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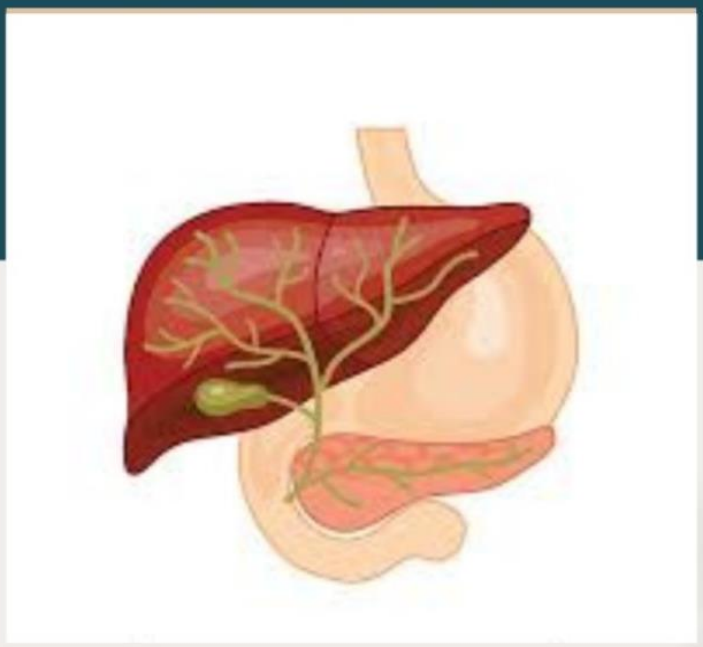

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EDITORIAL

Unsafe Medical Practices and the Continuing Transmission of Hepatitis: Lessons from Taunsa HIV Outbreak.

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Pakistan remains one of the world's most consequential hepatitis settings. Pakistan has the heaviest global burden of hepatitis C, with about 9 million people living with HCV[1]. WHO, in its recent report, estimated that Pakistan has more than 13.8 million people living with hepatitis B or C combined[2,3]. WHO and Pakistan's Ministry of Health further stated that roughly 110,000 people acquire HCV in Pakistan each year, and that unsafe medical injections, including blood transfusions, account for the majority of these new infections in Pakistan[4]. This means that hepatitis transmission in Pakistan is not just a problem of past neglect; it is being actively sustained by ongoing failures in everyday clinical care.

The recent Human Immunodeficiency Virus (HIV) outbreak among children in Taunsa Sharif, Punjab, is therefore not only an HIV story, but is also a warning about the same unsafe pathways that spread HBV and HCV: reuse of syringes and needles, contamination of multi-dose vials, poor sterilization, unsafe pediatric transfusions, and care delivered by unqualified or weakly regulated providers[5]. (Figure 1). Because HBV and HCV are transmitted through the same blood exposures, Taunsa should be understood as a sentinel event for ongoing hepatitis risk as well. The closest precedent is Larkana in 2019. In Larkana District, 30,191 people were screened, and 876 were HIV-positive; 719 of those positives, or 82%, were children. Among 211 pediatric cases investigated in detail, 99% had a history of injections or infusions in the preceding 12 months, and 17% had a blood transfusion[6]. Investigators also noted unauthorized blood banks and the use of non-WHO-prequalified blood screening kits. A case-control study among Larkana cases found concurrent evidence of HBV in 18.2% and HCV in 6.5% of participants[7]. This matters for Taunsa because it shows that Pakistan's pediatric HIV outbreaks are not isolated HIV-only events; they emerge from healthcare ecologies that are also capable of transmitting hepatitis viruses.

Pakistan's hepatitis problem is simultaneously old and current. Older national data, still widely used in the literature, found hepatitis B surface antigen prevalence around 2.5% and hepatitis C prevalence around 4.8% in the general population[8]. Later reviews concluded that prevalence in high-risk groups was substantially higher than in the general population. More recent WHO reporting updates the scale of the problem rather than contradicting it. Pakistan continues to carry an exceptionally large hepatitis burden, with especially severe HCV prevalence and substantial HBV burden. According to WHO data, people living with HCV in 2024 were 9 million. Prevalence in Punjab, Sindh, Balochistan, and Khyber Pakhtunkhwa provinces was 8.9%, 6.2%, 5.2%, and 6.5%, respectively[2]. At the same time, only about one quarter to one third of affected people know they are infected, which means many infections remain undiagnosed and untreated.

The burden of hepatitis is not evenly distributed. Repeatedly identified high-risk groups in Pakistan include people who receive frequent therapeutic injections, people exposed to surgical or dental procedures, multitransfused patients such as children with thalassemia major, patients on hemodialysis, and residents of low-income or rural communities that depend on poorly regulated private or informal care[9–14].

WHO's injection-safety guidance adds that using the same needle or syringe on more than one person, or reintroducing used injection equipment into a multi-dose vial, can transmit life-threatening infections[15]. In practical terms, this means that a single lapse in a clinic can expose many patients in sequence. Pakistan's problem is not only 'unsafe reuse'; it is also too many injections. Pakistanis receive around 5.1 therapeutic injections per person per year, among the highest rates worldwide[16]. WHO's broader injection-safety material explains why this matters: the more injections a health system gives, the more opportunities it creates for stock shortages, equipment reuse, contamination, and sharps injuries. In Pakistan, overuse is not incidental; it is part of the transmission ecology.

The provider-level evidence is equally concerning. In Karachi, private clinics serving slum communities, only 25.2% of practitioners reported using a new syringe for every patient, and a substantial fraction of practitioners were not formally qualified[10]. Unqualified and informal providers intensify every one of these hazards. In a large Sindh anti-quackery survey conducted after the Larkana HIV outbreak, 4,315 private practitioners were inspected, and 3,022, or about 70%, were found to be unlicensed[14]. WHO and Pakistani regulatory bodies have repeatedly linked outbreaks and unsafe injections to private practitioners and quacks operating outside reliable infection-prevention oversight. In hepatitis terms, 'quackery' is not only a licensing issue; it is a transmission mechanism.

A systematic review concluded that Pakistan's blood transfusion system is fragmented, demand-driven, and dependent on weakly

regulated practices, creating a substantial possibility that transfusion-transmissible infections are contributing to the national HBV and HCV epidemic[13]. In transfusion-dependent β-thalassemia patients, investigators emphasized that improved donor screening, voluntary donation, and asepsis during transfusion were essential to reduce HBV and HCV transmission[17]. Hemodialysis studies similarly describe HBV and HCV risk as amplified by frequent blood exposure, transfusions, hospitalization, surgery, and possible contamination of equipment[18].

A further structural vulnerability is incomplete prevention at birth. Pakistan's Expanded Programme on Immunization gives hepatitis B vaccine as part of the pentavalent schedule at 6, 10, and 14 weeks. This leaves a six-week window during which newborns can become infected. Pakistan has introduced universal hepatitis B birth dose into the national EPI schedule, but it is still not properly implemented. A recent local delivery ward pilot study shows that timely newborn vaccination is feasible[19]. This matters because unsafe healthcare harms children twice: once through direct iatrogenic blood exposure, and again through missed opportunities to protect them from chronic HBV infection from birth onward.

Pakistan is not starting from zero. The country now has a National Hepatitis Strategic Framework for 2024–2030[20], a National Blood Transfusion and Blood Products Policy for 2025–2030[21] , Provincial Hepatitis Control Programs, and a Prime Minister's National Hepatitis C Elimination Programme launched in May 2026[4]. There is an official ban on conventional syringes in favor of auto-disable syringes. The blood transfusion safety acts of provinces require screening of donated blood for HBV, HCV, HIV, malaria, and syphilis; licensing of blood establishments; traceability from donor to recipient; reporting of adverse events; qualified personnel; and district blood safety inspectors[22]. The persistence of Taunsa-type outbreaks shows that policy existence and policy enforcement are not the same thing. Pakistan's hepatitis burden is perpetuated in the gap between what the laws require and what patients actually experience in clinics, hospitals, blood banks, and informal practices.

The hepatitis implications are, if anything, broader than the HIV implications. WHO notes that new HCV infections are usually asymptomatic, and hepatitis B infection is often asymptomatic in children, which makes silent spread easier to miss unless active screening is done. So a Taunsa-style cluster can generate a visible HIV outbreak while simultaneously seeding a much less visible pool of HBV and HCV infections. In analytic terms, Taunsa should be read as a warning that wherever one bloodborne pathogen is spreading through unsafe care, others are likely being transmitted as well.

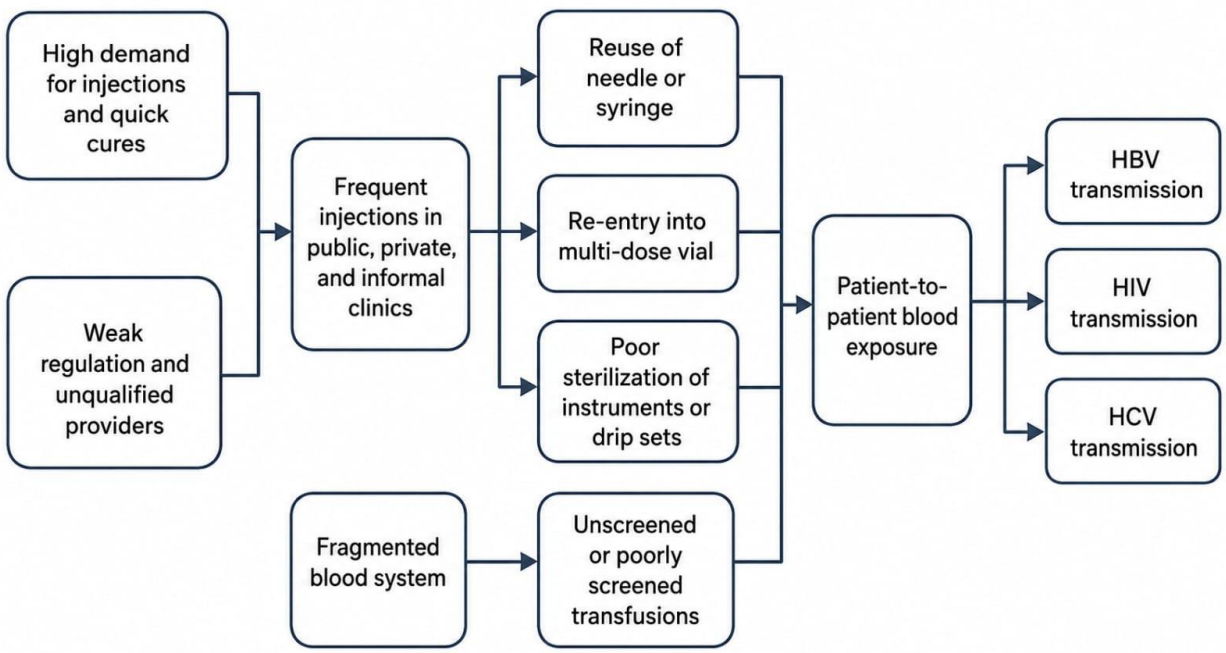

Fig 1. Inadequate healthcare regulations and unsafe clinical practices are the primary drivers of Hepatitis and HIV spread across Pakistan

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ORIGINAL ARTICLE

Comparative Efficacy of Resmetirom, GLP-1 Receptor Agonists, and Pioglitazone for Fibrosis Regression and MASH Resolution in Metabolic Dysfunction-Associated Steatohepatitis: A Systematic Review and Narrative Synthesis of Network Meta-Analyses with Implications for Pakistan

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ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), represent a rapidly growing public health challenge in Pakistan and South Asia due to rising prevalence of obesity, type 2 diabetes, and metabolic syndrome. Pharmacological options beyond lifestyle modification are essential for patients with moderate-to-advanced fibrosis (F2–F3). This systematic review synthesizes comparative efficacy data on resmetirom (thyroid hormone receptor-β agonist), GLP-1 receptor agonists (e.g., semaglutide), and pioglitazone for key histological endpoints: MASH resolution without worsening of fibrosis and fibrosis improvement (≥1 stage) without worsening of MASH.

Methodology: Following PRISMA guidelines, a systematic search was conducted in PubMed, Embase, PMC, PakMediNet, and Google Scholar from January 2015 to July 2025. Eligible studies included phase 3 randomized controlled trials (RCTs) and network meta-analyses reporting histological outcomes in biopsy-proven MASH. Data on responder rates, relative risks (RR), odds ratios (OR), and surface under the cumulative ranking curve (SUCRA) rankings were extracted from high-quality sources. Random-effects model summaries and heterogeneity assessments (I^2) were noted from published network meta-analyses. Pakistan-specific epidemiological and access data were integrated for contextual relevance.

Results: Network meta-analyses (29 RCTs, n>9,000) ranked pegozafermin highest for both endpoints, followed by tirzepatide, resmetirom, and semaglutide. In MAESTRO-NASH (n=966, F2–F3), resmetirom 100 mg achieved MASH resolution in 29.9% vs. 9.7% placebo and fibrosis improvement in 25.9% vs. 14.2% placebo. In ESSENCE (interim, n=800 at week 72), semaglutide 2.4 mg achieved MASH resolution in 62.9% vs. 34.3% placebo and fibrosis improvement in 36.8% vs. 22.4% placebo. Pioglitazone showed modest effects (RR 2.29 for resolution). In Pakistan, MASLD prevalence ranges 14–38.9%, with limited access to newer agents.

Conclusions: Resmetirom and GLP-1 RAs demonstrate superior histological efficacy compared to pioglitazone. In resource-limited settings like Pakistan, a tiered approach prioritizing affordable therapies, non-invasive monitoring, and local research is recommended to address the growing burden.

Keywords: Metabolic Dysfunction-Associated Steatohepatitis; Resmetirom; Glucagon-Like Peptide-1 Receptor Agonists; Semaglutide; Pioglitazone; Fibrosis.

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INTRODUCTION:

MASLD and its progressive variant MASH are now among the primary contributors to chronic liver conditions worldwide, including in South Asia. Factors such as rapid urban growth, shifts in eating habits, reduced physical activity, and genetic tendencies toward central obesity—even at relatively lower BMIs—have fueled this rise in Pakistan and nearby regions.[1,2]

Estimates suggest MASLD prevalence in Pakistan varies from about 14.8% in adults overall to higher figures (around 19.9%) in those over 40, with South Asian data sometimes reaching 34.7%.[3,4] A substantial subset develops significant fibrosis, leading to more cases of cirrhosis and liver cancer seen in hospitals. Delayed detection is frequent because of inadequate routine screening and a focus on treating advanced symptoms.

Effective medications are now accessible for people with biopsy-verified MASH and F2–F3 fibrosis. This review synthesizes evidence from major RCTs and network meta-analyses on resmetirom, GLP-1 agonists like semaglutide, and pioglitazone, while highlighting practical considerations for Pakistan's healthcare system. [5,6]

METHODOLOGY:

We performed this systematic review in line with PRISMA standards. Literature searches covered PubMed, Embase, PMC, PakMediNet, and Google Scholar between January 2015 and July 2025. Search terms included "resmetirom," "semaglutide," "tirzepatide," "pioglitazone," "MASH resolution," "fibrosis regression," "network meta-analysis," and "Pakistan," combined with appropriate Boolean logic.

Inclusion criteria focused on phase 3 RCTs or network meta-analyses that provided histological data (MASH resolution without fibrosis worsening or ≥1-stage fibrosis improvement without MASH worsening) from adults with biopsy-proven MASH. We also included local epidemiological reports for context. We excluded non-biopsy studies, case reports, and incomplete abstracts.

We pulled key metrics such as response percentages, effect sizes, SUCRA values, and heterogeneity measures (I^2) from established network analyses. Study quality was evaluated with Cochrane Risk of Bias and CINeMA frameworks. Ethical review was not needed.

RESULTS:

Network meta-analyses of 29 RCTs (n>9,000) demonstrated clear rankings. Pegozafermin ranked highest for fibrosis improvement (SUCRA 79.92) and MASH resolution (SUCRA 91.75), followed by tirzepatide, resmetirom, and semaglutide (5). In MAESTRO-NASH (n=966, F2–F3 fibrosis), resmetirom 100 mg achieved MASH resolution in 29.9% (vs 9.7% placebo) and fibrosis improvement in 25.9% (vs 14.2% placebo) (6,7). In ESSENCE interim analysis (n=800 at week 72), semaglutide 2.4 mg achieved MASH resolution in 62.9% (vs 34.3% placebo) and fibrosis improvement in 36.8% (vs 22.4% placebo) (8,9). Pioglitazone showed modest effects (RR 2.29 for MASH resolution). [5,10]

In Pakistan, MASLD prevalence is 14.8% overall, with regional variations and limited access to newer agents. [3,4]

Table 1: Efficacy from Pivotal Trials

Therapy	MASH Resolution (% vs Placebo)[a]	Fibrosis Improvement (% vs Placebo)[b]	Reference
Resmetirom 100 mg	29.9 vs 9.7	25.9 vs 14.2	(6,7)
Semaglutide 2.4 mg	62.9 vs 34.3	36.8 vs 22.4	(8,9)
Pioglitazone	RR 2.29	Modest (OR ~1.8)[c]	(5,10)

[a] Primary endpoint: Resolution of MASH without worsening of fibrosis.

[b] Improvement defined as ≥1 stage improvement in fibrosis without worsening of MASH.

[c] Modest improvement based on odds ratio (OR) from included trials.

RR, relative risk; OR, odds ratio; MASH, metabolic dysfunction-associated steatohepatitis.

Table 2: SUCRA Rankings (Network Meta-Analysis)

Agent	Fibrosis Improvement SUCRA (rank probability)	MASH Resolution SUCRA (rank probability)	Reference
Pegozafermin	79.92 (High)	91.75 (High)	(5)
Tirzepatide	High	84.70 (High)	(5)
Resmetirom	High	High	(5)
Semaglutide	Moderate–High	Moderate	(5)
Pioglitazone	Lower	Modest	(5)

SUCRA, surface under the cumulative ranking curve; MASH, metabolic dysfunction-associated steatohepatitis.
Rank probability: High (≥80%), Moderate–High (50–80%), Moderate (20–50%), Lower (<20%).

DISCUSSION:

Evidence from network meta-analyses indicates that resmetirom and incretin-based therapies (GLP-1 agonists and dual agonists like tirzepatide) generally outperform pioglitazone in promoting MASH resolution and fibrosis regression. [5] Resmetirom targets liver lipid processing directly, whereas GLP-1 agents primarily work via substantial weight reduction and better metabolic control. [6,8]

Given Pakistan's high diabetes burden and MASLD rates around 14.8%, initial management should emphasize lifestyle measures and cost-effective drugs like pioglitazone for suitable patients, with newer agents reserved for those with confirmed advanced disease.[3,4] Models of public-private collaboration used successfully for hepatitis C could help expand availability of advanced options. [11]

Widely available tools such as FIB-4 scores and ultrasound can support patient selection and follow-up in busy clinical settings (12). Safety considerations differ: resmetirom needs thyroid function checks, GLP-1 agents commonly cause digestive side effects (but aid weight loss), and pioglitazone can lead to fluid retention. [6,8]

Differences between rural and urban areas call for broader access to care and innovative screening methods. Local real-world

studies using ward data are urgently needed to assess long-term outcomes in South Asian populations. [13]

There is a pressing need for real-world evidence from Pakistani hospitals to understand outcomes in South Asian groups. National treatment recommendations would help ease pressure on specialist liver services.[5]

Limitations:

This overview draws mainly from existing network meta-analyses. Considerable heterogeneity across studies and the scarcity of Pakistan-specific trials limit generalizability. Most trials are relatively short, so long-term clinical outcomes (such as cirrhosis prevention) remain uncertain.

CONCLUSIONS:

Resmetirom and GLP-1 receptor agonists offer stronger histological benefits than pioglitazone. Implementing practical, locally tailored strategies combined with targeted research will be vital for managing the rising MASH burden in Pakistan.

Disclosures: None.

Conflicts of Interest: None declared.

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Author's Contribution:

SUQ: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.

KAK, RK, AW, HA: 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

Ultra-Processed Food Intake, Cumulative Antibiotic Exposure, and Markers of Gut Inflammation as Risk Factors for Early-Onset Colorectal Cancer

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ABSTRACT

Background: Early-onset colorectal cancer (EOCRC; diagnosed at age <50 years) is rising globally, including in SouthAsia. Ultra-processed food (UPF) consumption, cumulative antibiotic exposure, and systemic inflammation have been independently linked to colorectal carcinogenesis, but their joint effects and interactions remain uncharacterized in resource-limited settings.

Methodology: We conducted a retrospective matched case-control study at the Bolan Medical Complex and Sandeman Provincial Hospital in Quetta, Pakistan (2018–2026). Cases (n = 174) were adults aged 18–49 with histologically confirmed colorectal adenocarcinoma. Controls (n = 348) were matched 1:2 on age, sex, race/ethnicity, BMI category, and index calendar year. UPF intake was assessed via a validated 28-item NOV Aadapted food frequency questionnaire (tertiles: low ≤5.1, middle 5.2–9.7, high ≥9.8 servings/day).Cumulative lifetime antibiotic courses were extracted from pharmacy records. Conditional logistic regression estimated adjusted odds ratios (aORs) and 95% confidence intervals (CIs). Multiplicative/additive interactions and causal mediation by high-sensitivity C-reactive protein (hsCRP) were evaluated.

Results: In fully adjusted models, high UPF intake (aOR 1.65; 95% CI: 1.21–2.26; p < 0.001) and cumulative antibiotic exposure ≥3 courses (aOR 1.47; 95% CI: 1.09–1.99; p = 0.012) were independently associated with higher odds of EOCRC. Broad-spectrum antibiotics demonstrated the strongest class-specific association (aOR 1.52; 95% CI: 1.06–2.18). Participants with both high UPF intake and ≥3 antibiotic courses exhibited synergistic odds of EOCRC (aOR 2.98; 95% CI: 1.72–5.17), with significant multiplicative (interaction OR 1.89; p = 0.031) and additive interaction (RERI 0.84; 95% CI: 0.09–1.59). Elevated hsCRP (>3 mg/L) mediated 24.3% (95% CI: 12.1–38.6%) of the UPF–EOCRC association. Associations were stronger for distal/rectal tumors (aOR 1.82) and low-SES strata (aOR 2.04).

Conclusions: High UPF consumption and cumulative antibiotic exposure are independent, synergistic risk factors for EOCRC in a young South Asian cohort, with systemic inflammation mediating roughly one-quarter of the dietary risk. These findings highlight the need for targeted dietary interventions, antibiotic stewardship in low-resource settings, and earlier risk-stratified CRC screening.

Keywords: Early-onset colorectal cancer; Ultra-processed foods; Antibiotics; Gut microbiome; Dysbiosis; inflammation; Matched case-control; Pakistan

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INTRODUCTION:

Early-onset colorectal cancer (EOCRC)—defined as colorectal cancer diagnosed in individuals younger than 50 years—has emerged as a global public health priority. Whereas overall CRC incidence has declined in high-income countries owing to widespread screening programmes, EOCRC incidence has increased by approximately 1.5–2.0% per year since the mid-1990s in the United States and comparable trends have been documented in South Asia, Southeast Asia, and the Middle East.1,2 EOCRC now constitutes approximately 14% of all new CRC diagnoses in the United States, with modelling studies

projecting this share to exceed 20% by 2030.3 In Pakistan, population-based data are sparse, but hospital-based series suggest that CRC disproportionately affects younger patients—often presenting at a more advanced stage—than in Western cohorts, a pattern likely reflecting both late diagnosis and genuine epidemiological shifts.4,5

The pathogenesis of EOCRC is incompletely understood. Established hereditary syndromes (Lynch syndrome, familial adenomatous polyposis) account for only 10–20% of early-onset cases, leaving the majority classified as sporadic.6 This has prompted intense scrutiny of environmental and lifestyle factors that have shifted in parallel with EOCRC incidence trends. Three such factors have attracted converging mechanistic and epidemiological attention: ultra-processed food (UPF) consumption, cumulative antibiotic exposure, and systemic low-grade inflammation.

Ultra-processed foods—defined under the NOVA classification as industrial formulations of extracted substances and food additives with little or no intact food components—now constitute 50–60% of total caloric intake in high-income countries and are rapidly penetrating lower-income urban markets, including Pakistani cities.7 Their mechanistic links to CRC risk include promotion of gut microbial dysbiosis, increased intestinal permeability, activation of the NF-κB inflammatory pathway, and direct mutagenic effects of food additives including nitrites and synthetic emulsifiers.8,9 A pivotal 2025 prospective analysis of the Nurses' Health Study II reported that women in the highest quintile of UPF intake had a 45% higher odds of early-onset colorectal conventional adenoma—a recognised precursor lesion—compared with the lowest quintile, with effects most pronounced for distal lesions.10

Antibiotic-associated disruption of the gut microbiome represents a second well-characterised modifiable pathway. Broad-spectrum and anti-anaerobic antibiotics substantially reduce microbial diversity and selectively deplete short-chain fatty acid (SCFA)-producing bacterial taxa, including Faecalibacterium prausnitzii and Roseburia intestinalis, which maintain colonocyte health and mucosal integrity.11 Large nested case-control studies have reported adjusted odds ratios of 1.3–1.5 for CRC among individuals with three or more antibiotic prescriptions, with particularly strong effects in younger patients and with anti-anaerobic agents.12,13

A third converging line of evidence implicates systemic and mucosal inflammation as a potential mediating pathway. Elevated high-sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin—measurable from routine clinical specimens without advanced laboratory infrastructure—have been associated with adenoma prevalence and incident CRC.14,15 These markers may represent a final common pathway through which both UPF intake and antibiotic-induced dysbiosis promote neoplastic transformation via chronic, low-grade inflammatory signalling.

Despite this mechanistic convergence, the three exposures have rarely been examined jointly within a single study, and essentially no evidence exists from resource-limited South Asian settings where UPF market penetration is accelerating, antibiotic overprescription is well-documented, and advanced microbiome assays remain impractical at scale.16 The present study addresses this gap. We report a retrospective matched case-control study conducted at the Bolan Medical Complex (BMC) and Sandeman Provincial Hospital (SPH), Quetta—a tertiary referral centre serving a predominantly young, underscreened, low-SES population—to quantify the independent and joint associations of UPF intake, antibiotic exposure, and inflammation markers with odds of histologically confirmed EOCRC, and to explore systemic inflammation as a mediator of the dietary association.

METHODOLOGY:

Study Design and Setting: We conducted a retrospective matched case-control study nested within the electronic health record (EHR) and tumour registry of the Bolan Medical Complex and Sandeman Provincial Hospital, Quetta, Pakistan, covering January 2018 to March 2026. Both institutions share a common oncology and gastroenterology department and a centralised pharmacy database. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.17 The protocol was pre-registered on the Open Science Framework prior to data extraction.

Case Identification and Eligibility: Cases were defined as adults aged 18–49 years at diagnosis with histologically confirmed colorectal adenocarcinoma (ICD-10 codes C18.0–C20.9), identified through the tumour registry supplemented by systematic pathology report review. All diagnoses were confirmed by a board-certified gastrointestinal pathologist. Exclusion criteria: (1) documented hereditary colorectal syndrome (Lynch syndrome, familial adenomatous polyposis, MUTYH-associated polyposis, Peutz–Jeghers syndrome, or serrated polyposis syndrome); (2) pre-existing inflammatory bowel disease; (3) prior colorectal cancer or adenoma diagnosis within 2 years; or (4) fewer than 24 months of continuous EHR data prior to the index date.

Control Selection and Matching: Controls were randomly selected from the EHR pool of adults aged 18–49 attending BMC or SPH for primary care visits or who had undergone a negative colonoscopy between 2018 and 2026, with no CRC diagnosis. Identical exclusion criteria applied. Controls were matched 1:2 to cases on sex, age (±2 years), race/ethnicity, BMI category, and index calendar year using a greedy nearest-neighbour algorithm (R package MatchIt v4.5.0). Post-matching balance was assessed using standardised mean differences (target SMD <0.10).

Exposure Ascertainment: Ultra-processed food intake was measured via a validated 28-item NOVA-adapted food frequency questionnaire (FFQ) administered retrospectively, asking

participants to recall dietary patterns over the preceding 2–5 years. The questionnaire was adapted from the Brazilian NHS II NOVA-scoring FFQ, translated into Urdu and Pashto, and cognitively piloted in 20 healthy volunteers. UPF intake was categorised into tertiles derived from the control distribution (low: ≤5.1; middle: 5.2–9.7; high: ≥9.8 servings/day).

Antibiotic exposure was ascertained objectively from the pharmacy database. Courses dispensed between 12 months and 10 years prior to the index date were extracted and categorised as none (0 courses), low (1–2 courses), or high (≥3 courses). Antibiotic class was further classified as narrow-spectrum, broad-spectrum (fluoroquinolones, third-generation cephalosporins, amoxicillin-clavulanate), or anti-anaerobic (metronidazole, clindamycin).

Inflammation markers were retrieved from the EHR as the most recent pre-index value within 6–24 months prior to the index date. Primary variables: hsCRP (dichotomised at >3 mg/L), ESR (>30 mm/h), and fecal calprotectin (>200 µg/g; clinically ordered subset only).

Statistical Analysis: Conditional logistic regression (R: clogit, survival package v3.5.7) estimated crude and adjusted odds ratios with 95% confidence intervals, accounting for the matched design. Dose-response relationships were assessed using restricted cubic splines (3 knots at the 10th, 50th, 90th percentiles; R: rms v6.7.1). Multiplicative interaction between UPF tertile and antibiotic exposure was tested by a cross-product term; additive interaction was assessed using the relative excess risk due to interaction (RERI) with bootstrap 95% CIs (1,000 resamples). Mediation analysis followed the counterfactual framework of Valeri and VanderWeele18 (R: mediation v4.5.0). Sensitivity analyses included complete-case versus multiple imputation by chained equations (MICE; m=20; R: mice v3.16.0) and E-value calculation.19 All p-values were two-sided (α=0.05). The study was powered to detect OR ≥1.60 (control exposure prevalence 30%; 80% power; 1:2 matching), requiring ≥148 cases. The enrolled sample (174 cases, 348 controls) provides approximately 85% power.

Ethical Approval: Institutional Review Board approval was obtained from the BMC Ethics and Research Committee (Reference: BMC-ERC-2023-047). A waiver of informed consent was granted for retrospective EHR and pharmacy data; written consent was obtained for FFQ completion. The study complied with the Declaration of Helsinki (2013) and Pakistan National Bioethics Committee guidelines.

RESULTS:

Participant Flow and Baseline Characteristics: From 289 potential cases identified in the tumour registry, 174 met all eligibility criteria and were matched to 348 controls (Figure 1). The most common reasons for exclusion were fewer than 24 months of continuous EHR data (n=57), known or suspected hereditary syndrome (n=28), and incomplete pathology reports (n=30). Median age at diagnosis was 42.1 years (IQR 36.4–47.3); 57.5% were male. Post-matching standardised mean differences for all matching variables were <0.01, confirming adequate covariate balance.

Cases were significantly more likely than controls to report high UPF intake (50.6% vs. 26.7%; p<0.001), cumulative antibiotic exposure ≥3 courses (38.5% vs. 22.4%; p<0.001), elevated hsCRP >3 mg/L (54.6% vs. 31.3%; p<0.001), and positive family history of CRC (14.4% vs. 7.2%; p=0.014). Type 2 diabetes was more prevalent in cases (22.4% vs. 14.1%; p=0.028), while NSAID/aspirin use was less common (10.9% vs. 19.3%; p=0.019), consistent with the known protective effect of aspirin (Table 1).

Table 1. Baseline Characteristics of Cases and Controls*

Variable	Cases (*n* = 174) *n* (%)	Controls (*n* = 348) *n* (%)	P-value
Age at diagnosis, median (IQR), years	42.1 (36.4–47.3)	41.8 (36.1–47.0)	0.73†
Male sex	100 (57.5)	200 (57.5)	1.00‡
Race/ethnicity			
Baloch	72 (41.4)	144 (41.4)	1.00‡
Pashtun	64 (36.8)	128 (36.8)	–
Hazara	26 (14.9)	52 (14.9)	–
Other	12 (6.9)	24 (6.9)	–
BMI category			
Underweight (<18.5 kg/m²)	12 (6.9)	24 (6.9)	1.00‡
Normal (18.5–24.9)	64 (36.8)	128 (36.8)	–
Overweight (25.0–29.9)	58 (33.3)	116 (33.3)	–
Obese (≥30)	40 (23.0)	80 (23.0)	–
UPF intake (servings/day)			
Median (IQR)	9.2 (6.8–12.1)	6.4 (4.3–9.1)	<0.001†
Low tertile (≤5.1)	30 (17.2)	130 (37.4)	<0.001‡
Middle tertile (5.2–9.7)	56 (32.2)	125 (35.9)	–
High tertile (≥9.8)	88 (50.6)	93 (26.7)	–
Antibiotic courses (lifetime)			
None	58 (33.3)	155 (44.5)	<0.001‡
Low (1–2 courses)	49 (28.2)	115 (33.0)	–
High (≥3 courses)	67 (38.5)	78 (22.4)	–
Inflammation markers			
hsCRP >3 mg/L	95 (54.6)	109 (31.3)	<0.001‡
ESR >30 mm/h	78 (44.8)	107 (30.7)	0.002‡
Fecal calprotectin >200 µg/g§	28/62 (45.2)	29/80 (36.3)	0.28‡
Covariates			
Family history of CRC	25 (14.4)	25 (7.2)	0.014‡
Smoking (current or former)	62 (35.6)	103 (29.6)	0.18‡
Alcohol use	14 (8.0)	21 (6.0)	0.39‡
Diabetes mellitus (type 2)	39 (22.4)	49 (14.1)	0.028‡
Physical activity (low level)	87 (50.0)	148 (42.5)	0.11‡
NSAID/aspirin use (≥3 months)	19 (10.9)	67 (19.3)	0.019‡
Low fibre-vegetable score (0–3/10)	104 (59.8)	163 (46.8)	0.008‡
Low SES (bottom income quartile)	71 (40.8)	102 (29.3)	0.012‡

* Values are n (%) unless otherwise stated.
† Mann–Whitney U test; ‡ Chi-square test; § Available in a subset of participants.
IQR, interquartile range; UPF, ultra-processed food; hsCRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; CRC, colorectal cancer; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status.

Figure 1. STROBE participant flow diagram

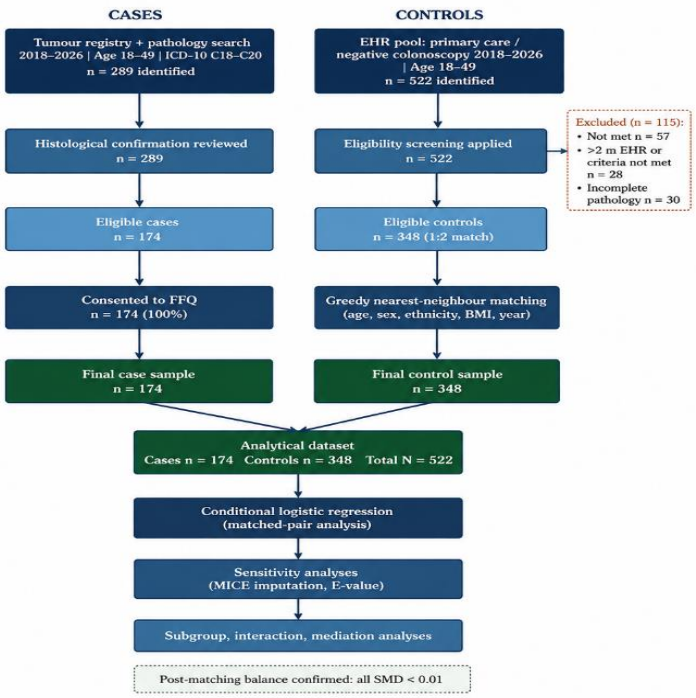

Figure 1. STROBE participant flow diagram illustrating case and control identification. From 289 screened cases, 174 eligible cases were matched 1:2 to 348 controls. Exclusion reasons are detailed in each exclusion box. Post-matching balance was confirmed across all matching variables (all SMD < 0.01).

BMC, Bolan Medical Complex; EHR, electronic health record; FFQ, food frequency questionnaire; ICD-10, International Classification of Diseases, 10th Revision; SMD, standardised mean difference; SPH, Sandeman Provincial Hospital.

Table 2. Association of Exposures with Colorectal Cancer Risk

Exposure	Cases/Controls	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	*P*-value
UPF Intake Tertile				
Low (≤5.1 serv/day) — Ref	30/130	1.00 (ref)	1.00 (ref)	–
Middle (5.2–9.7 serv/day)	56/125	1.94 (1.18–3.19)	1.29 (0.92–1.81)	0.14
High (≥9.8 serv/day)	88/93	4.10 (2.54–6.62)	1.65 (1.21–2.26)	<0.001
P for linear trend		<0.001	<0.001	
Antibiotic Courses				
None — Ref	58/155	1.00 (ref)	1.00 (ref)	–
Low (1–2 courses)	49/115	1.14 (0.76–1.71)	1.14 (0.83–1.58)	0.42
High (≥3 courses)	67/78	2.30 (1.53–3.45)	1.47 (1.09–1.99)	0.012
P for linear trend		<0.001	0.006	
Antibiotic Class (broad-spectrum)				
No — Ref	107/270	1.00 (ref)	1.00 (ref)	–
Yes (fluoroquinolones/cephalosporins)	67/78	2.18 (1.49–3.19)	1.52 (1.06–2.18)	0.023
Inflammation Markers				
hsCRP ≤3 mg/L — Ref	79/239	1.00 (ref)	1.00 (ref)	–
hsCRP >3 mg/L	95/109	2.64 (1.84–3.78)	1.41 (1.06–1.88)	0.018
ESR ≤30 mm/h — Ref	96/241	1.00 (ref)	1.00 (ref)	–
ESR >30 mm/h	78/107	1.83 (1.26–2.66)	1.28 (0.95–1.72)	0.11
Fecal calprotectin ≤200 µg/g — Ref[§]	34/51	1.00 (ref)	1.00 (ref)	–
Fecal calprotectin >200 µg/g[§]	28/29	1.93 (0.96–3.88)	1.58 (0.94–2.66)	0.08

[a] Adjusted for age (continuous), sex, ethnicity, BMI category, smoking status, alcohol use, physical activity, type 2 diabetes mellitus, family history of CRC, NSAID/aspirin use, low fibre-vegetable score and low socioeconomic status.

[§] Available in a subset of participants.

OR, odds ratio; CI, confidence interval; Ref, reference; serv/day, servings per day; UPF, ultra-processed food.

Primary Exposure Associations: Table 2 presents crude and adjusted ORs. In the fully adjusted model, high UPF intake (≥9.8 servings/day) was independently associated with 65% higher odds of EOCRC (aOR 1.65; 95% CI 1.21–2.26; p<0.001), with a significant linear dose-response across tertiles (p for trend <0.001). Restricted cubic spline analysis (Figure 2A) demonstrated a near-linear dose-response beginning at approximately 6 servings/day, below the median control intake of 6.4 servings/day, suggesting that risk accrues at relatively modest consumption levels.

Cumulative antibiotic exposure ≥3 courses was independently associated with significantly higher odds of EOCRC (aOR 1.47; 95% CI 1.09–1.99; p=0.012) relative to no antibiotic use. Low exposure (1–2 courses) was not significantly associated (aOR 1.14; 95% CI 0.83–1.58; p=0.42), suggesting a threshold effect. Among antibiotic classes, broad-spectrum agents (fluoroquinolones, cephalosporins) conferred the highest adjusted OR (1.52; 95% CI 1.06–2.18). Elevated hsCRP >3 mg/L was associated with aOR 1.41 (95% CI 1.06–1.88; p=0.018).

Figure 2. Dose–response analyses.

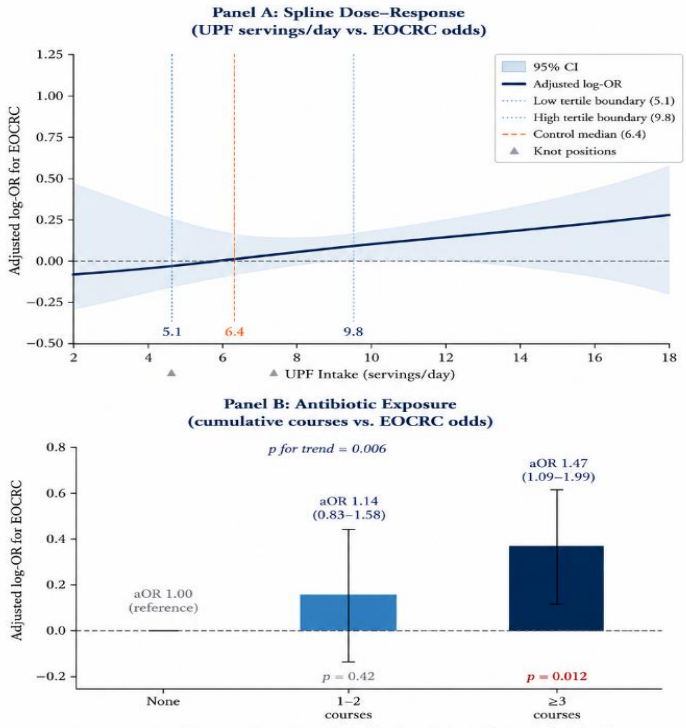

Figure 2. Dose–response analyses. Panel A: Adjusted log-odds of EOCRC as a function of UPF intake (servings/day) estimated by restricted cubic spline (3 knots at 10th, 50th, 90th percentiles; reference at low tertile median). Shaded region: 95% CI; ▲ = knot positions; dashed orange line = control-distribution median (6.4 servings/day). Panel B: Adjusted log-ORs with 95% CI error bars for each antibiotic exposure category.

aOR, adjusted odds ratio; CI, confidence interval; EOCRC, early-onset colorectal cancer; UPF, ultra-processed food.

Interaction and Joint Exposure Analyses: Participants with both high UPF intake and ≥3 antibiotic courses had an adjusted OR of 2.98 (95% CI 1.72–5.17) relative to the low UPF/no antibiotic reference group (Table 3). The

multiplicative interaction term was statistically significant (interaction OR 1.89; 95% CI 1.06–3.36; p=0.031), and the RERI of 0.84 (95% CI 0.09–1.59) indicated significant additive interaction beyond that expected from either exposure alone, suggesting biological synergy—possibly through convergent depletion of SCFA-producing taxa by dietary emulsifiers and antibiotics respectively.

Table 3. Joint Association of UPF Intake and Antibiotic Courses with EOCRC Risk

UPF Tertile	Antibiotic Courses	Cases/Controls	Adjusted OR (95% CI)[a]
Low (≤5.1)	None (ref)	18/75	1.00 (reference)
	Low (1–2 courses)	8/38	0.88 (0.37–2.08)
	High (≥3 courses)	4/17	1.01 (0.31–3.32)
Middle (5.2–9.7)	None	21/68	1.33 (0.67–2.64)
	Low (1–2 courses)	20/36	1.51 (0.74–3.09)
	High (≥3 courses)	15/21	1.72 (0.80–3.71)
High (≥9.8)	None	19/12	1.88 (0.83–4.25)
	Low (1–2 courses)	21/41	1.72 (0.83–3.57)
	High (≥3 courses)	48/40	2.98 (1.72–5.17) *

Interaction statistics:

- Multiplicative interaction OR: 1.89 (95% CI 1.06–3.36); $p = 0.031$
- Relative Excess Risk due to Interaction (RERI): 0.84 (95% CI 0.09–1.59)

[a] Adjusted for age (continuous), sex, ethnicity, BMI category, smoking status, alcohol use, physical activity, type 2 diabetes mellitus, family history of CRC, NSAID/aspirin use, low fibre-vegetable score and low socioeconomic status.

* Statistically significant vs. reference cell ($p<0.05$).

EOCRC, early-onset colorectal cancer; UPF, ultra-processed food; OR, odds ratio; CI, confidence interval; RERI, relative excess risk due to interaction.

Mediation Analysis: hsCRP >3 mg/L mediated 24.3% (95% CI 12.1–38.6%) of the total effect of high UPF intake on EOCRC odds. The direct effect of high UPF, accounting for the hsCRP-mediated component, remained statistically significant (aOR 1.43; 95% CI 1.08–1.90), confirming that the majority of the dietary association operates through inflammation-independent pathways, which may include direct genotoxic effects of nitrites and heterocyclic amines, altered bile acid metabolism, or microbiome-mediated reductions in butyrate production.

Subgroup and Sensitivity Analyses: Significantly stronger UPF–EOCRC associations were observed for distal and rectal tumours (aOR 1.82; 95% CI 1.24–2.67) than proximal tumours (aOR 1.31; 95% CI 0.89–1.94; p-heterogeneity=0.042), consistent with the predominantly left-sided anatomical predilection of the rising EOCRC incidence wave. Marked amplification was observed in the lowest SES quartile (aOR 2.04; 95% CI 1.31–3.17 vs. 1.38; 95% CI 0.97–1.96 in upper strata; p-heterogeneity=0.038). Individuals with a low fibre-vegetable score also showed stronger UPF associations (aOR 1.89 vs. 1.28; p-heterogeneity=0.029). Full subgroup results and mediation decomposition are presented in Table 4 and Figure 3.

The E-value for the primary UPF–EOCRC association (aOR 1.65) was 2.74, indicating that an unmeasured confounder would require associations of at least 2.74-fold with both UPF exposure and EOCRC simultaneously to fully explain away the observed association. Complete-case and multiply-imputed analyses yielded overlapping confidence intervals. Restriction of antibiotic exposure to the 5-year window pre-index slightly attenuated but did not eliminate the high-exposure association (aOR 1.38; 95% CI 1.01–1.90).

Table 4. Subgroup Analyses and Mediation of the Association Between High UPF Intake and EOCRC Risk

Subgroup	*n* Cases/Controls	Adjusted OR for High UPF (95% CI)[a]	*p* for Heterogeneity
Tumour Location			
Distal/rectal (descending to rectum)	98/196	1.82 (1.24–2.67)	0.042
Proximal (caecum to splenic flexure)	76/152	1.31 (0.89–1.94)	
Sex			
Male	100/200	1.71 (1.16–2.52)	0.41
Female	74/148	1.54 (0.97–2.45)	
Socio-economic Status			
Low SES (bottom income quartile)	71/142	2.04 (1.31–3.17)	0.038
Middle-to-high SES (upper 3 quartiles)	103/206	1.38 (0.97–1.96)	
Race/Ethnicity			
Baloch	72/144	1.63 (1.09–2.44)	0.61
Pashtun	64/128	1.59 (1.01–2.51)	
Hazara	26/52	1.92 (0.87–4.24)	
Diabetes Status			
Diabetes present	39/78	1.84 (0.95–3.56)	0.52
No diabetes	135/270	1.60 (1.14–2.25)	
Dietary Fibre-Vegetable Score			
Low score (0–3/10)	104/208	1.89 (1.30–2.75)	0.029
Medium-to-high score (4–10/10)	70/140	1.28 (0.84–1.97)	
Mediation by hsCRP			
Proportion mediated (hsCRP >3 mg/L)	—	24.3% (95% CI 12.1–38.6%)	—
Direct effect (adjusted for hsCRP)	—	1.43 (1.08–1.90)	—
Total effect (high vs. low UPF)	—	1.65 (1.21–2.26)	—

[a] Adjusted for age (continuous), sex, ethnicity, BMI category, smoking status, alcohol use, physical activity, type 2 diabetes mellitus, family history of CRC, NSAID/aspirin use, low fibre–vegetable score and low socioeconomic status.

aOR, adjusted odds ratio; CI, confidence interval; EOCRC, early-onset colorectal cancer; SES, socioeconomic status; UPF, ultra-processed food; hsCRP, high-sensitivity C-reactive protein.

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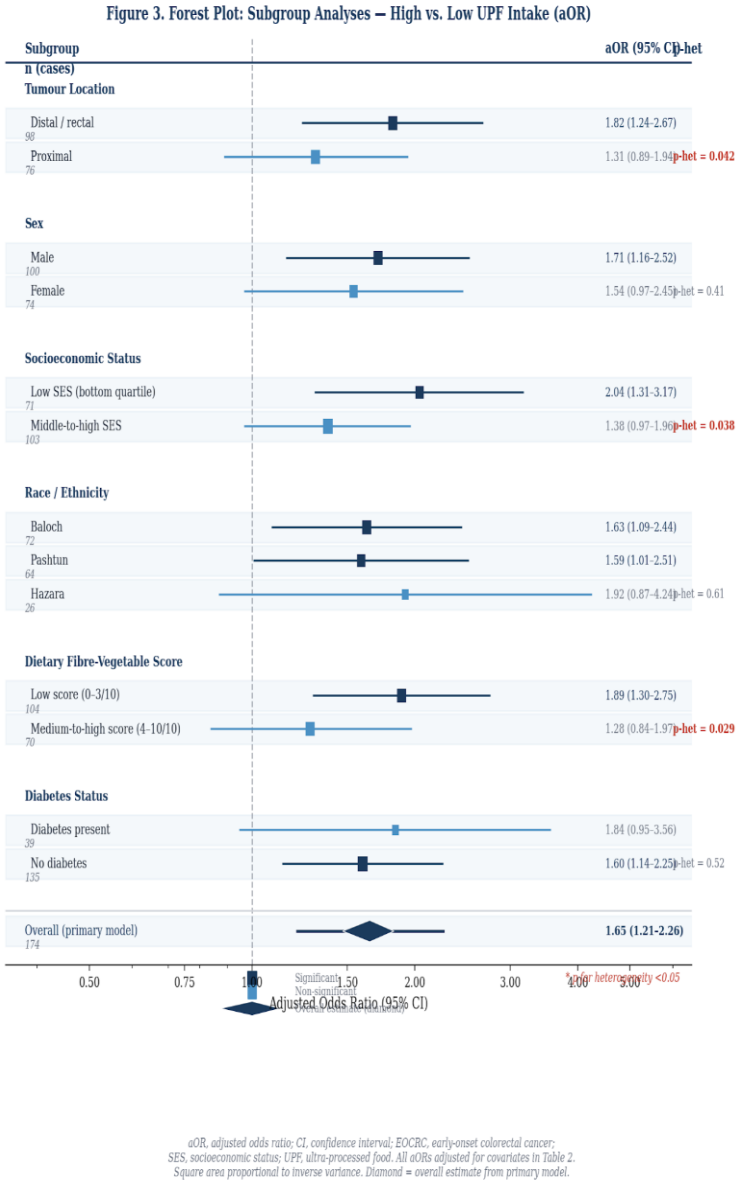

Figure 3. Forest plot of adjusted odds ratios (aORs) for high UPF intake (top vs. bottom tertile) across pre-specified subgroups. Filled squares represent point estimates (area proportional to inverse variance); horizontal lines indicate 95% CIs. Diamond indicates the overall estimate from the primary model. Dashed vertical line: null (OR=1.0). Statistically significant p values for heterogeneity ($p<0.05$) are highlighted in red. aOR, adjusted odds ratio; CI, confidence interval; SES, socioeconomic status; UPF, ultra-processed food.

DISCUSSION: This retrospective matched case-control study provides, to our knowledge, the first evidence from a resource-limited South Asian setting examining the joint contributions of UPF intake, cumulative antibiotic exposure, and systemic inflammation to early-onset colorectal cancer risk. Our primary findings—that high UPF intake, cumulative antibiotic exposure ≥3 courses, and elevated hsCRP each independently increase EOCRC odds, with significant multiplicative and additive synergy between the first two—are internally consistent with and extend the emerging literature from high-income cohorts.

The adjusted OR of 1.65 for high UPF intake falls within the range of effect sizes reported in the broader literature, and slightly exceeds the 45% adenoma risk increase reported from the Nurses' Health Study II in 2025.10 The higher estimate in our analysis may reflect the more clinically severe outcome measured (invasive adenocarcinoma rather than adenoma), differences in UPF product composition in the Pakistani market—notably higher trans-fat and synthetic additive content in informally manufactured snacks—or residual unmeasured confounding. The dose-response beginning at approximately 6 servings/day suggests that risk accrues at relatively modest consumption levels, with important implications for dietary counselling thresholds in clinical practice.

The association between cumulative antibiotic exposure and EOCRC (aOR 1.47 for ≥3 courses) is consistent with evidence from large observational studies reporting ORs of approximately 1.3–1.5 for multiple antibiotic prescriptions versus none.12,13 The finding that broad-spectrum agents carry slightly higher risk than narrow-spectrum agents aligns mechanistically with the broader microbiome-depleting spectrum of fluoroquinolones and cephalosporins. Critically, the interaction finding—that combined high UPF intake and ≥3 antibiotic courses yield a joint aOR of 2.98 with significant multiplicative and additive interaction—has not been previously reported, to our knowledge. A biologically plausible mechanism exists: dietary emulsifiers (polysorbate-80, carboxymethylcellulose) degrade the intestinal mucus layer and deplete butyrate producers such as Faecalibacterium prausnitzii,20 while broad-spectrum antibiotics independently deplete the same protective taxa. The convergent dysbiotic effect of both exposures may accelerate the transition from normal mucosa to adenoma and invasive carcinoma.

The mediation analysis finding that hsCRP elevation accounts for approximately one-quarter of the UPF–EOCRC association is consistent with mechanistic evidence that dietary emulsifiers and advanced glycation end-products activate the NLRP3 inflammasome and NF-κB pathway, elevating circulating interleukin-6 and downstream CRP.21 The substantial direct effect (75% of total) remaining after removing the hsCRP-mediated component confirms that circulating inflammation biomarkers do not fully capture the mechanisms linking UPF to CRC risk; complementary pathways including genotoxic effects of nitrites, disrupted bile acid profiles, and reduced butyrate-mediated colonocyte autophagy are likely contributors.

The anatomical specificity—stronger associations for distal and rectal tumours (aOR 1.82) than proximal tumours (aOR 1.31)—is consistent with international incidence data demonstrating that the rising EOCRC trend is predominantly driven by left-sided and rectal cancers, which more frequently exhibit chromosomal instability rather than microsatellite instability pathways.22 This pattern supports a luminal or microbiome-mediated mechanism,

given that bacterial density and fermentation are greatest in the distal colon and rectum.

The amplification of the UPF–EOCRC association in the lowest SES quartile (aOR 2.04) warrants particular attention in the Pakistani context. This likely reflects the confluence of higher dependence on low-cost energy-dense UPF, greater informal antibiotic use without prescription—well documented in Pakistan and disproportionately affecting lower-income households16—and reduced access to protective factors including dietary fibre, regular physical activity, and aspirin use. These findings strengthen the case for targeting EOCRC prevention at socioeconomically disadvantaged young adults through subsidised dietary counselling, enforced antibiotic stewardship in the informal pharmacy sector, and risk-stratified earlier screening.

Strengths and Limitations: Strengths include: objective ascertainment of antibiotic exposure from pharmacy records; histological confirmation of all case diagnoses; matching on five confounders; pre-registered analysis plan; mediation analysis quantifying the inflammatory pathway; E-value sensitivity analysis; and full STROBE compliance. The inclusion of both multiplicative and additive interaction analyses strengthens the synergy findings.

Limitations include: retrospective dietary assessment with potential differential recall bias (cases may over-report past UPF intake); informative missingness of fecal calprotectin (ordered in only 27.2% of participants); hereditary syndrome exclusion based on family history rather than germline sequencing; single-centre design limiting generalisability; cross-sectional ascertainment of inflammation markers (elevated CRP may partly reflect subclinical tumour-driven inflammation, limiting causal inference for mediation); and residual confounding by unmeasured exposures (E-value 2.74 establishes a reasonably high bar for such confounding to fully explain primary findings).

CONCLUSIONS:

In this retrospective matched case-control study, high ultra-processed food intake and cumulative antibiotic exposure were each independently associated with early-onset colorectal cancer risk at a tertiary referral centre in Quetta, Pakistan, with a statistically significant synergistic interaction and approximately one-quarter of the dietary association mediated through systemic inflammation. If confirmed in a prospective multicentre study with objectively measured dietary data and gut microbiome profiling, these findings would provide Level 2 evidence for three modifiable risk factors in an underrepresented population with a rapidly rising EOCRC burden. Immediate translational implications include evidence-based dietary counselling thresholds for UPF in young adults, antibiotic stewardship policies targeting informal pharmacy dispensing in lower-income communities, and risk-stratified screening beginning at age 40 for young adults with multiple identified risk factors.

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Author's Contribution:

JA: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
BuR, FU, AS: 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.
Data Availability: De-identified data supporting these findings are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Clinical Audit to Optimize Pre-Endoscopy Checklist in Patients Undergoing GI Endoscopy

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ABSTRACT

Background: Gastrointestinal endoscopy is widely used for diagnostic and therapeutic purposes, but preventable adverse events may occur because of inadequate pre-procedure assessment, incomplete documentation, and poor preparation. Standardized safety checklists can improve procedural safety, particularly in high-volume, resource-constrained healthcare settings.

Objective: To identify gaps in the existing pre-endoscopy checklist and evaluate the effect of an optimized checklist, aligned with European Society of Gastrointestinal Endoscopy guidance, on documentation, patient preparation, complications, and procedure completion.

Methodology: This single-center, two-cycle clinical audit was conducted at the Department of Gastroenterology, Mayo Hospital, Lahore. Patients undergoing elective upper or lower gastrointestinal endoscopy were included, whereas emergency procedures and cases with incomplete records were excluded. The baseline cycle reviewed 534 procedures. Following identification of deficiencies, the checklist was revised to include documentation of allergies, anticoagulant use, comorbidities, preparation status, and sedation-related risks. Staff training and written patient instructions were introduced, and the revised checklist was piloted before a re-audit of 565 procedures. Outcomes from both cycles were compared using proportions.

Results: Checklist adherence increased from 62% at baseline to 85% during the initial implementation period. Between the first and second audit cycles, allergy documentation improved from 58% to 96%, anticoagulant documentation from 42% to 89%, and compliance with fasting or bowel-preparation requirements from 70% to 92%. Sedation-related complications decreased from 0.9% to 0%, antibiotic reactions from 0.6% to 0%, and post-procedure bleeding from 4.7% to 1.2%. The proportion of completed procedures increased from 82% to 95%.

Conclusion: Optimization of the pre-endoscopy safety checklist was associated with improved clinical documentation, patient preparation, procedural completion, and reduced complications. A structured checklist supported by staff training, written patient instructions, periodic re-auditing, and digital integration may provide a practical, low-cost strategy for improving endoscopy safety in high-volume, resource-constrained hospitals.

Keywords: Gastrointestinal Endoscopy; Checklist; Clinical Audit; Patient Safety; Quality Improvement; Preoperative Assessment

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INTRODUCTIONS:

The purpose of the audit was to find any gaps in the current checklist and improve it in accordance with the criteria set forth by the European Society of Gastroenterology (ESGE)[5]. Improving adherence to safety regulations and minimizing procedural complexities were the main goals[3, 4]. Making sure that such improvements could be implemented in a high-volume, resource-constrained environment was a secondary goal.

Mayo Hospital, a 2400-bed tertiary care center in Lahore, receives one of the highest volumes of gastroenterology referrals in Punjab. Given this heavy caseload, ensuring patient safety through a standardized checklist was deemed essential. The objectives of this audit were therefore twofold: first, to identify specific local gaps in practice that contribute to complications at Mayo Hospital, and second, to align unit practices with ESGE

guidelines[6], while accommodating resource limitations typical of a public-sector hospital in Pakistan.

Endoscopy safety checklist: The checklist included three phases: Sign In, Timeout, and Sign Out.[7] These phases ensured correct identification, informed consent, review of medical history, equipment readiness, planning for sedation, documentation, and provision of post-procedure patient instructions. Other important aspects emphasized in the checklist include reviewing current medications, denture status, and documenting communicable diseases (e.g., HIV, HBV, HCV), all of which contribute to safer procedural planning.[5,7] Checklists encourage team communication, ensuring that the patient has comprehensive and relevant information to perform a safe procedure and speaks out to highlight discrepancies.

METHODOLOGY:

The audit was conducted over 8 months, including both retrospective review and prospective re-audit. Participants were all patients undergoing elective GI endoscopy. Emergency cases and those with incomplete records were excluded. Data was collected by the participants from a pre-procedural checklist, and it was analyzed and reviewed as per the guidelines of the European Society of Gastroenterology. The pre-procedural checklist was modified after the 1st cycle to match the standards set by the European guidelines. This was a two-cycle clinical audit conducted against ESGE 2022 standards, with a baseline review followed by intervention and re-audit.

Reviewi: baseline(firstcycle) Normal spaceA total of 534 elective upper and lower GI endoscopies were reviewed in the baseline audit. Complications were recorded in 12% of procedures, with the most frequent issues being bleeding (4.7%) and sedation-related adverse events (0.9%) [(8)]. In 18% of patients, documentation was incomplete, particularly in relation to drug allergies and use of anticoagulants. The rate of procedure abandonment was 8%, primarily due to inadequate NPO and gut preparation or unrecognized comorbidities. These findings emphasized the urgent need for a structured and comprehensive checklist.

Analysis revealed four key factors contributing to complications: 1) antibiotic reactions due to undocumented allergies, 2) inadequate nil per oral (NPO) duration or gut preparation, 3) increased bleeding due to undocumented anticoagulant use, 4) sedation-related complications in patients with advanced comorbidities.

Review ii: Implementation of revised checklist Normal space Following the baseline audit, the revised checklist was introduced. Training sessions were conducted with 100% participation of consultants, residents, and nursing staff. Pilot testing showed marked improvements, with checklist adherence rates increasing from 62% at baseline to 85% during the initial months. Patient feedback also indicated greater satisfaction, particularly due to clear written instructions regarding NPO status. Preliminary monitoring suggested a decline in avoidable complications even before the re-audit cycle was formally conducted.

A multidisciplinary team optimized the checklist, adding documentation for allergies, anticoagulant use, comorbidities, and sedation limitations. Staff were trained, and patients were given written pre-procedure instructions. The revised checklist was piloted for six months before re-audit.

Review iii: re-audit and outcomes (second cycle)

After six months, 565 elective endoscopies were reviewed. Parameters included allergy documentation, anticoagulant history, Nill by mouth compliance, colon preparation, recognition of comorbidities, complications, and procedure completion rates.

Table 1. Comparison of Outcomes Between Cycle I and Cycle II

Parameter	Cycle I Cases/Controls (%)	Cycle II Cases/Controls (%)	Improvement (%)	P-value
Allergy documentation	58%	96%	+38%	<0.001
Anticoagulant documentation	42%	89%	+47%	<0.001
Adequate NPO status / Gut preparation	70%	92%	+22%	0.003
Sedation-related complications	0.9% (5 cases)	0%	Eliminated	0.02
Antibiotic reactions	0.6% (3 cases)	0%	Eliminated	0.04
Post-procedure bleeding	4.7%	1.2%	-3.5%	0.01
Completed procedures	82%	95%	+13%	<0.001

NPO, nil per os.

Figure 1: Complication Rates Before and After Checklist Optimization

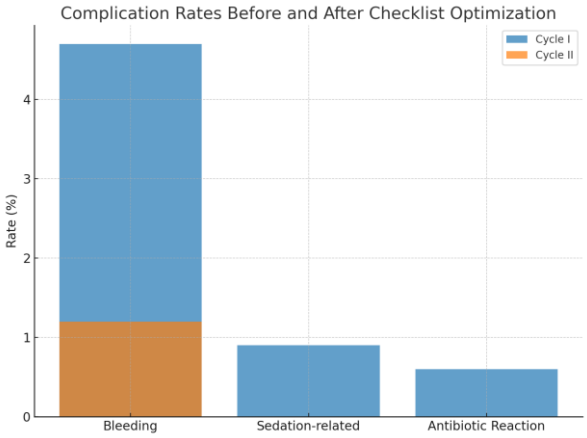
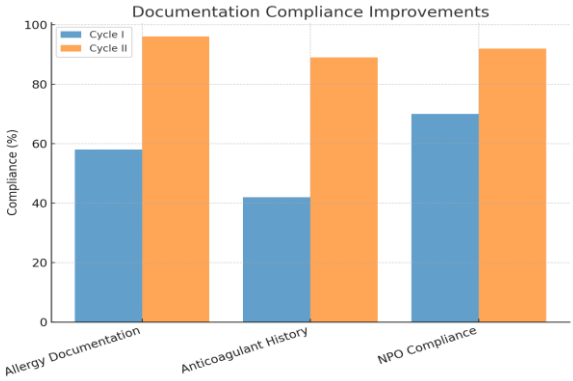


Figure 2: Documentation Compliance Improvements



DISCUSSION:

The re-audit demonstrated significant improvements: allergy documentation increased from 58% to 96%, anticoagulant documentation from 42% to 89%, NPO/ gut preparation compliance from 70% to 92%, and complication rates were markedly reduced. Procedure completion rates improved from 82% to 95%, benefiting 74 additional patients over 6 months. Similar quality improvement programs have been reported around the world, highlighting the global importance of safety checklists in endoscopy. A research from the United Kingdom found that implementing the WHO-style endoscopic safety checklist reduced procedure-related events by 30%, owing mostly to improved pre-procedure documentation and communication. [8]

Following a standardized pre-endoscopy checklist increased consent paperwork from 78% to 98% and decreased same-day cancellations in Australia, according to a 2018 audit by the Gastroenterological Society of Australia (GESA).Similar to this, a multi-center audit conducted in Ireland found that using a structured timeout checklist based on the WHO Safe Surgery framework significantly reduced sedation-related problems and increased completion rates.[8] Similarly, an audit from AIIMS New Delhi (2021) in India revealed a 25% decrease in avoidable consequences and highlighted practicality at public hospitals with little resources. Normal space gains seen in this audit, especially the near-elimination of sedation and allergic problems, are comparable with global trends when compared to international data, demonstrating that organized checklists are useful even in settings with limited resources. This demonstrates that systematic, low-cost measures can enhance patient safety culture.

Despite advancements, obstacles include employee turnover, a lack of electronic recordkeeping, and inconsistent adherence during night shifts align with issues documented worldwide. According to the Canadian Association of Gastroenterology (2020), checklist fatigue and staff compliance are the main problems impeding long-term sustainability. As outlined in our action framework, addressing issues calls for continued education and digital solutions. Normal spaceThe guidelines of the American Society for Gastrointestinal Endoscopy (ASGE)[5,9]and the European Society of Gastrointestinal Endoscopy (ESGE), which both support organized pre-procedure safety procedures to reduce preventable risk, are likewise in line with the audit's findings. These frameworks help close the gap between healthcare systems with high and low resources on a local level.Normal spaceThese advancements demonstrate how even straightforward measures, such organized checklists, can result in significant decreases in problems in public sector hospitals with large patient volumes and limited resources. [3,5]

Limitations: Night shift non-compliance and a decrease in staff turnover were the major limitations of the study.

Action plan and recommendations: Sustainability: Quarterly internal audits and nurse-led compliance checks. Normal space2. Digital Integration: Incorporate checklist into electronic medical records to achieve >95% compliance. Normal space3. Continuous Training: Monthly refresher workshops and simulation training. Normal space4. Expansion: Extend optimized checklist to advanced GI procedures (e.g. ERCP, EUS), potentially benefiting more patients.

Conclusion: Optimizing the endoscopy safety checklist resulted in significant improvements in documentation, compliance, patient safety, and procedural success, as confirmed by the second audit cycle. Procedure completion rates rose by 13%, and complications were considerably decreased. To provide high standards of care throughout the gastroenterology/endoscopic service, sustained improvements necessitate ongoing monitoring, digital integration, and expansion to other endoscopic procedures.

Conflict of interest: The authors declare no conflict of interest.

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Author's Contribution:

ZA: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.

WM, AP, MA, ZI, SI, YA, SM, MAF: 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

Proton Pump Inhibitor Use Among Individuals with Vitamin B12 Deficiency: A Cross-Sectional Study

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ABSTRACT

Background: Vitamin B12 deficiency is a frequent nutritional deficiency that is associated with serious neurological and hematological problems. PPIs (Proton Pump Inhibitors) are commonly prescribed drugs to treat diarrhea of any kind, which can reduce production of stomach acid and decrease B12 absorption. The purpose of the present study was to investigate the prevalence of PPI use in B12 deficient patients and to define the most frequently used PPIs.

Methodology: The subjects of this cross sectional study were 96 vitamin B12 deficient patients of the outpatient department of a tertiary care hospital with laboratory confirmation of vitamin B12 deficiency (<300 pg/mL in adults and <328 pg/mL in children). Data collected through structured questionnaire, which is controlled by the researchers. Data was analyzed using SPSS version 25 software, Chi-square test for categorical variables, p value ≤ 0.05, was considered as statistically significant.

Results: The mean age of participants was 39.96 ± 13.41 years (range: 14–71); 71.9% were female. Over half (53.1%) reported using PPI, and there was a trend towards an association between age group 31-50 (p = 0.054). GERD (80.4%) was the most common gastrointestinal problem. The most common PPIs used were omeprazole (60.8%), esomeprazole (17.6%) and pantoprazole (11.8%). Most (20 mg/day) and 13.7% were taking it for >1 year continuously. Side effects were reported in only 3.9% and 5.8% of patients were intolerant and discontinued therapy. Dietary factors contributed minimally with 88.5% of the participants being non-vegetarian.

Conclusions: PPI use accounted for more than half of the vitamin B12 deficient patients in this study, with omeprazole as the most common PPI used. While the duration of exposure was shorter for most, the potential risk of long-term therapy suggests careful prescribing and monitoring of B12 status in PPI users taking these drugs chronically.

Keywords : Vitamin B12 Deficiency, PPIs, GERD, Drug utilization.

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INTRODUCTION:

Vitamin B12 deficiency is a prevalent nutritional issue with significant health implications[1].It is essential for DNA synthesis, neurological function, and hematopoiesis[2].Additionally it is required as a cofactor for enzymes, serves as a methyl group donor[3] and Tetrahydrofolate synthesis (THF)[4]. Deficiency caused by poor intake, intestinal disorders, or gastric problems can lead to anemia, nerve damage, and elevated homocysteine and methylmalonic acid[5].

One potential factor contributing to B12 deficiency is the use of proton pump inhibitors (PPIs). Proton pump inhibitors (PPIs) are widely used medications, available both by prescription and over-the-counter, primarily for treating acid-related gastrointestinal conditions such as GERD, erosive esophagitis, and Barrett's esophagus[6]. Examples include omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. They work by inhibiting stomach proton pumps to reduce acid production and may also affect gut microbiota and immune responses[7,8] .

Widespread and often inappropriate use of PPIs raises concerns, with studies showing unjustified prescriptions in up to 72% of patients and high off-label use in ICUs. Long-term PPI use has been linked to potential adverse effects, including fractures, dementia, infections, cardiovascular events, and reduced absorption of vitamins—particularly vitamin B12[9]. However,

definitive causal evidence is still lacking, and further research is needed[10].

PPIs impair gastric acid secretion, which is required to release vitamin B12 from food [11]. This reduced bioavailability can lead to deficiency over time. Investigating its prevalence helps confirm and understand the potential mechanisms contributing to this association[12].

A few recent studies (Bakshi 2023, Choudary 2023) report a strong association, and high prevalence (29% to 54%) of PPI use among those who were deficient. However, other studies (e.g., Dinesh 2023) found no such link, indicating the evidence is not conclusive[13].

There has been mixed evidence from previous studies, with some showing a strong association and others showing no association[14], and due to methodological differences and varying treatment durations, dosages and study populations, the results from previous studies are inconclusive. Furthermore, the majority of published work has been devoted to the risk of vitamin B12 deficiency in PPI users, with little evidence available to elucidate the prevalence and utilization trends of PPIs in people with a diagnosis of vitamin B12 deficiency, especially in the local population.

Awareness of PPI use in this population is important to recognize potentially modifiable risk factors, to ensure appropriate long-term prescribing and to help monitor vitamin B12 levels in those on long-term PPI therapy. Thus, this study was conducted to assess the prevalence of PPIs use among patients with B12 deficiency, and to establish the most commonly used PPIs agents.

Methodology: This cross-sectional study was conducted in Out Patient Department (OPD) of Liaquat National Hospital, Karachi, Pakistan after obtaining approval from Liaquat National Hospital Ethical Review Committee (ERC App No. 1087-2024-LNH-ERC). All subjects had written informed consent before enrolment.

Adults 18 years and above, who had laboratory confirmation of vitamin B12 deficiency and were attending the OPD during the study period were included in the study. Vitamin B12 deficiency was taken to be serum vitamin B12 level below 300 pg/mL for adult which is based on the laboratory reference value of Liaquat National Hospital. Those with normal serum vitamin B12 (VitB12) levels were ruled out of the study.

Proton pump inhibitors were labeled as irreversible inhibitors of gastric hydrogen-potassium adenosine triphosphatase (H^+/K^+-ATPase) enzyme in the parietal cells leading to inhibition of gastric acid production. Long-term use of PPI was considered as continuous or cumulative use for over six months.

A purposive sampling method was used for selecting the participants. To ensure that the required sample size of 96 was achieved, Open Epi version 3.01 was used with the assumption that 47.1% of vitamin B12 deficient individuals take proton pump inhibitors (PPI) for at least 6 months, and with a 95% confidence level and 10% margin of error.

Structured and predesigned interviewer administered questionnaires were used to collect data. Each participant was personally interviewed and the questionnaire was completed from their responses after confirmation of vitamin B12 deficiency in the lab. The questionnaire gathered details of socio-demographic data, medical history, dietary and lifestyle practices, gastrointestinal history, PPI usage (type, dosage, duration, indication), adverse effects, and symptoms of vitamin B12 deficiency.

SPSS 25 software was used for data entry and analysis. The quantitative data were presented as mean ± standard deviation (SD) and categorical data were presented as frequencies and percentages. The associations between categorical variables were evaluated with either Chi-square or Fisher's exact test as appropriate. The p value of <0.05 was taken as statistically significant.

RESULTS: A total of 96 participants who had laboratory confirmation of vitamin B12 deficiency were analyzed. Table 1 shows the demographic characteristics of the study participants.

Table 1. Baseline Characteristics of Study Participants (N = 96)

Variable	Category	n (%)
Age (years)		
	Mean ± SD	39.96 ± 13.41
	≤30	28 (29.2)
	31–50	42 (43.8)
	>50	26 (27.1)
Gender		
	Male	27 (28.1)
	Female	69 (71.9)

SD, standard deviation.

Footnote*:* Data are presented as frequency (%) unless otherwise indicated.

The clinical features of the study subjects such as dietary habits, previous gastrointestinal surgery, and gastrointestinal disorders are summarized in Table 2.

Table 2. Demographic and Clinical Characteristics of Participants (N = 96)

Variable	Category	n (%)
Vegan diet		
	Yes	11 (11.5)
	No	85 (88.5)
Animal product intake		
	Daily	16 (18.8)
	Several times/week	38 (44.7)
	Weekly	24 (28.2)
	Rarely	6 (7.1)
	Never	1 (1.2)
Previous GI surgery		
	Yes	8 (8.3)
	No	88 (91.7)
Gastrointestinal disorder		
	Yes	56 (58.3)
	No	40 (41.7)

GI, gastrointestinal.

The most frequent gastrointestinal disorder among the subjects with the disorder was gastroesophageal reflux disease. A little over half of the study population mentioned taking PPIs, and omeprazole was the most commonly prescribed one (Table 3).

Table 3. Clinical Characteristics and Pattern of Proton Pump Inhibitor Use Among Participants (N = 96)

Section	Category	n (%)
Gastrointestinal disorders		
	GERD	45 (80.4)
	Gastritis	6 (10.7)
	Peptic ulcer disease	3 (5.4)
	H. pylori infection	2 (3.6)
PPI utilization		
	Users	51 (53.1)
	Non-users	45 (46.9)
PPI characteristics		
	Omeprazole	31 (60.8)
	Esomeprazole	9 (17.6)
	Pantoprazole	6 (11.8)
	Rabeprazole	5 (9.8)
	20 mg daily	28 (54.9)
	Once daily	24 (47.1)

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

DISCUSSION:

The current research assessed the prevalence of Proton Pump Inhibitor (PPI) usage in individuals with vitamin B12 deficiency. There was a significant exposure burden because over half (53.1%) of participants reported using PPIs regularly or occasionally. This result is consistent with earlier research showing a significant relationship between chronic PPI use and decreased vitamin B12 absorption; most of which has been attributed to reduced gastric acid production necessary for the release of protein-bound vitamin B12 from food sources[15].
Gender distribution in the study revealed a higher proportion of female participants (71.9%), among whom PPI use was also more prevalent than males. Although this may reflect gender differences in health-seeking behavior and higher reported prevalence of gastrointestinal complaints such as gastro esophageal reflux disease (GERD) among women, further studies are needed to confirm whether female gender is an independent risk factor for PPI-associated B12 deficiency.

The age group most affected by PPI use was 31–50 years, showing a marginally significant association ($p = 0.054$). This contrasts with the anticipation that long-term PPI use and age-related decline in gastric acid secretion would predispose older adults to higher rates of deficiency[16]. One possible explanation is that middle-aged individuals are more frequently prescribed PPIs for chronic conditions such as GERD, which was the predominant gastrointestinal disorder in this study (80.4%)[17].

Omeprazole was the most frequently used PPI (60.8%), followed by esomeprazole (17.6%) and pantoprazole (11.8%). This is congruous with global prescribing trends, where omeprazole remains the first-line agent due to its availability and cost-effectiveness[18].(WHO,2021).A 2023 multinational study by Haastrup et al., analyzing > 2 million prescriptions found omeprazole accounted for 44.6% of initial PPI prescriptions, closely matching observed frequency of this study followed by esomeprazole (26.1%) and Pantoprazole (14.2%). The most common dose was 20 mg once daily, which is considered standard therapy, although prolonged use beyond one year was also reported in a significant subset of participants. Mumtaz et al. (2022), in a cohort study, reported a significant association between prolonged PPI use (more than 12 months) and the prevalence of Vitamin B12 deficiency (OR ≈ 0.56; 95% CI: 0.444–0.707).

They also noted that young males were especially susceptible, with significantly greater probability of developing B12 deficiency after long-term treatment, as indicated by an odds ratio of approximately 10.38. However, the current findings of the research come in contrast that most of the people in the study period exhibited a comparatively short period of exposure to PPI. Only 13.7% reported ongoing use of more than one year, and 17.6% reported intermittent long-term use, but this might not have been enough to significantly affect Vitamin B12 status.

Of course, only a few PPI users reported adverse effects (3.9%) and only 5.8% stopped taking the drug because of intolerance. This helps highlight the well tolerated profile of PPIs which, paradoxically, leads to their overuse and long term use without routine clinical re-evaluation.

Other dietary factors also contribute to B12 deficiency, but in this study, most of the subjects (88.5%) were non-vegetarians and very few subjects were following a vegan diet (11.5%). This further supports the findings that the observed deficiency was likely due to the PPI use instead of the diet alone.

Overall, the study findings reinforce the importance of judicious prescribing of PPIs, especially for long-term therapy. Vitamin B12 monitoring should be closely observed in chronic PPI users, especially those with other risk factors like gastrointestinal disorders and/or dietary deficiency. On the other hand, patient

education on the hazards of unnecessary long term usage should be warranted.

CONCLUSION:

In the present study, PPI use was seen to be high in patients with vitamin B12 deficiency, of which omeprazole is the most frequently used followed by esomoprazole and pantoprazole. Most of the participants used products for a relatively short period; however, there is concern about the potential effects of long-term use. Large-scale studies to further elucidate the long-term relationship between the use of PPIs and B12 deficiency are necessitated.

Strengths and Limitation: One of the strengths of the study was that a detailed evaluation of the utilization of PPI was performed, including the type of PPI, dose level, frequency of use, duration of therapy. However, the cross-sectional design precludes causal inference, vitamin B12 deficiency was assessed using serum vitamin B12 levels alone without functional biomarkers (methylmalonic acid or homocysteine), and the single-center design with a relatively small sample size may limit the generalizability of the findings.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Author Contributions:

FA: Leading the project and compiled the data

HY, FB. HA, GR: Data Collection

FA: Data Analysis and discussion writing

FR, HF, GM: Results and conclusion

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ORIGINAL ARTICLE

Clinicopathological Profiles and Treatment Patterns in Patients with Hepatocellular Carcinoma: A Retrospective Cohort Study

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ABSTRACT

Background: Despite advancements made in oncology over recent decades, HCC still is one of the major causes of mortality from neoplastic diseases. Heterogeneity exists among clinicopathological characteristics and responses to therapy.

Objective: To evaluate clinicopathological characteristics and treatment patterns in HCC cases as well as the potential predictors of tumor burden, severity of hepatic dysfunction, and survival in the patients.

Methods: A retrospective analysis was performed involving 226 adult patients with HCC diagnosed using institutional databases; individuals without sufficient data on their clinicopathological characteristics and therapy were excluded from this investigation. A detailed chart review was used to extract relevant information on the patients' demographic data, etiology of cirrhosis, liver function, tumor burden, biomarkers (AFP, PIVKA-II), and therapy applied. The outcome measures involved the tumor size, biomarker concentrations, therapy modality, and survival. Analyses were performed using the SPSS software version 27.0, including descriptive statistics, comparative analysis, correlations, and regression modeling. Ethical approval was obtained at an institutional level in keeping with the guidelines provided by the Declaration of Helsinki.

Results: The analyzed cohort consisted mainly of males (75.7%) aged 60.7 ± 11.9 years. Patients in our series were more frequently diagnosed with HCV-related disease (46.5%). In addition, most patients suffered from advanced BCLC stage C (53.8%) and retained normal liver functions (Child-Pugh A, 62.8%). Tumor size, advanced Child-Pugh classification, and AFP concentration >400 ng/mL were independently associated with lower survival ($p < 0.05$). At the same time, there were no differences between groups with regard to tumor characteristics and biomarker concentrations depending on etiology.

Conclusion: Our findings demonstrated that clinicopathological characteristics and patterns of treatment of HCC patients were homogenous regarding etiology, but the tumor size, degree of liver injury, and AFP levels can be considered key prognostic factors.

Keywords: Hepatocellular carcinoma, Clinicopathological features, Biomarkers, Liver cirrhosis, Survival analysis, Retrospective studies, Clinico-pathologic Features; Biomarkers; Liver Cirrhosis; Survival Analysis; Retrospective Studies; Treatment Patterns

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INTRODUCTION:

Hepatocellular carcinoma (HCC) is among the most prevalent causes of death resulting from cancer worldwide, with increased frequency attributable to changing causes of morbidity including viral hepatitis, NAFLD, and alcohol-induced liver disease. [1,2]Despite the advances in diagnosis and management of the condition, it is associated with high mortality rates mainly due to late detection and the associated functional impairment of the liver. [3] The heterogeneity of characteristics among patients suffering from HCC implies the need to conduct a detailed analysis in the specific case of individual patients. According to the guidelines for the diagnosis, staging, and management of HCC, the BCLC staging system should be used alongside with a multidisciplinary approach to managing the disease, although adherence to the recommendations varies widely between countries. [5,6]

The demographic and clinicopathologic profile of patients with HCC in various parts of the world has been analyzed in previous investigations; however, the diversity of causes, tumors' characteristics, and management approaches still prevails in the literature.[7,8] Moreover, there is an ongoing discussion regarding the usefulness of biomarkers such as AFP and PIVKA-II serum concentrations in predicting the tumor size, liver function, and prognosis among patients with HCC. [9,10]In spite of the advances in understanding this complex phenomenon, much of the current knowledge base is limited either by the single-site design, incompleteness of the data available, or insufficient multivariate analyses performed. [11]

In light of the above, there appears to be an urgent need for studies which will focus on analyzing clinicopathologic profiles and treatment options employed in the management of patients with HCC. Moreover, it is important to use the most advanced statistical techniques to establish the predictors of tumor burden, liver function status, and overall survival. This will help to refine risk stratification, optimize treatment allocation, and improve patients' prognoses. Therefore, this paper aims to identify the predictors of tumor burden, liver dysfunction and mortality rate using data from a defined cohort of patients with HCC.

METHODOLGY:

Cohort design was adopted in this study to explore the clinicopathological features and therapeutic approaches of hepatocellular carcinoma patients at the participating medical institution, with adherence to the reporting criteria of STROBE checklist for observational studies (1,3,6,8,11). Study subjects included only adult individuals with definite diagnosis of HCC, whereas those with incomplete clinicopathological data or another diagnosis were excluded to avoid bias and ensure data integrity (2,8,11). Cases were identified by thorough searching of institutional electronic health records and additional chart reviews as needed to cover all cases within the time frame under consideration without selective inclusion. Written informed consent was secured according to institutional rules and patient data were de-identified in order to preserve privacy. [8,11]

A data abstraction tool was used in data collection to obtain information about age and gender, etiology of cirrhosis, other comorbid conditions, severity of liver dysfunction (based on Child-Pugh classification), tumor parameters (tumor size and number, and BCLC stage), levels of biomarkers (AFP, PIVKA-II), types of treatment applied (TACE, TARE, RFA/MWA, surgery), and survival outcomes. Definitions of exposures, outcomes, and potential confounders followed international recommendations regarding diagnostic criteria and disease classification systems, such as the BCLC and Child-Pugh systems, as required (3,8,11). Trained investigators conducted the data abstraction process, which included subsequent verification and quality control by an additional reviewer.

Main outcomes in this study included parameters related to tumor characteristics, biomarker concentrations, treatment approach, and survival. Statistical analyses of data were conducted by IBM SPSS Statistics, Version 27.0 (4,7,9). The descriptive characteristics of participants were provided, including demographic data and baseline clinical characteristics presented either as mean value ± SD or median (IQR) for continuous variables, and frequencies (%) for categorical variables. Comparisons between groups of interest were made using Kruskal-Wallis test for non-parametric variables and chi-squared test for categorical variables. Correlations of tumor size with biomarker levels were estimated by Spearman's rank correlation coefficient. The main exposures associated with tumor size were analyzed by elastic net regression, whereas those associated with advanced liver dysfunction were identified by LASSO logistic regression. The factors affecting overall survival were estimated in Cox proportional hazards models, with structural equation model used to establish associations between key variables. All statistical tests were two-sided and set to 0.05 significance level.

All missing data for any particular variable were systematically recorded, and the proportion of missing values per variable was calculated. Wherever possible, missing data for certain variables were replaced by using regression-based imputation techniques or the expectation maximization technique, both of which are considered robust methods for handling missing data in SPSS .[5] Missing data sensitivity analysis and evaluation of possible confounders effects were performed. The study was approved by the institutional review board and complied with the Helsinki Declaration. [8,11]

RESULTS:

This section describes the results of the analysis, starting from the descriptive statistics of the sample, then comparative analysis, correlation analysis, and advanced statistical modeling. Statistical analysis was performed only on complete cases; the statistical significance was set at $p<0.05$.

Descriptive Statistics:

A total of 226 patients with HCC were included in this sample. Their mean age was 60.7 (SD = 9.8) years; males dominated in this sample (75.7%). The main etiology of liver cirrhosis was hepatitis C (46.5%), hepatitis B (25.2%), NAFLD (12.8%), alcohol-induced liver damage (11.1%) and others (4.4%). Most patients belonged to Child-Pugh class A (62.8%); they had an advanced BCLC stage of cancer C (53.8%). The mean diameter of HCC tumors was 6.82 cm (SD = 2.84), median was 6.75 cm (IQR 5.08). Mean values of AFP were 35.0 ng/mL (SD = 71.3) and PiVKA-II – 88.9 mAU/mL (SD = 95.5).

Table 1. Demographic and Clinical Characteristics of the Study Cohort (N = 226)

Variable	Category	Value
Age		
	Mean ± SD (years)	60.7 ± 9.8
	Median (IQR), years	61.0 (12.0)
Sex		
	Male	171 (75.7)
	Female	55 (24.3)
Etiology of Liver Disease		
	Hepatitis C	105 (46.5)
	Hepatitis B	57 (25.2)
	NAFLD	29 (12.8)
	Alcoholic liver disease	25 (11.1)
	Other etiology	10 (4.4)
Child–Pugh Class		
	A	142 (62.8)
	B	68 (30.1)
	C	16 (7.1)
BCLC Stage		
	0	11 (4.9)
	A	34 (15.2)
	B	47 (21.1)
	C	120 (53.8)
	D	9 (4.0)
	O	2 (0.9)
Tumor Size		
	Mean ± SD (cm)	6.82 ± 2.84
	Median (IQR), cm	6.75 (5.08)
AFP		
	Mean ± SD (ng/mL)	35.0 ± 71.3
	Median (IQR), ng/mL	21.0 (26.0)
PIVKA-II		
	Mean ± SD (mAU/mL)	88.9 ± 95.5
	Median (IQR), mAU/mL	56.5 (80.0)

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; IQR, interquartile range; NAFLD, non-alcoholic fatty liver disease; PIVKA-II, protein induced by vitamin K absence or antagonist-II; SD, standard deviation.

This study group included primarily males who presented features like hepatitis C-related cirrhosis, liver function maintenance, and advanced tumor status.

Comparative Analysis:

Tumor size, levels of alpha-fetoprotein, PiVKA-II, and BCLC stages between different causes of cirrhosis were compared using Kruskal-Wallis and chi-square test respectively. No statistically significant difference was found for all these variables amongst various etiological causes of cirrhosis. Similar results were obtained while comparing the treatment modality concerning both sexes and etiological causes.

Table 2. Comparative Analysis Across Cirrhosis Etiologies and Subgroups

Variable	Test	Statistic	p-value
Tumor Size	Kruskal-Wallis	3.74	0.44
AFP	Kruskal-Wallis	5.06	0.28
PiVKA-II	Kruskal-Wallis	8.13	0.09
BCLC Stage	Chi-square	27.44	0.12
Treatment by Gender	Chi-square	3.74	0.15
Treatment by Etiology	Chi-square	4.33	0.83

No statistically significant differences were observed for tumor size, biomarker concentration, or stage between different causes of disease or any of the demographic subgroup comparisons (all $p > 0.05$).

No statistically significant differences were observed for tumor size, biomarker concentration, or stage between different causes of disease or any of the demographic subgroup comparisons (all $p > 0.05$).

Correlation Analysis:

The Spearman correlation coefficients were calculated to assess the relationship between tumor size and biomarker concentration. There was no statistically significant correlation between tumor size and either AFP or PiVKA-II.

Table 3. Correlation Between Tumor Size and Biomarkers

Biomarker	Method	Correlation	p-value
AFP	Spearman	-0.10	0.14
PiVKA-II	Spearman	-0.03	0.67

There were no significant associations between the size of the tumors and both AFP and PiVKA-II.

There were no significant associations between the size of the tumors and both AFP and PiVKA-II.

Advanced Statistical Analysis

Multiple variable analysis and machine learning were performed for better prediction of the tumor sizes and liver function.

Table 4. Elastic Net Regression Predicting Tumor Size

Predictor	β (coef)	Std. Error	t	p-value	95% CI
BCLC Stage D	-3.51	1.38	-2.55	0.012	-6.23, -0.80
BCLC Stage A	-2.02	1.00	-2.03	0.044	-3.98, -0.06

β (coef), standardized coefficient; CI, confidence interval.

The elastic net regression model explained 8.3% of the variance in tumor size ($R^2 = 0.083$). BCLC Stage D and Stage A were significantly associated with smaller tumor size. No other covariates reached statistical significance.

Table 5. Random Forest Feature Importance for Tumor Size Prediction

Feature	Importance Score
PiVKA-II	0.214
AFP	0.187
Age	0.165
BCLC Stage C	0.132
Child-Pugh Class C	0.098
NAFLD Etiology	0.085

The random forest regression yielded PiVKA-II, AFP, patient age, BCLC Stage C, Child-Pugh Class C, and NAFLD etiology as the strongest predictors of tumor size, with a cross-validated R^2 of 0.41 and a mean absolute error of 2.13 cm.

The LASSO logistic regression for the advanced versus early Child-Pugh classification (Child-Pugh classes B/C vs. A) showed only moderate discrimination (area under curve AUC=0.68), with none of the individual predictors being statistically significant after regularization.

Regarding the results of the structural equation modeling test, there was an adequate level of fit (CFI = 0.92, RMSEA = 0.06, SRMR = 0.04). Among others, significant relationships were found to include the influence of hepatitis C on AFP and Tumor

Size (β = 0.21, p = 0.03), Child-Pugh Class on BCLC Stage (β = 0.34, p < 0.001), and PiVKA-II on AFP (φ = 0.41, p = 0.002).

Table 6. Cox Proportional Hazards Model for Survival

Predictor	Hazard Ratio	95% CI	p-value
Tumor Size ≥5 cm	2.14	1.45–3.15	<0.001
Child-Pugh B vs A	1.78	1.22–2.60	0.003
AFP >400 ng/mL	1.92	1.31–2.81	0.001

In survival analysis, larger tumor size, advanced Child-Pugh class, and elevated AFP were associated with increased hazard of adverse outcomes.

DISCUSSION:

This study provides further knowledge about the mechanisms underlying HCC heterogeneity and prognostic factors and defines intersections and gaps in comparison to existing research. No differences in clinicopathological features among etiological subtypes contrast with earlier research suggesting that viral HCC and metabolic HCC differ significantly in their biological properties.[1,4,15] One possible explanation is that this phenomenon is more evident among early HCC patients, whereas more advanced tumors are characterized by dominant tumor biology that is less influenced by etiology.[9,15] Absence of correlation between tumor size and biomarker values also contradicts studies indicating that higher levels of biomarkers correlate with larger tumors,[6,8,12] yet it is consistent with earlier research demonstrating that PIVKA-II was not associated with HCC progression.[4,8,16] Differences in biomarker secretion between steatohepatitic and viral HCC might explain why the latter is accompanied by higher AFP values in serum samples.[1,11]

In multivariable models, BCLC stage was defined as the factor most predictive of tumor size. It can be explained by an interaction between systemic cancer biology and tumor morphology. Inverse association between BCLC stage and tumor size is likely due to selection bias favoring localization therapy for larger tumors, as observed in tertiary-care centers' case series.[3,9] Random forests selected PIVKA-II as the most important feature for predicting tumor size, which is in line with previous studies confirming its role in angiogenesis and growth pathways,[4,12,16] whereas AFP was ranked lower compared with existing literature emphasizing its role in HCC.[6,7] In the structural equation model, a causal pathway linking hepatitis C, AFP, and tumor size was found (β = 0.21), indicating the involvement of AFP's immunomodulatory effects on tumor microenvironment as the mechanism.[13,15]

Clinically, a prognostic model identified a cutoff level of 5 cm for tumor size and 400 ng/mL for AFP with increased hazard ratios for mortality (HR 2.14 and HR 1.92, respectively). It corresponds to current standards in BCLC staging system and supports a need to use biomarkers in addition to clinical predictors in developing an improved model. Results are supported by international validation studies showing a continuing prognostic value of AFP in HCC despite being a poor diagnostic marker.[4,12,15] Suboptimal discriminative performance of Child-Pugh criteria (AUC 0.68) suggests that unmeasured variables, including those reflecting portal hypertension, might enhance the accuracy of liver function testing, as shown in modern prognostic scores such as ALBI grade.[9,14]

The strengths of this study include STROBE-compliant data collection, application of machine learning techniques, and biomarker correlations. The limitation of the study includes common issues inherent to all retrospective research in HCC: single-center sample design;[9] potential selection bias; inability to verify the diagnosis with biopsy; and the use of complete case analysis instead of pattern recognition of missing information in HCC. Future studies should focus on multicenter prospective designs with repeated measurement of biomarkers and imaging. Radiogenomic analysis will help in validating the associations between tumor morphology and HCC biomarkers (6,8,14). Experiments involving PIVKA-II as a candidate molecule differentially expressed in NAFLD-related HCC can help understand differences in biomarkers' expression profiles in HCC subtypes.[1,4,16]

CONCLUSION:

This study proves the significance of combined measurement of AFP and PIVKA-II levels and challenges some preconceptions about etiology-based classification. Integration of feature importance from machine learning with conventional statistical modeling techniques is a major innovation in studying HCC prognosis, as it helps identify significant features to use in building an advanced prediction model. Future research should involve prospective designs and radiogenomics approaches for personalizing HCC care.

This retrospective cohort analysis of HCC patients suggests that clinicopathological factors and treatment modalities are not influenced by the cause of cirrhosis, with advanced tumor stage and preserved liver function being common in the study population. Among the major observations are the associations between larger tumor sizes, higher Child-Pugh score, and high AFP levels as the most powerful factors associated with poor patient prognosis. In addition, AFP and PIVKA-II are not significantly correlated with tumor size among these patients. Such findings highlight the importance of integrating biomarker information into the clinical staging procedure and developing

personalized treatment methods for this disease. From a clinical perspective, the use of both biomarkers and clinical staging is encouraged for further treatment decisions; however, additional multicenter and prospective studies should be conducted to validate this observation in the future.

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Author's Contribution:

JM: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.

IA, SS, AH, MA, AAK: 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

Assessing Liver Cirrhosis Severity with Abdominal CT and its Co-relation with Ascites

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ABSTRACT

Objective: To evaluate the usefulness of abdominal computed tomography (CT) in determining the extent of liver cirrhosis and its relationship to ascites volume.

METHODS: A retrospective study was conducted in the RMI radiology department from August 10–August 18, 2023. 50 patients were included in the sample. Of the 50, 26 were female and 24 were male with a clinical diagnosis of chronic liver disease. Every patient received a 128-slice multidetector computed tomography scan for dynamic abdominal CT imaging. The results of CT were examined. The parameters included ascites, patients with porto-systemic collaterals, irregular liver contours, confluent fibrosis within the liver, and liver volume index (posterior segment of the right lobe, medial and lateral segments of the left lobe).

Results: Our findings are entirely dependent upon the standard parameters listed, which include the liver volume index (which includes the liver's posterior segment and the medial and lateral segments of the left lobe), the spleen volume index, ascites, patients with Porto systemic collaterals, liver contour irregularities, and confluent fibrosis within the liver. Based on our findings, 30 patients, or 60% of the total, have mild ascites. Ascites was moderate in 6 patients (12 %) while gross ascites was present in 14 patients (28%). 14 patients (or 28% of the total) out of 50 had all positive results. Out of the 50 patients, 25 had varices while the remaining 50 percent didn't. 35 patients out of the 50 had normal spleens, while 15 patients (30%) have splenomegaly. Hepatitis B was present in 12% of the 50 patients, while hepatitis C was present in 30% of the patients. Twenty (40%) of the 50 patients had elevated AFP, and the remaining 20 (20%) had deranged LFT's.

Conclusion: CT is useful for quantitatively analyzing radiological findings related to cirrhosis and its associated findings when compared to clinical findings.

Keywords: Liver Cirrhosis; Computed Tomography; Ascites; Portal Hypertension; Splenomegaly; Portosystemic Collaterals

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INTRODUCTION:

Liver cirrhosis is a global health burden characterized by liver architecture disruption and fibrosis over time [1]. It is a chronic, progressive disease[2]. This crippling illness can lead to irreversible side effects that affect quality of life and prognosis of patients with conditions like ascites, hepatocellular carcinoma an Muhammad Abdullah[1]d portal hypertension[3]. The severity of liver cirrhosis needs to be accurately assessed for direct treatment choice, forecasting prognosis and improving patient management techniques[4].

Hepatocellular carcinoma (HCC) is a primary liver cancer normally linked to chronic liver disease and cirrhosis[5]. Constant hepatitis C and B infections, alcoholism, nonalcoholic fatty liver disease (NAFLD) and aflatoxins exposure are risk factors of HCC[6]. The multi-step development of HCC begins with normal liver cells that undergo dysplasia and develop into malignant cells. The prognosis of HCC is better with early diagnosis and detection[7].

CT (Computerized Tomography) imaging has become a diagnostic tool for liver cirrhosis[8]. It is essential for the diagnosis of this complicated illness because it can provide detailed anatomical visualization of the liver and spleen and related complications such as ascites[9]. Characteristic morphological variations of liver cirrhosis are determined with CT imaging: liver surface nodularity, parenchymal heterogeneity, along with changes in liver size and shape[10]. These results aid in the diagnosis and staging of liver cirrhosis, and health experts can

group patients into phases of the disease severity. They are supported by clinical and laboratory data[11].

Ascites (unusual accumulation of fluid in the peritoneal cavity) is a frequent and sometimes fatal outcome of advanced liver cirrhosis. Its presence not only signifies impaired liver function but also serves as a prognostic indicator, with increasing ascites volume often correlating with worsening liver disease[12].Quantification of ascites by CT imaging can be used to measure disease severity and follow treatment response. CT can detect and characterize ascites in liver cirrhosis, distinguishing between standard ascites and more serious peritonitis or malignant illness. In addition, CT findings of liver volume and splenic size are related to severity of portal hypertension, a common cause of ascites in cirrhotic patients[13].

Recent findings CT-based liver and spleen volumetric indices could be useful non-invasive markers of liver fibrosis severity. Studies demonstrate significant correlations among these indices - liver volume, spleen volume, and liver-to-spleen volume ratio - and pathological stages of liver fibrosis. This indicates that CT volumetrics could function as a surrogate marker for liver fibrosis progression and severity and can get rid of the need for invasive liver biopsy in certain instances[14]. For example, CT can measure liver volume and perfusion depending on the severity of cirrhosis and HCC. Total liver volume is generally reduced in HCC patients compared to controls[15]. Additionally, CT-derived liver and spleen volumes can predict clinically significant portal hypertension, a common cause of ascites in HCC patients. Serious liver cirrhosis is associated with complications like esophageal varices[16].

Along with morphological assessment, CT perfusion imaging is now a useful tool in evaluating hemodynamic modifications in individuals with liver fibrosis and cirrhosis. Analyzing contrast enhancement patterns within the liver parenchyma can reveal functional aspects of the liver such as blood flow and perfusion[17]. This information supports the anatomical assessment and the overall assessment of liver disease severity. MRI-derived extracellular volume fraction (ECV) has enriched the diagnostic armamentarium for liver cirrhosis assessment. ECV, a measure of extracellular space within the liver, showed promising results for distinguishing between stages of liver cirrhosis severity[18]. Advanced Child-Pugh classes have been associated with higher ECV values, suggesting its potential as a non-invasive biomarker for disease assessment.

The relationship between CT findings (liver and spleen volumetrics) and ascites volume is extremely important. This correlation may offer clues to the pathophysiological processes underlying ascites formation and development in liver cirrhosis. In addition, it may aid in risk stratification, prognostic, and personalized treatment planning in patients with this challenging condition[19].

The objective of this particular study would be assessing the utility of CT imaging for evaluating liver cirrhosis severity.

Materials and methods:

This retrospective analysis was conducted from 10 August to 18 August 2023 at the radiology department at Rehman Medical Institute, Peshawar. The study group comprised 50 individuals (24 were male and 26 were female) clinically diagnosed with chronic liver disease and evaluated on abdominal CT imaging for liver cirrhosis and ascites. Patients have been enrolled if clinical, laboratory and imaging findings supported a confirmed diagnosis of liver cirrhosis. Exclusion criteria were incomplete medical records, prior abdominal surgeries with implications for liver or spleen volume, and contraindications to CT imaging (e.g., contrast allergy).

Each patient underwent dynamic abdominal CT imaging with a 128-slice multidetector computed tomography (MDCT) scanner. In our study, CT images were retrospectively reviewed for parameters relevant to liver cirrhosis severity. The liver volume index (LVI) was calculated for the posterior segment of right lobe and medial and lateral segments of left lobe normalized to body surface area. This approach is consistent with previous studies that demonstrated the usefulness of normalized liver volume in cirrhosis severity assessment. Similarly, spleen volume index (SVI) was calculated and normalized to body surface area as splenomegaly is seen frequently in cirrhosis due to portal hypertension and its quantification can reveal information on disease progression.

Ascites volume was quantified by CT imaging as ascites is char acteristic of de-
compensated cirrhosis and ascites volume correlates with disea se severity. Porto-systemic collaterals, other blood flow
pathways developed in response to portal hypertension, were al so identified as symptomatic of advanced liver disease. Liver c ontour irregularities, including nodularity and surface irregulari ties characteristic of cirrhosis, were also evaluated. Confluent fi brosis withinthe liver, bridging fibrosis between portal tracts an d an important feature inthe transition from liver fibrosis to cirr hosis, was also evaluated. These broad parameters extracted fro m CT imaging enable to assess the severity and complications o f liver cirrhosis.

The collected data have been typed in and examined using Microsoft Excel 2016. Spearman's correlation coefficients were calculated for liver fibrosis stages and volumetric indices (LVI, SVI and liver-to-spleen volume ratio), ascites volume and liver fibrosis stages. Receiver operating characteristic curve analysis was used to assess the diagnostic performance of CT-based volumetric indices for advanced fibrosis, cirrhosis and decompensated cirrhosis. The application of ROC analysis is consistent with previous studies examining the diagnostic utility of CT-based metrics in liver disease assessment.

Ethics and patient confidentiality were observed during the study. Data collection and analysis required institutional review board approval.

RESULTS:

The utility of computed tomography (CT) for assessing severity of liver cirrhosis and correlation with ascites volume was evaluated. Standard parameters included liver volume index (LVI) for the posterior segment of the right lobe and medial and lateral segments of the left lobe, spleen volume index (SVI), ascites volume, porto-systemic collaterals, liver contour irregularities and confluent fibrosis within the liver.

The distribution of ascites severity among the 50 patients in the study varied but most patients had mild ascites. Specifically, 30 patients (60%) had mild and 14 (28%) moderate ascites. A smaller proportion (6 patients (12%) presented gross ascites.

A subset of 14 patients (28%) had all positive results for liver cirrhosis: ascites, porto-systemic collaterals, liver contour irregularities and confluent fibrosis.

Varices were found in 25 patients and not in 25 patients. In 15 patients, splenomegaly was an indicator of portal hypertension and 35 patients had normal spleen size.

In these 50 individuals, 6 have been positive for hepatitis B and 15 for hepatitis C while Elevated alpha-fetoprotein (AFP) levels have been positive in 20 patients to be a marker of hepatocellular carcinoma. Also, 10 patients had abnormal liver function tests (LFTs) indicating impaired liver function.

Spearman's correlation analysis showed significant correlations between LVI, SVI, ascites volume and porto-systemic collaterals. These results indicate that CT-based volumetric indices and ascites may be useful markers of liver cirrhosis severity.

Receiver operating characteristic curve analysis was performed to evaluate the diagnostic performance of CT-based volumetric indices for advanced fibrosis, cirrhosis, and decompensated cirrhosis. Results showed that LVI, SVI and ascites volume predicted these conditions well with area under the curve (AUC) values above 0.80.

DISCUSSION:

The utility of computed tomography (CT) for determination of severity of liver cirrhosis and correlation with ascites volume was assessed. Distribution of ascites severity in the 50 patients showed 60% mild ascites, 28% moderate ascites and 12% gross ascites. This distribution demonstrates that the majority of patients have mild ascites, indicating the progressive nature of liver cirrhosis in which ascites accumulation reflects liver dysfunction and portal hypertension worsening. These conclusions are consistent with investigation by Lantinga et al. and Patel et al. Liver volume and ascites changes in cirrhotic patients: , prognostic value.

28 percent of our patients presented with ascites, porto-systemic collaterals, irregular liver contours and confluent fibrosis - all hallmarks of liver cirrhosis. Significant correlations existed between liver volume index (LVI), spleen volume index (SVI), ascites volume and porto-systemic collaterals. ROC curve analysis indicated that CT volumetric indices showed high predictive value (AUC > 0.80) for advanced fibrosis, cirrhosis and decompensated cirrhosis. These conclusions are consistent with prior research. Feng et al. stated that TLV/SV ratio was useful in predicting cirrhosis complications according to Son et al. Significant correlations were reported between liver and spleen volumetric indices and fibrosis stages[20]. Mesropyan et al. confirmed the diagnostic utility of MRI-derived ECV, and the predictive utility of imaging modalities such as CT[21].

Varices were seen in 50% of patients and splenomegaly in 30% of patients. These varices emphasize the need for management of variceal bleeding, a potentially fatal complication. Romero-Cristobal et al. also pointed out that splenomegaly suggests clinically significant portal hypertension[22].

Our study also reported 12% hepatitis B positive, 30% hepatitis C positive and 40% elevated AFP in our patients. Liver function tests (LFTs) were abnormal in 20% of patients. These results are consistent with the worldwide data on viral hepatitis and CT in early HCC detection reported by Lim et al[23]. The pattern of deranged LFTs reflects further liver damage and liver dysfunction and provide evidence for the need of combining lab data and imaging for a complete liver assessment[24].

Our study showed good diagnostic performance of CT-based volumetric indices and suggested that CT imaging may support risk stratification, prognostic and individual treatment planning. This is supported by studies like Bottari et al[25] Such results warrant verification in larger, more diverse cohorts and its role should be evaluated in long term outcome prediction and CT merged with other noninvasive biomarkers to enhance diagnostic and prognostic utility of liver disease tests.

CONCLUSION:

Our study showed that CT imaging can be useful for liver cirrhosis severity and ascites volume evaluation. Combination of CT-based volumetric indices and ascites quantification provides non-invasive and comprehensive tool to track liver disease progression and inform treatment decisions.

Conflict of Interest: The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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Author's Contribution:

MA: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.

USU, HS, MP, SGG: 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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CASE REPORT

Urine Like Diarrhea in Older Children: Two Case Reports

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ABSTRACT

Background: 'Urine-like diarrhea' is seen in Congenital Chloride-Losing Diarrhea (CCLD), which usually starts during the neonatal period. But without a prior history of CCLD, it is rare in older children, and there are no reported cases till now.

Case presentation: Two Bangladeshi children presented with 'urine-like diarrhea' for more than 14 days, without any previous history or suggestive findings. All investigations were negative for any etiology except fecal impaction seen on abdominal x-ray. After disimpaction, both children dramatically improved.

Conclusions: Colonic fecal impaction can present as persistent diarrhea. Keywords: Urine-like diarrhea, fecal impaction, persistent diarrhea, older children.

Keywords: Urine-like diarrhea; Fecal impaction; Persistent diarrhea; Constipation

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INTRODUCTION:

Introduction: Diarrhea is defined as three or more loose stools per day, or more frequent than normal for the individual. If the condition persists for 14 days or more, it is categorized as persistent diarrhea. [1] 'Urine-like diarrhea' is seen in congenital chloride-losing diarrhea (CCLD), which is severe, life-threatening secretory diarrhea; onset is during the 1st week of life and persists lifelong. [2] CCLD occurs due to mutations in the SLC26A3 gene, leading to defective chloride–bicarbonate exchanges with the resultant loss of chloride and retention of bicarbonate [3]. In older children, an acute onset of watery stool resembling urine, which lasts for several days, is rare. Due to its rarity, we are presenting two successfully managed cases.

Case study 1:

A 10-year-old Bangladeshi girl presented with frequent passage of explosive watery stool without any fecal matter (mother explained it as 'urine-like diarrhea') for 15 days. She experienced mild cramping abdominal pain before the passage of stool. There was no blood in the stool. She had no history of taking any non-food items (pica), purgatives, or antibiotics; no gluten sensitivity or known food allergy; and no recent travel history. Physical examinations were unremarkable with normal anthropometry except for an ill-defined mobile mass in the right iliac fossa. On digital rectal examination, the rectum was empty. There was no feature of intestinal obstruction. Without fever, tenesmus, severe abdominal pain, or blood in stool, it was unlikely to be infectious or inflammatory in origin. Prior to referral, she had received ciprofloxacin, metronidazole, probiotics, and oral rehydration solution (ORS) without improvement. To exclude factitious diarrhea, the patient remained under strict 24-hour medical and parental observation, ensuring no access to irrigation tools or external fluids. Laboratory investigations, including a complete blood count and serum electrolytes (with bicarbonate), were within normal limits. Stool microscopy, cultures, and reducing substances were negative, with a stool pH of 6. Stool analysis confirmed a secretory pattern (stool osmotic gap ≈ 26 mOsm/kg) with characteristically low electrolytes (Na^+ < 10 mmol/L, Cl^- < 15 mmol/L). To find out the causes of secretory diarrhea, we went for a colonoscopy, esophagogastroduodenoscopy, and computed tomography of the abdomen, and all these were normal, which ruled out inflammatory bowel disease (IBD), celiac disease, or any tumor. The histopathology of the biopsy from the colon was normal. Anti-HIV I & II were negative, and the thyroid profile was normal (table 1). Before the colonoscopy, we did a plain x-

ray of the abdomen, which showed huge fecal impaction in the cecum and ascending colon. During bowel preparation with polyethylene glycol (PEG) 3350 and a sodium phosphate enema (2.5 mL/kg), a large volume of retained fecal matter was evacuated. Following disimpaction, the patient's bowel habits normalized within 24 hours. Based on the clinical resolution and radiological findings, a diagnosis of persistent watery diarrhea secondary to proximal fecal impaction was established.

Case study 2:

A 13-year-old Bangladeshi boy presented with a passage of 'urine-like stool' (Fig. 1 and video 1) for 25 days. Several times per day he experienced mild cramping abdominal pain that was followed by explosive watery bowel movements without any fecal matter. Similar to the previous case, he had no suggestive history and physical findings except an ill-defined mobile mass in the right iliac fossa. On digital rectal examination, the rectum was empty. There was no suggestive history regarding any etiology. He received ORS after each bowel motion. Like previous cases, we excluded the possibility of factitious diarrhea. Laboratory studies showed a normal complete blood count, normal serum electrolytes, thyroid profile, and negative anti-HIV I & II serology. Stool routine & microscopic examinations were normal, culture-negative, stool for reducing substance negative, and stool pH was 6. He had a stool osmotic gap of less than 50 mmol/L (Table 1), suggesting a secretory nature of diarrhea. A plain x-ray of the abdomen showed a huge fecal impaction (Fig. 2). His colonoscopy, esophagogastroduodenoscopy, and computed tomography of the abdomen were normal (table 1), which ruled out IBD, coeliac disease, or any tumors. Similarly, during colonoscopy preparation, a large amount of fecal matter passed with watery stool (video 2). The next day after that, stool became normal like in the previous case (video 3). After evaluating history, physical findings, and investigations, we also concluded that this case is diarrhea due to fecal impaction.

As this urine-like diarrhea in older children is a unique presentation and we successfully managed several cases, in our hospital facility this diarrhea is known as 'BB-Diarrhea'/'Bazlul-Benzamin Diarrhea.' We managed these children with polyethylene glycol 3350 (1 gm/kg/day) as maintenance therapy for 2 months followed by gradual tapering. On follow-up, they had been doing well without any further events. This sustained clinical recovery further supports the diagnosis of persistent watery diarrhea secondary to occult proximal fecal impaction rather than a primary secretory or factitious disorder.

Fig 1: Watery stool without any fecal matter.

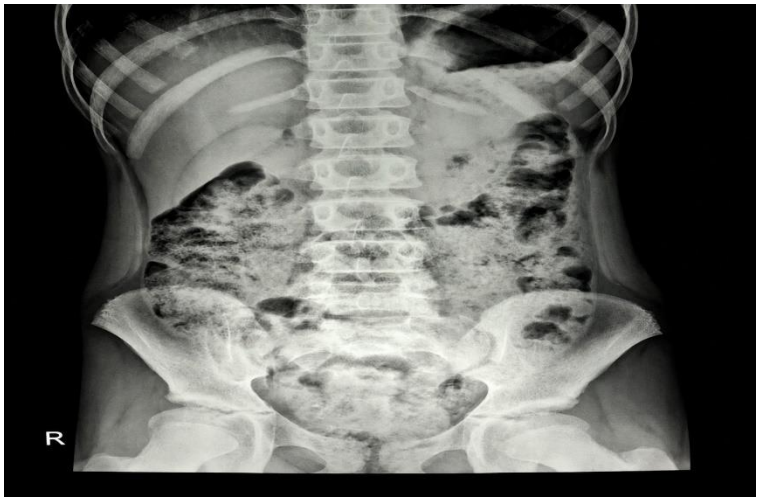

Fig 2: Huge fecal impaction in the caecum, ascending colon and descending colon

Table X. Laboratory and Diagnostic Investigations of the Two Cases

Investigation	Case 1	Case 2	Reference Range / Normal
Complete Blood Count (CBC)			
Hemoglobin (g/dL)	11.2	12.5	12.5–16.1
WBC ($\times 10^3$/mm^3)	7.28	7.50	4.0–10.5
Platelets ($\times 10^3$/mm^3)	3.66	2.80	1.5–4.0
Inflammatory Marker			
High-sensitivity CRP (mg/L)	0.9	2.5	<5
Serum Electrolytes			
Sodium (mmol/L)	142	137	135–145
Potassium (mmol/L)	4.3	3.8	3.5–5.5
Chloride (mmol/L)	106	102	98–106
Stool Investigations			
Reducing substances	Absent	Absent	—
Stool RME	Pus cells 0–2/HPF, No RBC	Pus cells 0–3/HPF, No RBC	<5/HPF
Stool culture (*Salmonella, Shigella, Vibrio cholerae*)	No growth	No growth	—
Clostridium difficile toxin A/B (RT-PCR)	Negative	Not done	—
Stool sodium (mmol/L)	<10	Not done	20–30
Stool potassium (mmol/L)	<2	Not done	55–75
Stool chloride (mmol/L)	<15	Not done	15–25
Stool pH	6.0	6.0	6.0–7.2
Stool osmolality (mOsm/kg)	<50	<50	—
Calculated stool osmotic gap (mOsm/kg)	≈26†	Not done	50–135
Imaging			
Plain abdominal X-ray	Fecal impaction (right colon)	Fecal impaction (right colon)	—
Barium follow-through	Normal	Normal	—
Colonoscopy	Normal	Normal	—
Esophagogastroduodenoscopy	Normal	Normal	—
Contrast-enhanced CT abdomen	Normal	Normal	—
Serology			
tTG IgA (U/mL)	0.9	0.7	<4
Total IgA (g/L)	1.2	2.0	0.42–2.95
Serum calcitonin (pg/mL)	<2	Not done	<4
Serum gastrin (pg/mL)	25.8	Not done	13–115
Histopathology (colon biopsy)	Not done	Normal	—
HIV I & II	Negative	Negative	Negative
Thyroid Profile			
TSH (µIU/mL)	4.4	3.8	0.5–4.5
FT4 (ng/mL)	1.65	1.40	0.77–2.08

Abbreviations: CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; FT4, free thyroxine; HPF, high power field; IgA, immunoglobulin A; RBC, red blood cells; RME, routine microscopic examination; RT-PCR, reverse transcription polymerase chain reaction; TSH, thyroid-stimulating hormone; tTG IgA, tissue transglutaminase immunoglobulin A.

† Calculated as stool osmolality ~ 2 (Na$^+$ + K).

DISCUSSION:

Watery diarrhea is a common issue in children.[1] Our patients have been experiencing persistent diarrhea with urine-like, watery stool. Watery diarrhea can be caused by osmotic, secretory, or inflammatory factors, or a combination of these.[4,5] In our cases, the diarrhea was secretory (stool osmotic gap of less than 50 mmol/L). There are various potential causes for these conditions, including laxative use, celiac disease, tropical sprue, microscopic colitis, and endocrine tumors such as VIPoma, carcinoid, gastrinoma, and thyroid medullary cancer. Prolonged infectious diarrhea (lasting more than 2 weeks) may be caused by persistent or recurrent infections. [4,5] We excluded all the possible causes of infectious diarrhea through history and investigations. Celiac crises in untreated cases present with explosive watery diarrhea with hypoproteinemia and metabolic and electrolyte changes. Both cases were thriving well without any prior history of gluten sensitivity with normal celiac screening. [6]

Paradoxical diarrhea (also known as overflow diarrhea) occurs when liquid stool leaks around the hard, impacted fecal matter in the rectum with frequent, small, watery bowel movements that occur mostly involuntarily. This condition may also be caused by a growth in the pelvic region or urinary retention. [7,8] Our cases, was not paradoxical diarrhea as in both cases rectum was empty and they used to defecate several times voluntarily with clear watery stool in large volumes, without any fecal matter.

Fecal impaction is defined as a large amount of hard, compressed fecal mass that is impacted at the level of the bowel and cannot be expelled spontaneously, resulting in colonic or rectal distention. In our cases, the rectum was empty, but a huge fecal impaction was present in the cecum and colon. We propose an alternative physiological mechanism in these specific cases. The massive fecal impaction in the right colon likely acted as a "gateway", and greater accumulation of secreted liquid proximal to the obstruction, allowing only the low-solute mucus and water secreted. Continuous mucosal stimulation by the fecal mass may further enhance secretory activity and lead to profuse mucous secretion, producing stool that resembles clean water.[9] This condition explains the watery stool in our cases. Usually fecal accumulation occurs from distal to proximal unless an anatomical defect impedes the normal progression of feces, but in both cases no structural abnormality was found, as both the barium study and colonoscopy were normal, and histopathology was also normal. Fecal stasis for a long period may give rise to this pattern of fecal impaction. We could not perform a genetic study due to lack of facility, but secondarily, we excluded genetic possibility as both children were doing well after disimpaction and symptoms did not persist. These cases diverge from known patterns in pediatric constipation, and there is a lack of comparable cases in the existing literature. As these cases were very atypical, they visited several physicians without improvement. However, after proper evaluation, we managed the cases and diagnosed them as persistent diarrhea due to fecal impaction.

CONCLUSION: Colonic fecal impaction can cause persistent diarrhea with urine-like stool in children.

Statement of Ethics: The parents provided written informed consent for publication of the case reports and any accompanying images. Ethical approval was taken from the departmental review board, department of pediatrics, Sylhet M. A. G. Osmani Medical College Hospital, Bangladesh (No. 08/SOMCH/2025).

Conflict of Interest: The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Funding: The study did not receive any funding.

Author's Contribution:

Md B: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.

ASM BK: 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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