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Editorial Note

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It is with immense pleasure that we present to you the next issue of *Pakistan Journal of Gastroenterology.* This milestone marks another step forward in our ongoing journey to provide a credible platform for advancement of gastroenterology and hepatology research in Pakistan and beyond.

The publication of this issue is a testimony to the trust placed in us by our respectable authors, who continue to contribute their high-quality and original research to this journal. We are particularly grateful to all the authors who considered *Pak J Gastro* as the home for their precious research work. At the same time, we extend our heartfelt thanks to our reviewers, whose timely and constructive evaluations ensure the academic integrity and scientific rigor of every article published.

This issue showcases a diverse range of scholarly endeavors, including an editorial, original articles, and a clinical review with updates in the field of gastroenterology. These contributions reflect the progress being made in clinical practice, research methodologies, and innovations that impact patient care.

While we celebrate this achievement, we also recognize that this is only the beginning of a committed journey. Our vision is to take the official *Journal of Pakistan Society of Gastroenterology* to the next level by striving for national indexing, international recognition, and eventual accreditation by established global academic authorities. With continued support from our authors, reviewers, and readers, we are confident that this goal will be realized.

Together, let us continue to build *Pakistan Journal of Gastroenterology* into a platform that effectively highlights academic advances in the field of gastroenterology & hepatology both at national and international levels.

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PAKISTAN JOURNAL OF GASTROENTEROLOGY

Editorial

Non-Invasive Assessment of Portal Hypertension: An Evolving Landscape

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Portal hypertension is a key pathophysiological consequence of chronic liver disease (CLD), and its progression plays a pivotal role in the development of complications such as variceal bleeding, ascites, hepatic encephalopathy, and spontaneous bacterial peritonitis. Early detection and staging of portal hypertension are crucial to delay or prevent these complications and to guide management strategies.

Traditionally, hepatic venous pressure gradient (HVPG) measurement has been considered the gold standard for assessing portal hypertension. However, HVPG is invasive, costly, and limited to specialized centers, making it impractical for routine or repeated use in many healthcare settings, especially in resource-limited regions. [1] Upper GI endoscopy for screening gastroesophageal varices is another accepted tool but is also invasive, not always readily accessible, and does not offer a quantitative measure of portal pressure. Overuse in asymptomatic patients adds unnecessary burden to healthcare systems and can lead to patient fatigue and financial stress.

Over the past decade, a range of non-invasive tests (NITs) have emerged to assess liver fibrosis and indirectly estimate portal hypertension[2] These include:

- ***Liver stiffness measurement (LSM) using transient elastography (TE) (e.g., Fibro Scan) or shear-wave elastography;*** When combined with platelet count, LSM becomes a valuable predictor of clinically significant portal hypertension (CSPH). This approach has been shown to potentially obviate the need for screening endoscopy in up to 30% of patients with compensated cirrhosis.[3]

- Spleen stiffness measurement (SSM); is gaining ground as a complementary tool to LSM. In advanced fibrosis, where liver stiffness may plateau, spleen stiffness continues to correlate with increasing portal pressure. The Baveno VII consensus suggests SSM values 50 kPa to rule in CSPH. [4] Other studies suggest thresholds between 46– 55 kPa for optimal sensitivity and specificity. [5]

- Doppler ultrasound of the abdomen, when performed by an experienced radiologist, can reveal surrogate markers of portal hypertension, such as collateral circulation, splenomegaly, and altered portal vein flow dynamics.

- Magnetic resonance elastography (MRE) is more sensitive and reproducible than ultrasound-based modalities, especially in obese patients or those with ascites, and can help confirm fibrosis staging when TE results are equivocal. [6]

- FIB-4 index remains a useful, FIB-4 inexpensive scoring tool for estimating advanced fibrosis, particularly in primary care and outpatient settings.

- Artificial intelligence-based imaging and deep learning models are being developed to interpret liver and spleen elastography data with higher precision, although their current clinical utility is limited by cost and availability. [7]

The Baveno VII consensus (2022) made significant strides in validating the use of noninvasive tools to assess compensated advanced chronic liver disease (cACLD) and CSPH.[4] It proposed the following criteria:

- LSM 150 × 10^9/L: CLD is likely, but endoscopy can be avoided. - LSM 15–20 kPa: suggests possible cACLD. - LSM >20 kPa and platelet count >150 × 10^9/L: CLD is likely, but endoscopy can be avoided. - LSM 15–20 kPa: suggests possible cACLD. - LSM >20 kPa and platelet count <150 x 10^9 /L: indicates a significant risk of CSPH.

In viral alcohol or MASH related cACLD. The ANTICIPATE model may be applied in patients with LSM value between 20-25 kPa, where the risk of CSPH may exceed 60% in the presence of thrombocytopenia.[8]

Conclusion:

Non-invasive assessment of portal hypertension has moved from a research interest to a clinical imperative. When properly applied, these tools improve risk stratification, reduce unnecessary endoscopies, and offer safer, more efficient patient care. In Pakistan and other resource-limited settings, embracing non-invasive models is not only practical but essential. Continuous validation and adaptation of these methods—guided by international recommendations like Baveno VII—will enhance our ability to provide timely and costeffective care to patients with chronic liver disease.

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Narrative Review

Stem Cell Therapy for Liver Cirrhosis - Prospects and challenges

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Abstract:
The burden of liver diseases and their impact on health is a global concern. While liver transplant remains the curative option for end-stage liver diseases, it has many shortcomings restricting its widespread availability and adaptation. The quest for an effective alternative to slow down progression of liver cirrhosis and restoration of function of cirrhotic liver is therefore ongoing, where stem cell therapy is on the table which. However, although in many cases the results are encouraging with stem cells in liver diseases, it still has a long way to go before it can be recommended in regular clinical practice. We have significant experience of treating liver cirrhosis patients with human progenitor stem cells. Here we present a blend of our own experience and review of recent literature to assess where we stand today with stem cells as an option at our disposal for treating liver diseases.
Keywords: Stem cell, liver cirrhosis.

How to Cite this article:

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Introduction:

There are approximately 500 million people in the world who are at risk of developing liver cirrhosis and complications.[1,2] Liver diseases were responsible for over 1.3 million deaths globally in 2017; 1-year mortality being 57%.[3,4] It has been estimated that these diseases account for 2.4% of the global death burden .[4] At present, liver transplantation remains the only curative option for end-stage liver disease. However, it has several limitations, like shortage of organs, organ rejection and high cost .[5,6] Patients on waiting list awaiting donor organ, have high mortality rate.[7,8] Moreover, liver transplantation is still not available in Bangladesh. Liver support devices like, MARS act as 'bridge' to transplant, but studies have shown that these devises including MARS do not reduce mortality significantly compared to standard medical care .[9]

On the other hand, the potential of stem cells to differentiate into multiple cell lines makes it a potential candidate to induce regeneration in failing organs, particularly the liver which has excellent regenerative capacity .[10,11] Contrary to

our previous understanding, we now know that liver cirrhosis is not completely irreversible and therefore stem cells may represent an option for restoration of normal or near normal liver function even in established liver cirrhosis.[12, 13, 14, 15] Besides, stem cell therapy will have several advantages over liver transplantation. A donor will be able to donate stem cells to multiple recipients. The technique is simple and cost effective compared to liver transplantation and there will be no need to remove the recipient liver.[16]

The history of cell therapy for liver diseases dates back to 1976 when allogenic hepatocyte transplantation was performed via portal vein in congenital enzyme deficient rat.[17] Later hepatocytes were transplanted into spleen. The hypothesis was that spleen would play the role of ectopic liver.[18] Subsequently in humans, in end-stage liver disease, hepatocytes transplanted via splenic artery remained viable and the post-transplant spleen displayed hepatic cord structure.[19]

Discussion:

Mesenchymal stem cells

Mesenchymal stem cells (MSC)s are mesoderm derived pluripotent stem cells. They can be isolated from bone marrow, umbilical cord, fat, pulp, placenta, endometrial tissue, limbus and amniotic membrane. MSCs have several advantages like multi-directional differentiation, immunomodulatory and pro-angiogenic effect, secretion of growth factors, cytokines and regulators through paracrine signaling and other pathways.[20, 21] They decrease the expression of inflammatory molecules like interleukin-12 (IL-12) and tumor necrosis factor-α (TNF-α), while secreting interferon-ϒ (IFN-ϒ) and IL-10. This leads to an increase in the number of regulatory T cells.[22] They also increase CCL18 and improve monocyte survival.[23] They improve anti-inflammatory effect of macrophage by secreting prostaglandin E2 (PGE2),stimulated gene/protein 6 and indolemine 2,3-deoxygenase (IDO) and inhibit antibody production, secretion and proliferation of activated B lymphocytes.[24, 25, 26] It has also been observed that MSCs inhibit non-apoptotic death of hepatocytes by ferroptosis by decreasing intra-cellular reactive oxygen species (ROS) and ferrous level.[27] Another advantage with MSCs is that these do not induce host immune response due to low immunogenicity.[21] MSCs express specific cell surface markers, like CD105, CD73 and CD90 and can improve immune response [28]. All these, in turn, may contribute to hepatic regeneration. Besides, MSCs are associated with low risk of carcinogenicity.[29]

MSCs secrete IL-10, which inhibit activation of hepatic stellate cells (HSC) and extracellular matrix (ECM) formation during hepatic regeneration. MSCs also induce apoptosis of HSC through FasL pathways.[30] Macrophages are crucial in hepatic fibrosis as they secrete fibrotic factors like transforming growth factor-β (TGF-β) and platelet derived growth factor (PGDF).[31, 32] Macrophages are characterized as pro-inflammatory or M1type and pro-repair or M2 type.[33] MSCs polarize macrophages to M2 state and promote their death.[34, 35, 36] Thus, MSCs reduce hepatic inflammation and fibrosis. Therefore, it is no wonder that till 2022, there were around 1300 publications in PubMed and more than 50 clinical trials registered in ClinicalTrials.gov using MSCs in treating liver diseases.

A phase II clinical trial with autologous bone marrow derived MSCs in 71 alcoholic liver cirrhosis patients has shown improvement of liver function and fibrosis and Child-Pugh and Model for End Stage Liver Disease (MELD) scores compared to control group, however no significant difference was observed between single and double MSC infusions.[37] Another study involving 110 acute on chronic liver failure (ACLF) patients also reported improvement of liver function and MELD score, better infection control and reduced mortality at 24 weeks follow up.[38] A Chinese group has extensively studied MSCs in wide range of liver diseases including decompensated liver cirrhosis, primary biliary cholangitis (PBC), ACLF and liver transplant recipients. They have observed improvement in liver function and hepatic functional reserve in addition to reduced transplant rejection and post-transplant complications and improvement of quality of life and survival.[39, 40, 41, 42] Besides, at 75 month follow up, none of the 219 liver

cirrhosis patients who received MSC therapy developed hepatocellular carcinoma (HCC).[43]

MSCs also improve complications of liver cirrhosis like, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy and hepatic failure.[44,45,46] In fact, a meta-analysis showed that MSCs are associated with statistically significant improvement in serum albumin and total serum bilirubin in decompensated liver cirrhosis.[47] Furthermore, significant reduction of serum biomarkers of hepatic fibrosis namely, procollagen III C terminal peptide, procollagen III N terminal peptide (PIIINP), serum laminin, hyaluronic acid and type IV collagen following MSC infusion have also been reported.[48,49] Having said so, it needs also be mentioned that there are several published studies in the literature, which failed to reveal any improvement of liver function with MSC.[50,51,52] Such inconsistencies may be attributed to source of MSC, sample size, inclusion and exclusion criteria, study end point etc. Another limitation with MSC therapy is that the mechanism of MSC induced improvement in liver diseases have been studied only in vitro and not in humans, as technical and ethical issues remain concern.[53,54]

Haemopoietic progenitor stem cells:

MSCs therapy however remains challenging for resource constrained countries like Bangladesh, as extremely high tec, sophisticated and expensive instruments and good manufacturing practice (GMP) are pre-requisite for MSC therapy. This is also clearly defined in the national guideline on stem cell and cell based products of Bangladesh Government.[55] In such a scenario, haemopoietic progenitor stem cells provide a visible option. These improve the damaged liver through paracrine signaling between donor and host cells, which induces cytokines and growth factors.[56,57,58] After partial hepatectomy in humans, haemopoietic progenitor stem cells have shown to reduce IL-1 mediated inflammation on one hand, while on the other hand facilitate CD39 dependent liver regeneration.[59]

Granulocyte colony stimulating factor (GCSF) is a haemopoietic growth factor that mobilizes haemopoietic progenitor stem cells to peripheral circulation.[60] GCSF induced proliferation of haemopoietic progenitor stem cells have shown to induce hepatic regeneration in acute and chronic liver damage models.[61,62]

In one of our studies involving 34 decompensated liver cirrhosis patients, we saw improvement in ascites and serum albumin following infusion of haemopoietic progenitor stem cells via hepatic arterial route.[63] We had similar experience after administrating haemopoietic progenitor stem cells via portal venous route in 20 more decompensated liver cirrhotics via portal venous route.[64] In both studies, the mortality appeared to be low. In a large study, it was demonstrated that GCSF in combination with haemopoietic progenitor stem cells infusion improved liver function, Child-Pugh score and survival in acute liver failure.[65] In addition, human menstrual blood stem cells have shown to reduce progression of hepatic fibrosis in animal model.[66] Besides, researchers from our region have shown that the CD34 cell population rises in the liver following GCSF administration.[67] Studies from our region have also found that GCSF administration leads to improvement in Child-Pugh and MELD scores, prevents development of sepsis and hepato-renal syndrome and improves survival in decompensated cirrhosis.[12,13] He also had satisfactory results with GCSF injections in a group of 17 decompensated cirrhosis patients.[68]

Improvement in serum albumin level has also been reported following MSC infusion. A meta-analysis demonstrated that there was significant improvement in serum albumin following both intravenous and hepatic arterial infusion of MSCs compared to control group [47]. The exact explanation of the improvement in serum albumin level in our patients is difficult to explain. Only human albumin injection does not improve serum albumin and ascites so drastically as experienced by us. It tempts us to hypothesize that combination of human albumin and haemopoietic progenitor stem cells may have potentiating impact on ascites.[63]

None of our patients developed HCC. A study found that umbilical cord-derived MSC infusion is also not associated with increase in frequency of HCC.[69]

Other types of stem cells:
Clinical trials with human embryonic stem cells (hESCs) have ethical and legal concerns as these cells are associated with carcinogenesis and immune rejection.[53] Similar issues are also associated with induced pluripotent stem cells (iPSCs).[70] Human hepatocytes also have immunogenicity issues. Besides impaired proliferative ability of hepatocytes as well as insufficient cell migration and limited space within the unhealthy liver also limit the use of human hepatocytes.[71]

Route of administration:
Route of administration is a major issue in stem cell therapy. Most preferred route of MSC administration is intravenous infusion. However, in different studies MSCs have been administered through hepatic artery, portal vein, intra-hepatic vein and intra-splenic vein.
The main aim remains to deliver transplanted stem cells to the hepatic sinusoids. Another frequently adapted route is the portal vein either by puncture of an intra-hepatic splenic vein tributary or an intra-hepatic portal vein tributary or an intra-hepatic portal shunt via jugular vein through hepatic venous system.[72, 73, 74]However, liver cirrhosis patients often have portal hypertension, which makes it difficult for transplanted cells to reach the hepatic sinusoids and usually all remaining cells get eliminated by macrophages with 24 hours. Besides, the portal vein is susceptible to embolism.[75]
While the hepatic arterial route has high rate of MSC colonization and survival, the peripheral venous route is straightforward and can be easily repeated.[76] However, the fourth i.e. intraperitoneal route should better be avoided, as it is associated with risks of secondary bacterial peritonitis, adhesion and interference with MSC migration.[77]
In our case, we injected GCSF to mobilize haemopoietic progenitor stem cells to the peripheral circulation from bone marrow. We use apheresis machine (COM.TEC, Fresenius Krabi AG, Hamburg, Germany) to collect enriched population of haemopoietic progenitor stem cells without any risk of contamination.[63,64] P1YA kit (Fresenius Krabi AG, Hamburg, Germany) was used to harvest haemopoietic progenitor stem cells from peripheral blood.[63,64] Number of haemopoietic progenitor stem cells was calculated by flow cytometry (Bacton Dickenson FACSVerse, Bacton Dickenson Biosciences, San Jose, CA, USA).[63] We administered haemopoietic progenitor stem cells through both hepatic arterial and iportal venous routes.[63,64]

Dose of administration:
Dose of MSCs remain a major issue for clinical application in liver disease. The usual dose of MSC in peripheral intravenous infusion is between $5x10^5$ to $1x10^6$ cells/kg.[78] Dose escalation study has shown that upto $2x10^8$ cells/time after 3 cycles of umbilical cord derived MSC infusion was safe in decompensated liver cirrhotics.[79]

Conclusion:
While stem cell therapy appears to be a safe and prospective treatment alternative for liver cirrhosis, there are still many gray areas that need to be answered like establishing a standard treatment protocol, choice between MSC and human progenitor stem cell, route, dose and frequency of administration and in-depth appreciation of in vivo mechanism of action. Further interest and more randomized, multi-center clinical trials involving different liver diseases of different aetiologias will probably establish this promising modality as an effective one for the management of advanced liver diseases in the future.

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Author's Contribution:

MAM: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
SMN, ALM, AR, MM, SMFA: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

PAKISTAN JOURNAL OF GASTROENTEROLOGY

Original Article

Exploring Viral and Non-Viral causes of Alanine Aminotransferase Spikes above 1000 in a South Asian Cohort

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Abstract:

Background

Elevated ALT levels greater than 1000 U/L indicate severe hepatic injury. In Western studies, ischemic hepatitis and drug-induced liver injury (DILI) are common causes.[1,2] However, in South Asia, hepatitis E (HEV) predominates, contributing to a different clinical pattern. This study explores the causes and outcomes of ALT >1000 U/L in a South Asian cohort.

Methods

we prospectively analyzed 151 patients with ALT >1000 U/L from AIMS Hospital. Data on demographics, etiology, clinical presentation (acute hepatitis, acute liver failure [ALF], acute-on-chronic liver failure [ACLF]), hospital stay, and 30-day outcomes were collected. Statistical analysis was performed using IBM SPSS Version 22.

Results

Viral hepatitis was the leading cause (86.1%), with hepatitis E being the most frequent (55.6%). Non-viral causes, including ischemic hepatitis (4.6%) and DILI (3.3%), were rare. Acute hepatitis (63.6%) was the most common presentation, and hepatitis E was responsible for 63.5% of these cases. ALF occurred in 11.9%, primarily due to hepatitis E. The majority of patients (78.1%) had a short hospital stay (<48 hours), with 94% showing improvement. Severe cases (ischemic hepatitis, ACLF) resulted in a 4% mortality rate, and 2% were referred for liver transplantation.

Conclusion

Our study highlights the dominance of hepatitis E in ALT >1000 U/L in South Asia, contrasting with Western trends where ischemic hepatitis and DILI are more prevalent.[1, 2] These findings suggest the need for regional-specific diagnostic strategies, particularly in endemic areas.

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Introduction:

Hepatitis E virus (HEV) is a significant cause of acute viral hepatitis globally, with Southeast Asia bearing a disproportionately high burden. HEV infections contribute to substantial morbidity and mortality, especially in regions with poor sanitation and limited access to safe drinking water. In Southeast Asia, HEV is responsible for 25–30% of acute hepatitis cases, with a prevalence reaching as high as 50% in endemic areas. Pregnant women and immune compromised individuals are particularly vulnerable, often experiencing severe outcomes,

including fulminant hepatitis. Despite advancements in public health initiatives, the burden of HEV remains a critical concern in the region, underscoring the need for region-specific data on the clinical course and outcomes associated with HEV infections.[1,2]

This study focuses on understanding the etiological distribution and clinical manifestations of patients presenting with severe hepatic injury, defined by ALT levels exceeding 1000 U/L, in a South Asian cohort. By analyzing the causes, clinical profiles, and outcomes of these cases, this study aims to shed light on the role of viral hepatitis particularly HEV and its contribution to severe liver disease. Furthermore, the study explores non-viral causes, such as ischemic hepatitis and drug-induced liver injury (DILI), to establish a comprehensive understanding of the spectrum of conditions leading to marked ALT elevation. Such findings are essential to guide regionally relevant diagnostic and therapeutic strategies.

Several studies in both global and regional contexts have investigated ALT elevations and their etiologies. Western studies frequently report ischemic hepatitis and DILI as leading causes of ALT spikes exceeding 1000 U/L.[3] Conversely, research from South Asia, including Pakistan and India, has highlighted viral hepatitis, predominantly HEV, as the principal etiology (4). For instance, Sharma et al. observed ischemic hepatitis as the leading cause in a Western cohort, while Khan et al. found HEV to account for over half of the cases in a South Asian setting.[4,5] Additionally, studies on HIV-positive cohorts in Asia suggest a multi factorial interplay between viral hepatitis co-infections and ALT elevations, emphasizing the complexity of hepatic injuries in the region.[6] These differences underline the necessity of region-specific investigations to address unique epidemiological patterns.

Despite extensive research on ALT elevation and its causes, significant gaps remain in understanding the clinical trajectory and outcomes of patients with HEV-related ALT spikes in South Asia. Most studies have focused on viral prevalence or clinical presentations without delving into comparative analyses of viral versus non-viral causes. Additionally, the role of non-viral etiologies like ischemic hepatitis in South Asia remains underexplored. Our study addresses this gap by providing a detailed analysis of 151 patients with ALT >1000 U/L, highlighting the dominance of HEV and its clinical outcomes. By comparing our findings with global data, we aim to contribute to the growing understanding of hepatic injuries in diverse populations and advocate for tailored diagnostic and management approaches.

Methodology:

Study Design and Setting

This prospective cross-sectional study was conducted at the Department of Gastroenterology, Asian Institute of Medical Sciences (AIMS) Hospital, Hyderabad, Pakistan, from January 2023 to December 2024. The study aimed to evaluate the etiological factors, clinical presentations, and outcomes of patients with alanine aminotransferase (ALT) levels exceeding 1000 U/L.

Study-Population:

A total of 151 patients presenting with ALT >1000 U/L during the study period were included in the analysis. Patients were selected consecutively based on the inclusion and exclusion criteria.

Inclusion Criteria:

1. Patients aged 18 years or older.
2. ALT levels exceeding 1000 U/L at presentation.
3. Availability of complete clinical, laboratory, and imaging data to determine the etiology and outcomes.

Exclusion Criteria:

1. Patients with pre-existing chronic liver disease or cirrhosis.
2. Those undergoing ongoing treatment for conditions associated with ALT elevation (e.g., chemotherapy or antiretroviral therapy).
3. Patients with autoimmune liver disease or metabolic liver conditions such as Wilson's disease or alpha-1 antitrypsin deficiency.
4. Incomplete or missing critical data in medical records.

Data Collection:
Data were collected at the time of hospital admission using a standardized data collection form. Key variables included:

- **Demographics**: Age, gender, and relevant medical history.
- **Etiological Factors**: Viral hepatitis (A, B, C, D, E), and non-viral causes (ischemic hepatitis, drug-induced liver injury, sepsis).
- **Clinical Presentations**: Acute hepatitis, acute liver failure (ALF), and acute-on-chronic liver failure (ACLF).
- **Investigations**: Laboratory findings (ALT, AST, bilirubin, prothrombin time, albumin) and viral serologies (e.g., anti-HEVIgM, HBsAg, anti-HCV antibodies). Imaging studies, including ultrasound and CT scans, were performed as required.

Outcome-Measures:
The primary outcomes included clinical improvement, discharge, and adverse outcomes such as referral for liver transplantation or in-hospital mortality.

Statistical-Analysis
Data were analyzed using IBM SPSS Statistics Version 22. Categorical variables were reported as frequencies and percentages. Chi-square tests were used for categorical data comparisons, while t-tests or Mann-Whitney U tests were applied for continuous variables. Logistic regression analysis identified factors associated with adverse outcomes, p-value <0.05 was considered statistically significant.

Results:
In our cohort of 151 patients with ALT >1000 U/L, the majority were male (74.2%) and younger than 40 years old (69.5%). Most patients (68.2%) weighed ≥70 kg, and 67.5% had no co-morbidities. Among those with co-morbidities, diabetes (19.3%), ischemic heart disease (14.6%), and chronic liver disease (6.0%) were most common as shown in Table-1.

Viral hepatitis was the leading cause of elevated ALT levels, accounting for 86.1% of cases. Hepatitis E virus (HEV) was the most prevalent, responsible for 55.6% of cases, followed by hepatitis A (8.6%) and hepatitis B (7.3%). HEV was notably over-represented in pregnant women, emphasizing the heightened vulnerability in this group. Drug-induced liver injury (DILI) was the second most common non-viral cause, contributing to 3.3% of cases, primarily due to medication overdoses or idiosyncratic reactions.
Clinical outcomes revealed that the majority of patients improved without complications, with 142 (94.0%) showing recovery. Liver transplant was required in three cases, while six patients succumbed to their conditions. Mortality was highest among patients with hepatitis D (25.0%) and HEV (3.6%), underscoring the need for targeted prevention and management strategies in these high-risk groups clearly depicted in Table-2.

Table-1: Demographic variables at Presentation

Variable		n=151 (%)
Age	<40 years	105 (69.5%)
	≥ 40 years	46 (30.5%)
Gender	Male	112(74.2%)
	Female	39 (25.8%)
Weight	<70 kg	48 (31.8%)
	≥ 70 kg	103 (68.2%)
Comorbidities	No co-morbidities	102 (67.5%)
	Diabetic	14 (19.3%)
	Hypertension	4 (2.6%)
	Ischemic Heart Disease	16 (14.6%)
	Chronic Liver Disease	9 (6.0%)
	Chronic Kidney Disease	6 (4.0%)

Table-2: Causes of ALT >1000 vs. Outcomes in 30 days

Cause	Improved	Referred for Liver transplant	Died	Total	% of Total
Hepatitis A	13	0	0	13	8.6%
Hepatitis B	11	0	0	11	7.3%
Hepatitis C	14	0	0	14	9.3%
Hepatitis D	5	1	2	8	5.3%
Hepatitis E	80	1	3	84	55.6%
Ischemic Hepatitis	6	1	0	7	4.6%
DILI / Non-Acetaminophen	5	0	0	5	3.3%
Sepsis	2	0	0	2	1.3%
Hepatitis B + E	2	0	0	2	1.3%
Hepatitis B + D	1	0	1	2	1.3%
Hepatitis C + A	1	0	0	1	0.7%
Hepatitis B + A	1	0	0	1	0.7%
Hepatitis C + E	1	0	0	1	0.7%
Total	142	3	6	151	100.0%

Discussion:

Our findings underscore regional differences in severe ALT elevation. Globally, a meta-analysis showed ischemic hepatitis in ~51% of ALT>1000 cases, with viral and DILI each ~13%.[7] By contrast, hepatitis E featured prominently in our cohort, consistent with its high prevalence in South Asia.[8,9] The pooled seroprevalence of HEV IgG in Southeast Asia is ~21% and rising over time,[10] reflecting ongoing transmission. HEV genotypes 1–2 cause outbreaks via contaminated water, disproportionately affecting young adults and pregnant women.[9,11] Indeed, HEV-related acute liver failure (HEV-ALF) carries significant mortality – estimated at ~32% in non-pregnant patients and >60% in pregnant patients in India.[8] This aligns with historical data (e.g. 30% fatality in third-trimester HEV) and emphasizes the need for vigilance.[8,11] By contrast, acetaminophen overdose is less common in our setting, although we counsel all ALF patients to avoid hepatotoxins. Per WHO guidance, diagnosis of HEV relies on anti-HEV IgM testing or RNA detection. Acute HEV treatment is mainly supportive; no specific antiviral is approved. Prevention (improving sanitation) and vaccination (a recombinant HEV239 vaccine is licensed in China) are key long-term strategies.[9] Meanwhile, prompt identification of ischemic or toxic causes is critical: ischemic hepatitis has markedly worse prognosis (our data mirror a 21-fold higher mortality vs. other causes.[7] Where available, N-acetylcysteine can be administered empirically in suspected DILI, and early transplant referral should be considered for fulminant cases.

Conclusion:

Our study emphasizes the multifactorial nature of severe liver injury and the need for a comprehensive approach to diagnosis and treatment. The findings suggest that both viral and non-viral causes contribute to severe transaminase elevations, and early intervention is critical to improving patient outcomes. Further research is needed to explore the long-term effects of these conditions and to develop more effective treatments, particularly for hepatitis E, which poses a growing public health challenge worldwide.

Ethical-Considerations:

The study was reviewed and approved by the AIMS Hospital Ethical Review Committee. All participants provided written informed consent, and the study adhered to the ethical guidelines of the Declaration of Helsinki.

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Author's Contribution:

SM: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
FN, BK, SS, MZ, ND, US, UG, MB, SK: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

PAKISTAN JOURNAL OF GASTROENTEROLOGY

Original Article

Platelet count to prothrombin(PLT/PT) ratio to predict esophageal varices in patients with hepatitis C related chronic liver disease

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Abstract:

Background: Variceal haemorrhage is a serious complication of portal hypertension in patients with chronic liver disease caused by various etiologies. In order to identify varices at earlier stages many non-invasive predictors have been studied to avoid unnecessary EGD and reduce bleeding related mortality.

Objective: To identify the relationship of PLT/PT ratio with presence of esophageal varices in patients with HCV-CLD.

Methods: In this cross-sectional study 140 patients with HCV related CLD were included. They distributed into those with and without esophageal varices. Variceal group was further subdivided into those low risk (Grade-I) and high-risk Varices (Grade-II/III). All patients were subjected to detailed history and examination. Laboratory tests. Ultrasound abdomen and EGD was performed.

Results: Median age of patients was 54+/- 10.18 years. 61.4% patients were male (n=86) and 38.6% were female (n=54). 86.4% (n=121) had EVs and 13.5%(n=19) had no varices. PLT/PT ratio at cut off value of ≤12384 predicted esophageal varices with sensitivity of 85.12%. Specificity of 73.68%, PPV of 95.37%, NPV of 43.74% and diagnostic accuracy of 83.57% with AUC of 0.817. PLT/PT ratio at cut-off value of ≤11145.03, with AUC of 0.707, sensitivity of 88.64%, specificity of 54.55%, PPV of 83.87%, NPV of 64.29% and diagnostic accuracy of 79.34%.

Conclusion: PLT/PT ratio has significant association with both the presence of esophageal varices and advanced grades of varices.

Keywords: Platelet count to prothrombin time (PLT/PT) ratio, Esophageal varices, HCV-related chronic liver disease**.**

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Introduction:

Chronic liver disease (CLD) is characterized by progressive decline in liver functions which include production of clotting factors, detoxification and excretion of bile. It is a process of liver parenchymal inflammation, destruction and regeneration resulting in fibrosis and cirrhosis which consists of scarring and regenerative nodules. CLD is caused by different etiologies like Hepatitis B and C, alcohol and Steatosis. [(1)] The number of cases worldwide is estimated to be at 1.5 billion.[2] Around 1.32 billion people were reported to have died from CLD in 2017.[3] Amongst Asian countries Pakistan is noted to have the highest incidence of CLD.[4]

A grave consequence of this disease is portal hypertension(pHTN), which is a pathological rise in the venous pressure of the portal system.[5] Physiological adaptations of the body, result in the formation of collaterals that divert blood from the portal venous system to the inferior and superior vena cava such as, the gastro-esophageal collaterals that drain into the azygos vein and development of esophageal varices(EVs).[6] Rupture of EVs, and bleeding is

a significant complication of pHTN.[7] A less frequent complication to be considered is gastric variceal bleeding.[8] About half of these may resolve on their own.[9]

Esophagogastroduodenoscopy (EGD) is considered the gold standard for diagnosis of EVs.[10] Various imaging modalities such as contrast-enhanced MRI, CT with contrast, angiography, doppler ultrasonography, endoscopic ultrasound, and Fibroscan have been evaluated for use in diagnosing EVs.[11] However most of these modalities are not widely available and have financial implications. Liver stiffness measurement (LSM) along with platelet count has been utilized a predictor of low risk of EVs.[12,13] The Baveno VI/ VII guidelines recommended against screening EGD in patients with LSM < 20kPa or platelet counts >150x10^9. [14]

The high prevalence of CLD, but limited with the availability of invasive screening modalities for EVs, such as EGD in regions like Pakistan raises the need for further investigation into alternative non-invasive methods that can be employed in developing regions.

Materials and Methods:

This was a cross-sectional study, performed in the outpatient department of Hepato-gastroenterology at Shifa International Hospital Ltd. Islamabad, approved by the Ethical Review Committee (IRB). Non-probability consecutive sampling was used for recruitments of patients. Based on the previously studied sensitivity of 93.5% and specificity of 88.75% of platelet count to prothrombin time ratio (PLT/PT ratio) and 95% confidence level, a sample size of 97 patients was required.[15]

A written consent was obtained from all the patients. A total of 140 patients, aged > 18 years, both male and female, who had been variables were non-normally distributed, quantitative variables were expressed as median (IQR). The Chi-square test or the Fisher exact test as appropriate was used for the comparison of qualitative data between two groups and the Mann–Whitney U test was employed to assess differences in non-normally distributed quantitative data between the two groups. The receiver operating characteristic curve was used in assessing the diagnostic significance of significant predictors that had been associated with esophageal and advanced varices. A p-value of 0.05 or lower was regarded as statistically significant.

suffering from HCV-related chronic liver disease (HCV-CLD) for a period of at least six months were included. They were classified in two groups (Variceal and Non-variceal), the variceal groups were sub grouped into those with low risk/non-advanced EVs (Grade-1) and those with high risk/ advanced varices (Grade-2/3 EVs).

Patients with BMI>30, severe life-threatening comorbidities such as congestive heart failure (NYHA-III and IV), end-stage renal disease were excluded. Exclusion criteria also extended to patients who were of post-sclerotherapy status, or with a history of any previous intervention of EVs, hepatocellular carcinoma or portal vein thrombosis, patients already on a beta blocker or anticoagulation therapy, or patients having a haematological disorder affecting their platelet count.

All patients were subjected to a full medical history, while strictly following the inclusion and exclusion criteria, clinical assessment, and laboratory studies including complete blood count, HBsAg,Anti HCV, liver functions tests, Prothrombin time (PT), albumin, renal function tests. PLT/PT ratio was calculated and statistically analysed. Abdominal ultrasonography was performed by an experienced radiologist for measuring splenic diameter and assessing for features of CLD (Portal vein diameter, portal venous flow, Liver contour and echogenicity). Screening EGD was performed for EVs in endoscopy department.

Data analysis:

IBM SPSS Statistics, Version 26.0. (IBM, NY, USA) MedCalc version 19.4.1 was used for data entry and analysis. Qualitative data were reported as numbers and percentages. As the Kolmogorov-Smirnov test indicated that most

Results:

Amongst the total 140 patients, 86 (61.4%) were male and 54 (38.6%) female with overall median age of 54+/- 10.18 years. 86.4% (n=121) had EVs and 13.5 %(n=19) had no varices. Different clinical, laboratory and imaging features were compared between these two groups. (Table.1)

	Esophageal varices Yes (n=121 No (n=19)		
	n (%) Median (IQR)		p-value
Age	55 (50-60)	51 (49-65)	0.850
Gender			
Female	43 (35.5)	11 (57.9)	0.078
Male	78 (64.5)	8 (42.1)	
aspartate transaminase	47.0 (35.0-70.0)	37.0 (28.0-49.0)	0.084
Alanine transaminases	33.0 (23.0-48.0)	25.0 (20.0-48.0)	0.315
Total bilirubin	1.29 (.92-1.96)	.79 (.50-1.20)	0.002
Haemoglobin	10.20 (8.90-11.90)	12.80 (10.80-13.20)	0.001
Total leukocyte count	5470.0 (4120.0-8910.0)	5600.0 (4500.0-6600.0)	0.891
Platelets	101000.0 (70000.0-140000.0)	155000.0 (125000.0-183000.0)	0.000
Prothrombin time	13.00 (11.90-14.50)	10.50 (10.00-11.50)	0.000
International normalized ratio	1.25 (1.12-1.40)	1.09 (1.00-1.20)	0.000
Albumin	3.00 (2.70-3.50)	4.00 (3.50-4.00)	0.000
Sodium	135.0 (131.0-139.0)	136.0 (135.0-140.0)	0.235
Blood urea nitrogen	15.00 (12.00-23.54)	15.00 (11.00-20.00)	0.692
Creatinine	.92 (.70-1.20)	.72 (.50-1.00)	0.054
PV diameter	11.00 (10.00-13.00)	10.00 (10.00-11.00)	0.208
Spleen size	14.00 (12.80-16.10)	13.00 (12.00-13.40)	0.002
MELD sodium	13.0 (10.0-17.0)	10.0 (7.0-12.0)	0.001
AST to platelet ration index	1.10 (.70-1.90)	.60 (.30-1.20)	0.007
Fibrosis-4 score	4.90 (3.17-8.46)	2.40 (2.00-3.47)	0.001
Platelet to prothrombin time ratio	7342.50 (4797.29-10857.14)	15124.37 (9652.00-17700.00)	0.000
Platelet to splenic diameter ratio	7166.60 (4625.00-10160.00)	12500.00 (8141.59-15625.00)	0.000
Ascites			
Mild	44 (36.4)	1 (5.3)	0.009
Moderate	15 (12.4)	1 (5.3)	
Gross	4 (3.3)	0	
No ascites	58 (47.9)	17 (89.4)	
Child Pugh score			
Class A	46 (38.0)	16 (84.2)	0.001
Class B	62 (51.2)	3 (15.8)	
Class C	13 (10.7)	0	

In patients with varices the median age was found to be 55 years and in those without it was 51 years. The varices group contained 35.5% females and 64.5% males, in the non-varices group 57.9% were females and 42.1% males(p=0.078). No significance was found in AST, ALT and renal function tests between the two groups (p> 0.05). However, bilirubin levels, PT and albumin were statistically significant(p<0.05), along with haematological parameters such as haemoglobin levels(p=0.001) and platelet count(P=0.000). PT and INR were higher while the albumin levels were found to be lower in the variceal group as compared to those without varices (p=0.000). In imaging parameters, PV diameter showed no significance(p=0.208) however, patients with varices were found to have a larger splenic size which proved to be significant(p=0.002).

MELD (model for end stage liver disease) scoring, which involves the use of INR, renal function tests and albumin levels for assessment of need for the liver transplant in patients with CLD, was found to be significantly higher in the variceal group (p=0.001). Similarly, the AST to Platelet ratio index (APRI) (p=0.007) and the Fibrosis-4 score(p=0.001) were both also significant.

PLT/PT ratio was significantly lower in the varices group in comparison with non-variceal group (7342.50 vs 15124.37, p=0.000). Moreover, platelet to spleen diameter ratio (PLT/SD ratio) and the presence of mild ascites were both significant (P=0.000) and (p=0.009) respectively. 51.2% patients in variceal group had CTP Class-B while most of the patients in Non-variceal group had CTP-A, indicating increased rate of development of EVs with progressive stages of CLD. Higher values of PT, INR, and MELD score, APRI, FIB-4 and CTP Score while lower platelet count, albumin and PLT/PT were observed in patients with advanced high-risk varices. (Table.2).

Variceal Subgroups			
Nonadvanced/Low risk Grade-I (n=33)		Advanced/High risk varices Grade-II &Grade-III (n=88)	
n (%) Median (IQR)			p-value
Age	54 (48-57)	55 (50-62)	0.189
Gender			
Female	12 (36.4)	31 (35.2)	1.00
Male	21 (63.6)	57 (64.8)	
aspartate transaminase	42.0(30.0-64.0)	48.0 (38.5-70.5)	0.127
Alanine transaminases	32.0 (21.0-39.0)	34.0 (24.0-49.0)	0.356
total bilirubin	1.30 (.69-1.80)	1.29 (.92-2.07)	0.313
Hemoglobin	11.00 (9.60-12.70)	10.00 (8.85-11.55)	0.112
Total leukocyte count	5200.0 (4570.0-9240.0)	5520.0 (3875.0-8910.0)	0.528
Platelets	135000.0 (81000.0-151000.0)	97000.0 (65100.0-128000.0)	0.005
Prothrombin time	11.90 (11.01-13.60)	13.05 (12.20-14.75)	0.001
international normalized ratio	1.12 (1.05-1.28)	1.27 (1.15-1.44)	0.001
Albumin	3.30 (3.00-3.50)	3.00 (2.60-3.35)	0.009
Sodium	134.0 (130.0-136.0)	137.0(132.5-139.5)	0.027
Blood urea nitrogen	15.00 (10.00-18.00)	16.00 (12.00-25.00)	0.051
Creatinine	.96 (.65-1.07)	.91 (.70-1.23)	0.641
PV diameter	10.20 (10.00-12.00)	12.00 (10.00-13.00)	0.137
spleen size	13.50 (12.60-15.00)	14.20 (12.95-16.50)	0.144
MELD sodium	11.0 (10.0-15.0)	13.5(11.0-18.5)	0.035
AST to platelet ration index	.80 (.50-1.40)	1.30 (.75-2.00)	0.004
Fibrosis-4 score	3.30 (2.20-5.29)	5.28 (3.57-8.84)	0.002
Platelet to prothrombin time ratio	11200.00 (6330.11-13589.00)	6769.93(4218.17-9761.90)	0.000
platelet to splenic diameter ratio	9806.45(6000.00-12230.00)	6607.66(4394.97-9026.15)	0.015
Ascites			
Mild	8 (24.2)	36 (40.9)	0.070
Moderate	3 (9.1)	12 (13.6)	
Gross	0	4 (4.5)	
No ascites	22 (66.7)	36 (40.9)	
Child Pugh score			
Class A	22 (66.7)	24 (27.3)	0.000
Class B	9 (27.3)	53 (60.2)	
Class C	2 (6.1)	11 (12.5)	

Among the different non-invasive scores calculated in this study PLT/PT ratio at cut off value **≤12384** had the highest AUC (0.817) for prediction of EVs with increased sensitivity, specificity, PPV and diagnostic accuracy after FiB-4 score. (85.12%, 73.68%, 95.37%, and 83.57% respectively) as shown in table. Moreover, PLT/PT ratio also showed significant association with advanced grades of varices with sensitivity of 88.64% and diagnostic accuracy of 79.34%.

Discussion:

In this study PLT/PT ratio at cut off value of **≤12384** predicted EVs with sensitivity of 85.12%. Specificity of 73.68%, PPV of 95.37%, NPV of 43.74% and diagnostic accuracy of 83.57% with AUC of 0.817. Further PLT/PT ratio at the cut-off value of ≤11145.03, with AUC of 0.707, sensitivity of 88.64%, specificity of 54.55%, PPV of 83.87%, NPV of 64.29% and diagnostic accuracy of 79.34%.

Although PV diameter, PLT/SD, Fib-4. APRI was found to be significant for the prediction of EVs but PLT/PT ratio had the highest AUC, i.e. 0.817 and 0.707 for the presence of EVs and high-risk varices respectively. Further PLT/PT ratio had the highest diagnostic accuracy for detecting varices assessment of high-risk varices.

Moreover, a great variability has been observed between variceal and non-variceal group in terms of various prognostic scores such as MELD, CTP score, APRI, FiB-4 which indicate synthetic functions of liver as well as parenchymal and structural outline and similar changes were noticed in PLT/PT ratio, which reflects both the hepatic synthetic function (prothrombin time) and outcomes of portal hypertension (Low platelet count).

PHTN is a serious complication of CLD which is the main reason for the development of EVs, gastric varices and portal hypertensive gastropathy.[16] The American Association for the Study of Liver Diseases guidelines advise that EGD be carried out every 2 to 3 years minimum for the screening of varices.[17] However, due to the limited nature of such resources in developing countries, a need was felt to explore further non-invasive techniques, such as laboratory testing for biochemical markers etc for screening of EVs in patients with CLD.

Although the role of PLT/SD ratio has been studied in different populations for non-invasively predicting EVs but a systemic review by Chawla et al concluded it as inadequate parameter for the assessment of varices.[18] Our study also agreed with this statement because both Platelet count and splenic size only indicate PHTN which could be secondary to causes other than liver cirrhosis such as isolated PV thrombosis or splenic vein thrombosis. Therefore, the PLT/PT ratio could be a better alternative which reflects both the liver function and portal hypertension.[18]

A study of MN Islam et al showed a positive correlation of prolonged PT with presence EVs with sensitivity of 56.67% and specificity of 73.33%. This study also reported association between Child Pugh score and presence EVs but no relationship with advanced grades of esophageal varices. Our study endorsed these results but the sensitivity and specificity could have been increased even more, if these variables could have been combined with Platelet count.[19]

Similarly, in another Indian study by Cherian et al, Low platelet count, CTP-B/C, splenic diameter (SD) and portal vein (PV) diameter were found significantly as independent variables in prediction of EVs and presence of high-risk varices. These variables were comparable with the present results in terms of sensitivity and specificity.[20]

Recently combined platelet count and albumin were compared with Baveno-VI and Transient Elastography (TE) in patients with HCV-CLD who were cured with direct acting antivirals (DAAs) and created HCV-RESIST criteria for prediction of high-risk varices. These criteria included platelet count and plasma albumin level. The Negative predictive value (NPV) of platelet count more than 120 x 10^9/L and Albumin level > 3.6g/dl for prediction of High-risk varices were 97.2% and 94.7%, respectively. The performance of these combined variables was almost similar to that of Elastography based algorithm and hence avoided unnecessary EGD in many patients. [21]

Tijana Glisic et al in another study in Serbia assessed various non-invasive scores such MELD score, AST to ALT ratio (AST/ALT), APRI, fibrosis-4-index (FIB-4), albumin-bilirubin (ALBI) score, and platelet-albumin-bilirubin (PALBI). This study concluded that ALBI and PALBI could be utilized for predicting presence of EVs with AUC of 0.603, and 0.606, respectively whereas APRI and MELD for high risk varices and variceal bleeding with AUC of 0.662 and 0.637 respectively which also endorse the results of our study but still the PLT/PT ratio had the highest AUC (0.817 and 0.707)[22]

PLT/PT ratio is easy to calculate which require simple blood test with no associated potential complications related to invasive procedures and imagine modalities. Still no data is available to find out its association with LSM. So further studies are required to focus at the association of PLT/PT ratio with LSM with hope that we can cooperate it into the algorithm for evaluation of portal hypertension and hence avoid unnecessary EGDs in these patients.

The main limitations of this study include single centre and cross-sectional study.

Conclusion:

PLT/PT ratio has significant association with both the presence of EVs and advanced grades of EVs.

Table 3. Diagnostic value of significant factors associated with E. varices (EVs)

Parameters	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
PV Diameter	>11	0.589	49.59	78.95	93.75	19.74	53.57
Fibrosis-4 score	>2.5	0.732	88.43	68.42	94.69	48.14	85.71
APRI	>0.7	0.692	68.60	63.16	92.22	24.00	67.86
PLT/SD ratio	≤10714	0.779	80.99	73.68	95.14	37.83	80.00
PLT/PT ratio	≤12384	0.817	85.12	73.68	95.37	43.74	83.57

Table 4. Diagnostic value of significant factors associated with advanced varices

Parameters	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
PV Diameter	>12.5	0.587	32.95	87.88	87.88	32.95	47.93
Fibrosis-4 score	>3.39	0.682	76.14	60.61	83.75	48.78	71.90
APRI	>0.5	0.669	93.18	39.39	80.39	68.41	78.51
PLT/SD ratio	≤9618.32	0.643	79.55	54.55	82.36	50.00	55.23
PLT/PT ratio	≤11145.03	0.707	88.64	54.55	83.87	64.29	79.34

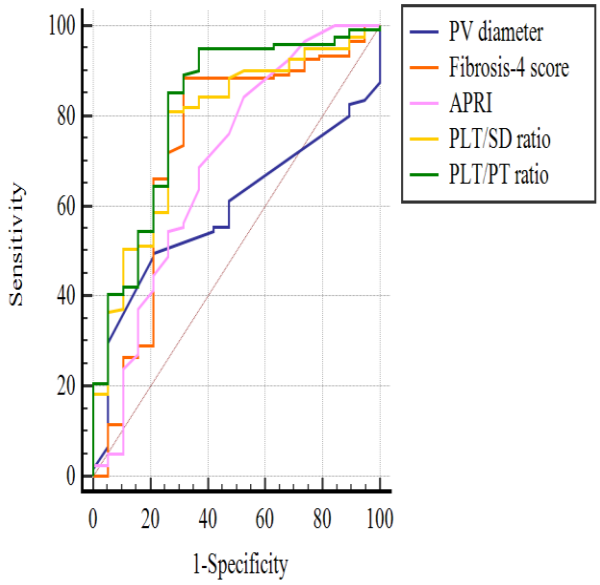
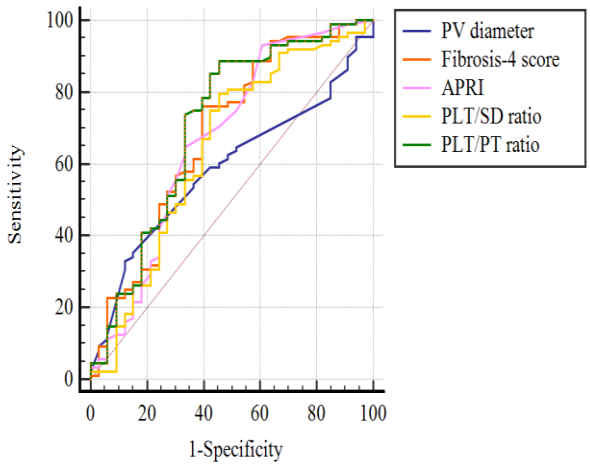


Figure: 2



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Author's Contribution:

MA: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
MA, SR, MS, AK, MBB: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

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Original Article

Diagnostic accuracy of serum - ascites albumin gradient (SAAG) for detection of esophageal varices in patients with liver cirrhosis

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Abstract:

Introduction: Identifying patients with compensated cirrhosis who are at risk of developing esophageal varices (EVs) is crucial for effective management. The Serum Ascites Albumin Gradient (SAAG) is a non-invasive laboratory tool that can predict the presence of EVs in cirrhotic patients, with a cutoff value of >1.4 g/dL indicating the need for clinical attention. SAAG can potentially reduce the need for repeated upper endoscopies.

Objective: To evaluate the diagnostic accuracy of SAAG in diagnosing esophageal varices in patients with cirrhosis, using endoscopy as the gold standard.

Materials and Methods: This cross-sectional study was conducted between April 2023 and October 2023 at the North Medical Ward, Department of Medicine, Mayo Hospital, Lahore. A total of 270 patients with cirrhosis and ascites (age 20-60 years) from both the genders were enrolled using non-probability consecutive sampling. 5cc blood and ascitic fluid samples were collected and sent to the hospital's laboratory for SAAG assessment. Patients underwent endoscopy to determine the presence of EVs, with varices considered present if the esophageal veins measured >5 mm in diameter.

Results: The diagnostic performance of SAAG in detecting EVs was evaluated, with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) calculated. The results showed that SAAG had a sensitivity of 87.5%, specificity of 59.86%, PPV of 66.27%, and NPV of 84.16%.

Conclusion: SAAG is a non-invasive, cost-effective tool with high sensitivity but low specificity for diagnosing esophageal varices in cirrhotic patients. Therefore, while SAAG can help reduce the frequency of endoscopy, it should be used in conjunction with other diagnostic methods for more accurate patient management.

Key Words: Serum ascites albumin gradient (SAAG), Esophageal Varices, Liver Cirrhosis, Endoscopy.

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Introduction:

Progressive liver dysfunction is a hallmark of liver cirrhosis. In the early stages, the liver retains its ability to compensate for normal functions, and with timely diagnosis and treatment, liver function can be sustained for a longer period. However, in the advanced stages of cirrhosis, patients may experience several complications, one of which is gastrointestinal bleeding.[1]

A significant complication of cirrhosis is the development of esophageal varices (EV), with a bleeding risk ranging between 25% and 35%.[2] Approximately 30-40% of patients with compensated cirrhosis (Child-Pugh class A) present with EV, while this figure increases to 60-85% in patients with decompensated cirrhosis

(Child-Pugh classes B and C).[3] Overall, about 50-60% of cirrhosis patients will eventually develop EV.[4] A study conducted in Pakistan found that 14.6% of cirrhotic patients had EV.[5] Identifying patients at risk for EV is crucial in managing cirrhosis effectively.[6]

Non-invasive methods are now available for assessing EV, including scoring systems based on laboratory investigations, which help minimize the need for repeated endoscopies.[7] The Serum Ascites Albumin Concentration Gradient (SAAG), which is derived from the comparison of albumin levels in ascitic fluid and serum, serves as a useful tool. A high SAAG score (>1.1 g/dL) typically indicates portal hypertension, a leading cause of EV.[8] The incidence of EV can thus be evaluated through a high SAAG score, reducing the necessity for endoscopic procedures.[9] The sensitivity and specificity of the SAAG for detecting EV are reported to be 91% and 50%, respectively, with a positive predictive value (PPV) of 91%, a negative predictive value (NPV) of 50%, and an overall accuracy of 85%.[10] A study by Patel et al. demonstrated a sensitivity of 95.2% and specificity of 44.4%. Another study found a sensitivity of 100%, specificity of 23.1%, PPV of 89.7%, NPV of 100%, and accuracy of 90%.[11]

Endoscopic evaluation of patients at risk for EV also carries the potential risk of exposing individuals to transmissible infections such as hepatitis B and C.[12] As a result, SAAG can be a useful alternative to invasive endoscopic procedures for diagnosing EV. Although the literature has highlighted SAAG's potential as a non-invasive diagnostic tool, its diagnostic accuracy for identifying EV remains a topic of debate.[12]

The goal of this study is to assess the diagnostic accuracy of SAAG for identifying EV in cirrhotic patients, using endoscopy as the gold standard. Endoscopy remains the routine method for diagnosing EVs, but there is an increasing need for non-invasive diagnostic approaches to reduce patient risk, particularly in cases where esophageal bleeding is not present.

Material and Methods:

This cross-sectional study was conducted over six months (April 9, 2023, to October 9, 2023) at Mayo Hospital Lahore, utilizing a non-probability, consecutive sampling technique. A total of 270 patients were enrolled, with a 95% confidence interval and an expected prevalence of esophageal varices (EV) of 14.5% in cirrhotic patients. The patients were aged 20-60 ye
ars, from either gender, with cirrhosis (defined by ALT >40 IU, coarse liver on ultrasound for >1 year, and ascites >50 mL on ultrasound), and ascites. SAAG was considered positive if the serum ascites albumin concentration gradient (SAAG) was ≥1.1 g/dL and negative if <1.1 g/dL. Endoscopy was used as the gold standard for diagnosing EVs, defined as positive if esophageal veins were >50% larger than normal. All the diabetic patients (blood sugar >186 mg/dL), those with liver or esophageal carcinoma or those who received EV treatment within the last two months were excluded from the study.

A written informed consent was obtained from all participants. Demographic data (age, sex, BMI, duration of cirrhosis) was recorded and a 5cc venous blood and ascitic fluid samples w collected for SAAG analysis. The blood samples were processed in the hospital's laboratory and EV status was determined based on the SAAG result. Patients also underwent endoscopy, which classified varices as mild (<3 mm), moderate (3–6 mm), or severe (>6 mm) based on direct visualization.

Data analysis was performed using SPSS version 22. Descriptive statistics (mean, standard deviation) were calculated for quantitative variables (age, BMI, duration of cirrhosis). Frequency and percentage were determined for categorical variables (gender, EV status). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of SAAG were calculated using endoscopy as the gold standard. Stratified analyses by age, gender, BMI, and cirrhosis duration were also performed.

Results:

Mean age of patients included in this study was 39.24±11.57 years. Among patients 137(50.7%) were male and 133(49.3%) were females. As per body mass index criteria 96(35.6%) patients body mass index was normal. As per SAAG findings 169(62.6%) patients were positive for esophageal varices. As per endoscopic findings 128(47.4%) patients were positive for esophageal varices.

Diagnose accuracy parameters calculation showed that sensitivity and specificity of SAAG was 87.5% and 59.86% respectively. PPV and NPV for SAAG was 66.27% and 84.16% respectively (**Table-1).** An increasing trend was seen in specificity as increase in age. In younger age groups specificity of SAAG was lower as compared to elderly age group patients. However, for sensitivity opposite trend was seen. In younger age group sensitivity was higher as that of elderly age group patients (**Table-2).** Among male patients sensitivity and specificity of SAAG was 86.67% and 54.55% and among female patients it was 88.24% and 66.15% respectively (**Table-3)** Among obese patients sensitivity (83.72%) and specificity (57.45%) of SAAG was lower as that of patients with normal body mass index [Sensitivity: 93.48% & Specificity: 56%] and overweight patients [Sensitivity: 84.62% & Specificity: 66.67% (**Table-4**) Patients with duration of cirrhosis as 2-3(years) among them sensitivity and specificity of SAAG was 86.11% and 55.13% respectively. While patients with duration of cirrhosis as 4-5(years) among them sensitivity and specificity of SAAG was 89.29% and 65.63% respectively (**Table-5).**

Table-1: Diagnostic Accuracy of SAAG taking Endoscopy as Gold Standard for diagnosis of esophageal varices in patients with liver cirrhosis

SAAG	Endoscopy		Total
	Positive	Negative	
Positive	112(87.5%)	57(40.1%)	**169**
Negative	16(12.5%)	85(59.9%)	**101**
Total	**128**	**142**	**270**

Sensitivity=87.5% (80.66, 92.16)
Specificity=59.86% (51.64, 67.56)
Positive Predictive value=66.27% (58.85, 72.97)
Negative Predictive value=84.16% (75.81, 90.01)
Diagnostic accuracy=72.96% (67.37, 77.91)

Table-2: Diagnostic Accuracy of SAAG taking Endoscopy as Gold Standard stratified for age for diagnosis of esophageal varices in patients with liver cirrhosis

SAAG		Endoscopy		Total
		Positive	Negative	
20-30	**Positive**	28(93.3%)	24(49%)	**52**
	Negative	2(6.7%)	25(51%)	**27**
31-40	**Positive**	32(91.4%)	12(37.5%)	**44**
	Negative	3(8.6%)	20(62.5%)	**23**
>40	**Positive**	52(82.5%)	21(34.4%)	**73**
	Negative	11(17.5%)	40(65.6%)	**51**

	20-30	31-40	>40
Sensitivity	93.33%	91.43%	82.54%
Specificity	51.02%	62.5%	65.57%
PPV	53.85%	72.73%	71.23%
NPV	92.59%	86.96%	78.43%
DA	67.09%	77.61%	74.19%

Table-3: Diagnostic Accuracy of SAAG taking Endoscopy as Gold Standard stratified for Gender for diagnosis of esophageal varices in patients with liver cirrhosis

		Endoscopy		Total
		Positive	Negative	
Male	**Positive**	52(86.7%)	35(45.5%)	**87**
	Negative	8(13.3%)	42(54.5%)	**50**
Female	**Positive**	60(88.2%)	22(33.8%)	**82**
	Negative	8(11.8%)	43(66.2%)	**51**

	Male	Female
Sensitivity	86.67%	88.24%
Specificity	54.55%	66.15%
PPV	59.77%	73.17%
NPV	84%	84.31%
DA	68.61%	77.44%

Table-4: Diagnostic Accuracy of SAAG taking Endoscopy as Gold Standard stratified for body mass index for diagnosis of esophageal varices in patients with liver cirrhosis.

		Endoscopy		Total
		Positive	Negative	
Normal	Positive	43(93.5%)	22(44%)	**65**
	Negative	3(6.5%)	28(56%)	**31**
Overweight	Positive	33(84.6%)	15(33.3%)	**48**
	Negative	6(15.4%)	30(66.7%)	**36**
Obese	Positive	36(83.7%)	20(42.6%)	**56**
	Negative	7(16.3%)	27(57.4%)	**34**

	Normal	Overweight	Obese
Sensitivity	93.48%	84.62%	83.72%
Specificity	56%	66.67%	57.45%
PPV	66.15%	68.75%	64.29%
NPV	90.32%	83.33%	79.41%
DA	73.96%	75%	70%

Table-5: Diagnostic Accuracy of SAAG taking Endoscopy as Gold Standard stratified for duration of Cirrhosis for diagnosis of esophageal varices in patients with liver cirrhosis.

	Endoscopy			Total
	Positive	Negative		
2-3 years	Positive	62(86.1%)	35(44.9%)	**97**
	Negative	10(13.9%)	43(55.1%)	**53**
4-5 years	Positive	50(89.3%)	22(34.4%)	**72**
	Negative	6(10.7%)	42(65.6%)	**48**

	2-3	4-5
Sensitivity	86.11%	89.29%
Specificity	55.13%	65.63%
PPV	63.92%	69.44%
NPV	81.13%	87.5%
DA	70%	76.67%

Discussion:

The risk of bleeding from esophageal varices (EV) is a critical concern in patients with cirrhosis and portal hypertension. Several diagnostic tools, including ultrasound and biochemical tests, help assess this risk. One key biochemical measure is the Serum Ascites Albumin Gradient (SAAG), a reliable indicator of portal hypertension. A SAAG value greater than or equal to 1.1 g/dL typically indicates portal hypertension, whereas values lower than 1.1 g/dL suggest non-portal hypertensive causes of ascites. Correcting SAAG levels may reduce the risk of bleeding from varices by identifying and managing portal hypertension effectively.[13]

Several studies have highlighted the role of SAAG in assessing EV in cirrhotic patients. Eldeeb GS et al. demonstrated that SAAG had a sensitivity of 87.5%, specificity of 59.86%, positive predictive value (PPV) of 66.27%, and negative predictive value (NPV) of 84.16%.[14] Another study, conducted by Sharma et al. in India reported a SAAG sensitivity of 81% and a specificity of 100%.[15] However, the discrepancy in SAAG levels observed in this study, when compared to its sensitivity, was in contrast with the findings from other studies, suggesting a potential issue in standardization or population differences. In addition, a study by Das BB reported a SAAG sensitivity of 91% and specificity of 50%, with an overall accuracy of 85%, a PPV of 91%, and an NPV of 50%.[16] Similarly, Chaurasia AK found a sensitivity of 95.2% and specificity of 44.4%[17] and Kumar S reported a sensitivity of 100% and a specificity of 23.1%, with a PPV of 89.7% and an NPV of 100%.[18] A common trend in these studies is the higher sensitivity of SAAG, coupled with lower specificity, which indicates that SAAG is more reliable in detecting patients at risk of variceal bleeding but may result in false positives. This variation in diagnostic performance across studies could be attributed to differences in sample size, sample selection criteria, and the cut-off points used for SAAG.

SAAG also serves to determine the severity of portal hypertension. A higher SAAG (≥1.1 g/dL) indicates significant portal hypertension, while a lower SAAG (<1.1 g/dL) suggests the absence of portal hypertension.[19,20] The threshold of 1.1 g/dL is crucial as it provides clinicians with an indication of whether further investigation, such as endoscopy, is warranted to assess EV risk.

Endoscopy remains the gold standard for diagnosing EV, gastric varices, and portal hypertensive gastropathy.[21] However, SAAG provides a valuable alternative for evaluating portal hypertension and estimating the risk of variceal bleeding. Using SAAG as a screening tool could help identify patients who may not

require immediate endoscopic evaluation, potentially reducing healthcare costs, minimizing patient discomfort, and alleviating the burden on endoscopy units.[22,23] By using SAAG to stratify patients based on their risk, healthcare systems could optimize the allocation of resources, ensuring that high-risk patients receive timely intervention while low-risk patients are spared unnecessary procedures.

CONCLUSION:

The results of this study indicate that the Serum Ascites Albumin Gradient (SAAG) demonstrates high sensitivity but low specificity in diagnosing esophageal varices in cirrhotic patients. Hence, SAAG is an important non-invasive screening tool to detect EV in selected group of patients to avoid undergoing unnecessary endoscopic procedure.

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Author's Contribution:

DN: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
MSA, IUH, AAK, SH, MKY: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

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Original Article

Peri-Operative FLOT Chemotherapy in Locally-Advanced Gastric and Gastroesophageal Carcinoma: Outcomes in South Asian Population

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ABSTRACT:

Objective: To compare oncological outcomes of perioperative FLOT chemotherapy in terms of tumor response, tumor margin clearance and average positive number of lymph nodes retrieved in surgical resection specimens of locally advanced gastric and gastroesophageal carcinoma.

Materials and Methods: The patients presenting in Department of General Surgery, Shifa International Hospital, Islamabad from July 2020 to March 2023 were included in the study**.** Out of total 108, we included 37 patients who undertook perioperative FLOT chemotherapy in for resectable, locally advanced gastroesophageal cancer. Response to therapy was assessed based on per operative findings, R0 resection and D2 lymphadenectomy and disease regression on histopathology specimens. Patients were also assessed according to post-operative recovery time, mean ICU and hospital stay, as well as post chemo and post-operative complications.

Statistical Analysis: Appropriate statistical analysis was performed using SPSS version 26.

Results: There were a total 37 patients with mean age 57.21 ± 10.04 years. 4(10.8%) had well-differentiated adenocarcinoma, 19(51.4 %) had moderately-differentiated and 14(37.8%) had poorly-differentiated cancer. Perioperative completion rate of 4 cycles of chemotherapy was 100%. 4 patients had dose reduction due to neutropenia. 100% of the patients had R0 resection. Average positive lymph nodes on histopathology were 2.04 ± 3.01 in 13 patients (35.1%). 24 out of 37 patients (64.9%) had no nodal involvement. Histopathology, evaluated for treatment response according to CAP (College of American Pathologists) -TRG criteria, 7 (18.9%) patients out of 37 showed no tumor regression. 22(59.5%) had partial response and 8(21.6%) patients had complete response.

Conclusion: Perioperative FLOT shows highly favorable results in patients with resectable, locally-advanced gastric and gastroesophageal cancer. Considering the burden of this disease in the South Asian population, an optimal therapeutic regime is an absolute requirement. Our initial data in this study provides favorable results to use of perioperative chemotherapy with the FLOT-4 regime in our population.

Keywords: gastroesophageal cancer, neo-adjuvant, locally-advanced, negative margins, chemotherapy

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Introduction:

Gastric and gastroesophageal cancers are commonly occurring malignancies in Asia and the prognosis for advanced disease remains bleak, highlighting the importance of need of more innovative therapeutic approach for management and eradication of gastric and gastroesophageal cancers.[1] Neoadjuvant chemotherapy has been agreed upon as standard of care to achieve curative resections even in advanced gastric and gastroesophageal cancer however differences of practice still occur in regard with type and combinations chemotherapy regimens.[2]

Despite its widespread presence in East, there is an obvious dearth of trial-based data and information originating from these countries. Some data has originated from Japan in the last few decades but it is lacking in providing

applicable information about neo-adjuvant chemotherapy for resectable, locally advanced tumors.[3] German centers have published studies showing FLOT as superior therapy to ECF and ECX therapies.[4] China with an incidence rate of >45% with 50% mortality rate of the total Gastroesophageal cancer cases in the world, has presented results, based on two large scale trials RESONANCE and RESOLVE, pointing at chemo regimens based on a combination of SOX and XELOX.[5,6]

Over the years, advancement in surgical technique has led to considerable improvement in the disease management, but metastasis and recurrence have remained the main causes of morbidity and mortality in gastric and gastroesophageal cancer patients. The need for control of metastasis as well as recurrence, led to the consideration of neoadjuvant therapy, and especially since the MAGIC and FNCLCC/FFCD trials, the purely surgical approach to locally advanced gastric and esophageal cancers has undergone a drastic change. The 2006 MAGIC trial consisted of perioperative intervention with fluorouracil, epirubicin and cisplatin (ECF), and the French FFNCLCC/FFCD trial used a 5- FU and Cisplatin based regimen[7,9]. Both sets of data have revealed a significant role of neoadjuvant chemotherapy in the overall survival rate although debate still exists on the exact combination of the perioperative chemo agents.[10]

The neoadjuvant approach to management of locally advanced gastric and gastroesophageal cancers must include an objective purpose of the chemotherapy as well as the effect it has on the surgical intervention such as gastrectomy or esophagectomy that follows. Overall survival, disease free survival, down-staging of tumor, rate of local recurrence, pathological response, R0 resection and the adverse effects of chemotherapy leading to reduced tolerability and susceptibility, are all important factors to be considered.

Although evidence does exist on the superior benefit of FLOT (fluorouracil, leucovorin, oxaliplatin and docetaxel) over neoadjuvant ECF when considering the number of curative surgeries following chemotherapy and survival without disease progression[7], there is still a paucity of evidence on the topic, especially considering the South Asian populations where the incidence rate of gastric and gastroesophageal cancers is high. Countries such as Japan have conducted trials on neoadjuvant chemotherapy, but the regimens were comparatively conservative compared to documented Western chemotherapy regimens.[2]

In our study, the findings of FLOT 4 perioperative chemotherapy in locally advanced gastric and gastroesophageal cancers are discussed. Our study includes 37 cases of locally advanced gastric and gastroesophageal cancers that were managed with FLOT 4 perioperative chemotherapy and subsequently underwent gastrectomy or esophagectomy. The aim of the study was to assess the oncological and pathological efficacy of FLOT 4 as well as the peri-operative morbidity and mortality, lymph node retrieval and to evaluate the feasibility of FLOT regimen in the South Asian population.

Materials and Methods:

This was a retrospective study and it was carried out at the Department of General Surgery, Shifa International Hospital, Islamabad from July 2020 to March 2023. Approval of IRB was sought before commencing data collection. We reviewed data of 108 patients out of which data of 37 patients with diagnosed, histologically positive, locally advanced (stages cT1b–cT4a; cM0), resectable gastric and esophageal carcinomas who took FLOT-4 regimen as perioperative chemotherapy was analyzed. Staging investigations included CT scans, endoscopic ultrasounds and biopsies for all patients. PET scans, MRI, or bone scans were used if clinically indicated according to the availability. Patients included were those with ages 18 to 80 years with no prior anti-tumor therapies, locally advanced gastric and gastroesophageal cancer (stage cT3 – 4 and N+ M0) according to EUS and CECT. Patients had normal hematopoietic, renal and hepatic function. Excluded patients were those who were clinically unfit for systemic chemotherapy or surgery, had locally advanced inoperable disease or distant metastases, or had undergone prior radiotherapy. FLOT was administered intravenous according to NCCN guidelines recommended dose (4 cycles preoperative and 4 cycles postoperative: Fluorouracil 2600 mg/m^2 IV continuous infusion over 24 hours, Leucovorin 200 mg/m^2, Oxaliplatin 85 mg/m^2, Docetaxel 50 mg/m^2: repeated every 14 days). Exclusion criteria included patients with gastroesophageal cancer had either undergone

upfront surgery, had metastatic disease at the time of surgery or had a different neoadjuvant chemotherapy regimen.

The TNM categories were according to the Union for International Cancer Control tumor-node-mets classification. The clinical efficacy response was evaluated using the response evaluation criteria in solid tumors (RECIST) guidelines. Adverse effects of neoadjuvant chemotherapy were graded (0-IV) according to the Common Terminology Criteria for Adverse Events (CTCAE). The surgical procedure data was extracted from operative notes. The pathological response assessment was scored using the tumor regression grade (TRG) of the Becker criteria. Postoperative complications were defined as any anomaly that occurred within 30 days after surgery stratified using the Clavien-Dindo classification. Descriptive statistics were calculated for patients' characteristics using mean, standard deviation, and percentages using the SPSS 26.0 statistics software. Results is presented in graphs and tables along with inference. The work has been reported in line with the STROCSS criteria.[8]

Results:

Initially, data of 108 patients was analyzed however 37 patients were included in the study according to our inclusion criteria. Out of these 37, 24 (64.9%) were male and 13(35.1%) were female. Mean age was 57.21 ± 10.04 years. All 37 patients completed 04 cycles of perioperative FLOT chemotherapy at an average of 21 days before surgery. 04 patients had dose reduction because of grade 3 neutropenia however all other non-hematological complications were grade 1 or 2 and required supportive therapy only.

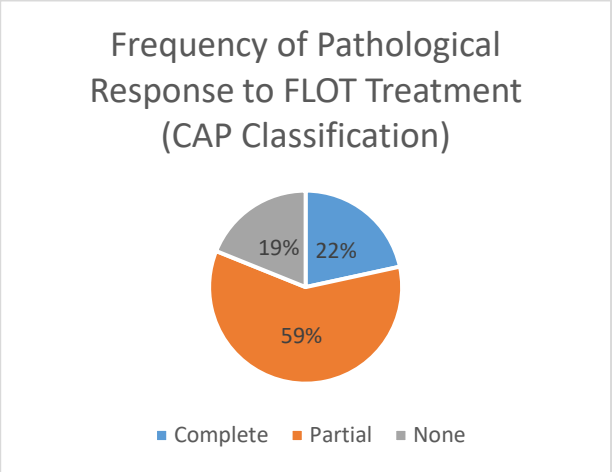
21(56.8%) patients underwent total gastrectomy with D2 lymph node dissection and 16(43.2%) underwent esophagectomy for gastroesophageal carcinoma.

All 37 patients had R0 resection. All margins namely circumferential, radial, proximal and distal were tumor free. Average number of lymph nodes retrieved were 22 with a minimum of 12 lymph nodes and a maximum of 37 lymph nodes. Average positive lymph nodes on histopathology were 2.04 ± 3.01 in 13 patients (35.1%). 24 out of 37 patients (64.9%) had no nodal involvement.

Of 37 patients, 4(10.8%) had well-differentiated adenocarcinoma, 19(51.4 %) had moderately-differentiated and 14(37.8%) had poorly-differentiated tumor. (Table 2) Histopathology samples was evaluated for treatment response according to CAP (College of American Pathologists) -TRG criteria.

7 (18.9%) patients out of 37 showed no tumor regression (Minimal/ no tumor killed or extensive residual cancer). 22(59.5%) had partial response (Single cells or small groups of cancer cells) and 8(21.6%) patients had complete response (No viable cancer cells). (Figure 1)

Figure 1: Frequency of Pathological Response to FLOT Treatment (CAP Classification)



Mean post-op stay in hospital was 6 ±1 days. Grade 2 Clavien-Dindo post-op complications were noted in 5 out of 37 patients.

One patient, known case of COPD, developed shortness of breath requiring gradually tapered oxygen therapy. Patient was discharged on day 9. No immediate life-threatening complication or all-cause mortality was noted in 30 day follow up period. These patients are being followed up at year 1, year 3 and year 5 post operatively to see long term outcomes in terms of Overall Survival (OS) and Disease-Free Survival (DFS).

Discussion:

Since the advent of neoadjuvant chemotherapy, the management of gastroesophageal carcinoma has drastically transformed since early 90s. Several regimens have been studied with regards to their efficacy and safety. The major breakthrough was in 2006 with the MAGIC Trial, a randomized phase III clinical trial from nine centers across UK. This was the largest trial which analyzed the effects of neoadjuvant chemotherapy in gastric and gastroesophageal cancer. Patients were

randomly divided in two groups: one underwent surgery alone, the other underwent surgery and perioperative chemotherapy, three cycles in each preoperative and postoperative period. Epirubicin, cisplatin, and fluorouracil (ECF) regimen was used. The results demonstrated significantly better surgical as well as long term outcomes in patients with ECF. Reduction in tumor size and stage lead to more R0 resections and significantly improved progression-free and 5-year overall survival (36% compared to 23% in upfront surgery P = 0.009). [9]

Another significant phase III trial was the 2011 French FFCD9703, with a similar design to the MAGIC trial but used a Cisplatin and 5-Flourouracil based regimen. 224 patients were divided into two groups: a control group which had surgery alone, the other group had 2-3 cycles of FU/Cis regime preoperatively. Again, similar results to MAGIC trial were seen where patients with chemotherapy had better rates of R0 resection (84% vs. 73%, P = 0.04) survival advantage over group who had surgery alone (38% vs. 24%, P = 0.02), and greater disease-free survival for 5 years (34 v. 19%, P = 0.01).[10] Both these trials cemented the superiority of perioperative chemotherapy regardless of tumor location and were widely adopted throughout the globe.

The role of Docetaxel as combination therapy for gastric carcinoma has been studied in several settings demonstrating improved outcomes in terms of overall survival, response rate, time-to-disease progression. The V-325 study was notable in this series.[11] However, that addition of docetaxel to a frequently used regimen of cisplatin and 5-fluorouracil was associated with severe toxicities and was not tolerated well by the patients.[12] Despite this, several authorities continued to study docetaxel with modified regimens because it appeared to have a significantly higher response rate as compared to the classic duet. However further modification was needed to improve safety and convenience of patients with advanced GE junction and gastric carcinoma so that its usage maybe widely accepted.

In 2008 Al-Batran et al. put forward the docetaxel based FLOT regimen which included, fluorouracil, leucovorin, oxaliplatin and docetaxel.[13] This challenged the earlier ECF regimen and its modified versions as trials validated its efficacy and safety. In 2016 FLOT4 phase II trial was published, demonstrating a significant advantage to patients who received FLOT compared to those who had ECF/ECX in terms of tumor regression (44% vs 27%, P = 0.01) and R0 resections (85% vs 74%, P = 0.02) in 300 patients.[14] However, Phase III showed side effects of both the regimens were same. The median overall survival (50 months compared to 35 months, P = 0.012) and median disease-free survival (30 months compared to 18 months, P = 0.0036) were also significantly longer than those of the ECF/ECX group.[14] This superiority of results led to category 1 recommendation of FLOT as a preferred therapy by NCCN guidelines in 2018. [15]

Several studies have been conducted throughout the world based on these recommendations. However, due to regional differences in practice of number and completion of doses before and after surgery, head-on comparisons of results are lacking.[16] Generally, the fluorouracil-based regimens are widely adapted in Asian regions, while the ECF and FLOT regimen are practiced in European countries.[17]

A Chinese study conducted on 23 patients showed that FLOT is safe and effective in terms of clinical efficacy (69.6%) and R0 resections (91.3%). 13% patients had complete remission. The most common adverse event from chemotherapy was neutropenia (30.4%).[18] However, Favi et al. in Germany observed no significant difference in terms of prognosis and rather better primary tumor response in CROSS-group as compared to FLOT-group: 43% vs 27% in a total of 40 patients.[19]

A Chinese study by Li et.al concluded excellent response and good tolerance in 73 patients who received FLOT with 64% partial response and 6% complete response with 86% R0 resections achieved. Leukopenia was commonest side effect and grade 3 or 4 side effects or treatment-related deaths were noted.[20]

To our knowledge no such trial has been or is being conducted in Pakistan at the moment to assess the response and tolerability of FLOT regimen in the Pakistani or South Asian population. The delay in the initiation of study and limitation of number of patient recruited in the study is attributed to economic constraints, for example, unavailability of 5-FU pump and patients who could afford a porta-cath insertion. The results of our study show a cumulative frequency of 78.3% in patients who had either complete or partial tumor regression to

perioperative FLOT regimen which is comparable to 73.1 % for similar responses in a study conducted in China, which is favorable for achieving a high number of R0 resections.[18] Our study demonstrated a ypN0 of 52.2% which is comparable to 56.3% demonstrated in a Dutch study.[21]

In several small centers across our country, D2 lymphadenectomy is not well-documented and upfront surgery is still being offered to many patients; hence compromising chances of an R0 resection and therefore disease -free as well as overall survival of the patient.These results not only add the knowledge and application in local population but also adds the south Asian pool which has no considerable data on FLOT regimen despite sharing a significant disease burden.

Current clinical trials are being looked up for a consensus on superiority, safety and efficacy of FLOT. The ESOPEC trial is being conducted on 438 patients with locally advanced gastroesophageal adenocarcinoma, comparing two groups, one on CROSS, the other on FLOT, both followed by surgery. The patients will be followed up for 36 months at the minimum also aiming to compare disease-free and progression-free survival in these groups.[22]

Another phase III trial registered in 2020, the RACE trial will compare 340 patients on two limbs: one given FLOT regimen as induction therapy, the other given only FLOT as neoadjuvant therapy. Both groups will undergo surgery followed by adjuvant FLOT. Only patients with locally-advanced disease will be included. The objective of this trial is to demonstrate the superiority of combined treatment with FLOT in terms of progression-free survival.[23]

The limitations of our study included small number of patients who could fit our inclusion criteria, this relatively newer regimen in our part of the world is less opted for due to higher costs and lack of infusion pumps leading to constrained practice by medical oncologists to prescribe FLOT regimen. Several patients present with advanced disease as there are no national screening or disease awareness programs. The initial data shows promising results, therefore, a larger number of patients could be reviewed from multiple centers for validation of our results. Further trials and analyses from our side of the world are needed to further solidify this treatment option and validate its efficacy for overall survival(OS) and disease-free survival (DFS) in such patients.

Conclusion:

Considering the burden of this disease in the South Asian population, an optimal therapeutic regime is an absolute requirement. Our initial data in this study, backed by recommendations and previous literature coming sporadically from around the continent, gives us enough evidence to continue the use of perioperative chemotherapy with the FLOT-4 regime.

Table 1: Total and Positive Numbers of Lymph Nodes Retrieved in D2 Lymphadenectomy

	MINIMUM	MAXIMUM
Total Number of LN retrieved	12	37
Frequency of Positive LN seen on Histopathology	0(64.9%)	9(2.7%)

Table 2: Frequency of Histopathological Grade of Tumor

TUMOR GRADE	FREQUENCY (n=37)	PERCENTAGE %
Well-Differentiated	4	10.8
Moderately Differentiated	19	51.4
Poorly Differentiated	14	37.8
Total	37	100.0

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Author's Contribution:

YM: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
RA, MBB, HMK: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

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Original Article

Relationship between Upper GI symptoms and Endoscopic findings with Gastric H Pylori density.

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Abstract:

Objective: Helicobacter pylori affect many individuals in developed and developing countries. Inflammation caused by H pylori differs depending on the virulence factors, bacterial density and host response of bacteria. This study is designed to investigate the association between density of H Pylori colonization in gastric mucosa in biopsy specimens and severity of gastric mucosal inflammation.

Methods: This study of 75 patients was done at Department of Gastroenterology, Ghurki Trust Teaching Hospital Lahore. These patients presented with GI symptoms and got endoscopy done between June 2023 to June 2024. Their histopathology reports were retrospectively screened and severity of inflammation and H Pylori density were analyzed by Sydney scoring. Data analysis was done using SPSS software version24.

Results: The analysis of H. pylori density and its association with gastrointestinal symptoms and endoscopic findings reveals that most gastrointestinal symptoms, including epigastric pain, nausea, and retrosternal burning, show no significant association with H. pylori density. On endoscopy findings evaluation only esophagitis is associated with higher H. pylori densities ($p < 0.001$), indicating a potential link between the bacterium and this condition. Other findings, such as moderate gastritis and duodenitis, show trends toward association but are not statistically significant.

Conclusion: Our study shows that density of H Pylori infection has no influence over Upper GI symptoms and also endoscopic findings cannot be taken as evidence of H pylori infection.

Keywords: Endoscopy, H Pylori, Esophagitis, Gastritis, Duodenitis.

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Introduction:

Helicobacter pylori are flagellated, spiral-shaped, microaerophilic, Gram-negative bacteria, which infect Gastric mucosa of almost half of the world's population.[1] Poor sanitation conditions and non-availability of safe and clean water make it a common infection in the under-developed world. Its colonization in gastric Mucosa leads to mucosal inflammation, which can lead to a wide variety of diseases ranging from Gastritis, Peptic Ulcer Disease to Gastric Carcinoma and MALT Lymphoma.[2] Along with H Pylori infection, several host factors such as life habits, Genotype and immunological response also contribute towards disease severity. This finding is based on the fact that prevalence of H Pylori in PUD varies in different geographical areas and only 10 % of infected people develop clinically significant disease.[3] Furthermore, it has been seen that eradication of H pylori leads to worsening or development of Gastroesophageal Reflux disease.

H. Pylori induced gastritis is highly prevalent in developing countries. In Pakistan as well, a high prevalence is reported. According to a local research, 88 percent of dyspeptic gastritis patients had H. Pylori infection.[4] Inflammation of Gastric

mucosa leads to atrophy, intestinal metaplasia, dysplasia and gastric carcinoma.[5] In the data from developed world as well, intestinal metaplasia and atrophy are considered as premalignant disorders associated with H. Pylori induced chronic gastritis.[6] So, it means that fundamental step which leads to complications is Gastric atrophy. Hence, the role of H. Pylori should be studied at all levels, i.e., initial infection, atrophy and its associated symptoms, and the intestinal metaplasia and possible carcinoma or lymphoma. Moreover, the bacterial density has been correlated with gastric inflammation. Another local study showed that the density of H. Pylori on biopsy proven gastritis is positively correlated with histological evidence of chronic inflammatory infiltrate.[7] In another local study it was found that greater the load of H. Pylori infection, the higher is the degree of neutrophilic activity, atrophy and intestinal metaplasia.[8]

The objectives of present study were not limited to chronic gastritis alone, but also included evaluating the bacterial density in relation to the severity of all endoscopic findings, as well as the common GI symptoms with which patients presented for upper GI endoscopy.

Methods:

This cross-sectional correlational study was carried out at Gastroenterology and Endoscopy department of Ghurki Trust Teaching Hospital in collaboration with Pathology department of LMDC/GTTH. A total of 75 patients who presented with upper GI symptoms and underwent endoscopy with biopsy were evaluated from July 2024 to December 2024.

Indications of endoscopy like pain epigastrium, nausea, retrosternal Burning etc. were noted (Table 1) Endoscopy was performed by same Endoscopist using Olympus Endoscope XQ160 series to clear the interobserver variation. Seventy-five Gastric antral biopsies of chronic gastritis patients were included in the study. Gastric biopsies of patients who were on anti H Pylori therapy or had received H. Pylori eradication treatment in past were excluded.

Baseline data which included age, gender, symptoms, history, concomitant medication (especially antibiotics) and endoscopic findings were entered in patient's proforma. Gastric biopsy tissue was processed by same histopathologist after staining with hematoxylin and eosin. Giemsa stain was then used for H. Pylori demonstration. The Sydney System of classification of Histopathological features of Chronic Gastritis was used and gastritis was classified as none, mild, moderate and severe on a scale of 0-3. Similarly, density of H pylori was evaluated based upon histopathological evaluation.

The H. Pylori density was graded as follows:

0: none
1: H. Pylori seen only in one place
2: just a few H. Pylori seen
3: dispersed H. Pylori seen in separate foci
4: numerous H. Pylori in separate foci
5: almost complete coverage of gastric surface by layer of H. Pylori
6: uninterrupted coverage of gastric surface by a dense layer of H. Pylori

None was considered when no H Pylori was seen. Mild was 1-2, Moderate was 3-4 and severe was 5-6.

This classification provided numerical data for statistical analysis and is widely used. Before grading these specimens, two pathologists agreed with a consensus on the scoring of gastritis.

SPSS (Statistical Package for Social Sciences) for Windows 20.0 program was used for the statistical analysis. Descriptive statistics for continuous variables was summarized as mean and standard deviation, and descriptive statistics for categorical data was summarized as percentage. The Chi-Square test was used to compare the data in the categorical structure. Correlation between parameters was done by using Pearson correlation analysis. The results were evaluated with a confidence interval of 95% and in a significance level of $p < 0.05$.

Results:

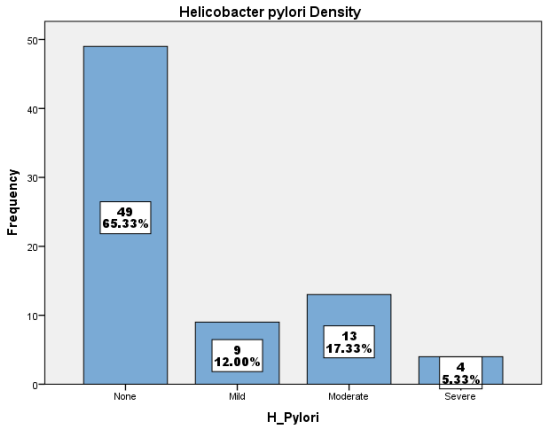
In this study, a total of 75 patients were diagnosed with upper gastrointestinal symptoms; among these, more than half of the cases, 47(62.7%), were females, while fewer were males, 28(37.3%), with a mean age of 38.84 ± 14.52 ranging from 17-84 years. The mean age of male and female patients was 36.68±14.32 and 40.13±14.64 years, respectively.

Table 1: *Distribution of patients according to gastrointestinal symptoms & Endoscopic Findings*

Parameters	N(%)	
Gastrointestinal symptoms	**Yes**	**No**
Epigastric_pain	60(80)	15(20)
Nausea	35(46.7)	40(53.3)
Vomiting	14(18.7)	61(81.3)
Retrosternal burning	36(48)	39(52)
Malena	1(1.3)	74(98.7)
Hematemesis	1(1.3)	74(98.7)
Burping	3(4)	72(96)
Belching	3(4)	72(96)
Endoscopic Findings		
Esophagitis	54(72)	21(28)
Gastritis Mild	3(4)	72(96)
Gastritis Moderate	25(33.3)	50(66.7)
Gastritis Severe	12(16)	63(84)
Duodenitis	28(34.7)	49(65.3)
Antral Gastritis	33(44)	42(56)
Gastric Ulcer	1(1.3)	74(98.7)
Duodenal Ulcer	5(6.7)	70(93.3)
Evaluation of H. pylori	**Positive**	**Negative**
Esophagitis	54(72)	21(28)
	26(34.7)	49(65.3)

The above table evaluates the distribution of gastrointestinal symptoms and endoscopic findings in patients, aiming to understand their correlation with H. pylori density. The most common gastrointestinal symptoms reported among patients were epigastric pain (80%), retrosternal burning (48%), and nausea (46.7%). Less frequently observed symptoms included vomiting (18.7%), melena (1.3%), hematemesis (1.3%), burping (4%), and belching (4%). Endoscopic examination revealed that esophagitis was the most prevalent finding, affecting 72% of the patients. Other significant findings included Antral Gastritis (44%), Duodenitis (34.7%), Moderate Gastritis (33.3%), and Severe Gastritis (16%). Mild gastritis was observed in only 4% of the cases, while gastric ulcers and duodenal ulcers were found in 1.3% and 6.7% of the patients, respectively. The evaluation for H. pylori presence showed that 34.7% of the patients tested positive for the bacterium. This significant presence indicates that H. pylori plays a notable role in the development of gastrointestinal symptoms and associated pathologies.

Figure 1 shows the distribution of patients according to H. pylori density.



The figure presents the distribution of H. pylori density among 75 patients, categorized into four levels: None, Mild, Moderate, and Severe. The majority of patients, 49 out of 75 (65.3%), showed no detectable H. pylori presence, indicating that a significant portion of the patient cohort does not have an active H. pylori infection. H. pylori density was classified as mild in 9 patients, representing 12.0% of the total sample, suggesting that a smaller segment of the population has a low level of H. pylori infection. A moderate density of H. pylori was found in 13 patients, accounting for 17.3% of the cohort, indicating a clear prevalence of moderate infection levels among the patients. Only 4 patients (5.3%) had a severe density of H. pylori, reflecting a relatively low prevalence of high-density infections in the studied population.

Table 2: Association between H. pylori density, gastrointestinal symptoms & Endoscopic Findings

		H. pylori density				
Parameters		None	Mild	Moderate	Severe	p-value
Epigastric pain	*Yes*	39(65.0)	7(11.7)	11(18.3)	3(5.0)	.966
	No	10(66.7)	2(13.3)	2(13.3)	1(6.7)	
Nausea	*Yes*	22(62.9)	5(14.3)	6(17.1)	2(5.7)	.947
	No	27(67.5)	4(10.0)	7(17.5)	2(5.0)	
Vomiting	*Yes*	7(50.0)	3(21.4)	2(14.3)	2(14.3)	.206
	No	42(68.9)	6(9.8)	11(18.0)	2(3.3)	
Retrosternal burning	*Yes*	21 (58.3)	5(13.9)	9(25.0)	1(2.8)	.270
	No	28(71.8)	4(10.3)	4(10.3)	3(7.7)	
Malena	*Yes*	1(100)	-	-	-	.911
	No	48(64.9)	9(12.2)	13(17.6)	4(5.4)	
Hematemesis	*Yes*	1(100.0)	-	-	-	
	No	48(64.9)	9(12.2)	13(17.6)	4(5.4)	.911
Burping	*Yes*	2(66.7)	-	1(33.3)	-	.800
	No	47(65.3)	9(12.5)	12(16.7)	4(5.6	
Belching	*Yes*	2(66.7)	-	1(33.3)	-	.800
	No	47(65.3)	9(12.5)	12(16.7)	4(5.6)	
Esophagitis	*Yes*	33(61.1)	9(16.7)	12(22.2)	-	**<.001
	No	16(76.2)	-	1(4.8)	4(19.0)	
Gastritis Mild	*Yes*	3(100)	-	-	-	.646
	No	46(63.9)	9(12.5)	13(18.1)	4(5.6)	
Gastritis Moderate	*Yes*	20 (80.0)	-	3(12.0)	2(8.0)	.077
	No	29(58.0)	9(18.0)	10(20.0)	2(4.0)	
Gastritis Severe	*Yes*	7(58.3)	2(16.7)	3(25.0)	-	.657
	No	42(66.7)	7(11.1)	10(15.9)	4(6.3)	
Duodenitis	*Yes*	14(53.8)	5(19.2)	6(23.1)	1(3.8)	.326
	No	35(71.4)	4(8.2)	7(14.3)	3(6.1)	
Antro gastritis	*Yes*	20(60.6)	6(18.2)	6(18.2)	1(3.0)	.442
	No	20(64.5)	1(3.2)	7(22.6)	3(9.7)	
Gastric Ulcer	*Yes*	1(100)	-	-	-	.911
	No	48(64.9)	9(12.2)	13(17.6)	4(5.4)	
Duodenal Ulcer	*Yes*	3(60)	-	2(40)	-	.468
	No	48(65.7)	9(12.9)	11(15.7)	4(5.7)	

***statistically significant at 0.01 level of significance*

The analysis of H. pylori density and its association with gastrointestinal symptoms and endoscopic findings reveals that most gastrointestinal symptoms, including epigastric pain, nausea, and retrosternal burning, show no significant association with H. pylori density. However, vomiting is more common in patients with severe H. pylori density, though not significantly. Notably, esophagitis is significantly associated with higher H. pylori densities ($p < 0.001$), indicating a potential link between the bacterium and this condition. Other findings, such as moderate gastritis and duodenitis, show trends toward association but are not statistically significant. These insights highlight the importance of considering H. pylori density in the context of esophagitis and potentially other gastrointestinal conditions. (Table 2)

Table 3: Association between H. pylori & gastrointestinal symptoms

Parameters	**N(%)**		
Gastrointestinal symptoms	**Positive**	**Negative**	**p-value**
Epigastric_pain			
Yes	21(35)	39(65)	.903
No	5(33.3)	10(66.7)	
Nausea			
Yes	13(37.1)	22(62.9)	.673
No	13(37.1)	27(67.5)	
Vomiting			
Yes	7(50.0)	7(50.0)	.220
No	19(31.1)	42(68.9)	
Malena			
Yes	-	1(100)	1.000
No	26(35.1)	48(64.9)	
Retrosternal burning			
Yes	15(41.7)	21(58.3)	.221
No	11(28.2)	28(71.8)	
Hematemesis			
Yes	-	1(100)	1.000
No	26(35.1)	48(64.9)	
Burping			
Yes	1(33.3)	2(66.7)	1.000
No	25(34.7)	47(65.3)	
Belching			
Yes	1(33.3)	2(66.7)	1.000
No	25(34.7)	47(65.3)	

Table 3 presents the association between various gastrointestinal symptoms and the presence of H. pylori. The parameters considered include epigastric pain, nausea, vomiting, melena, retrosternal burning, hematemesis, burping, and belching. For each symptom, the table provides the number and percentage of positive and negative H. pylori cases, along with the p-value, to indicate statistical significance.

For epigastric pain, 35% of positive cases and 65% of negative cases were reported, with a p-value of .903, indicating no significant association with H. pylori. Similarly, nausea showed no significant association, as 37.1% of positive cases and 62.9% of negative cases had a p-value of .673. Vomiting had a higher percentage of positive cases at 50%, compared to 31.1% of negative cases, but the association was not statistically significant (p = .220). For melena, data was missing for positive cases, and the p-value was 1.000, suggesting no significant association.

Retrosternal burning was reported in 41.7% of positive cases and 58.3% of negative cases, with a p-value of .221, showing no significant association. Hematemesis also had missing data for positive cases and a p-value of 1.000, indicating no significant association. Both burping and belching showed similar results, with 33.3% positive cases and 66.7% negative cases and a p-value of 1.000, suggesting no significant association with H. pylori.

DISCUSSION

H. Pylori is a gram negative, spiral-shaped bacterium which is responsible for Gastric inflammation and possible complications like Gastric Atrophy, Intestinal metaplasia and MALT lymphoma[1 2]. A lot of studies have been done to establish the relationship of these findings and density of H Pylori with variable results.[3,4,5] Similarly, it has been attempted in past to predict the presence of H pylori based upon the symptomatology but no clear association has been established.[7] Our study had two objectives. First, to find out symptoms associated with presence of H Pylori and secondly the possible association of severity of endoscopic findings and degree of colonization of H pylori.

Detection of H. pylori by optical microscopy is considered to be an efficient method This method is highly rated because of its potential of definite diagnosis of H. pylori infection, thus indicating gastric inflammation.[8] In the study by Lobo Gatti and collaborators, histological test was found to be most sensitive for H. pylori detection, compared to others like urease test and culture tests. This is the reason that we used this test for evaluation of H pylori. Our results show that 34 % of patients were found to be positive for H pylori. This value is far less than the values seen in other studies of third world countries. Two studies from Brazil showed an incidence of 85% and 78 %,[10] while a Jordanian study[11] showed a value of 82 %. Global prevalence of H pylori has been estimated by WHO to be around 35 % which is quite close to our numbers. While another local data from Pakistan shows a value of 73%[8]. So, it can be concluded that exact value varies amongst various communities, sample cohort and symptomatology.

H. pylori do play a role in the pathogenesis of various gastric diseases (gastritis, ulcer, cancer) because it leads to mucosal destruction. Exact mechanism of this mucosal damage is unknown, but it is found out that proteases released by H Pylori damage the mucus structure by increasing the gastric acid secretion. The most common gastrointestinal symptoms reported among patients were epigastric pain (80%) followed by retrosternal burning (48%) but only 35% of patients were H pylori positive, which was statistically in-significant. Majority of those patients who experienced epigastric pain did not have H Pylori infection. So, it means that merely pain is not a positive indicator for presence of H Pylori infection. This symptom correlation has been studied in various studies. According to local data, pain has been related to H Pylori infection.[7,8] Main reason for this difference of result may be due to multiple reasons, especially, NSAIDs intake and various different cohort of patients. When it comes to most common endoscopic finding in patients having infection, only esophagitis was found to be statistically significant while gastritis, duodenitis and presence of ulcer were not found to be related to H Pylori infection. It is, in contrast to previous work done in the region[19] where gastritis was found to be the major endoscopic finding.

Although amongst the available data there was a statistically significant relation between the intensity of H. pylori and the severity of inflammation in study by sarin. This study revealed that as the intensity of H. pylori increases, there is increase in the severity of inflammation as well.[13] In another study done by Yakoob, et al. a significant relationship was found between intensity of H. pylori colonization and chronic inflammatory gastric activity.[14] In a study

performed on Histopathological examination of endoscopic biopsy specimens of 461 patients, Türkay, et al. also concluded that as the intensity of H. pylori increased, the intensity of inflammation also increased proportionately.[15] Similarly, in another work done by Alagöz, et al. a significant correlation was observed between lymphoplasmacytic cell infiltration and inflammation activation and severity of H Pylori infestation[16].In contrast, to these positive associations in a study of 272 gastric biopsy specimens by Ardakani, et al. no significant relationship was found between the density of H. pylori and the severity of chronic gastritis activity. These findings are in strong agreement to our findings that there is no well-defined association of H pylori infection and degree of gastric inflammation.[17] In a study done in India Choudhary, et al. also found no statistically significant relationship between H. pylori density and chronic gastritis.[18] This is also in agreement to our findings. But variation between studies is because of variation in genomic structure of h pylori and life style differences and antimicrobial resistance of organism in different strains.

CONCLUSION:

Our study concludes that H pylori infection has a variable symptom profile depending upon demographics and concomitant risk factors. Similarly, endoscopic findings cannot be taken as evidence of H pylori infection. For proper detection we have to rely on investigations of H Pylori.

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Author's Contribution:

AM: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
II, UA, SS, MF, SSQ, UH: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

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