After that, endoscopic resection of the mass was done, and it was sent for histopathology. Histopathology reveals proliferation of benign Brunner's gland in the submucosal region and Lamina propria is infiltrated with chronic inflammatory cells (Figure 3).

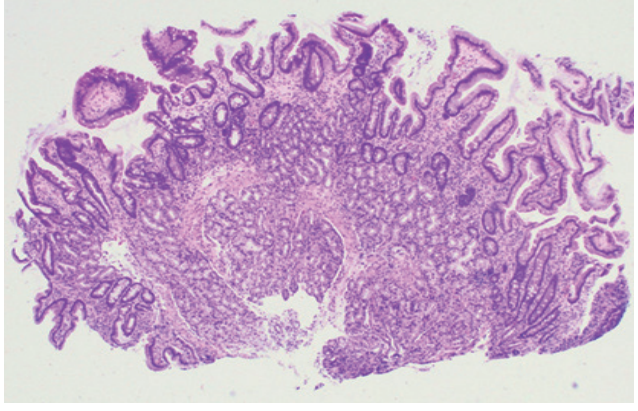

Figure 3: Histologic image

So, based on the clinical presentation, UGIT endoscopy, EUS and histopathology findings, the diagnosis of Brunner's gland adenoma was confirmed.

Discussion:

Brunner's gland adenoma (BGA) is a rare, benign neoplasm arising from the Brunner's glands in the duodenum. Brunner's glands are primarily found in the submucosa of the duodenum. They secrete mucus and bicarbonate, which protect the duodenal mucosa from gastric acid and digestive enzymes. A benign neoplasm arising from these glands is called Brunner's gland adenoma.[9] It is infrequent and diagnosed incidentally during endoscopy or imaging procedures.

Brunner's glands are predominantly found in the duodenum proximal to the ampulla of Vater. The most common site is the duodenal bulb.[10] However, they may extend up to the proximal jejunum. They play a key role in protecting the duodenal mucosa.[11] It arises from the hyperplasia of Brunner's glands and is often presented as a pedunculated mass or nodule in the submucosal layer of the duodenum. These lesions can range from small, benign tumors to larger growths. These lesions can cause abdominal pain, obstruction, or gastrointestinal bleeding.[12]

BGA is linked to factors such as middle age, male gender, and specific genetic conditions. Additionally, it is suggested that chronic irritation of the duodenal lining, possibly from acid reflux or Helicobacter pylori infection, could contribute to its pathogenesis.[13,14]

Brunner's gland adenomas are typically asymptomatic. However, some patients may present with symptoms like epigastric pain, nausea, vomiting, gastrointestinal bleeding, or a palpable mass.[12] In large adenomas, obstruction or intussusception may also occur.

Endoscopy is the most common diagnostic tool for diagnosis. On endoscopy, the adenoma usually appears as a polypoid mass within the duodenum. Ultrasound or CT scans can also help to identify larger tumors.[15,16] However, definitive diagnosis and characterization of the lesion requires histopathology. Most of the cases are histologically benign. However, there have been isolated reports of malignant transformation. Incidence is extremely rare.[17]

The treatment of Brunner's gland adenoma depends upon the symptoms and size of the tumor. In asymptomatic cases, conservative observation may be sufficient. Periodic follow-up by endoscopy should be done to monitor for any changes. In symptomatic conditions like bleeding, obstruction, or a risk of malignant transformation, endoscopic or surgical intervention may be necessary.[18]

The prognosis for patients with Brunner's gland adenoma is generally excellent. Recurrence is rare. However, long-term follow-up may be required, especially in cases that have undergone more conservative management or biopsy.[19]

Conclusion:

Brunner's gland adenoma is a rare benign tumor of the duodenum. It is often asymptomatic but may present with gastrointestinal symptoms in certain cases, requiring endoscopic or surgical intervention. The prognosis is generally good. Further research into its pathogenesis and potential links to gastrointestinal diseases would help refine diagnostic and treatment approaches.

Conflicts of Interest: There is no conflict of interest.

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References:

1. Lu Y, Fröbom R, Lagergren J. Incidence patterns of small bowel cancer in a population-based study in Sweden: increase in duodenal adenocarcinoma. *Cancer Epidemiology.* 2012 Jun 1;36(3):e158-163.

2. Zar N, Holmberg L, Wilander E, Rastad J. Survival in small intestinal adenocarcinoma. *European Journal of Cancer.* 1996 Nov 1;32(12):2114-2119.

3. Stewart ZA, Hruban RH, Fishman EF, Wolfgang CL. Surgical management of giant Brunner's gland hamartoma: case report and literature review. *World Journal of Surgical Oncology.* 2009 Dec;7:1-4.

4. Cruveilhier J: Anatomy of the Human Body. New York, Harper and Bros, 1844.

5. Lu L, Li R, Zhang G, Zhao Z, Fu W, Li W. Brunner's gland adenoma of duodenum: report of two cases. *International Journal of Clinical and Experimental Pathology.* 2015 Jun 1;8(6):7565-7569.

6. Rocco A, Borriello P, Compare D, De Colibus P, Pica L, Iacono A, Nardone G. Large Brunner's gland adenoma: case report and literature review. *World journal of gastroenterology:* WJG. 2006 Mar 28;12(12):1966-1968.

7. Vyas S, Skipworth JR, Lytras D, Smyth C, Mee A, Hatfield A, Imber C, Webster G. Rare presentation of Brunner's gland adenoma: another differentiation in patients with recurrent "idiopathic" pancreatitis. *Hepatobiliary and Pancreatic Diseases International.* 2012 Feb 15;11(1):107-110.

8. Sorleto M, Timmer-Stranghöner A, Wuttig H, Engelhard O, Gartung C. Brunner's Gland Adenoma–A Rare Cause of Gastrointestinal Bleeding: Case Report and Systematic Review. *Case Reports in Gastroenterology.* 2017 Jan 27;11(1):1-8.

9. Levine JA, Burgart LJ, Batts KP, Wang KK. Brunner's gland hamartomas: clinical presentation and pathological features of 27 cases. *American Journal of Gastroenterology* (Springer Nature). 1995 Feb 1;90(2): 290.

10. Marine D, Jones B, Ghahremani GG, Hamilton SR, Bayless TM. Hyperplasia of Brunner glands: the spectrum of its radiographic manifestations. *Gastrointestinal radiology.* 1991 Dec;16:104-108.

11. Zhu M, Li H, Wu Y, An Y, Wang Y, Ye C, Zhang D, Ma R, Wang X, Shao X, Guo X. Brunner's gland hamartoma of the duodenum: a literature review. *Advances in Therapy.* 2021 Jun;38(6):2779-2794.

12. Ramay FH, Papadimitriou JC, Darwin PE. Brunner's Gland Adenoma with High-Grade Dysplasia. *ACG Case Reports Journal.* 2018 Jan 1;5(1):e81.

13. Stolte M, Schwabe H, Prestele H. Relationship between diseases of the pancreas and hyperplasia of Brunner's glands. *Virchows Archiv A.* 1981 Dec;394:75-87.

14. Yadav D, Hertan H, Pitchumoni CS. A giant Brunner's gland adenoma presents as gastrointestinal hemorrhage. *Journal of Clinical Gastroenterology.* 2001 May 1;32(5):448-450.

15. Gourtsoyiannis NC, Zarifi M, Gallis P, Mouchtouris A, Livaditou A. Radiologic appearances of Brunner's gland adenoma: a case report. *European journal of radiology.* 1990 Nov 1;11(3):188-190.

16. Block KP, Frick TJ, Warner TF. Gastrointestinal bleeding from a Brunner's gland hamartoma: characterization by endoscopy, computed tomography, and endoscopic ultrasound. Official journal of the American College of Gastroenterology| *ACG.* 2000 Jun 1;95(6):1581-1583.

17. Koizumi M, Sata N, Yoshizawa K, Kurihara K, Yasuda Y. Carcinoma arising from Brunner's gland in the duodenum after 17 years of observation–a case report and literature review. *Case Reports in Gastroenterology.* 2008 Oct 12;1(1):103-109.

18. Desai G, Yadav K, Pande P, Sali P, Tampi C, Wagle P. Brunner gland adenoma masquerading as a duodenal gastrointestinal stromal tumor with intussusception: CASE report. ABCD. *Arquivos Brasileiros de Cirurgia Digestiva (São Paulo).* 2017 Jan;30:71-72.

19. Xiang Y, Liu J, Tang D, Wang L, Xu G, Huang Q. The characteristics and treatment outcomes of 71 duodenal Brunner's gland adenomas with endoscopic submucosal dissection. *Digestive Diseases.* 2023 Dec 11;41(6):852-859.

Case Series

Vonoprazan Associated Gastric Mucosal Changes in Bangladeshi Patients: A Case Series

S Dey[1], SMA Hasan[2], SK Bhowmick[3]

Abstract

Background: Vonoprazan, a potassium-competitive acid blocker (P-CAB), has emerged as an effective therapy for gastroesophageal reflux disease (GERD) and Helicobacter pylori eradication. Since its global launch in 2015, several endoscopic mucosal changes associated with its long-term use have been reported, including white globe appearance (WGA), web-like mucosa (WLM), and gastric cracked mucosa (GCM). In Bangladesh, vonoprazan has only recently been introduced, and limited data exist regarding its mucosal effects.

Objective: To report three cases from Bangladesh showing characteristic gastric mucosal changes following vonoprazan therapy.

Result: All three patients developed distinct mucosal changes after vonoprazan use, including longitudinal erythema, web-like mucosa, and hemorrhagic gastric polyps. Mucosal abnormalities regressed or improved following cessation of vonoprazan and initiation of alternative acid-suppressive therapy (proton pump inhibitors or H2 blockers). All these mucosal changes occur at upper part of stomach.

Conclusion: This case series highlights the emergence of vonoprazan-associated gastric mucosal changes in Bangladeshi patients. Clinicians should remain vigilant and consider endoscopic follow-up during long-term P-CAB therapy.

Keywords: Vonoprazan, P-CAB, Web-like mucosa, White globe appearance, Gastric cracked mucosa, GERD, Helicobacter pylori, Bangladesh.

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Introduction:

Potassium-competitive acid blockers (P-CABs) represent a novel class of potent acid-suppressive medications. Vonoprazan, introduced in Japan in 2015, is the most clinically established P-CAB to date and is widely used for treating GERD, Helicobacter pylori infection, and PPI-resistant esophagitis.[1] Unlike PPIs, vonoprazan directly inhibits gastric H+/K+ ATPase without requiring activation under acidic conditions, resulting in rapid and sustained acid suppression.

Long-term use of vonoprazan has been associated with unique gastric mucosal changes. Recent literature describes newly recognized endoscopic findings such as web-like mucosa (WLM), white globe appearance (WGA), stardust gastric mucosa, and gastric cracked mucosa (GCM), which are distinct from changes due to autoimmune gastritis or Helicobacter pylori infection. The mechanisms remain unclear but may involve hypergastrinemia, epithelial remodeling, and microbiota alterations due to profound hypochlorhydria.

In Bangladesh, vonoprazan is relatively new, and data on its adverse mucosal effects are scarce. This case series presents three patients from Bangladesh who developed characteristic gastric mucosal changes during vonoprazan therapy.

Case 1:

A 36-year-old female presented with upper abdominal discomfort and heartburn persisting for the last six months, predominantly occurring after meals. She had a medical history of hypothyroidism and nonalcoholic fatty liver disease. Her medications included thyroxine (50 mcg daily), ursodeoxycholic acid (300 mg twice daily), vonoprazan (20 mg daily), domperidone (10 mg as needed), and losartan (50 mg daily). On clinical examination, her BMI was 31 kg/m². Blood pressure was 140/90 mmHg, heart rate was 110 bpm, and mild hepatomegaly was noted without tenderness. Laboratory tests showed hemoglobin of 13 g/dL, ALT 51 U/L, random blood sugar 6.8 mmol/L, HbA1c 5.4%, and TSH 8 mIU/mL. Ultrasonography confirmed grade II fatty liver disease. Fibroscan revealed a CAP score of 369 dB/m and liver stiffness of 7.4 kPa. An upper GI endoscopy performed six months ago showed Grade B reflux esophagitis and rapid urease test was negative. On follow-up endoscopy, conducted while she was on vonoprazan, longitudinal erythema was noted in the gastric body and fundus. Vonoprazan was discontinued, and esomeprazole was prescribed. Repeat endoscopy performed two months later showed complete resolution of the mucosal changes (Figure 1).

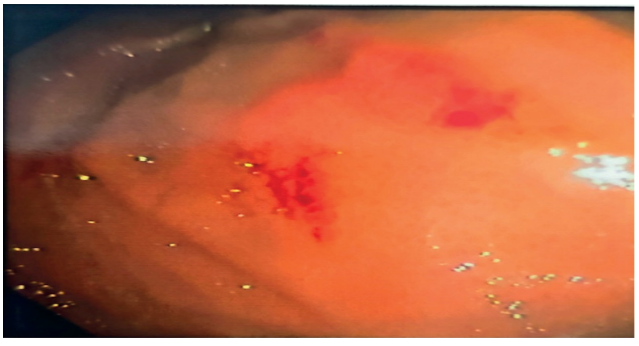

Figure 1: The Stomach shows longitudinal erythema in the fundus after 6 months of vonoprazan intake.

Case 2:

An 84-year-old male, a retired farmer and chronic smoker, presented with a six-month history of productive cough and epigastric pain that worsened with food intake. He denied vomiting, weight loss, hematemesis, or altered bowel habits. On examination, his BMI was 19 kg/m². Vital signs were stable. Respiratory examination revealed prolonged expiration. Laboratory investigations revealed hemoglobin of 12 g/dL and ALT of 34 U/L. Chest X-ray demonstrated hyperinflated lung fields. ECG showed right bundle branch block. Abdominal ultrasonography was normal. An endoscopy performed four months prior had shown mild antral gastritis, and the CLO test was negative. A follow-up endoscopy, done after four months of vonoprazan therapy, revealed a thick, adherent web-like mucosa in the body and fundus of the stomach. The patient had been receiving vonoprazan 20 mg twice daily for acid-related dyspepsia. He was switched to H2-receptor antagonists, and a follow-up endoscopy was scheduled to monitor the mucosal changes (Figure 2).

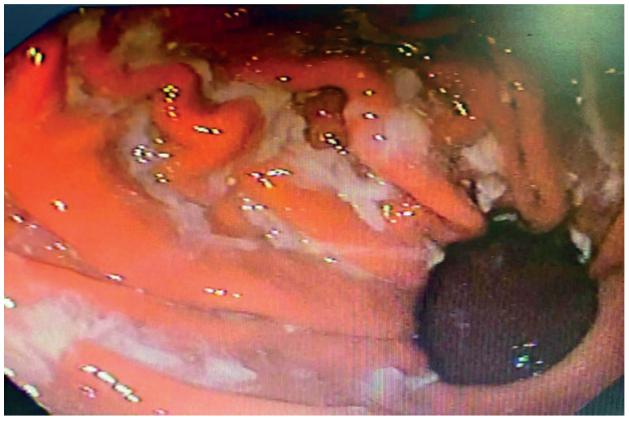

Figure 2: Web-like mucosa in a patient following vonoprazan intake.

Case 3:

A 32-year-old male known case of spondyloarthritis presented with burning upper abdominal pain for six months. He had been on sulfasalazine and intermittent indomethacin for joint symptoms. Physical examination revealed a BMI of 20 kg/m² and grade I joint tenderness. Laboratory investigations showed hemoglobin of 10.5 g/dL, CRP 20 mg/L, and positive HLA-B27. Abdominal ultrasonography was normal. Initial endoscopy revealed antral erosions with multiple duodenal ulcers. He was started on vonoprazan-based triple therapy by a local physician. After four months, follow-up endoscopy showed a bleeding sessile polyp at the fundus. Histopathology confirmed it to be a hyperplastic polyp, and the rapid urease test was negative. Vonoprazan was discontinued, and esomeprazole therapy was initiated. The patient was advised to undergo surveillance endoscopy (Figure 3).

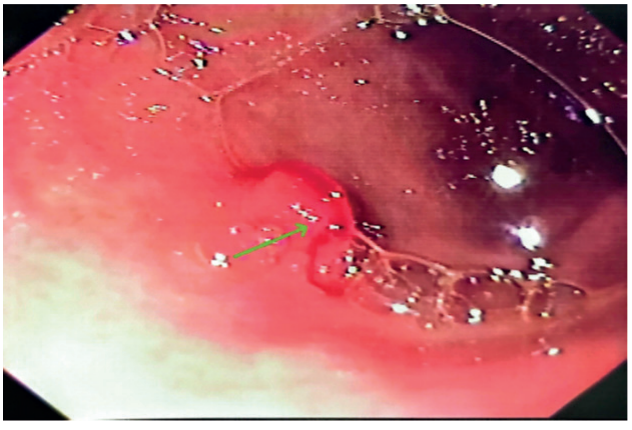

Figure 3: A hemorrhagic gastric polyp in a patient following 4 months of vonoprazan.

Discussion:

Vonoprazan's strong acid suppression efficacy makes it suitable for GERD and *Helicobacter pylori* eradication, particularly in PPI-resistant cases.[2] P-CAB drugs have similar efficacy to PPI in triple therapy.[3,4] Vonoprazan can be used even at a low dose for PPI-refractory reflux esophagitis.[5,6] However, with its increased use, novel gastric mucosal findings have emerged. These include web-like mucosa, described as a spider web or clot-like mucus pattern in the upper stomach and reported in 19 to 21 percent of users; white globe appearance, consisting of white, globe-like protrusions; gastric cracked mucosa, characterized by linear mucosal breaks possibly related to chronic hypochlorhydria; stardust gastric mucosa, a white granular appearance and hemorrhagic gastric polyp more commonly seen in long-term users and females patients.[7-11]

The pathogenesis of these mucosal changes is not fully understood but may involve hypergastrinemia-induced epithelial proliferation, hypochlorhydria-related alterations in gastric flora, and mucosal remodeling.[12-14] Notably. most of these mucosal changes resolve upon discontinuation of vonoprazan and substitution with PPIs or H_2 blockers. Our case series is consistent with these international findings, with patients developing reversible mucosal changes following vonoprazan therapy.

Conclusion:

Vonoprazan-associated mucosal changes are now being recognized globally. Here we have documented these changes for the first time in Bangladeshi patients. So endoscopic surveillance may be warranted in long-term users of vonoprazan. Further multicentric, prospective studies are necessary to define pathogenesis, risk factors, and optimal management strategies in this regard.

Conflicts of Interest: There is no conflict of interest.

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Referencess:

1.Scarpignato C, Hunt RH. Potassium-competitive Acid Blockers: Current Clinical Use and Future Developments. *Current gastroenterology reports.* 2024;26(11):273-293.

2.Miyazaki H, Igarashi A, Takeuchi T, Teng L, Uda A, Deguchi H, et al. Vonoprazan versus proton-pump inhibitors for healing gastroesophageal reflux disease: A systematic review. *Journal of gastroenterology and hepatology.* 2019;34(8):1316-1328.

3.Jung YS, Kim S, Kim HY, Noh SJ, Park JH, Sohn CI, et al. Efficacy and Tolerability of 14-Day Tegoprazan- versus Rabeprazole-Based Triple Therapy for Eradication of Helicobacter pylori: A Real-World Evidence Study. *Gut and liver.* 2023;17(5):711-721.

4.Tanabe T, Hoshino S, Kawami N, Hoshikawa Y, Hanada Y, Takenouchi N, et al. Efficacy of long-term maintenance therapy with 10-mg vonoprazan for proton pump inhibitor-resistant reflux esophagitis. *Esophagus : official journal of the Japan Esophageal Society.* 2019;16(4):377-381.

5.Hoshino S, Kawami N, Takenouchi N, Umezawa M, Hanada Y, Hoshikawa Y, et al. Efficacy of Vonoprazan for Proton Pump Inhibitor-Resistant Reflux Esophagitis. *Digestion.* 2017;95(2):156-161.

6.Mizuno H, Nishino M, Yamada K, Kamiyamamoto S, Hinoue Y. Efficacy of Vonoprazan for 48-Week Maintenance Therapy of Patients with Healed Reflux Esophagitis. *Digestion.* 2020;101(4):411-421.

7.Iwamuro M, Kono Y, Tanaka T, Kawano S, Ikeda N. Vonoprazan-Associated Mucosal Redness: A Report of Two Cases. *Cureus.* 2024;16(10):e71325.

8.Suda H, Eto S, Sakurai K. Profound gastric mucosal changes and severe rebound acid hypersecretion after long-term Vonoprazan use: A case report. *DEN open.* 2025;5(1):e70046.

9.Kubo K, Kimura N, Matsuda S, Tsuda M, Mabe K, Kato M. Vonoprazan-associated Gastric Mucosal Redness: A Report of Four Cases. *Internal medicine* (Tokyo, Japan). 2020;59(4):507-511.

10.Shinozaki S, Sakamoto H, Osawa H, Yano T, Yamamoto H. Prevalence and factors associated with web-like mucus in the stomach after vonoprazan use. *Biomedical Reports.* 2024;22.

11.Miwa W, Hiratsuka T, Sato K, Fujino T, Kato Y. Development of white globe appearance lesions in the noncancerous stomach after vonoprazan administration: a report of two cases with a literature review. *Clinical Journal of Gastroenterology.* 2021;14(1):48-58.

12.Yoshizaki T, Morisawa T, Fujinami M, Matsuda T, Katayama N, Inoue K, et al. Propensity score matching analysis: incidence and risk factors for "stardust" gastric mucosa, a novel gastric finding potentially induced by vonoprazan. *Alimentary Pharmacology and Therapeutics.* 2021;53(1):94-102.

13.Kaneko H, Sato H, Suzuki Y, Ikeda A, Kuwashima H, Ikeda R, et al. A Novel Characteristic Gastric Mucus Named "Web-like Mucus" Potentially Induced by Vonoprazan. *Journal of clinical medicine.* 2024;13(14).

14.Kubo K, Kimura N. Long-term follow-up of patients developing gastric mucosal lesions after initiating the potassium-competitive acid blocker vonoprazan. *Clin Endosc.* 2024;57(4):549-551.

Review Article

Assessment of NUDT15 before Thiopurine Treatment in Inflammatory Bowel Disease: An Asian Perspective

MY Arafat[1], M Saifuddoula[2], TK Majumder[3], MI hossain[4], R Hasan[5]

Abstract

Background: Thiopurines, consisting of mercaptopurine and azathioprine, are used as immunosuppressants in treating inflammatory bowel disease. They are used to maintain remission of IBD patients. These drugs sometimes cause severe adverse effects, particularly myelosuppression, hepatoxicity, and pancreatitis. Recent advancements in pharmacogenomics have identified different genetic variants, including TMPT and Nudix hydrolase-15 (NUDT15). NUDT15 polymorphisms have been shown to play an important role in thiopurine-induced adverse reactions in Asians. This review article provides an insight into the NUDT15 testing before initiating thiopurine therapy in Asian patients with IBD.

Conclusion: In this article, the metabolism and pharmacogenetics of thiopurines, the prevalence and impact of NUDT15 variants in Asia, clinical guidelines for the importance of NUDT15 testing, dose adjustment based on NUDT15 genotypes, and monitoring and follow-up of the patients being treated are discussed.

Key words: Inflammatory bowel disease, Thiopurine metabolism, NUDT15 genotypes.

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Introduction:

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is responsible for chronic inflammation of the gastrointestinal tract and requires long-term management strategies.[1,2]

An imbalance between pro-inflammatory and anti-inflammatory responses contributes to persistent inflammation in IBD.[3] Multidisciplinary management is often required, which includes a combination of medications, nutritional support, lifestyle changes, and, in severe cases, surgical interventions.[1] Thiopurines, including azathioprine (AZA) and 6-mercaptopurine (6-MP), are effective immunomodulators for maintaining remission in inflammatory bowel disease (IBD). However, these drugs require careful monitoring to identify toxicity.[4] Adverse effects of these drugs include myelosuppression, hepatotoxicity, and pancreatitis. Myelosuppression is characterized by decreased bone marrow function, which can lead to severe anemia and neutropenia. Regular blood count monitoring is essential to avoid such serious side effects.[5] Therefore, we should weigh the benefits of thiopurines against these potential risks and implement appropriate monitoring strategies to ensure patient safety.[4,5]

The identification of genetic polymorphisms in thiopurine metabolism has significantly enhanced the management of adverse effects associated with thiopurine therapy. While TPMT genotyping is a well-established method for predicting toxicity, its effectiveness is limited in Asian populations due to the lower prevalence of TPMT variants.[6] NUDT15 is under Nudix (nucleoside diphosphate linked to x) hydrolase superfamily. Recent research has highlighted the NUDT15 gene as a crucial factor in thiopurine-induced myelosuppression among Asians, particularly in patients with inflammatory bowel disease (IBD), which contrasts with that of European descent. Testing for NUDT15 variants is crucial for personalized medicine approaches, allowing healthcare providers to tailor treatment strategies and minimize the risk of adverse effects. By integrating NUDT15 testing into clinical practice, clinicians can optimize thiopurine therapy for Asian patients, ensuring safer and more effective treatment outcomes. Thus, NUDT15 testing should be prioritized before initiating thiopurine therapy in this demographic.[7,8]

Thiopurine metabolism and pharmacogenetics

Thiopurines, like azathioprine and 6-mercaptopurine, are prodrugs. These require intracellular activation to produce their immunosuppressive effects. Azathioprine is converted to 6-mercaptopurine (6-MP). Thereafter, it is metabolized through competitive pathways. The primary pathway involves the conversion of 6-MP to active 6-thioguanine nucleotides (6-TGNs). It is crucial for immunosuppression. However, 6-MP can also be inactivated by thiopurine methyltransferase (TPMT) by converting it to 6-methylmercaptopurine (6-MMP). In addition, xanthine oxidase (XO) transforms it into 6-thiouric acid.[9-11]

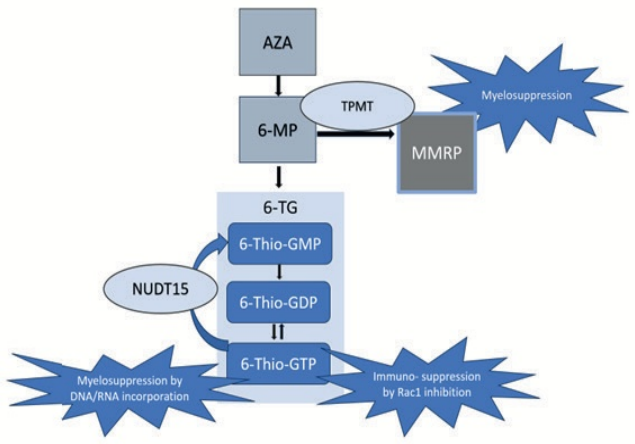

Figure 1. Overview of NUDT15 role in thiopurine metabolism. The azathioprine (AZA) and 6-mercaptopurine (6-MP) undergo a series of reactions that result in the active species, 6-thio-GTP, which are then incorporated into DNA/RNA or can inhibit Rac1 activity (6-thio-GTP). NUDT15 hydrolyzes 6-thio-GTP to the corresponding monophosphates and thereby reduce risk of toxicity by reducing the concentration of active metabolites (6-Thio-GTP) in cells.

AZA, azathioprine; MP, 6-mercaptopurine; 6-MMPR, 6-methyl-mercaptopurine ribonucleotides; 6-TG, 6-tioguanine;6-Thio-GTP, 6-thio-guanosine triphosphate; 6-Thio-GDP, 6-thio-guanosine diphosphate; 6-Thio-GMP, 6-thio-guanosine monophosphate; Rac1, Ras-related C3 botulinum toxin substrate.[1]

thiopurine medications (Figure 1). The balance among these metabolic pathways is essential, as high levels of 6-TGNs correlate with therapeutic efficacy but also heighten the risk of myelosuppression. Understanding these dynamics is vital for optimizing thiopurine therapy.[12]

Variability in thiopurine metabolism is significantly influenced by genetic polymorphisms in key enzymes, particularly TPMT and NUDT15. TPMT variants can reduce enzyme activity and increase myelosuppression risk. However, their prevalence is significantly low in Asian populations, which reduces their utility for thiopurine toxicity in these populations.[13,14] On the other hand, NUDT15 has emerged as a critical genetic determinant of thiopurine-induced myelosuppression among Asians. It inactivates thiopurine metabolites. Variants like c.415C>T (p.Arg139Cys) are strongly associated with diminished enzyme activity. This results in increased levels of the active metabolites 6-TGTP and 6-TdGTP and can lead to thiopurine intolerance and increased toxicity, particularly myelosuppression.[14-17] Understanding these genetic factors is essential to reducing the risk of adverse effects. Therefore, they can guide treatment decisions and improve patient safety.[14,18]

NUDT15 Variants in Asian populations and their impact on thiopurine toxicity

The prevalence of NUDT15 variants varies significantly among different ethnic groups. In Asian populations, the incidence of NUDT15 allelic mutations is 8.5–16%.[19-21] The mutation variant is rare in Caucasians, with frequencies of less than 1%22. In IBD patients, the frequency is 12% and 10.4%, respectively. The frequency is as high as 32.1% in China with autoimmune hepatitis.[23] The c.415C>T variant is the clinically most significant mutation and is associated with thiopurine-induced leukopenia, particularly in Asian populations. However, other NUDT15 variants, such as rs746071566 (c.55_56insGAGTCG), rs186364861 (c.52G > A), c.137C > G, and c.138T > G, have also been identified and are associated with reduced enzyme activity.[19,24,25] Studies suggested that the predictability of the NUDT15 variant allele for leukopenia is 36%-42.3%.[26,27] Patients carrying one or two copies of the c.415C>T variant are at significantly higher risk of developing severe myelosuppression, often requiring dose reduction or discontinuation of thiopurine therapy. Several studies have been conducted on the clinical utility of NUDT15 genotyping, revealing its significant potential to predict thiopurine toxicity. For example, a study in Japanese patients with IBD found that the c.415C>T variant was associated with a 35.6% risk of leukopenia in heterozygous patients and a 100% risk in homozygous patients, compared to a 7.6% risk in wild-type patients.[28]

Guidelines for NUDT15 testing

Given the high prevalence and significant impact of NUDT15 variants in Asian populations, several clinical guidelines now recommend NUDT15 testing before initiating thiopurine therapy in Asian patients with IBD. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for thiopurine recommends NUDT15 testing, particularly for Asian patients.[29] They recommend adjusting starting doses of thiopurines based on TPMT and NUDT15 genotypes (Table 1). The Korean Association for the Study of Intestinal Diseases (KASID) recommends NUDT15 testing before starting thiopurine to minimize the risk of myelosuppression.[30] The current British Society of Gastroenterology (BSG) guideline recommends NUDT15 genotype testing for IBD patients, if available. The Chinese Society of Gastroenterology (CSG) guidelines for IBD management include NUDT15 genotyping as a recommended pretreatment test. The guidelines suggest that patients with NUDT15 variants should be closely monitored by 6-thioguanine nucleotide levels to guide dosage adjustments.[31] While NUDT15 testing is not yet widely recommended in international guidelines, the American Gastroenterological Association (AGA) and the European Crohn's and Colitis Organization (ECCO) have acknowledged the importance of NUDT15 genotyping in Asian populations. These organizations suggest that NUDT15 testing may be considered in Asian patients, particularly those with a family history of thiopurine-induced toxicity.

Dose adjustment based on NUDT15 genotype

One of the important applications of NUDT15 testing is dose adjustment based on genotypes. Several non-functional alleles of the NUDT15 gene determine the tolerated thiopurine dosage of the patient.[21,22] Patients with NUDT15 variants may require lower starting doses of thiopurines to reduce the risk of myelosuppression. The 2018 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline update suggests that patients with intermediate

metabolizers should start with 30% to 80% of the standard dose.[18,29] However, this type of patient has some variability in the tolerated thiopurine dosages. A small proportion of these patients do not require significant thiopurine dose reduction.[22,32] Therefore, this allele-based dose adjustment applies mainly to starting doses; decisions about subsequent doses can be taken on regular monitoring of clinical myelosuppression. Patients with homozygous NUDT15 variants are at high risk of severe myelosuppression and may consider alternative therapies.[29] As alternative therapies to thiopurines, biologic agents like anti-tumor necrosis factor (TNF) therapies and small-molecule drugs like Janus kinase (JAK) inhibitors can be considered. However, the choice of alternative treatment should be based on disease severity, patient pReferencess, and other clinical factors.[33,34]

Studies suggest that East Asian descent has a significant proportion of NUDT15 poor metabolizers, which is about one in every 50 patients. This frequency is more common than the TPMT poor metabolizer phenotype in Europeans. This can explain the importance of testing NUDT15 genotyping in the Asian populations.[22]

Dosing of thiopurine by NUDT15 phenotype[18,29]

Table 1: Dosing of thiopurine by NUDT15 phenotype

Types	Risk	Dosing recommendation
Normal Metabolizer -Two normal function alleles(NUDT15*1/*1)	↔	Normal starting dose‡
Intermediate metabolizer -One normal function allele and one non-functional allele (NUDT15*1/*2, NUDT15*1/*3) OR Possible Intermediate Metabolizer -One uncertain function allele and one non-function allele (e.g., NUDT15*2/*5, NUDT15*3/*6)	↑	30% to 80% of normal starting dose‡
Poor Metabolizer -two non-functional alleles (NUDT15*2/*2, NUDT15*2/*3, NUDT15*3/*3)	↑↑	Consider Alternative therapy
* Allele. ‡Allow 2-4 weeks to reach steady-state after each dose adjustment in accordance with the risk level. ‡Adjust doses of thiopurine based on the degree of myelosuppression		

Monitoring and follow-up

British Society of Gastroenterology (BSG) suggests complete blood count (FBC), urea and electrolytes, and liver function tests (LFT) at baseline and at 2, 4, 8, 12 weeks, and thereafter every three months.[35] Even with dose adjustment, this is crucial to detecting signs of toxicity early with NUDT15 variants, especially the c.415C>T mutation cases.[18] It is recommended to reduce or temporarily stoppage of the thiopurine dose with regular follow-up when toxicities develop. For myelosuppression, reduction of thiopurine dose (when white cell count (WCC) < 3.5x109/L) or stoppage (when WCC <1.5x 109/L) with close white cell monitoring is vital. Thioguanine (TGN) and methyl mercaptopurine nucleotide (MeMP) levels should be assessed before considering thiopurine again.

For hepatotoxicity, the drug should be withheld until normalization of the LFT. Once toxicity resolves, re-challenge with a low dose of thiopurine with allopurinol can be an option. For pancreatitis, alternative treatment should be considered.[35,36] Physicians should make the patients aware of the symptoms of myelosuppression, hepatotoxicity, and other potentially serious side effects, such as fever, fatigue, abdominal pain, and bruising, and advise seeking medical attention as early as possible.[37,38]

Challenges and future directions

There are multiple challenges to practicing NUDT15 testing, especially in the Asian population. The cost of genetic testing can be an issue in the widespread adoption of NUDT15 testing, particularly in resource-limited settings. Though the cost of genotyping has decreased in recent years, preventing severe adverse effects may justify the investment. Efforts to increase the accessibility of NUDT15 testing, such as through insurance coverage and public health initiatives, are needed to ensure that all patients who could benefit from testing have access to it.[39]

Thiopurine dose adjustment should be based on the NUDT15 genotype. However, there is no standard guideline for IBD patients on the optimal dosing strategy for patients with NUDT15 variants. Further research is needed to establish a standardized dosing consensus in IBD patients. It will reduce the risk of toxicity and ensure the need for effective immunosuppression.[29,40] In addition to the NUDT15, other factors like TPMT and ITPA, environmental factors, concomitant medications, and infections can influence thiopurine metabolism and toxicity. Future research should explore the interaction between NUDT15 and other genetic and environmental factors to develop more comprehensive predictive models for thiopurine toxicity.[40]

Conclusion:

The prevalence of NUDT15 variants is high in Asian populations, which is the reason behind their strong association with thiopurine-induced myelosuppression in this group of people. It is therefore important to assess NUDT15 genotyping to minimize the adverse effects and optimize treatment outcomes. By identifying the genetic mutation of NUDT15, the risk of thiopurine-induced toxicity can be prevented by tailoring the treatment strategies. The integration of NUDT15 testing into clinical practice can make a significant advancement in personalized medical care for IBD. Clinical guidelines and consensus now recommend NUDT15 testing, especially for the Asian population. Dose adjustment based on genotype should be a standard practice. However, Cost, availability of the test, and standardized dosing guidelines are the current challenges for this genetic testing. Future research should focus on addressing these challenges. In addition, interaction between NUDT15 and other genetic and environmental factors should be explored. By integrating NUDT15 testing into clinical practice, we can improve the safety and efficacy of thiopurine therapy for Asian patients with IBD.

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References:

1. Gionchetti P, Rizzello F, Habal F, Venturi A, Campieri M, Poggioli G, et al. Standard treatment of ulcerative colitis. *Dig Dis.* 2003;21(2):157–167. doi:10.1159/000073247

2. Weinberg M, Peppelenbosch M, Hommes D. Biological therapy in the management of recent-onset Crohn's disease: why, when and how? *Drugs.* 2006;66(11):1431–1439. doi:10.2165/00003495-200666110-00002

3. Dieleman LA, Peña AS, Meuwissen SG, van Rees EP. Role of animal models for the pathogenesis and treatment of inflammatory bowel disease. *Scand J Gastroenterol Suppl.* 1997;223:99-104.

4. Sparrow MP. Use of allopurinol to optimize thiopurine immunomodulator efficacy in inflammatory bowel disease. *Gastroenterol Hepatol (N Y).* 2008;4(7):505-511.

5. Gledhill T, Hurst A, Brown L, Bliss P. Monitoring thiopurine methyltransferase (TPMT) activity in inflammatory bowel disease: is it worth it? *Gut.* 2011;60(Suppl 1):A145. doi:10.1136/gut.2011.239301.307

6. Winter JW, Marinaki AM, Sanderson JD, Mills PR. TPMT genotype and the response to azathioprine in inflammatory bowel disease: authors' reply. *Aliment Pharmacol Ther.* 2007;26(7):1084-1085. doi:10.1111/-j.1365-2036.2007.03448.x

7. Zhang A, Yang J, Li J, Xu Y, Zhang X. Further evidence that a variant of the gene NUDT15 may be an important predictor of azathioprine-induced toxicity in Chinese subjects: a case report. *J Clin Pharm Ther.* 2016;41(5):572–574. doi:10.1111/jcpt.12420

8. Liang DC, Yang CP, Liu HC, Jaing TH, Hung IJ, Yeh TC, et al. NUDT15 gene polymorphism related to mercaptopurine intolerance in Taiwanese Chinese children with acute lymphoblastic leukemia. *Pharmacogenomics J.* 2016;16(6):536–539. doi:10.1038/tpj.2015.75

9. Hiratsuka M, Inoue T, Omori F, Agatsuma Y, Mizugaki M. Genetic analysis of thiopurine methyltransferase polymorphism in a Japanese population. *Mutat Res.* 2000;448(1):91-95.doi:10.1016/S0027-5107(00)00004-X

10. Katara P, Kuntal H. TPMT polymorphism: when shield becomes weakness. *Interdiscip Sci Comput Life Sci.* 2016;8(2):150-155. doi:10.1007/s12539-015-0111-1

11. Peng Y, Feng Q, Wilk D, et al. Structural basis of substrate recognition in thiopurine S-methyltransferase. *Biochemistry.* 2008;47(23):6216-6225. doi:10.1021/bi800102x

12. Cara CJ, Peña AS, Sans M, et al. Reviewing the mechanism of action of thiopurine drugs: towards a new paradigm in clinical practice. Med Sci *Monit Int Med J Exp Clin Res.* 2004;10(11):RA247-254.

13. Gearry RB, Barclay ML. Azathioprine and 6-mercaptopurine pharmacogenetics and metabolite monitoring in inflammatory bowel disease. *J Gastroenterol Hepatol.* 2005;20(8):1149-1157. doi:10.1111/j.1440-1746.2005.03832.x

14. Yang JJ, Bhojwani D. Thiopurine S-methyltransferase pharmacogenetics in childhood acute lymphoblastic leukemia. In: Czader M, editor. *Hematological Malignancies.* Vol. 999. Methods in Molecular Biology. New York: Humana Press; 2013. p. 273–284. doi:10.1007/978-1-62703-357-2_20

15. Jang IJ, Shin SG, Lee KH, et al. Erythrocyte thiopurine methyltransferase activity in a Korean population. *Br J Clin Pharmacol.* 1996;42(5):638-641. doi:10.1111/j.1365-2125.1996.tb00061.x

16. Nguyen ML, Hoang AV, Duong BT, Phung NTN. The influence of NUDT15 variants on 6-mercaptopurine-induced neutropenia in Vietnamese pediatric acute lymphoblastic leukemia. *Hum Genet Genomics Adv.* 2023;4(2):100183. doi:10.1016/j.xhgg.2023.100183

17. Winter JW, Gaffney D, Shapiro D, et al. Assessment of thiopurine methyltransferase enzyme activity is superior to genotype in predicting myelosuppression following azathioprine therapy in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2007;25(9):1069-1077. doi:10.1111/j.1365-2036.2007.03301.x

18. Khaeso K, Udayachalerm S, Komvilaisak P, et al. Meta-analysis of NUDT15 genetic polymorphism on thiopurine-induced myelosuppression in Asian populations. *Front Pharmacol.* 2021;12:784712. doi:10.3389/f-phar.2021.784712

19. Kakuta Y, Kinouchi Y, Shimosegawa T. Pharmacogenetics of thiopurines for inflammatory bowel disease in East Asia: prospects for clinical application of NUDT15 genotyping. *J Gastroenterol.* 2018;53(2):172-180. doi:10.1007/s00535-017-1416-0

20. Sutiman N, Chen S, Ling KL, et al. Predictive role of NUDT15 variants on thiopurine-induced myelotoxicity in Asian inflammatory bowel disease patients. *Pharmacogenomics.* 2018;19(1):31–43.doi:10.2217/pgs-2017-0147

21. Yang SK, Hong M, Baek J, et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. *Nat Genet.* 2014;46(9):1017-1020. doi:10.1038/ng.3060

22. Yang JJ, Landier W, Yang W, et al. The inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. *J Clin Oncol.* 2015;33(11):1235–1242. doi:10.1200/-JCO.2014.59.4671

23. Fei X, Shu Q, Zhu H, et al. NUDT15 R139C variants increase the risk of azathioprine-induced leukopenia in Chinese autoimmune patients. *Front Pharmacol.* 2018;9:460. doi:10.3389/fphar.2018.00460

24. Muhammad M, Saifo M, Aljamali M, Alali M, Ghanem KM. The frequency of NUDT15 rs116855232 and its impact on mercaptopurine-induced toxicity in Syrian children with acute lymphoblastic leukemia. *Front Oncol.* 2024;14:1334846. doi:10.3389/fonc.2024.1334846

25. Zhang F, Amat G, Tang Y, et al. NUDT15 genetic variants in Chinese Han, Uighur, Kirghiz, and Dai nationalities. *Front Pediatr.* 2022;10:832363. doi:10.3389/fped.2022.832363

26. Fan X, Yin D, Men R, Xu H, Yang L. NUDT15 polymorphism confers increased susceptibility to thiopurine-induced leukopenia in patients with autoimmune hepatitis and related cirrhosis. *Front Pharmacol.* 2019;10:346. doi:10.3389/fphar.2019.00346

27. Miao Q, Yan L, Zhou Y, et al. Association of genetic variants in TPMT, ITPA, and NUDT15 with azathioprine-induced myelosuppression in southwest China patients with autoimmune hepatitis. *Sci Rep.* 2021;11(1):7984. doi:10.1038/s41598-021-87095-0

28. Matsuoka K. NUDT15 gene variants and thiopurine-induced leukopenia in patients with inflammatory bowel disease. *Intest Res.* 2020;18(3):275-281. doi:10.5217/ir.2020.00002

29. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. *Clin Pharmacol Ther.* 2019;105(5):1095–1105. doi:10.1002/cpt.1304

30. Lee KM, Kim YS, Seo GS, Kim TO, Yang SK; IBD Study Group of the Korean Association for the Study of Intestinal Diseases. Use of thiopurines in inflammatory bowel disease: a consensus statement by the Korean Association for the Study of Intestinal Diseases (KASID). *Intest Res.* 2015;13(3):193. doi:10.5217/ir.2015.13.3.193

31. Inflammatory Bowel Disease Group, Chinese Society of Gastroenterology, Chinese Medical Association; Inflammatory Bowel Disease Quality Control Center of China. 2023 Chinese national clinical practice guideline on diagnosis and management of Crohn's disease. *Chin Med J (Engl).* 2024;137(14):1647-1650. doi:10.1097/CM9.0000000000003222

32. Moriyama T, Nishii R, Perez-Andreu V, et al. NUDT15 polymorphisms alter thiopurine metabolism and hematopoietic toxicity. *Nat Genet.* 2016;48(4):367-373. doi:10.1038/ng.3508

33. Hanauer SB. Clinical perspectives in Crohn's disease. Turning traditional treatment strategies on their heads: current evidence for "step-up" versus "top-down." *Rev Gastroenterol Disord.* 2007;7 Suppl 2:S17-22.

34. Meier J, Sturm A. Current treatment of ulcerative colitis. *World J Gastroenterol.* 2011;17(27):3204-3212. doi:10.3748/wjg.v17.i27.3204

35. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut.* 2019;68(Suppl 3):s1-106. doi:10.1136/gutjnl-2019-318484

36. Konidari A, Matary WE. Use of thiopurines in inflammatory bowel disease: safety issues. *World J Gastrointest Pharmacol Ther.* 2014;5(2):63-76. doi:10.4292/wjgpt.v5.i2.63

37. Baradaran H, Hashem Zadeh A, Dashti-Khavidaki S, Laki B. Management of drug-induced neutropenia, thrombocytopenia, and anemia after solid organ transplantation: a comprehensive review. *J Clin Pharm Ther.* 2022;47(12):1895-1912. doi:10.1111/jcpt.13775

38. Meijer B, Mulder CJ, van Bodegraven AA, de Boer NKH. How do I treat my inflammatory bowel disease patients with thiopurines? *World J Gastrointest Pharmacol Ther.* 2016;7(4):524-530. doi:10.4292/wjgpt.v7.i4.524

39. Goh LL, Lim CW, Leong KP, Ong KH. TPMT and NUDT15 testing for thiopurine therapy: a major tertiary hospital experience and lessons learned. *Front Pharmacol.* 2022;13:837164. doi:10.3389/fphar.2022.837164

40. Schaeffeler E, Jaeger SU, Klumpp V, et al. Impact of NUDT15 genetics on severe thiopurine-related hematotoxicity in patients with European ancestry. *Genet Med.* 2019;21(9):2145-2150. doi:10.1038/s41436-019-0448-7

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