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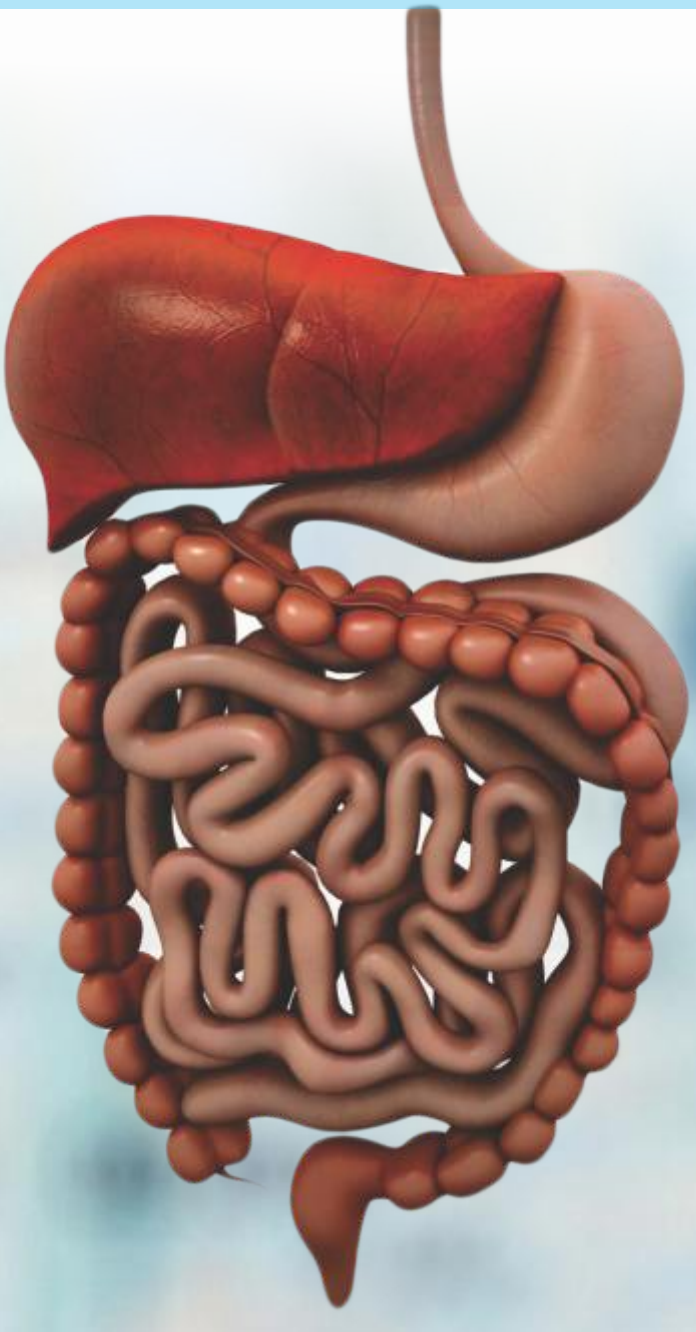

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PRESIDENT'S MESSAGE

A Warm Welcome to the South Asian Journal of Gastroenterology.

On behalf of the Sri Lanka Society of Gastroenterology (SLSG), it is with immense pleasure that I extend my warmest greetings to the readers of the inaugural issue of the South Asian Journal of Gastroenterology (SAJG). The SLSG is proud to initiate this landmark endeavour, a much-needed platform for sharing vital knowledge and fostering collaboration in the field of Gastroenterology not only in Sri Lanka but across South Asia.

The gastrointestinal (GI) landscape of South Asia presents unique challenges. Our region grapples with the burden of GI disorders like steatotic liver disease, cirrhosis and inflammatory bowel disease. Additionally, limited resources and diverse healthcare systems across South Asian nations necessitate a collaborative approach to address these issues effectively.

The SAJG serves as a beacon of hope in this regard. This peer-reviewed journal will bridge the knowledge gap by publishing high-quality research on GI diseases relevant to the South Asian context.

Original research papers, insightful case reports, and comprehensive reviews will equip healthcare professionals with the latest advancements in diagnosis, treatment, and preventive strategies for GI diseases prevalent in our region.

The SLSG is confident that the SAJG will become a premier forum for Sri Lankan and South Asian gastroenterologists to share their expertise and experiences. This knowledge exchange will not only benefit individual nations but also lead to the development of region-specific guidelines and best practices tailored to address the unique GI healthcare needs of South Asia.

I encourage SLSG members and all gastroenterologists across the region to actively participate in this endeavour by submitting their valuable research and engaging in scholarly discourse through the journal. The SLSG extends its unwavering support to the SAJG and I wish it continued success in the years to come.

Professor Madunil Niriella

President, Sri Lanka Society of Gastroenterology

CHIEF EDITOR'S MESSAGE

Warmest seasonal greetings to our esteemed readers and contributors,

It is with great privilege and excitement that I write to you on this momentous occasion: the launch of the inaugural issue of the South Asian Journal of Gastroenterology (SAJG) as the Editor-in-Chief. This juncture, will be a historic landmark in the history of Sri Lankan Society of Gastroenterology (SLSG), an organization that has been at the forefront of scientific inquiry into gastroenterological diseases since its establishment in 1965.

In an era where the boundaries between Surgery and Medicine are increasingly blurred within the discipline of gastroenterology, the necessity for dedicated forums for scientific discourse becomes ever more apparent. As healthcare providers in Sri Lanka, grappling with gastrointestinal disorders on a daily basis, we have long felt the absence of a forum for region-specific scientific knowledge. Hence, the establishment of this peer-reviewed journal, the South Asian Journal of Gastroenterology, is a long-awaited endeavour that promises to enrich not only our present but also the generations to come.

Sri Lanka bears a significant burden from gastrointestinal diseases that affect all strata of our society, yet much of the available data and guidelines are derived from Western populations.

It is imperative that this knowledge gap be addressed. The establishment of SAJG represents not merely a starting point, but rather a pivotal milestone in our collective journey towards bridging this gap. It aspires to become a veritable "knowledge hub," serving as a repository of scientific data in the field of gastroenterology.

The Sri Lankan Society of Gastroenterology (SLSG) is poised to embark on this venture of curating and disseminating the ever-changing landscape of gastroenterological research.

We urge our esteemed members to actively participate in this journey by contributing their invaluable research and sharing their expertise, both within Sri Lanka and to the wider global community.

Together, let us embark on this journey of advancing knowledge in the realm of gastroenterology, guided by the spirits of excellence, integrity, and collaboration.

Warm regards,

Dr. Duminda Subasinghe

Editor SLSG
Joint Editor, South Asian
Journal of Gastroenterology

EDITORIAL TEAM

ORIGINAL ARTICLE

The shift in aetiology of cirrhosis in a lower-middle income country in Southeast Asia over a decade –- a single centre study from Sri Lanka

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ABSTRACT

Background

Owing to its increasing prevalence globally, non-alcoholic steatohepatitis (NASH) is fast becoming the most common cause of cirrhosis, replacing viral hepatitis and alcohol respectively. This study aimed to describe the aetiology of cirrhosis among patients followed up at a specialised tertiary centre in Sri Lanka and to compare it with data collected at the same centre a decade ago.

Methods

We analysed the data from randomly selected patients diagnosed with cirrhosis who attended the Gastroenterology outpatient clinic at Colombo North Teaching Hospital, Ragama, Sri Lanka in 2022.

These patients were confirmed to have cirrhosis based on standard clinical, biochemical and radiological criteria. The causes of cirrhosis in these patients were compared with the findings of a previous study conducted at the same tertiary centre in Sri Lanka in 2012.

Results

Out of 303 patients, 126 (41.6%)were found to have NASH-cirrhosis. Alcohol-related cirrhosis was present in 94 (31.0%). Autoimmune hepatitis (AIH) was diagnosed in 44 (14.5%)patients, whilst a further 13 (4.3%) patients had cryptogenic cirrhosis.

Other less common causes included Wilson's disease, hemochromatosis, Budd Chiari syndrome (BCS) and chronic portal vein thrombosis (PVT).Only two (0.7%) patients had hepatitis B and one (0.3%)patient had Hepatitis C.

In comparison with the data set from 2012, out of 381 patients, ARLD was seen in 54.7%, with 38.3 % diagnosed to have cryptogenic cirrhosis, 3.4% with Hepatitis B and Wilsons disease in 1.9%. The remaining cases were attributed to other less common causes as Primary biliary cholangitis (PBC) and hemochromatosis.

Conclusion

The main aetiology of liver cirrhosis remains NASH at present. Whilst in 2012, alcohol-related cirrhosis was the most prevalent cause, accounting for over half of the cases, by 2022 it had significantly decreased. Cryptogenic cirrhosis also showed a significant reduction over the past decade. This study highlights a significant shift in trend in the aetiology of cirrhosis over the past decade in a developing, lower middle income country in South east Asia. Future changes in aetiology must be considered in establishing preventive and developing new treatment strategies.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) remains the most common chronic liver disease worldwide 1. Consequently, Non-alcoholic steatohepatitis (NASH), the more active form of NALFD characterised with underlying hepatic steatosis and inflammation, is fast becoming the leading cause of cirrhosis and hepatocellular carcinoma (HCC) globally 2. NAFLD affects approximately 25% of the global population, with NASH being a critical concern due to its potential to progress to cirrhosis, its complications, liver failure and HCC.

Sri Lanka, a lower middle-income country in Southeast Asia, has experienced notable changes in the aetiology of cirrhosis in recent years, which reflect both local epidemiological shifts and the larger global trends. Historically, ARLD and cryptogenic cirrhosis were the predominant causes of liver cirrhosis in Sri Lanka. However there has been a noticeable rise in cases of cirrhosis related to NASH, which has now become the leading cause of cirrhosis 3. Alcohol consumption has long been a major public health issue in the region, contributing significantly to the burden of liver diseases. Additionally, cryptogenic cirrhosis, where the underlying cause remains unidentified despite thorough investigation, further accounted for a substantial proportion of cirrhosis diagnoses. It is probable that the limited diagnostic capabilities in the past and the lack of awareness of other potential aetiologies such as autoimmune hepatitis (AIH) and NASH may have attributed to the diagnosis of cryptogenic cirrhosis. Whilst it is appreciated that causes for the development of cirrhosis are multifactorial, in recent years there has been a significant epidemiological transition worldwide.

·Epidemiological transition:

Sri Lanka, like many other developing countries, is undergoing an epidemiological transition characterized by a decrease in infectious diseases and a rise in chronic non communicable diseases (NCDs). This transition has led to a higher prevalence of conditions that predisposes an individual to NAFLD and NASH.4 Urbanisation with adaptation of unhealthy diets, increasing sedentary lifestyles, rise in obesity, increasing age are all thought to contribute to the shift in the aetiology of cirrhosis. Hence NASH has emerged as the prominent cause of cirrhosis. This shift mirrors global trends where the incidence of NASH is rising due to the increasing prevalence of obesity, diabetes, and metabolic syndrome. Extrahepatic cancers and cardiovascular disorders are the main causes of death in patients with NAFLD due to the strong correlation between metabolic syndrome and NAFLD 5.

In comparison, improved diagnostics, vaccination coverage as well as effective anti-viral treatment against Hepatitis B and Hepatitis C viral infections have attributed to a reduction in viral hepatitis induced cirrhosis 6. Whilst ARLD remains a major aetiological factor in cirrhosis, in Southeast Asia prevalence ARLD associated cirrhosis are lower than those in western populations 7.

·Changing diet and food habits:

The traditional Sri Lankan diets consist of high in fibre, vegetable and grain. However, owing to the colonial impact and globalization, Sri Lanka has over the years slowly adopted western dietary habits on its way to urbanization and development. Western diets whilst are high in sugar, salt and oil, they are of lower production costs with longer shelf lives. Hence for ease, availability and reduce cost, most people opt to follow a western diet. These dietary changes have significantly contributed to obesity and metabolic syndrome, which are significant risk factors for NASH.8,9

·Increase in Non-Communicable Diseases:

The incidence of diabetes, hypertension, and cardiovascular diseases is rising in Sri Lanka. These conditions are closely linked with metabolic syndrome and NAFLD, driving the rise in NASH-related cirrhosis. A recent study demonstrated that Sri Lanka has a higher prevalence of diabetes than previous estimates at 23%, which is higher than current global estimates for any other Asian country 10. Furthermore, the incidence and prevalence of metabolic syndrome appears to be high and is comparable to other parts of Asia 11. The World Health Organization (WHO) has also reported a growing burden of NCDs in Sri Lanka, which correlates with the rising cases of NASH .12 The increasing prevalence of NASH cirrhosis poses new challenges for healthcare providers in Sri Lanka. Early identification and management of NAFLD and NASH are crucial to prevent the progression to cirrhosis.

Hence improved screening programs, public health initiatives aimed at promoting healthy lifestyles and enhanced clinical awareness among healthcare professionals are required. Moreover, as the landscape of liver disease changes, there is a need for updated clinical guidelines and resource allocation to effectively manage, treat NASH as well as other emerging causes of cirrhosis.

The European Association for the Study of the Liver (EASL) emphasizes the importance of the early introduction of comprehensive management strategies for NAFLD and NASH, including lifestyle modifications, pharmacotherapy, and regular monitoring of liver function.13

METHODS

We analysed the data of a randomly selected sample of patients with cirrhosis, who attended the Gastroenterology outpatient clinic at the Colombo North Teaching Hospital, Ragama, Sri Lanka. This study was conducted over 4 weeks in June 2022.

All patients diagnosed with cirrhosis registered in our clinic were eligible for inclusion in the study. Cirrhosis was diagnosed on clinical, biochemical, abdominal imaging, and endoscopic criteria and, when possible or required, confirmed by liver biopsy. Alcohol-related cirrhosis had a history of consuming alcohol above the accepted safe limits (Asian standards: <14 units of alcohol per week in men and <7 units per week of alcohol in women) before the diagnosis of cirrhosis. NASH-cirrhosis were patients who had metabolic risk factors but did not drink alcohol above the safe limit, had no history of contributory drug or herbal product use and in whom Hepatitis B and C, autoimmune disease, haemochromatosis, Wilson's disease, and alpha-1 antitrypsin deficiency were excluded. Patients who were found to have hepatocellular carcinoma at diagnosis were excluded from the study.

Ethics approval for this study was obtained from the Colombo North Teaching Hospital, Ragama, Sri Lanka. Informed consent was taken from all participating patients and their families regarding obtaining information.

Data were entered into a spreadsheet (Microsoft Excel, Richmond, WA, USA). Statistical analysis was done using SPSS ver. 28.0(SPSS, Chicago, IL, USA). Continuous and categorical data were described using mean and standard deviations and percentages, respectively. Bivariate analysis was done using the c2-test.P < 0.05 was considered as significant. The causes of cirrhosis were compared with the previous findings collected at the same centre in 2012 14.

RESULTS

Three hundred and three patents were included in the study.

Table 1. Basic characteristics of the patients with cirrhosis

		Age		Sex	
	n	**Mean**	**95% CI**	**Female**	**Male**
Autoimmune hepatitis (AIH)	44	56.18	51.87- 60.49	35	9
				80%	20%
ARLD	94	55.28	53.55 - 57	2	92
				2%	98%
Cryptogenic cirrhosis	13	57.77	48.4 -67.13	9	4
				69%	31%
NASH	126	61.40	59.3 - 63.48	64	62
				51%	49%
Wilson's Disease	8	36.38	26.59 - 46.15	5	3
				63%	38%

Table 1 summarizes the basic characteristics of patients with cirrhosis, revealing distinct demographic patterns based on the underlying cause.

Patients with NASH had the highest mean age of 61.40 years with an almost equal gender distribution noted. Those patients with ARLD were noted to be mostly male (98%) with a mean age of 55.28 years.

Those patients with cryptogenic cirrhosis notably were female (69%) with a mean age of 57.77 years. Autoimmune hepatitis (AIH) patients had a mean age of 56.18 years and were predominantly females (80%). Those with Wilson's disease were much younger in age with a mean age of 36.38 years and had a female predominance (63%). Based on the aetiology of cirrhosis, these data show considerable differences in the age and gender distribution across the patients.

Table 2. Aetiology of cirrhosis among the patients

Aetiology	Number	Percentage
AIH	44	14.52
ARLD	94	31.02
NASH	126	41.58
Cryptogenic	13	4.29
Hepatitis B	2	0.66
Hepatitis C	1	0.33
Drugs	2	0.66
Primary sclerosing cholangitis (PSC)	1	0.33
Wilsons	8	2.64
Hemochromatosis	2	0.66
Budd Chiari Syndrome (BCS)	1	0.33
Chronic Portal vein thrombosis (PVT)	4	1.32
Biliary atresia	1	0.33
total	303	100

Table 2 above details the aetiological breakdown of cirrhosis among 303 patients, highlighting significant diversity in underlying causes. NASH was the most common cause, accounting for 41.58% of cases followed by ARLD representing 31.02%. AIH contributed to 14.52% of cases, while cryptogenic cirrhosis accounted for 4.29%.

The less frequent aetiologies of cirrhosis included Wilson's disease (2.64%), chronic portal vein thrombosis (PVT) (1.32%), and other rare causes such as viral hepatitis such as hepatitis B and C, drug-induced cirrhosis, hemochromatosis, biliary atresia, primary sclerosing cholangitis (PSC), and Budd-Chiari syndrome (BCS), each constituting less than 1% of the total. This distribution underscores the predominance of metabolic and lifestyle-related factors in the current cirrhosis landscape.

Table 3. Complications of cirrhosis

		AIH		ARLD		cryptogenic		NASH		Wilsons	
	n	44		94		13		126		8	
SBP	ABSENT	43	98%	88	94%	13	100%	120	95%	8	100%
	PRESENT	1	2%	6	6%	0	0%	6	5%	0	0%
PVT	ABSENT	44	100%	92	98%	11	85%	122	97%	8	100%
	PRESENT	0	0%	2	2%	2	15%	4	3%	0	0%
HCC	ABSENT	44	100%	90	96%	10	77%	116	92%	8	100%
	PRESENT	0	0%	4	4%	3	23%	10	8%	0	0%
HE	ABSENT	42	95%	67	71%	11	85%	115	91%	6	75%
	PRESENT	2	5%	27	29%	2	15%	11	9%	2	25%
HRS	ABSENT	44	100%	92	98%	13	100%	122	97%	8	100%
	PRESENT	0	0%	2	2%	0	0%	4	3%	0	0%
UGIB	ABSENT	6	14%	6	6%	1	8%	17	13%	2	25%
	PRESENT	38	86%	88	94%	12	92%	109	87%	6	75%
ascites	ABSENT	40	91%	47	50%	9	69%	89	71%	6	75%

ascites		0	0%	0	0%	0	0%	0	0%	0	0%
	PRESENT	4	9%	47	50%	4	31%	37	29%	2	25%
splenomegaly		40	91%	76	81%	10	77%	98	78%	5	63%
	ABSENT	4	9%	14	15%	2	15%	21	17%	3	38%
	moderate	0	0%	0	0%	0	0%	1	1%	0	0%
	PRESENT	0	0%	4	4%	1	8%	6	5%	0	0%
CTP	A	35	80%	14	15%	5	38%	51	40%	3	38%
	B	8	18%	65	69%	7	54%	66	52%	3	38%
	C	1	2%	15	16%	1	8%	9	7%	2	25%

Table 3 summarizes the complications experienced by patients with cirrhosis across different aetiologies. Most AIH patients had early-stage cirrhosis (Child-Turcotte-Pugh (CTP) class A). Whilst upper gastrointestinal bleeding (UGIB) was notably high, ascites and splenomegaly due to portal hypertension were relatively uncommon. Hepatic encephalopathy (HE) was present in a small fraction of patients. In AIH, spontaneous bacterial peritonitis (SBP) was rare, with only one patient having reported. Furthermore, there were no reported AIH patients with portal vein thrombosis (PVT) HCC and hepatorenal syndrome (HRS).

Conversely in ARLD, SBP, PVT, and HCC were more frequent compared to AIH. HE and UGIB were also prevalent, with significant numbers experiencing ascites and splenomegaly. Hence many ARLD patients were in the intermediate to advanced stages of cirrhosis (CTP class B and C).

Patients with cryptogenic cirrhosis showed no SBP but had a higher incidence of PVT and HCC. HE and UGIB were also common, with a considerable number experiencing ascites and splenomegaly. Most were in the intermediate stage of cirrhosis (CTP class B).

NASH patients exhibited a low occurrence of SBP, PVT, and HCC but had frequent cases of UGIB. Ascites and splenomegaly were less common, and most were in the intermediate stage of cirrhosis (CTP class B).

Those patients with Wilson's disease had no SBP, PVT, HCC, or HRS. HE was present in a quarter, with moderate cases of UGIB, ascites, and splenomegaly. They were evenly distributed across CTP classes A through to class C.

Table 4. Comparison of cirrhosis aetiologies according to the times

	2012[14]	2012	2022	2022	
Aetiology	**Number**	**Percentage**	**Number**	**Percentage**	**Significance**
alcohol	381	54.74	94	31.02	<0.001
NASH			126	41.58	
cryptogenic	270	38.79	13	4.29	<0.001
Hepatitis B	13	1.87	2	0.66	0.12
Wilsons	13	1.87	8	2.64	0.6
Autoimmune	7	1.01	44	14.52	<0.001
Drug induced	4	0.57	2	0.66	n/a
Hepatitis C	3	0.43	1	0.33	n/a
Hemochromatosis	3	0.43	2	0.66	n/a
PBC	1	0.14	2	0.66	n/a
Traditional herbs	1	0.14			n/a
Biliary atresia			1	0.33	n/a
Chronic PVT			4	1.32	n/a
BCS			1	0.33	n/a
Total	696	100	308	100	

Table 4 compares the aetiologies of cirrhosis between 2012 and 2022. In 2012, ARLD was the most prevalent cause, accounting for over half of the cases, but this has significantly decreased by 2022. NASH has emerged as the leading cause in 2022, representing a substantial shift in aetiological trend.

Notably Cryptogenic cirrhosis also showed a significant reduction over the decade. Cases attributed to AIH has markedly increased, reflecting a significant change in the landscape of cirrhosis aetiology. The prevalence of Wilson's disease and hepatitis B remained relatively stable, showing no significant changes.

Drug-induced cirrhosis, hepatitis C, hemochromatosis, primary biliary cholangitis (PBC), traditional herb use, biliary atresia, chronic PVT, and BCS had very low incidence rates in both years, with some conditions newly appearing in 2022.

This data hence highlights a significant epidemiological shift over the past decade, with a decrease in alcohol-related and cryptogenic cirrhosis and an increase in NASH and autoimmune hepatitis cases, emphasizing the evolving nature of cirrhosis aetiologies in Sri Lanka.

DISCUSSION

In Sri Lanka, the demographic characteristics of patients with cirrhosis reveal significant variations based on the underlying aetiology of disease. Patients with AIH tend to be older, with a mean age of 56.18 years, and are predominantly female (80%). This observation aligns with the global trends where AIH is more common in females and often diagnosed in middle-aged individuals 15. Conversely in patients with ARLD, males were more commonly affected (98%), with a mean age of 55.28 years. The male predominance in ARLD is consistent with the global patterns, reflecting higher alcohol consumption rates among men compared to females. 12,16

With regards to patients with cryptogenic cirrhosis, most patients were female with a mean age of 57.77 years. This category often includes patients with occult NASH, which is more prevalent among older females. Patients with NASH appeared to be older, with a mean age of 61.40 years and nearly equal gender distribution, highlighting the impact of metabolic syndrome and obesity, conditions that are rising in both genders due to lifestyle changes .17,18 Those with Wilson's disease were younger in age with a mean age of 36.38 years and female predominance (63%) was seen, reflecting the genetic nature and earlier onset of this disorder .19The demographic differences highlight the necessity of implementing customised public health initiatives and clinical methodologies to effectively manage and prevent cirrhosis in Sri Lanka, given its multifaceted aetiology.

When comparing complications across different aetiologies of cirrhosis, there appears to be distinct patterns in disease progression and clinical manifestations. With AIH, complications such as SBP were rare, consistent with findings suggesting a lower incidence of SBP in AIH compared to other aetiologies. Conversely, with ARLD, there appears to be a higher prevalence of SBP, reflecting the increased risk associated with alcohol-related immunosuppression and bacterial translocation 20, 21. Similarly, whilst HCC was absent in AIH, there was increased prevalence noted among ARLD cirrhosis aligning with the well-established association between chronic alcohol consumption and HCC development. 22, 23

Conversely, patients with cryptogenic cirrhosis displayed an intermediate pattern of complications, with no SBP but a higher incidence of PVT and HCC, suggesting a distinct disease course compared to the known aetiologies.

Those with NASH exhibited a lower occurrence of SBP and HCC, consistent with studies highlighting the lower incidence of bacterial infections and liver cancer in NASH compared to other aetiologies.

Those with Wilson's disease had a unique profile, with no SBP, PVT, or HCC, but a quarter experienced HE, indicating the neurological burden associated with copper accumulation in this disorder. 24

Overall, these findings emphasize the importance of considering the underlying aetiology of cirrhosis when assessing disease complications and management strategies. Further the findings highlight the need for tailored approaches to optimize patient outcomes.

Comparing cirrhosis aetiologies between 2012 and 2022 reveals a notable epidemiological shift in Sri Lanka. Alcohol-related cirrhosis, once predominant, saw a significant decline over the decade, aligning with global trends of decreasing alcohol consumption with rising awareness of liver health 25.

Conversely, NASH has emerged as the leading cause in 2022, mirroring the global epidemic of metabolic syndrome and obesity-related liver diseases 26,27. This shift underscores the impact of changing lifestyles and dietary habits on liver disease patterns. Cryptogenic cirrhosis also declined significantly, suggesting improved diagnostic capabilities or reclassification of cases due to better understanding of underlying aetiologies 28.

The notable increase in AIH reflects growing recognition and diagnosis of autoimmune liver diseases, potentially influenced by improved screening methods and heightened awareness among clinicians 29.

The stable prevalence of Wilson's disease and hepatitis B indicates consistent disease burden and management practices over the years. Low incidence rates of drug-induced cirrhosis, hepatitis C, hemochromatosis, PBC, traditional herb use, biliary atresia, chronic PVT, and BCS emphasize their rarity as cirrhosis causes in Sri Lanka.

Overall, these findings highlight the dynamic nature of aetiologies of cirrhosis, which are influenced by various factors such as societal changes, healthcare advancements, and evolving disease paradigms. Understanding these trends is crucial for implementing targeted prevention and management strategies to address the shifting burden of liver disease effectively.

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ORIGINAL ARTICLE

Prevalence of childhood obesity and its associations among adolescents: a cross-sectional, urban, community-based, birth cohort study from South Asia

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ABSTRACT

Background

There are few community-based data on childhood obesity. We investigated the community prevalence and associations of adolescent obesity in a birth cohort from an urban community in Sri Lanka.

Methods

The study population consisted of 14-year-olds (Year-2000 birth-cohort), from the Ragama MOH area were invited to participate in the study. Demographic and lifestyle data were collected, and standard blood biochemistry was performed. Body mass index (BMI), waist circumference (WC) and blood pressure were measured. Total body fat percentage (TBF) was measured using the impedance method. Wilcoxon Rank Sum test, linear models, generalized linear models and Multivariate analysis of covariance were used for the analysis of data.

Results

508 [260 (51.2%) girls; median birth weight 2.9 (IQR: 2.6-3.2) kg] participated in the study. Prevalence of central obesity (CO) was 26.7% (95% CI: 23.1% - 30.8%), general obesity (GO) was 1.8% (95% CI: 0.6% - 2.9%) and global obesity was 1.6% (0.4% - 2.7%). Girls showed a higher prevalence of CO compared to boys (37.8% vs 15.8% respectively, P <0.001).

GO was associated with lower birth order (P=0.044), CO with female sex (P<0.001) and higher birth weight (P=0.05), and global obesity with gestational diabetes (P=0.055). After adjusting for antenatal and postnatal factors, GO, and CO showed positive associations with blood pressure, lipid and glucose metabolism and alanine transaminase (ALT) and fatty liver.

Conclusion

In this cohort of adolescents, CO was more prevalent than GO. CO was commoner among the girls than in boys. GO was associated with lower birth order while CO showed association with higher birth weight. After adjusting for these, both GO and CO showed association with metabolic traits.

Key words:

Obesity, childhood, adolescence, epidemiology, risk factors, South Asia

INTRODUCTION

Childhood obesity, which was traditionally considered a health issue in developed countries, is now an emerging problem in many low and middle-income countries such as Sri Lanka (1-3). Childhood obesity is a complex disorder with the interaction between genetics, lifestyle, physical activity and eating habits. The increased prevalence of childhood obesity in recent years appears to be mainly due to environment and lifestyle influences, rather than genetic factors (2).

Obesity among adolescents is known to have a significant impact on both physical and psychological health.

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Childhood obesity predisposes to obesity and numerous other metabolic derangements in adulthood, including insulin resistance, diabetes, hypertension, dyslipidemia and fatty liver (4). Therefore, childhood obesity can progress to the development of cardiovascular disease in adulthood. Furthermore, adolescence is a key period in development for the establishment of obesity-related metabolic derangements in the future (5). Thus, steps should be taken to prevent and treat obesity as early as possible in adolescence, and environmental and behavioural determinants of childhood should be identified in order to design effective interventions.

The prevalence of obesity [the equivalent of body mass index (BMI) >23 kg/m2 or more] among 2-20-year olds in developing countries in both boys and girls has almost doubled from 1980 to 2013; 8.1% to 12.9% for boys and 8.4% to 13.4% for girls. The prevalence in developed countries is substantially higher among children and adolescents compared to developing countries; 23·8% of boys and 22·6% of girls were overweight or obese in 2013 (6). The previously reported prevalence of childhood and adolescent (2-20 years) overweight and obesity in Sri Lanka was 5% and 1.9% for boys and 8.9% and 2.2% for girls, respectively (6).

Majority of previous studies from Sri Lanka have been conducted among cohorts of school children. None of these studies has been from true community-based cohorts. Therefore, there is a lack of geographically defined, community-based information on childhood obesity and its associations from Sri Lanka. We investigated the community-prevalence and associations of childhood obesity in a birth cohort of adolescents from an urban-community in Sri Lanka.

METHODS

Study design, population and location

The present study was a cross-sectional, community-based study, conducted in 2014, in the Ragama Medical Officer of Health (MOH) administrative area of the Gampaha District, Sri Lanka. This urban population had a multi-ethnic composition. The study was conducted as part of the Ragama Health Study (RHS): collaborative research between the International Medical Centre of Japan and the Faculty of Medicine, University of Kelaniya, Sri Lanka. RHS is a community-based investigation of non-communicable diseases.

Population

The study population consisted of adolescents belonging to the year 2000 birth cohort.

They were 14-year olds when the study was conducted. A sample of 456 adolescents was required to obtain a 95±2% confidence interval, with an estimated 1000 births for the year 2000 in the Ragama MOH area, and expected response rate of 50%, and for an estimated obesity prevalence of 5%. Therefore, all adolescents belonging to the year 2000 birth cohort were invited in writing or by telephone to participate in the study. The objectives, procedures involved and benefits and risks of the study were explained in detail to both parents and children. Written consent from the parents and assent from the adolescents were obtained prior to enrollment in the study. The same study population was described earlier in a previous paper reporting non-alcoholic fatty liver disease in this population (7).

Data collection

All participants attended a special clinic at the Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka. They were requested to present after a 12 hour fast and along with all available medical records. Participants were interviewed by trained interviewers to obtain socio-demographic characteristics, birth history, history of breastfeeding, lifestyle habits of the child and details of the parents' medical history. All available medical records, including Child Health Development records, were also reviewed (7).

A complete physical examination was conducted on adolescents. This included anthropometric measurements (weight, height and waist circumference). Subjects were asked to remove shoes and empty their pockets before body weight was measured using a calibrated digital weighing scale, accurate to the nearest 0.1 kg, placed on an even concrete floor (Seca 893). The height was measured using a portable upright plastic stadiometer with a graduation of 1 mm (Seca 213). BMI was calculated as weight in kilograms divided by height squared in meters (kg/m2). Waist circumference (WC) was measured using a measuring plastic flexible tape with a graduation of 1 mm (Seca 203) (Seca Deutschland, Medizinische Messsysteme und Waagen. Hamburg, Germany). WC was measured midway between the highest point of the iliac crest and the lower point of costal margin in the mid-axillary line, at the end of normal expiration with the subject having minimum clothing at the waist area (7).

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured two times, with an interval of 3 min, using an automated blood pressure monitor (Omron Healthcare Co LTD Kyoto, Japan).

The average of the two values for both systolic and diastolic pressures was recorded. Total body fat (TBF) and visceral fat percentage (VFP) were measured using a body composition monitor employing a bioelectrical impedance method. TBF and VFP measurements were done according to the instruction manual (Omron HBF-362 body composition monitor, Omron Healthcare Co LTD Kyoto, Japan).

All participants had an ultrasonography examination of the liver. (5-MHz 50 mm convex probe; Mindray DP-10 Ultrasound Diagnostic Systems, Mindray Medical International Limited, Shenzhen, China). The ultrasound examinations were performed by five doctors who had special training in liver ultrasonography (7).

10 mL of venous blood was obtained from each participant was used to determine fasting serum triglycerides (TG), high-density lipoproteins cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), serum alanine transaminase activity (ALT), fasting plasma glucose (FBS) levels and serum insulin.

Definitions

General obesity (GO) was defined by the BMI for age method as BMI > equivalent of >25 kg/m2 among adults. For boys, GO was BMI >27.63 kg/m2 and for girls GO was BMI >28.57 kg/m2 (8). Central obesity (CO) was defined by WC > age and sex equivalent. For boys, CO was WC >76.1cm, and for girls, it was WC >70.0cm (8). Global obesity was defined by the presence of both GO and CO. Abnormal TBF was defined as values more than for age and sex equivalent. For boys, abnormal TBF was >25% and for girls >32%.

Fatty liver was diagnosed in the presence of two or more of the following ultrasound criteria: increased echogenicity of the liver compared to the spleen or the kidney, blurring of the liver vasculature and deep attenuation of the ultrasonography signal (9). This has an adequate threshold for the detection of steatosis within more than 33% of hepatocytes on liver histology (10). Non-alcoholic fatty liver disease (NAFLD) was defined as the presence of fatty liver on ultrasound with safe or absent alcohol consumption.

The homeostasis model assessment for insulin resistance (HOMA-IR score was calculated by using the following formula: HOMA-IR score = (fasting insulin [μU/ml] X Fasting glucose [mmol/ L])/22.5 (11).

Statistical analysis

Data were entered to a custom database created in EpiData version 3 (The EpiData Association, Odense, Denmark) and logical and random checks were done to minimize errors in data entry. Statistical analysis was done using R programming language 3.5.1. Continuous data were summarized using median and interquartile range (IQR). Group comparisons were made with Wilcoxon Rank Sum Test.

Generalized linear models were used to assess the relationships between antenatal and postnatal exposure variables with binary response variables where separate models were developed for CO, GO and global obesity. Generalized linear models with binomial distribution assumptions showed under-dispersion in CO and global obesity models while over-dispersion was observed in the GO model; therefore, quasi-binomial models were adopted in all three instances. $P<0.05$ was considered significant.

Ethical approval

Ethical approval for the study was obtained from the Ethics Review Committee, Faculty of Medicine, University of Kelaniya, Sri Lanka(approval reference number: P/191/09/2014).

Results

508 adolescents participated in the study, and 260 (51.2%) were girls. Median birth weight was 2.9 (IQR 2.6-3.2) kg. Nine (1.8%) had maternal gestational diabetes mellitus (GDM). The median age of menarche among the girls was 12 (IQR 11-13) years. The characteristics of the study population for boys and girls are summarized in Table 1.

The prevalence of CO in the cohort was 27.0% (95% CI: 23.2% - 30.9%) (Table 2). Girls showed a higher prevalence of CO compared to boys ($P<0.001$). GO was seen among 1.8% (95% CI: 0.6% - 2.9%) without gender differences($P=0.747$). Global obesity was observed among 1.6% (95% CI:0.5% - 2.7%) of the cohort without gender differences as well (Table 2).

Distribution of blood pressure, biochemical investigations and TBF of the adolescents with and without and CO and GO are shown in Table 3. Centrally obese adolescents had higher SBP and DBP, ALT, serum insulin, HOMA-IR, total cholesterol, LDL, VLDL, total cholesterol/HDL ratio, triglyceride levels and TBF, compared to centrally non-obese adolescents (figure 1).

Adolescents with general obesity showed higher SBP, ALT, serum insulin, HOMA-IR levels and TBF. FBSwas not different between the two groups (figures 2).

CO showed a positive association with increasing birth weight (OR: 1.17, 95% CI: 1.05 - 1.31 for every 250 grams increment) and CO was higher among girls (OR: 3.77, 95% CI: 2.43 - 5.99). There was an inverse relationship between GO and birth order of the child in the family. Each child with high birth order showed less GO (OR: 0.15, 95% CI: 0.01 - 0.62). GDM showed a positive tendency towards global obesity (OR: 8.79, 95% CI: 0.44 - 58.49), however, there were only eight adolescents with global obesity which resulted in a wide 95% CI (Supplementary Tables 1 and 2).

We observed similar rates of GO of 1.5-2.0%. GO was higher among boys than among girls in the present study, but this difference was not statistically significant. Previously published studies have reported females to be at a higher risk of developing GO and its consequences (12). Fat deposition begins early in females with the onset of puberty and continues unless consciously controlled. We observed higher rates of CO among the girls compared to the boys, which is in keeping with the above observations.

Previous studies from Sri Lanka have reported GO rates of 2.7% among girls and 1.7% among boys (10-15-year-olds) and 4.2% overall (5-15 years olds) (13, 14).

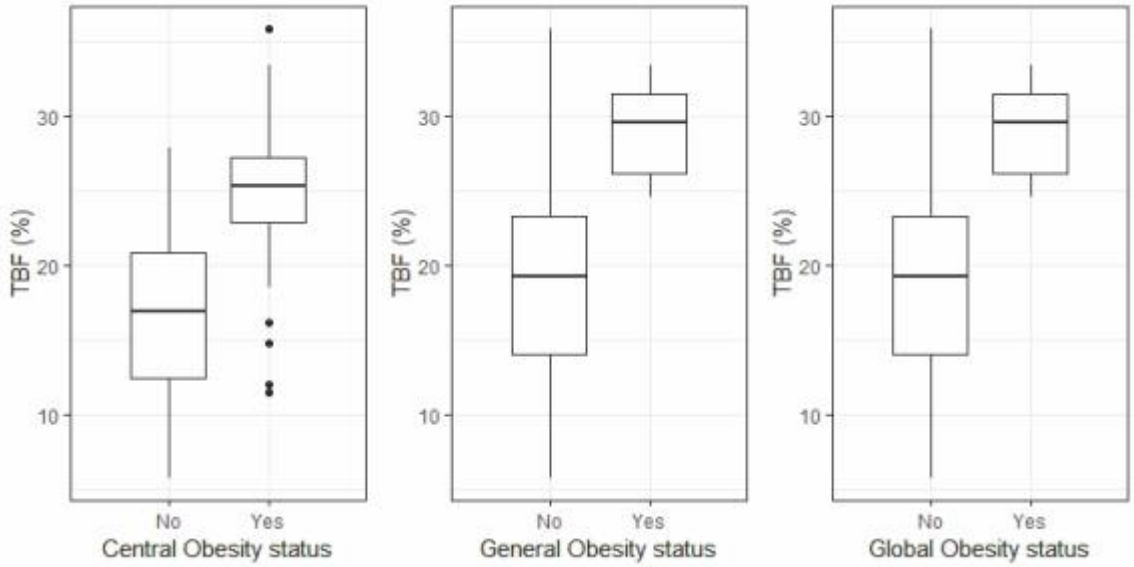

Figure 1: Distribution of total body fat among those with- and without central, general and global obesity

Discussion

In this first community-based study from a birth cohort of 14-year-old adolescents from an urban community in Sri Lanka, we found CO to be more common than GO. CO was significantly higher among girls than in boys (37.7% vs 15.7%). GO was observed among 2% of boys and 1.5% of girls. CO was independently associated with female gender and increasing birth weight while GO was independently associated with lower birth order. We also found that both CO and GO were independently associated with metabolic traits such as blood pressure, glucose and lipid metabolism and the presence of fatty liver.

Estimated rates of GO among children and adolescents (2-20 years) from Sri Lanka is 1.9% for boys and 2.2% for girls (6).

In another study of school girls aged 14-18 years from Sri Lanka, the rate of CO was 21.6% while GO was 5.5% (15). We observed comparable but lower GO rates among boys and girls but higher CO rates among girls in the present study. The observed rates of GO in the present study are also comparable but towards the lower end of the reported rates for GO among 5-19-year-old in other low- and middle-income countries (16). The reported rates of GO include 5.4% (among 5-18 year olds) from Argentina, 1.2 % (among 17-19 year olds) from Brazil, 1.6% (among 12-18 year olds) from China, 6.2% (among 11-19 year olds) from Egypt, 2.8-5.3% (among 8-18 year olds) from India, 7.9% (among 11-19 year olds) from Mexico, 6-6.7% (among 1-18 year olds) from Saudi Arabia, 9.4% (among 6-15 year olds) from Thailand and 3.7% (among 6-16 year olds) from Turkey (17-24).

In a previous study from Sri Lanka, being the firstborn was associated with GO in school girls aged 14-18 years (25). This finding is compatible with our finding of an inverse association between GO and birth order of the child. We also observed that CO had a positive association with female gender and increasing birth weight, while global obesity had a trend towards positive association with GDM. However, we could not elicit associations between breastfeeding and prematurity with GO in our study, although it has been shown that breastfeeding is a protective factor for GO and prematurity is associated with GO (26-28). We had only nine adolescents with global obesity, and it is possible that the non-significance of these factors are due to the small number of adolescents in the sample leading to low statistical power in our models.

Adolescence is identified as a critical period for the development of obesity-related metabolic derangements (29). We have also previously reported 8.4% prevalence of NAFLD in this same cohort with CO and GO being significantly associated with NAFLD (7). The consequences of childhood obesity include earlier puberty and menarche in girls, type 2 diabetes and increased incidence of the metabolic syndrome in youth and adults, and obesity in adulthood. These changes are associated with cardiovascular disease as well as with several cancers in adults, most likely to be mediated through insulin resistance and production of inflammatory cytokines (30). We observed many metabolic associations with childhood obesity in the present study.

There were high systolic and diastolic blood pressures, ALT, serum insulin, HOMA-IR, total cholesterol, LDL, VLDL, total cholesterol/HDL ratio and TG in adolescents with CO, compared to the adolescents without CO. However, FBS levels were not different between the two groups indicating that these adolescents are still able to maintain FBS despite high serum insulin and HOMA-IR levels. This is compatible with the finding that many children were able to control glucose within normal limits with evidence of early development of insulin resistance, in a previous study from Sri Lanka (31). Adolescents with GO had higher SBP, ALT, serum insulin and HOMA-IR levels compared to those without GO, but there was no difference in total cholesterol, LDL, VLDL, total cholesterol/HDL ration and triglyceride levels. The failure to demonstrate statistical significance in comparisons between those with and without global obesity is likely to be due to the low statistical power of the Wilcoxon Rank Sum test, as there were only eight adolescents with global obesity out of 508.

The strength of the present study is that it is a true community based, birth cohort study eliminating the bias of recruiting subjects from hospital clinics or educational institutions. We were able to achieve a response rate of approximately 50% from among those invited to participate (we calculated a response rate of 46% to power the study adequately). All participants were of the same age - 14 years (born in the year 2000) at the time of the survey. By selecting a group of adolescents of the same age, we were able to minimize rapid age-related changes in metabolism and fat distribution with the age group. However, there were some limitations. Diet is an essential factor in the development of obesity. In the present study, the data collected on dietary practices were considered too unreliable for analysis. Furthermore, data obtained on gestational and early feeding practices tend to have recall bias, but we were able to minimize this by checking the child health development records of the adolescents. Similarly, recall bias could have been present when assessing physical activity and sedentary time, but probably to a lesser extent.

A high prevalence of obesity and associated metabolic complications has been reported among children and adolescents in several low- and middle-income countries from previous studies (17, 32). These findings have been confirmed again in the present study. These prevalence figures are likely to increase further in the coming years (32). Therefore, therapeutic lifestyle changes, including healthy diet and maintenance of regular physical activity through parental initiative and social support interventions are the most important strategies to tackle childhood obesity. Screening of high-risk populations and effective health education programs are urgently needed to tackle the growing problem of childhood obesity and to prevent future adulthood diseases related to obesity.

Conclusion

In this cohort of adolescents from the same birth year, CO was more prevalent than GO. CO was commoner among the girls. GO was associated with lower birth order while CO showed association with female gender and higher birth weight.

Abbreviations

ALT - serum alanine transaminase activity
BMI - body mass index
CO - Central obesity
GDM - gestational diabetes mellitus
GO - General obesity
HDL - high-density lipoproteins cholesterol

HOMA-IR- homeostasis model assessment for insulin resistance
IQR- interquartile range
LDL - low-density lipoprotein cholesterol
MANCOVA - Multivariate analysis of covariance
MOH – Medical Officer of Health
NAFLD - Non-alcoholic fatty liver disease
RHS – Ragama Health Study
TBF - Total body fat percentage
TG - serum triglycerides
VFP - visceral fat percentage
VLDL - very low-density lipoprotein cholesterol
WC - Waist circumference

DECLARATIONS

Author contribution
MAN, SR and HJdeS conceptualized the study. AK, STDeS, DCG, YCJ and APDeS was involved in data collection. DS and AP with the assistance of MAN and HJdeS analyzed the data. MAN, DSE, AVGAMJ drafted the manuscript. All authors critically revised the manuscript. All authors read approved the final version of the manuscript.

Ethics approval and consent to participate
Ethical approval for the study was obtained from the Ethics Review Committee, Faculty of Medicine, University of Kelaniya, Sri Lanka. Written consent from the parents and assent from the adolescents were obtained prior to recruitment.

Availability of data and materials
The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author disclosure statement
All authors declare they have no competing interests to declare.

Consent for publication
Not applicable

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Supplementary Tables 1: Fitted generalized linear models for CO, GO and global obesity (variables in binary format)

Dependent variable	Independent variables	Estimate	Std. Error	Z value	P
Central obesity	Intercept	-3.58061	0.70816	-5.056	<0.001
	Female sex	1.328	0.223	5.780	<0.001
	Birth weight (every 250 grams)	0.15811	0.05568	2.840	0.005
	Dispersion parameter	1.02			
	Residual deviance	523.9	Degrees of freedom		476
General obesity	Intercept	-1.4204	1.1048	-1.286	0.199
	Birth order	-1.9189	0.9495	-2.021	0.044
	Dispersion parameter	0.85			
	Residual deviance	82.2	Degrees of freedom		482
Global obesity	Intercept	-4.253	0.381	-11.150	<0.001
	GDM	2.173	1.129	1.925	0.055
	Dispersion parameter	1.00			
	Residual deviance	79.9	Degrees of freedom		506

supplementary tables 2: odds ratios with 95% confidence intervals for the variables associated with central obesity, general obesity and global obesity.

Dependent variable	Independent variables	odds ratio (95% confidence interval)	P value
Central obesity	Birth weight (for every 250 grams)	1.17 (1.05 - 1.31)	0.005
	Female sex	3.77 (2.43 - 5.99)	<0.001
General obesity	Birth order (for every high order)	0.15 (0.01 - 0.62)	0.044
Global obesity	Gestational Diabetes Mellitus	8.79 (0.44 - 58.49)	0.055

Table 1: Characteristics of the study population

Variable	Girls (260) Median (IQR)	Boys (248) Median (IQR)
Height (cm)	154.3 (150.7 – 158.0)	159.7 (153.2 – 164.9)
Weight (cm)	67.0 (62.0 – 74.4)	63.7 (59.9 – 70.7)
BMI (kg/m^2)	18.7 (16.7 – 20.8)	17.0 (15.7 – 19.0)
Total body fat percentage (%)	22.8 (20.0 – 25.7)	14.3 (11.2 – 18.5)
Systolic blood pressure (mmHg)	103.0 (95.0 – 110.6)	104.0 (94.9 – 112.5)
Diastolic blood pressure (mmHg)	65.5 (60.5 – 70.5)	62.0 (57.0 – 69.0)
ALT (IU/L)	11.0 (10.0 – 14.5)	13.0 (11.0 – 17.0)
Fasting blood glucose (mg/dL)	78.0 (73.0 – 82.5)	80.0 (75.0 – 85.0)
Serum insulin (μU/mL)	9.9 (7.4 – 14.4)	8.3 (6.4 – 11.4)
Total cholesterol (mg/dL)	166.0 (149.0 – 188.5)	153 (139.0 – 171.2)
HOMA- IR	130.3 (90.6 – 185.1)	112.8 (82.1 – 150.4)
HDL cholesterol	48.0 (47.0 – 49.0)	47.0 (47.0 – 48.0)
LDL cholesterol	102.2 (84.5 – 121.9)	88.0 (74.2 – 105.8)
VLDL cholesterol	16.8 (13.8 – 21.3)	15.8 (12.2 – 21.2)
Total cholesterol/HDL ratio	3.5 (3.2 – 3.9)	3.2 (2.3 – 3.6)
Triglycerides	84.0 (69.0 – 106.5)	79.0 (61.0 – 106.2)

Table 2: Prevalence of General obesity, Central obesity and Global obesity with 95% Confidence intervals

Indices	Overall	Boys	Girls	P value
Central obesity	26.7% (23.2% - 30.9%)	15.8% (11.2% – 20.3%)	37.8% (31.9% – 43.7%)	<0.001
General obesity	1.8% (0.6% - 2.9%)	2% (0.3% - 3.8%)	1.5% (0.1% – 3.0%)	0.747
Global obesity	1.6% (0.4% - 2.7%)	1.6% (0.1% - 3.2%)	1.5% (0.1% - 3.0%)	1.000

Table 3: Distribution of blood pressure and biochemical investigations among adolescents with respect to presence and absence of central obesity and general obesity

Variable	Central obesity (CO)			General obesity (GO)		
	Presence	Absence	P value	Presence	Absence	P value
Systolic blood pressure (mmHg)	110.5 (101.5- 117.0)	101.5 (93.0- 109.0)	<0.001	114.5 (111.0- 121.5)	103.0 (95.0- 111.5)	0.002
Diastolic blood pressure (mmHg)	67.0 (62.0- 72.5)	63.0 (58.0- 68.5)	<0.001	66.0 (63.0- 73.0)	64.0 (59.0- 69.5)	0.130
ALT (IU/L)	14.0 (10.0 – 20.0)	12.0 (10.0- 15.0)	<0.001	25.0 (14.0- 39.0)	12.0 (10.0-15.7)	0.002
Fasting blood glucose (mg/dL)	79.0 (74.0- 85.0)	79.0 (74.0- 83.0)	0.493	79.0 (77.0- 86.0)	79.0 (74.0-84.0)	0.466
Serum insulin (µU/mL)	13.8 (10.3- 18.0)	8.0 (6.3 -10.5)	<0.001	21.1 (15.2- 26.3)	9.0 (6.8- 12.8)	<0.001
HOMA- IR	181.1 (136.5- 225.5)	105.3 (80.2-141.0)	<0.001	278.4 (195.1-351.5)	118.7 (85.2-170.5)	<0.001
Total cholesterol (mg/dL)	170.0 (153.0- 192.0)	156.0 (141.0- 175.0)	<0.001	165.0 (143.0- 193.0)	159.0 (142.2- 180.0)	0.549
HDL cholesterol	48.0 (47.0- 49.0)	47.0 (47.0- 48.0)	0.003	48.0 (47.0- 48.0)	48.0 (47.0- 48.0)	0.967
LDL cholesterol	103.4 (86.6- 122.0)	92.3 (75.9 -109.0)	<0.001	88.4 (73.6- 111.4)	95.4 (78.0- 112.3)	0.980
VLDL cholesterol	17.4 (14.4- 22.6)	16.0 (12.4- 20.4)	<0.001	22.6 (14.6- 27.8)	16.4 (12.8- 21.2)	0.117
Total cholesterol/HDL ratio	3.6 (3.3- 3.9)	3.3 (3.0- 3.6)	<0.001	3.4 (3.0- 3.9)	3.4 (3.0- 3.7)	0.520
Triglycerides	87.0 (72.0- 113.0)	80.0 (62.0- 102.0)	<0.001	113.0 (73.0- 139.0)	82.0 (64.0- 106.0)	0.118
Total body fat distribution (TBF)	25.4 (22.9 – 27.3)	17.0 (12.5 – 20.9)	<0.001	28.5 (25.4 – 31.2)	19.3 (14.1 – 23.3)	<0.001

REVIEW ARTICLE

Resmetirom: the new kid on the block for at risk MASH

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent condition, affecting approximately 30% of individuals worldwide.

A significant portion of these cases progress to metabolic dysfunction-associated steatohepatitis (MASH), a more severe form of MASLD. MASH-induced cirrhosis has become a primary reason for liver transplants and the most frequent cause of liver cancer.

Until recently, there were no liver-directed therapies for MASH. However, the Food and Drug Administration's (FDA) conditional approval of resmetirom marks a significant advancement in MASH treatment. This new therapy is specifically designed for patients with moderate to advanced MASH who have not yet developed cirrhosis, particularly those with fibrosis stages 2 or 3.

The introduction of resmetirom brings both opportunities and challenges to the medical community. One key issue is developing accurate non-invasive methods to identify patients with stage 2-3 fibrosis who are suitable candidates for the treatment. Additionally, it's crucial to exclude patients with more advanced disease, as the safety and efficacy of resmetirom in these cases remain uncertain.

This article examines the current research on identifying appropriate candidates for resmetirom treatment and proposes guidance for when to discontinue therapy. By addressing these aspects, we aim to optimize the use of this new treatment option for MASH patients.

INTRODUCTION

Resmetirom is an oral, liver-directed, thyroid hormone receptor beta-selective agonist targeted for the treatment of metabolic dysfunction-associated steatohepatitis (MASH), the progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD) (1).

On March 14, 2024, the Food and Drug Administration (FDA) granted conditional approval to resmetirom for treating fibrotic (stage 2 or 3) MASH (1).

This marks a significant milestone in MASH treatment, as previous attempts to gain regulatory approval for MASH liver-directed therapies had been unsuccessful despite numerous clinical trials(2-6).

The FDA's decision to grant conditional approval was based on resmetirom meeting specific histological endpoints in noncirrhotic MASH patients with moderate to advanced fibrosis. These endpoints include resolving steatohepatitis without worsening fibrosis or improving fibrosis by one stage without exacerbating steatohepatitis (7). Full FDA approval will require demonstrating favourable liver-related and overall clinical outcomes in MASH patients, a process that typically requires extensive time.

Resmetirom's approval for treating patients with moderate to advanced fibrosis, excluding those with cirrhosis, represents a breakthrough after over 20 years of research(8). It is currently the only liver-directed therapy supported by successful phase 3 clinical trial data from the MAESTRO NASH study (1).

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The FDA's initial approval specifies that resmetirom is indicated for adults with noncirrhotic MASH and moderate to advanced liver fibrosis (stages F2 to F3), in conjunction with diet and exercise (9). This target population, often referred to as "at-risk MASH" in literature, aligns with recent AASLD guidance on patients most likely to benefit from liver-directed treatments (10).

Based on trial data and established benchmarks, this article aims to guide identifying suitable candidates for resmetirom treatment and assessing treatment response. As this guidance is being written shortly after drug approval, future analysis of emerging data, including real-world evidence, is expected to further refine best practices, particularly regarding monitoring treatment response and adverse effects.

RESMETIROM USE IN CLINICAL PRACTICE.

Identifying Suitable Patients for Resmetirom Treatment

1. Diagnosing MASLD:
Before considering resmetirom treatment, a diagnosis of MASLD must be established. While the MAESTRO-NASH trial used older terminology, the overlap between old and new nomenclature is approximately 99% (8). It's crucial to rule out other liver conditions, particularly alcohol-associated liver disease, iron overload, viral hepatitis, and autoimmune hepatitis (10). Special attention should be given to excluding autoimmune liver disease, as its inclusion in MASH trials has led to concerns about elevated liver enzymes (8). Alcohol intake should be assessed through patient history and, if necessary, biomarkers like phosphatidylethanol (PEth) (11).

2. Confirming Fibrosis Stage:
Ideally, a liver biopsy within the past 12 months showing MASH with stage 2 or 3 fibrosis is the gold standard for patient selection. However, non-invasive tests (NITs) can be used when biopsy is not available or practical(8). While FIB-4 is useful for screening high-risk patients, it's not ideal for deciding on resmetirom treatment initiation or assessing response. Instead, a combination of NITs is recommended, with specific cut-offs provided for various tests like VCTE, ELF, and others (10).

In the absence of a recent biopsy, several non-invasive criteria are proposed, preferably including liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE) (10).

Multiple NITs can increase precision in staging hepatic fibrosis and predicting clinical outcomes.These recommendations are based on the MAESTRO-NASH trial and current AASLD guidelines (10).

3. Understanding "At-Risk" MASH:
Patients with "at-risk" MASH (steatohepatitis with stage 2 fibrosis or higher) face a significantly increased risk of liver-related morbidity and mortality (12). The disease spectrum ranges from MASL to cirrhosis, with non-cirrhotic significant liver fibrosis (stages 2-3) being the target for resmetirom treatment (9).

The MAESTRO-NASH study included patients with at least 3 cardiometabolic risk factors and specific VCTE results. Baseline characteristics and NIT results from this study provide valuable context for patient selection in clinical practice (13).

After confirming eligibility, patients should be dosed according to their weight. The FDA label recommends weight-based dosing: 80mg for patients under 100 kg and 100mg for those over 100 kg.Regular monitoring through liver chemistry tests and yearly liver stiffness measurements is recommended to assess safety and disease progression (8).

This approach aims to identify patients most likely to benefit from resmetirom while minimizing the risk of treating those with either too early or too advanced disease stages.

Patients Not Recommended for Resmetirom Treatment

1. Patients with Confirmed or Suspected Cirrhosis:
Given the challenges in precisely determining disease stages using non-invasive tests (NITs), it's advisable to err on the side of caution. Patients likely to have established cirrhosis should not be treated with resmetirom, as its efficacy and safety in this population are still being evaluated in ongoing clinical trials (8).

Indicators of advanced cirrhosis that would exclude patients from treatment include (8):
- Previous liver biopsy showing stage 4 fibrosis
- Imaging evidence of portal hypertension, ascites, or varices
- History of hepatic decompensation
- Clinical or laboratory signs of portal hypertension or liver dysfunction, such as:
* VCTE stiffness > 20 kPa or MR elastography> 5 kPa
* Platelet count <150,000/µl without alternative explanation
* ELF score > 11.3
* Unexplained hepatic nodularity on imaging
* Elevated bilirubin or other signs of impaired liver function

When using the ELF test alone, a score between 10.4-11.3 should be corroborated with additional NITs to confirm F2 or F3 disease and rule out cirrhosis (8).

The ongoing MAESTRO OUTCOMES trial is expected to provide comprehensive data on resmetirom's efficacy and safety in patients with compensated cirrhosis, which will inform future treatment decisions for this group (13).

2. Patients with Early-Stage Disease:
Individuals with early-stage MASLD (fibrosis stages 0 or 1) should not be considered for resmetirom treatment. These patients have a low risk of adverse liver-related outcomes and should instead be managed through lifestyle interventions and optimization of cardiometabolic health, as recommended by AASLD practice guidance (10).

In summary, resmetirom treatment should be reserved for patients with confirmed moderate to advanced fibrosis (stages F2 to F3) without cirrhosis. Careful assessment using a combination of clinical history, imaging, and non-invasive tests is crucial to identify suitable candidates and exclude those with either too early or too advanced disease stages.

Assessment of Treatment Response to Resmetirom

Evaluating response to resmetirom treatment involves analyzing changes in non-invasive tests (NITs) that may indicate histological improvement (14,15). While the relationship between NIT changes and histological response is still evolving, practitioners need to make clinical assessments using available tools.

Key indicators of potential histological response include:
1. ALT improvement: A reduction of 17 U/L or 20% has been associated with histological improvement in some studies. However, in the MAESTRO-NASH trial, many patients showed histological improvement without significant ALT changes, so this should be interpreted cautiously (1,16,17).

2. VCTE (FibroScan) stiffness: A reduction of 30% or more may indicate a meaningful change, given the test's coefficient of variation (18,19,20).

3. MRI-PDFF: A relative reduction of >30% was a strong predictor of histological response in the MAESTRO-NASH trial (1).

4. Other scores: Improvements in FAST, MAST, Agile 3+, Agile 4, and MEFIB scores have shown a correlation with liver-related outcomes, but require further validation in the context of pharmacological intervention (15,21,22).

It's important to note that failing to meet these thresholds doesn't necessarily indicate treatment failure (8). Many patients in the MAESTRO-NASH trial showed histological improvement without meeting these NIT thresholds.

Suggested Assessment Timeline:
1. Initial assessment (Week 12): Focus on safety and tolerability. Avoid efficacy judgments at this early stage.

2. 6-month assessment: Monitor disease progression. Consider VCTE or PDFF, but lack of response at this point may not indicate treatment failure.

3. 12-month assessment and annually thereafter:
- Continue treatment if:
  * Aminotransferases improve or normalize
  * Aminotransferases are stable but other improvements are present (e.g., MRI-PDFF reduction ≥30%)
- Consider discontinuation if:
  * No response in MRI-PDFF (if baseline measurement available)
  * >30% increase in liver stiffness or worsening in >2 NITs
  * Drug is not tolerated

Treatment failure may be indicated by worsening VCTE values (>30% increase), increased liver enzymes (>20%), or lack of improvement in MRI-PDFF (<30% reduction) (8). However, given the variability in NITs, worsening in at least two NITs should be considered before determining treatment failure.

Long-term real-world data on resmetirom treatment will further inform expected treatment duration and outcomes. The 54-month assessment of the MAESTRO-NASH study will provide crucial data on preventing progression to cirrhosis (8).

In cases of discrepant data or when a definitive assessment is needed, a liver biopsy can be considered (8). Regular monitoring of liver stiffness measurement (LSM) using a consistent method is recommended.

Safety Considerations for Resmetirom

Based on data from the combined safety phase 3 population (2,019 patients from MAESTRO-NASH and MAESTRO-NAFLD-1 trials), resmetirom has demonstrated a favorable safety and tolerability profile. The package insert details adverse reactions reported in more than 5% of patients in the MAESTRO-NASH trial, using exposure-adjusted incidence rates (EAIRs) per 100 person-years (8).

Key safety considerations include:
1. Gastrointestinal Effects:
- The most common adverse reactions were mild to moderate gastrointestinal disorders.

- Primary symptoms included nausea, diarrhoea, constipation, abdominal pain, and vomiting.
- These effects were dose-dependent.
- Diarrhea onset: Median 17 days (80 mg group) and 6 days (100 mg group), lasting about 20 days in both groups (8).
- Nausea onset: Median 28 days (80 mg group) and 5 days (100 mg group), lasting 26-28 days (8).
- In the 100 mg group, diarrhoea and nausea led to treatment discontinuation in 8 per 100 person-years (8).

2. Liver Enzyme Elevations:
- Early increases in liver enzymes were observed in the first 4 weeks, particularly in patients on statins.
- Mean ALT and AST increases were less than 1.5 times baseline (8).
- Enzyme levels typically normalized within 8 weeks without treatment discontinuation (8).
- This pattern is similar to other drugs in development that cause rapid decreases in liver fat content (23,24).
- One isolated case of potential hepatotoxicity was reported, resolving after treatment interruption (8).

3. Patient Education:
- Informing patients about potential gastrointestinal side effects is crucial to prevent unnecessary treatment discontinuations and improve real-world persistence rates.

4. Monitoring:
- Regular monitoring of liver enzymes, especially in the first 8 weeks of treatment, is advisable.
- Particular attention should be given to patients concurrently taking statins.

5. Dose Considerations:
- Adverse events were generally more frequent at the higher dose (100 mg per day).
- Clinicians should consider starting with the lower dose and titrating up as tolerated.

6. Long-term Safety:
- Continued monitoring and real-world data collection will be important to further establish the long-term safety profile of resmetirom.

By understanding these safety considerations, healthcare providers can better manage patient expectations, monitor for potential issues, and optimize treatment outcomes with resmetirom.

Considerations for Discontinuing Resmetirom Treatment

1. Initial Assessment Period:
- Conduct liver enzyme tests at 12 weeks after starting treatment
- This timing is crucial to properly assess potential hepatotoxicity (8)
- Early, mild, and transient increases in liver enzymes may occur and are consistent with the drug's efficacy profile

2. Avoiding Premature Discontinuation:
- Do not make decisions to stop treatment before the 12-week mark
- Early data interpretation can be challenging and potentially misleading (8)

3. Patient Education:
- Inform patients about potential signs of hepatotoxicity, including fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash (8)
- Emphasize the importance of reporting these symptoms promptly

4. Ongoing Monitoring:
- Continue regular liver enzyme tests throughout the treatment
- Be vigilant for any persistent and significant elevations

5. Criteria for Considering Discontinuation:
- Persistent and significant elevation of liver enzymes at any point during treatment
- Refer to specific thresholds and guidelines for liver enzyme elevations that warrant discontinuation (These should be based on current medical guidelines and the drug's prescribing information)

6. Individual Assessment:
- Consider each case individually, taking into account:
  * The patient's overall clinical picture
  * The severity and persistence of liver enzyme elevations
  * The presence of any symptoms indicative of liver dysfunction
  * The balance between potential benefits and risks of continuing treatment

7. Consultation:
- In complex cases, consider consulting with a hepatologist or other specialists experienced in managing NASH and drug-induced liver injury

By following these guidelines, healthcare providers can make informed decisions about when to discontinue resmetirom treatment, balancing the potential benefits of the medication against the risk of hepatotoxicity. Regular monitoring, patient education, and individualized assessment are key components of this approach.

Additional Considerations for Resmetirom Use

Resmetirom is metabolized by CYP2C8 and transported by OATP1B1 and OATP1B3. Therefore, concurrent use with potent CYP2C8 inhibitors (such as gemfibrozil) or OATP1B1/B3 substrates (like cyclosporine) should be avoided.

When using moderate CYP2C8 inhibitors (e.g., clopidogrel), consider reducing the resmetirom dose and monitoring patients more closely for adverse effects (8).

In late-stage clinical trials, resmetirom elevated plasma concentrations of certain statins. While this could theoretically increase statin-related side effects, none have been observed so far (8). As a precautionary measure, daily doses of statins should be limited as follows when used with resmetirom:

- Rosuvastatin and simvastatin: 20 mg maximum
- Pravastatin and atorvastatin: 40 mg maximum

These dosage limits align with or exceed standard maximum doses and are consistent with those used in the MAESTRO-NASH study population (8).

The FDA recommends adjusting doses of specific statins when used alongside resmetirom. Notably, in phase 3 safety data supporting resmetirom's approval (involving over 2,000 patients), about half were taking statins at baseline. This subgroup showed similar efficacy and safety profiles compared to those not on statins (8).

The authors do not anticipate issues with reducing statin doses as per the drug package insert, given resmetirom's significant effect on LDL reduction. After 52 weeks of treatment, patients with elevated baseline LDL levels experienced reductions of 14% and 20% in the 80 mg and 100 mg resmetirom groups, respectively, compared to no change in the placebo group (8).

Consequently, lowering statin doses in patients treated with resmetirom is not expected to negatively impact outcomes. Healthcare providers should continue to target appropriate LDL levels in high cardiovascular-risk patients, adjusting statin doses or using alternative agents as needed (8).

Endocrinological Considerations for Resmetirom Treatment

Resmetirom's effect on thyroid function has raised some questions. After 52 weeks of treatment, serum-free T4 levels decreased by approximately 16% to 19%. However, phase 3 trials reported no increase in endocrine-related adverse events, and TSH and T3/FT3 levels remained within normal physiological ranges (8). Resmetirom's mechanism involves upregulating T4 to T3 conversion through type 1 deiodinase (DIO1) specifically in the liver, mediated by thyroid hormone receptor beta (THR-β). Current evidence does not suggest central regulation of the hypothalamic-pituitary-thyroid (HPT) axis by resmetirom.

If central mediation occurred, a greater decrease in fT4 would be expected in patients without thyroid pathology compared to those on full hormone replacement therapy. However, the average fT4 decrease was similar between these groups (8).

Animal studies have shown that increased DIO1 leads to enhanced T3 clearance, which aligns with the stable T3/fT3 and TSH levels observed in resmetirom-treated patients (25). While resmetirom can be co-administered with thyroid hormone replacement therapy without interference, future research will assess any potential impacts on thyroid monitoring or bone health.

Resmetirom treatment also elevated sex hormone-binding globulin (SHBG) levels, indicating target engagement. This resulted in minor changes in sex hormone levels.

Although this has prompted some concerns about potential long-term effects, free testosterone levels remained stable, and no changes in bone mineral density were observed (8). Current safety data do not indicate a cause for alarm, but ongoing monitoring will continue to assess any long-term implications.

In summary, while resmetirom affects certain endocrine parameters, current evidence suggests these changes are manageable and do not pose significant health risks. However, continued research and monitoring are essential to fully understand the long-term endocrinological implications of resmetirom treatment.

Concomitant Use of Resmetirom with GLP-1 or GLP-1/GIP Dual Agonists

The use of GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists is becoming increasingly common for treating obesity and type 2 diabetes in the United States. These conditions often coexist with metabolic dysfunction-associated steatohepatitis (MASH) (26).

For patients already on GLP-1-based therapies who have active MASH with stage 2 or 3 fibrosis, initiating resmetirom treatment is recommended. In the MAESTRO-NASH trial, approximately 14% of patients were on GLP-1 receptor agonist therapy at baseline, and this did not appear to affect resmetirom's tolerability or efficacy (8).

However, due to a lack of evidence supporting the safety and efficacy of starting both GLP-1-based therapy and resmetirom simultaneously, this combination is not recommended for treatment-naïve patients (8).

For patients who have not previously used either GLP-1 agonists or resmetirom and have MASH with F2 or F3 fibrosis, clinicians should carefully weigh the risks and benefits of each therapy based on the individual patient's profile. It's important to note that to date, only resmetirom has demonstrated effects on both MASH resolution and fibrosis regression in a large phase 3 registration trial. These recommendations align with the most recent European Association for the Study of the Liver (EASL) guidelines for MASH diagnosis and treatment (27).

Currently, resmetirom is the only FDA-approved liver-directed therapy for MASH.

SUMMARY

Resmetirom received FDA approval for MASH treatment on March 14, 2024. It is indicated for patients with "at-risk MASH" who have developed stage 2 or stage 3 fibrosis. Patients with cirrhosis or early (F0-1) fibrosis should not be treated with resmetirom at this time.

Liver biopsy or non-invasive tests can be used to identify suitable candidates for resmetirom treatment, monitor safety, and assess treatment efficacy. As new data emerges, particularly regarding non-invasive assessment of treatment response, it is likely to further refine patient selection criteria, safety monitoring, and efficacy evaluation methods.

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The authors have no conflicts of interest to declare

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MINI REVIEW

Revisiting The Clinical Use of Proton Pump Inhibitors

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INTRODUCTION

Proton Pump Inhibitors (PPI) are among the widely prescribed medications in clinical practicein managing range of conditions related to gastric acid secretion. They serve as the cornerstone in management of peptic ulcer disease, gastro esophageal reflux disease, Non - Steroidal Anti Inflammatory Drugs(NSAID) induced ulcers, Helicobacter pylori eradication and Zollinger Ellison syndrome. Moreover, there are occasions where PPIs are used "off-label" to prevent symptoms associated with acid secretion.

Apart from its therapeutic advantages there is a rising concern regarding the adverse effects associated with the prolonged or higher doses of PPIs beyond recommended dosages or indications where their benefits are less certain and drug interactions.

The aim of this article is to address the appropriate uses and potential adverse consequences linked to PPIs.

REVIEW

PPIs are weakly basic prodrugs belonging to the Benzimidazole class and are susceptible to degradation by gastric acid. They are absorbed in the proximal small intestine and selectively accumulate in the acidic secretory canaliculi of gastric parietal cells. Here, they undergo acid-catalyzed conversion into a reactive component (thiophilic sulfonamides), which then interacts with H-K ATPase, the ultimate step in gastric acid secretion. (7)

To hinder premature activation and breakdown by gastric acid in the stomach, many of these medications are encased in diverse delivery formats such as enteric-coated tablets, gelatin capsules, or coated granules.(7)

TIMING OF PPI

The level of H-K-ATPase in the parietal cell reaches its highest point following a period of fasting, whereas proton pump inhibitors (PPIs) exhibit their greatest effectiveness when the parietal cell is stimulated to produce acid postprandially. This correlation holds significant clinical importance regarding the most suitable timing for PPI administration. PPIs are typically given prior to the initial meals of the day, approximately thirty minutes to one hour before eating. (5)

INDICATIONS FOR PPI

The fundamental aspect of PPI therapy entails identifying the correctindication and use them for appropriate duration. PPIs are typically prescribed for either short-term or long-term use, depending on the underlying condition being treated.

In 2022, the American Gastroenterological Association (AGA) released an update on deprescribing PPIs, outlining short-term usage as ≤8 weeks and long-term usage as exceeding 8 weeks.

According to this clinical practice update the indications necessitating prolonged PPI usage are limited and includepeptic strictures, Barrett's esophagus, Zollinger-Ellison syndrome, eosinophilic esophagitis, Gastroprotection in users of Aspirin /non steroidal anti-inflammatorydrugs at high risk of bleeding and prevention of progression of Idiopathic pulmonary fibrosis.

Apart from those, PPI responsive conditions where they recur on withdrawal of PPI can be considered for long term use such as endoscopy-negative reflux disease, functional dyspepsia, upper airway symptoms ascribed to laryngopharyngeal reflux. Additionally, in refractory steatorrhea in chronic pancreatic insufficiency and secondary prevention of peptic ulcers long -term PPI can be considered.

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This update doesn't support long-term use of PPI in nonerosive reflux disease or functional dyspepsia when there is no sustained response to high dose PPI therapy and regular steroid therapy unless they on concomitant aspirin/NSAID.

Definitive indications for short-term use of PPI include Helicobacter pylori eradication, NSAID related peptic ulcers, prophylaxis for stress ulcers in ICU patients and uninvestigated reflux disease or dyspepsia. Short-term use of PPI is conditionally indicated in prevention of rebleeding from Mallory-Weiss tears and ulcer prevention after sclerotherapy or band ligation treatment of nesophagealvarices. (1,5)

EFFICACY OF PPIs

Direct comparisons of the efficacy of various PPIs in clinical trials are scarce, and the findings of systematic reviews of trials have yielded inconclusive results, with no single PPI consistently demonstrating superiority across all measures.

However, due to variations in formulations that can impact drug absorption and bioavailability, there can be difference in acid suppression or symptom alleviation. Nonetheless, they are generally considered as exhibiting similar effectiveness in acid suppression and symptom relief.

The efficacy of PPIs in acid suppression can vary among individuals. Although PPI s are frequently considered equivalently effective in acid suppression, several factors including differences in the oral bioavailability of PPIs, the timing of food intake in relation to the activation of ATPase pumps, and genetic variations in enzyme activitycan influence the pharma cokinetic parameters of PPIs.

Switching between different PPI formulations or adjusting the dosage may be beneficial for patients who do not respond adequately to initial therapy or experience side effects. (3,5)

Further, PPIs do not typically exhibit a tolerance phenomenon even with long-term use.

REASON FOR PARTIAL RESPONSE OR POOR RESPONSE

Reduced efficacy over time could stem from alterations in the underlying condition being treated such as deterioration of gastroesophageal reflux disease (GERD) or the emergence of complications like Barrett's esophagus.

Inadequate dosing, poor compliance, or variations in individual response to the medication may result in incomplete acid suppression even with standard PPI doses, leading to persistent symptoms despite treatment.

The manifestation of symptoms related to rebound acid hypersecretion (RAHS) may pose challenges when discontinuing PPI therapy.

DRUG INTERACTION

PPIs have been known to interact with a wide range of medications, impacting their efficacy or potentially increasing the risk of adverse effects by altering gastric acidity levels and inhibiting the CYP2C19 metabolism.

These are few clinically significant interactions involving PPIs such as Warfarin, Digoxin, Methotrexate, SSRIs (Selective Serotonin Reuptake Inhibitors) and Benzodiazepine where the PPIs have the potential to raise the drug levels of these medications in blood.

furthermore, PPIs can impair the absorption of certain drugs like antiretroviral, antifungal drugs reducing the efficacy. It is advisable to administer these medications separately or consider alternative treatment options to achieve the optimal outcome.

ADVERSE EFFECTS

While PPIs are generally considered safe for short term use, there is growingrecognition of adverse effects particularly with prolonged usage. These effects can be categorized into those related to acid inhibition and those unrelated and the acid suppression-related adverse effects are mostly evident during extended PPI therapy.

PPIs have been linked to changes in composition of gut microbiome potentially impacting gastrointestinal and overall health. These adverse effects include increased susceptibility to enteric infections including Clostridium difficile infection , reduced absorption of essential vitamins and minerals, potential aggravation of osteoporosis and bone fractures, susceptibility to pneumonia, and gastrointestinal malignancies.(5,7)

DEPRESCRIBING

Long-term use of PPIs without an ongoing indication or evidence of benefit contributes to increased pill burden, increased medicationrelated costs, and potential adverse effects. If an appropriate indication is not present, consider deprescribing the PPI.

The manifestation of symptoms related to rebound acid hypersecretion (RAHS) may pose challenges when discontinuing PPI therapy. The dose tapering regimen may need to be adapted based on patient-specific factors, but as a general strategy slowly taper off the PPI over 2-4 weeks as there is no specific method for discontinuing PPI therapy has been proven effective, and no approach is universally accepted. (2)

CONCLUSION

•PPIs should be prescribed for appropriate condition for an appropriate duration.

•Regular reassessment of the need for continued PPI therapy, especially in patients on long-term treatment aids in identifying whether the patient still requires PPI therapy or can be deprescribed.

•Deprescribing strategies (stopping or stepping down or reducing to intermittent use or on-demand use) should be employed when appropriate, aiming to taper or discontinue PPIs in patients where ongoing therapy may no longer be necessary.

•Patients who discontinue long-term PPI therapy should be advised regarding the chance of developing transient upper gastrointestinal symptoms due to rebound acid hypersecretion and when discontinuing PPI therapy, the dose should be tapered graduallyespecially in patients on PPIs for longer than six months. (1,2)

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NARRATIVE REVIEW

Unmasking the mimics: Navigating the diagnostic labyrinth of gastrointestinal tuberculosis and Crohn's disease

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ABSTRACT

Intestinal Tuberculosis (ITB) and Crohn's disease (CD) are chronic granulomatous conditions that often affect the terminal ileum. Historically, ITB was more prevalent in developing countries, while CD was more common in developed nations. However, recent shifts in epidemiology have blurred these distinctions.

Distinguishing between ITB and CD is crucial due to their differing treatment approaches. ITB requires anti-tubercular therapy (ATT), whereas CD is managed with immunosuppressants. Therefore, misdiagnosis or delayed diagnosis can have serious consequences. The challenge in differentiation lies in the lack of definitive diagnostic criteria for either condition. Clinical presentations, endoscopic findings, imaging results and even histology often overlap. Microbiological confirmation of ITB (through acid-fast bacilli detection, mycobacterial culture, or TB-PCR tests) is possible in only a subset of cases. Therefore, for both diseases, diagnosis typically relies on a combination of clinical, endoscopic, radiological, and histological evidence.

In TB-endemic areas, clinicians sometimes initiate a trial of ATT to assess response. Early mucosal improvement at two months can indicate ITB. However, prolonged ATT in CD patients may lead to fibrosis and stricture formation. Therefore, early and accurate differentiation is essential to avoid complications and ensure timely, appropriate treatment for CD.

KEYWORDS

Tuberculosis, intestinal tuberculosis, Crohn's disease, diagnosis

INTRODUCTION

Intestinal tuberculosis (ITB) and Crohn's disease (CD) present a significant diagnostic challenge due to their similar clinical, radiological, endoscopic, and histopathological features [1].

Despite these similarities, the two conditions have distinct origins and require different treatment approaches, making accurate diagnosis crucial [2,3].

CD is a form of inflammatory bowel disease (IBD), characterized by chronic inflammation that can affect any part of the gastrointestinal tract, often in a discontinuous pattern. Its development is thought to result from a complex interplay between genetic predisposition and environmental factors, leading to alterations in gut microbiota and immune response. Genetic studies have identified several CD-associated genes, many of which are involved in bacterial recognition and innate immunity. Environmental risk factors may include smoking, early-life antibiotic exposure, certain medications, and dietary habits [4].Patients with CD typically experience a gradual onset of symptoms, which vary depending on the disease location and behaviour (inflammatory, stricturing, or penetrating). Common presentations include abdominal pain, persistent diarrhoea, and weight loss. Rectal bleeding may occur in cases involving the colon, and perianal complications are frequent [4].

Tuberculosis, primarily caused by Mycobacterium tuberculosis, is an infectious disease that can affect various organs, including the gastrointestinal tract. While often associated with developing countries, ITB cases continue to occur in developed nations, particularly among immigrant populations and immunocompromised individuals. In endemic areas, many ITB cases may occur without identifiable risk factors.ITB, like CD, leads to chronic intestinal inflammation and granuloma formation. Common symptoms include abdominal pain, fever, diarrhoea, appetite loss, weight reduction, and occasionally rectal bleeding.

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Patients may also experience obstructive symptoms or present with right lower quadrant pain or mass. ITB can originate in the intestines or spread from pulmonary infection, most commonly affecting the terminal ileum and ileocecal region, but potentially involving any part of the gastrointestinal tract [5].

The distinction between ITB and CD remains a significant challenge for medical professionals worldwide. The overlapping clinical presentations of ITB and CD underscore the importance of careful diagnostic evaluation to ensure appropriate treatment and optimal patient outcomes. This review compiles current evidence to aid in differentiating these conditions and highlights ongoing research that may enhance diagnostic accuracy.

MISDIAGNOSIS

The prevalence of IBD including CD, is increasing in developing countries traditionally considered tuberculosis-endemic regions[6]. Simultaneously, developed nations continue to see TB cases, particularly in immunocompromised individuals, making this a global diagnostic challenge[7]. This shift has highlighted the need for effective strategies to differentiate between ITB and CD (Table).

Distinguishing between ITB and CD is crucial due to their similar presentations but differing treatment approaches. Misdiagnosis can lead to serious complications. Treating CD as ITB may result in unnecessary exposure to anti-tubercular therapy (ATT), potentially causing hepatotoxicity and increasing the risk of stricture formation[8]. Conversely, misdiagnosing ITB as CD and administering immunosuppressive therapy can lead to disseminated tuberculosis with potentially fatal outcomes[9].

While some studies suggest potential benefits of ATT in CD, growing evidence indicates that its use in CD patients may increase the risk of stricturing or penetrating disease [8,10,11]. This underscores the importance of early and accurate diagnosis. If initial differentiation is challenging, close monitoring and early follow-up colonoscopy are recommended when empirical ATT is initiated.

The difficulty in distinguishing these conditions stems from their similar clinical manifestations and the limited sensitivity of microbiological tests for ITB[3]. Studies have shown significant rates of misdiagnosis in both directions [12]. This emphasizes the need for improved diagnostic strategies and a careful approach to treatment decisions. Given the potential consequences of misdiagnosis and inappropriate treatment, there is a pressing need for more accurate diagnostic methods and clearer guidelines for differentiating ITB from CD. Future research should focus on developing and validating more reliable diagnostic tools and algorithms to aid clinicians in making this critical distinction.

CLINICAL PRESENTATION

Both CD and ITB can manifest with overlapping intestinal and extraintestinal symptoms, making differentiation challenging. However, certain clinical features may help distinguish between the two conditions, although none are definitively diagnostic.

CD typically presents with a more prolonged, indolent course, while ITB often has a shorter symptom duration (usually less than 6 months) [13]. Constitutional symptoms, particularly evening fever, are more indicative of ITB. Fever in CD is generally associated with complications like abscesses or infections.

Pulmonary symptoms such as cough, sputum production, and hemoptysis may suggest ITB, as a subset of patients can have concurrent pulmonary involvement [14]. Conversely, extraintestinal manifestations, perianal disease, diarrhoea, and hematochezia are more common in CD. A palpable abdominal mass is relatively rare in CD but may occur in ITB due to complications like bowel adhesions or loculated ascites[15].

A meta-analysis revealed that abdominal pain is equally common in both conditions, while chronic diarrhoea, hematochezia, and perianal signs are more frequent in CD. Constitutional symptoms like fever and night sweats are more prevalent in ITB [16].

The pathogenesis of ITB involves mucosal penetration by the organism, often from swallowed-infected sputum. However, only about 20-25% of ITB patients have concurrent pulmonary involvement [17, 18]. The presence of exudative ascites favours ITB over CD, as tuberculosis can affect both the intestine and peritoneum [19].ITB commonly presents with abdominal pain, weight loss, and fever, with diarrhoea occurring in only about 20% of cases [17]. An abdominal mass in the right lower quadrant is palpable in 25-50% of ITB patients [17]. In contrast, CD more frequently features diarrhoea, rectal bleeding, and perianal complications [13].

While these clinical features can provide valuable clues, it's important to note that they are not specific to either condition and should be considered alongside other diagnostic criteria for accurate differentiation between CD and ITB.

SEROLOGICAL EVALUATION

Tuberculin skin tests (TST) and Interferon-gamma release assays (IGRA) are used to identify past or latent tuberculosis infection. However, their utility in differentiating ITB from CDis limited. TST can yield false positives due to BCG vaccination or non-tubercular mycobacterial infections. While IGRAs are more specific for Mycobacterium tuberculosis, their sensitivity and specificity for distinguishing ITB from CD are not perfect [20].

A negative result from either test doesn't conclusively rule out ITB, and positive results in TB-endemic regions may reflect exposure rather than active disease.Some studies have explored using specific IGRA cutoff values to differentiate ITB from CD, with higher levels potentially indicating more severe ITB [21]. However, these findings require further validation.

CD is associated with various antimicrobial antibodies, including Anti-Saccharomyces cerevisiae antibody (ASCA) [22]. However, the diagnostic accuracy of ASCA for CD is limited, and studies have shown no significant difference in ASCA prevalence between ITB and CD patients. Additionally, ASCA levels don't correlate with disease characteristics in either condition [23].Other antibodies, such as those against zymogen granule glycoprotein GP2 (aGP2) and anti-I2 (Pseudomonas fluorescens-associated sequence), have been proposed as potential discriminators between ITB and CD. However, these findings need further validation [24].Most studies, particularly from India, don't support the use of ASCA or other antibodies for differentiating ITB from CD [23,25,26]. Currently, these serological tests are not routinely used for this purpose in clinical practice.

While various serological tests have been investigated, none have proven sufficiently reliable for definitively distinguishing between ITB and CD. The search for more accurate biomarkers continues, and clinicians must rely on a combination of clinical, radiological, and histopathological findings for diagnosis.

ENDOSCOPIC FINDINGS

Endoscopy plays a crucial role in diagnosing and managing both ITB and CD. Ileocolonoscopy is the preferred method for examining these conditions. While certain endoscopic features can suggest one diagnosis over the other, none are entirely specific to either disease.

In CD, endoscopic findings often include aphthous ulcers, linear ulcers, cobblestone appearance, and skip lesions. ITB, on the other hand, more frequently presents with circumferential ulcers, transverse ulcers, and a patulous ileocecal (IC) valve. Left-sided lesions tend to be more indicative of CD, although both conditions commonly affect the ileocecal region [2].

CD can involve any part of the bowel, while ITB primarily affects the ileocecal area but can also involve other colonic regions. Isolated jejunal involvement is rare in ITB but can occur in CD. ITB may also present with strictures or hypertrophic lesions like polypoidal masses, and rectal involvement is uncommon [27].

A comparative study of colonoscopy findings identified four features more common in CD (aphthous ulcers, longitudinal ulcers, cobblestone appearance, and anorectal involvement) and four more frequent in ITB (transverse ulcers, patulous IC valve, pseudopolyps, and involvement of fewer than four segments) [28].

Colonoscopy also provides an opportunity for tissue sampling. Biopsies should be taken from ulcer margins for histological and microbiological testing, including mycobacterial culture and molecular tests [29].

While the optimal number of biopsy samples is not standardized, more samples generally increase the likelihood of a positive TB result. Recent guidelines from the Indian Council of Medical Research suggest taking at least six biopsy samples in sterile saline for microbiological analysis [30].

It's important to note that while these endoscopic features can provide valuable diagnostic clues, they should be considered alongside other clinical, radiological, and laboratory findings for a comprehensive diagnosis.

IMAGING FEATURES

Imaging techniques play a crucial role in evaluating and differentiating ITB from CD. While plain radiographs have limited utility, they may be useful in emergencies or for detecting pulmonary TB in ITB patients [31]. Barium studies, though less common now, can reveal characteristic findings in both conditions.

Ultrasound (US) offers a non-invasive, cost-effective option for assessing bowel diseases. In CD, the US can detect increased bowel wall thickness, enhanced colour Doppler signal, and mesenteric changes. For ITB, the US can identify bowel thickening, lymphadenopathy, ascites, and peritoneal changes [32]. The US also facilitates tissue sampling but has limitations related to bowel gas, obesity, and operator experience.

Computed tomography (CT) and CT-enterography (CTE) provide comprehensive evaluation of intestinal and extraintestinal lesions in both conditions. In ITB, CT typically shows circumferential wall thickening and homogeneous mucosal enhancement in the ileocecal region, along with extraintestinal findings like lymphadenopathy and ascites [33]. Necrotic lymph nodes are particularly indicative of ITB.

In CD, CTE often reveals asymmetrical circumferential wall thickening, with more prominent involvement of the terminal ileum. Active disease is characterized by mucosal enhancement and mural stratification. Mesenteric changes, including the "comb sign" (prominent vasculature), fibrofatty proliferation, and fat stranding, are common. CT can also detect fistulas, which are more frequent in CD than ITB [34].

A meta-analysis of CT features found that necrotic lymph nodes are highly specific for ITB, while the comb sign and skip lesions are more indicative of CD [31]. However, it's important to note that no single imaging feature is pathognomonic, and diagnosis should be based on a combination of clinical, endoscopic, and imaging findings.

These advanced imaging techniques have largely supplanted older methods like barium studies due to their ability to provide more comprehensive information about both luminal and extraluminal pathology. They play a crucial role in diagnosis, assessment of disease activity, and monitoring treatment response in both ITB and CD.

Magnetic Resonance Enterography (MRE) offers similar findings to CT enterography but with superior soft tissue resolution and without ionizing radiation. MRI can differentiate active inflammation from fibrosis, with fibrotic strictures appearing hypointense on T2-weighted images and showing no diffusion restriction [34].Emerging imaging techniques, such as contrast-enhanced intestinal ultrasonography, dynamic contrast-enhanced MRI, and PET/MRI, show promise in distinguishing ITB from CD. A recent Indian study suggested that perfusion-CT parameters could help differentiate these conditions [35].

Radiological methods, particularly intestinal ultrasonography (IUS), have proven valuable in monitoring treatment response for both ITB and CD. IUS has shown comparable efficacy to endoscopy and MRE in assessing IBD response, with the added advantage of evaluating transmural healing [36]. For ITB, IUS has demonstrated high sensitivity in evaluating response to anti-tubercular therapy (ATT) [37]. MRI-based parameters, such as changes in apparent diffusion coefficient, have also been explored for assessing ATT response [38].

Imaging studies help differentiate ITB from CD based on several factors:

1. Site involvement: ITB more commonly affects the cecum and right-sided colon, while CD more frequently involves the left-sided colon.
2. Pattern: Skip lesions are more prevalent in CD (99%) than ITB (15%) [39].
3. Bowel wall characteristics: CD typically shows asymmetric, thicker (>6 mm) bowel walls with stratification [40].
4. Strictures: Eccentric strictures with sacculation suggest CD, while concentric strictures are more common in ITB.
5. Extraintestinal findings: Peritoneal thickening, omental caking, ascites, cocoon formation, and necrotic mesenteric lymph nodes are more indicative of ITB.
6. Fistulas: Enteroenteric and perianal fistulas, along with mesenteric fibrofatty proliferation, are more characteristic of CD.

These imaging features, combined with clinical and endoscopic findings, contribute to a more accurate differentiation between ITB and CD.

HISTOPATHOLOGY

Distinguishing ITB from CD remains challenging due to overlapping histological features.

However, endoscopic biopsy has emerged as a valuable diagnostic tool, revealing subtle mucosal differences between the two conditions.

Granuloma detection rates vary widely in both diseases, ranging from 10-80% in ITB and 15-65% in CD [29, 41]. Multiple biopsies from various sites, including the colon, rectum, and ileum, are recommended for accurate diagnosis. Longitudinal ulcers often yield the highest granuloma detection rates [42].

Macroscopically, ITB typically presents with short strictures, inflammatory thickening, fibrosis, and adhesions. Ulcers are often transverse and circumferential with ill-defined edges. CD, in contrast, shows longer strictures, fistulae, sinuses, and extra-intestinal abscesses. Ulcers in CD vary from deep longitudinal fissures to smaller ones creating a cobblestone pattern. Microscopically, ITB is characterized by multiple, large, confluent caseating granulomas with acid-fast bacilli, found throughout the intestinal wall and lymphoid tissue. CD typically shows smaller, discrete microgranulomas, deep fissuring ulcers, distorted mucosal architecture, and chronic inflammation with a patchy distribution[29].

A meta-analysis identified three highly specific histological features for ITB: caseating necrosis, confluent granulomas, and macrophage-lined ulcers. While these features have excellent specificity, their sensitivity is poor [43].

Immunohistochemistry (IHC) has been explored to differentiate between ITB and CD, with mixed results. Some studies suggested CD73 as a potential marker for ITB, but subsequent research has challenged its exclusivity [44,45].

Despite these advancements, conclusive histopathological diagnosis often remains elusive, underscoring the diagnostic challenges in distinguishing ITB from CD.

MICROBIOLOGY

Microbiological confirmation is considered the gold standard for diagnosing gastrointestinal tuberculosis (ITB), typically through acid-fast bacillus (AFB) staining, culture, or polymerase chain reaction (PCR) based techniques. However, these methods often have low sensitivity in intestinal tissue samples.

AFB positivity in intestinal tissue is particularly low (less than 5%), limiting its diagnostic utility for ITB [46]. Mycobacterial culture can improve diagnostic yield and provide drug sensitivity information, with reported positivity rates ranging from 7% to 79% [14]. The Mycobacterium Growth Indicator Tube 960 (MGIT) offers quicker results and better sensitivity (40-52.8%) compared to traditional culture methods [47].

PCR-based tests provide rapid diagnosis by targeting specific DNA sequences, typically IS6110, which is specific to Mycobacterium tuberculosis. A meta-analysis of MTB-PCR (IS6110) studies reported a pooled sensitivity of 47% and specificity of 95% for diagnosing ITB and differentiating it from Crohn's disease. However, the absence of IS6110 in some Indian strains may limit its sensitivity in certain populations [48].

The Xpert-MTB/RIF, a point-of-care platform, has shown high specificity (100%) but low sensitivity (23%) in intestinal tissue samples [49]. Multiplex PCR targeting multiple genes (IS6110, MPB64, and Protein B) has demonstrated improved sensitivity and specificity [50].

A chip-based real-time PCR assay (True NAT MTB Plus) offers rapid diagnosis and drug sensitivity testing. An Indian study reported 70% sensitivity and 100% specificity for ITB diagnosis, though further real-world studies are needed to establish its role in differentiating ITB from CD [50].

Combining PCR techniques with histopathology can significantly improve detection rates, with one study reporting 97.5% detection of ITB using this approach [51]. However, data on newer PCR-based tests like Xpert-Ultra in this context is currently lacking.

In summary, while microbiological confirmation remains the gold standard for ITB diagnosis, the low sensitivity of these techniques in intestinal samples presents a significant challenge. Combining multiple diagnostic approaches, including newer molecular techniques, may offer the best chance for accurate diagnosis and differentiation from Crohn's disease.

MULTI-PARAMETER PREDICTION MODELS

Various attempts have been made to develop comprehensive models or nomograms for distinguishing ITB from CD, as individual clinical, endoscopic, and laboratory parameters are not exclusive to either condition.

A notable study by Limsrivilai et al. employed a Bayesian model incorporating gender, clinical manifestations, endoscopic features, and laboratory findings. This model achieved 91.8% accuracy in diagnosing ITB, with 90.9% sensitivity and 92.6% specificity [16]. A subsequent validation study demonstrated its superiority over other models across multiple centres, with the lowest rate of misdiagnosing ITB as CD [52].

An Indian study developed a multivariate logistic model using clinical, endoscopic, and histological findings. This model, based on four variables (blood in stool, weight loss, sigmoid colon involvement, and focally enhanced colitis), achieved 81.1% accuracy in differentiating the two diseases [13].

Li et al. analyzed clinical and endoscopic features using logistic regression, reporting that a combination of factors including hematochezia, intestinal surgery history, perianal disease, pulmonary tuberculosis, ascites, and positive Mantoux test could differentiate ITB from CD with 90.3% sensitivity and 76.8% specificity [53].Other studies have incorporated additional parameters such as night sweats, specific ulcer types, granuloma presence, radiological findings, and serological markers (ASCA and IGRA) into their models, with varying degrees of success [54].

While these multiparametric models show promise in differentiating ITB from CD, they have limitations. Most studies have small sample sizes and lack validation cohorts (except the Limsrivilai model). Additionally, the complex formulas used to calculate scores in some models limit their practical application in day-to-day clinical settings.

In summary, while progress has been made in developing predictive models for distinguishing ITB from CD, further research with larger, diverse populations and external validation is needed to establish more robust, clinically applicable diagnostic tools.

RESPONSE TO ATT

The differentiation between ITB and CD remains challenging in some cases, even with comprehensive diagnostic approaches. In such situations, a therapeutic trial of ATT has been a long-standing method to diagnose ITB and distinguish it from CD [55]. However, this approach requires careful, objective, and timely assessment of treatment response.

While using steroids or immunosuppressants as a diagnostic tool is generally avoided in TB-endemic regions due to the risk of TB dissemination, the ATT trial approach is not without risks [56]. These include ATT-induced hepatitis and potential delays in CD diagnosis, which could lead to stricturing disease and increased surgical risk.

Logan's seminal work established criteria for assessing ATT response in anorectal TB by evaluating lesion healing. However, relying solely on clinical responses can be misleading, as CD patients may show symptomatic improvement and reduction in inflammatory markers like CRP with ATT [57]. Additionally, ITB patients might remain symptomatic due to underlying strictures [58].

Mucosal healing of ulcers during ATT is considered the gold standard for confirming ITB [57] . Early colonoscopy at two months of ATT not only helps differentiate ITB from CD but can also prevent complications by allowing timely initiation of CD therapy if necessary [59]. This early reassessment provides diagnostic certainty and an opportunity to evaluate potential reasons for non-response, such as multidrug-resistant ITB or CD.

Non-invasive markers have also been explored as response criteria for ATT. An Indian study found that monitoring CRP levels at baseline and two months can help evaluate ATT response, with CRP normalization at two months predictive of mucosal response. However, fecal calprotectin was found to be a better marker of mucosal healing than CRP, as some CRP decline can occur with ATT in CD patients as well [60].

Radiological methods, including ultrasound and MRI, have also been investigated for assessing ATT response, as discussed in the imaging section.

In summary, while the ATT trial remains a valuable tool in differentiating ITB from CD in challenging cases, it requires careful monitoring and interpretation of response using multiple parameters, including endoscopic, biochemical, and radiological markers. This approach aims to ensure accurate diagnosis and appropriate management while minimizing potential risks associated with delayed or incorrect treatment.

GUIDELINE RECOMMENDATIONS

The Asia-Pacific guidelines from 2016 address the challenge of distinguishing between ITB and CD. They suggest an 8-12 week empirical antituberculosis treatment (ATT) for cases with unclear diagnoses, aiming to prevent potentially fatal complications from inappropriate immunosuppressive therapy. These guidelines recommend follow-up colonoscopies and biopsies at 8-12 weeks for non-responders and at six months for responders to assess mucosal healing [61].

The guidelines advise against simultaneous treatment for both ITB and CD, except in severe cases requiring immediate intervention, as this approach could lead to long-term diagnostic confusion. However, it's important to note that an 8–12-week empirical ATT period might delay appropriate CD treatment, potentially worsening the condition and its complications [21].

In 2020, updated recommendations from Asian gastroenterology organizations emphasized ruling out ITB before diagnosing inflammatory bowel disease (IBD). They suggested that persistent symptoms after three months of ATT might indicate CD. The 2021 World Gastroenterology Organisation Global Guidelines propose a 2–3-month empiric ATT with weekly assessments, focusing on symptom resolution and weight gain as response indicators [62].

While a complete symptom response without relapse during follow-up suggests ITB, it's crucial to conduct repeat colonoscopies at two months for all patients on empirical ATT, regardless of clinical response. This approach is necessary because clinical responses to ATT can be misleading in both CD and ITB patients. Some CD patients may show symptomatic improvement with ATT, while ITB patients might remain symptomatic due to strictures.

CONCLUSION

For cases in tuberculosis-endemic areas where standard clinical, endoscopic, radiological, histopathological, and microbiological evaluations fail to provide a definitive diagnosis, a systematic approach should be employed(Figure) [63]. This is particularly relevant in regions with high TB prevalence.

As CD becomes more prevalent in developing nations and ITB incidence rises in developed countries, clinicians face ongoing diagnostic challenges. To address these issues effectively, it's crucial to employ an evidence-based strategy that utilizes objective criteria for timely diagnosis and assessment of treatment response. This approach aims to provide a structured framework for healthcare providers navigating the complex landscape of IBD in various global contexts [63].

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MAN conceptualised and outlined the contents of the paper. VSR collected and analysed the evidence and drafted the manuscript. MAN and VSR were substantially involved in the revision of the manuscript. All authors checked the final manuscript before submission.

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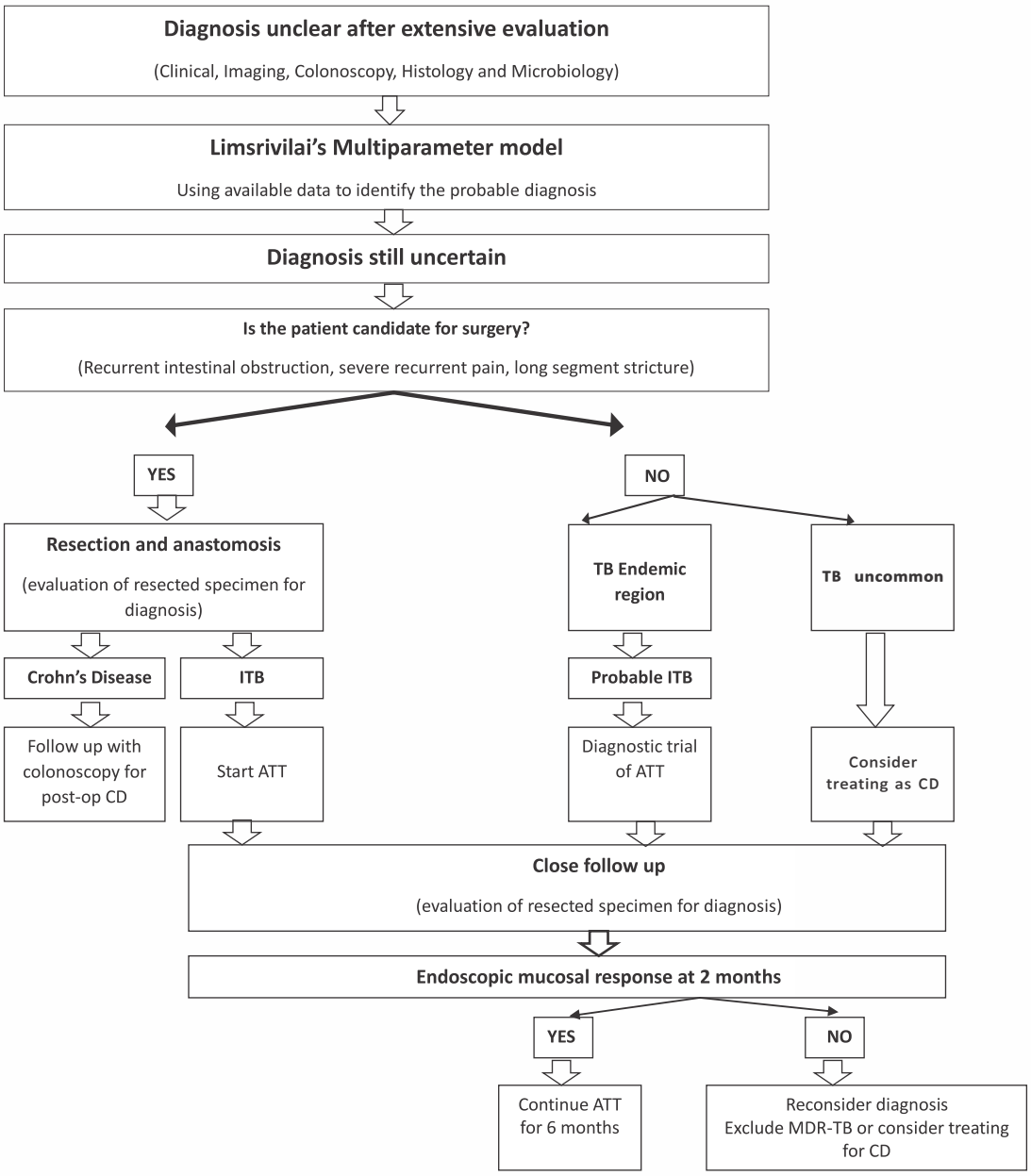
Table 1 - The main distinguishing features between ITB and CD across various diagnostic modalities as described in the article

Feature	Intestinal Tuberculosis (ITB)	Crohn's Disease (CD)
Clinical Presentation	• Shorter symptom duration (<6 months) • Constitutional symptoms like evening fever are more common • Pulmonary symptoms may be present. • An abdominal mass is more common	• A more prolonged, indolent course • Chronic diarrhoea more common • Hematochezia is more frequent • Perianal disease more common
Endoscopic Findings	• Circumferential ulcers • Transverse ulcers • Patulous ileocecal valve • Primarily affects ileocecal area	• Aphthous ulcers • Linear ulcers • Cobblestone appearance • Skip lesions • Can involve any part of bowel
Imaging Features	• Circumferential wall thickening • Homogeneous mucosal enhancement	• Asymmetrical wall thickening • Mucosal enhancement with stratification

	• Necrotic lymph nodes • Ascites	• "Comb sign" • Fistulas more common
Histopathology	• Multiple, large, confluent caseating granulomas • Acid-fast bacilli may be present	• Smaller, discrete microgranulomas • Deep fissuring ulcers • Distorted mucosal architecture
Microbiology	• Positive acid-fast bacilli staining (rare) • Positive culture or PCR for M. tuberculosis	• Negative for TB markers

Figure 1 – An algorithmic approach and follow up in a patient with diagnostic confusion between intestinal tuberculosis (ITB) and Crohn's disease (CD) after standard evaluation



MINI REVIEW

A Digest of Acute Pancreatitis

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INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas with high morbidity and mortality if not managed properly. Reported mortality rates from the USA of this condition range from 3% for patients with interstitial oedematous pancreatitis1 up to 20–40% for those with severe pancreatitis.2 The most common causes of AP are gallstone disease (40-70%) and alcohol (25-35%)3. Other less common causes are iatrogenic (thiopurines, valproate, post-endoscopic retrograde cholangiopancreatography), metabolic disorders (hypertrigly-ceridaemia, hypercalcaemia), congenital abnormalities (pancreas divisum, annular pancreas, choledochal cysts), tumours (pancreatic tumours, periampullarytumours), pancreatic trauma, autoimmunity, genetic, toxic (venom), viral infections and obstruction by parasites (ascariasis). This review will mainly focus on the initial management steps in acute pancreatitis since management decisions in this period can alter the course of the disease and decide whether the patient will devel- op multi-organ failure within the next few days.

REVIEW

The diagnosis of acute pancreatitis requires the presence of ≥2 of the following criteria:4 Abdominal pain consistent with pancreatitis – sudden onset severe epigastric pain that may radiate to the back and is usually relieved by bending forward Serum amylase or lipase >3 x upper limit of normal Characteristic findings from abdominal imaging- ultrasound (US) / contrast-enhanced computer tomography (CECT) / Magnetic resonance cholangiopancreatography (MRCP)

In most instances, US abdomen is adequate for the diagnosis. CECT and MRCP are generally reserved for patients in whom the diagnosis is unclear even after US imaging. Further imaging by CECT / MRCP may be warranted later on in the disease process for evaluation of local complications if the patient does not clinically improve.

Since the extent of pancreatic necrosis may not be clearly defined during the initial few days of the disease, imaging at 3-4 days after the onset of acute pancreatitis is more reliable.5

For identification of the aetiology of acute pancreatitis, liver biochemistry within 48 hours after the onset of symptoms may be important. An alanine aminotransferase (ALT) level >150 U/L discriminates biliary pancreatitis with a positive predictive value of >85%. Alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and bilirubin levels also may indicate the possibility of gallstone pancreatitis. US abdomen may show a dilated biliary tree from an obstructed gallstone.5

Further testing may be warranted once the patient has recovered from the acute illness when a clear aetiology is not revealed by the history and basic investigations. CECT abdomen may identify gallstones not detected by US and may reveal pancreatic or ampullary masses. Depending on availability, MRCP or endoscopic ultrasound should be performed when conventional imaging is negative as they are the best investigations for microlithiasis (tiny biliary calculi), pancreatic duct abnormalities and small pancreatic masses and periampullary masses.5

Serum triglyceride and serum calcium should also be part of the routine screening process for an aetiology.

CLASSIFICATION

The Revised Atlanta Classification system (2012) is an internationally accepted system that categorizes acute pancreatitis according to severity into mild acute pancreatitis, moderately severe acute pancreatitis and severe acute pancreatitis depending on the presence or

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absence of local complications (peripancreatic fluid collections, gastric outlet obstruction, splenic or portal vein thrombosis, colonic necrosis) and systemic complications (respiratory, cardiovascular or renal organ failure or exacerbation of pre-existing co-morbidity precipitated by acute pancreatitis).4

Mild acute pancreatitis is where there are no local or systemic complications of acute pancreatitis. These patients typically improve and are able to start feeding by 48 hours. The diagnosis of moderately severe acute pancreatitis requires fulfilment of one or more of the following criteria: local complications, transient organ failure lasting <48 hours, and exacerbation of any co-morbid diseases due to acute pancreatitis. Severe acute pancreatitis is defined by the presence of persistent organ failure lasting >48 hours.4

An issue with categorizing patients according to this system into moderately severe acute pancreatitis and severe acute pancreatitis is that the final categorization is only possible retrospectively after 48 hours have elapsed. Because of this, all patients with organ failure will have to be managed initially as potentially having severe acute pancreatitis.

In the past, much emphasis was placed on scoring systems (e.g. APACHE II, Ranson, modified Glasgow) in predicting severe acute pancreatitis. However, these scores are cumbersome to calculate and typically require 48 hours to become accurate, by which time the disease severity is obvious regardless of the score. Currently, the best marker for predicting acute severe pancreatitis is considered as fulfilment of systemic inflammatory response syndrome (SIRS) criteria on admission (≥2 of the following: PR >90/ min, RR >20/min or PaCO2 <32 mmHg, temperature>38 °C (100.4 °F) or <36 °C (96.8 °F), WBC >12,000or <4,000 cells/mm3 or >10% immature neutrophils).

The best strategy to predict the outcome of acute pancreatitis is considering a combination of 3 factors: host risk factors e.g. age (>55 years indicating poor prognosis), co-morbidity, body mass index (obesity indicating poor prognosis); clinical risk stratification e.g. SIRS; monitoring response to initial therapy e.g. persistent SIRS, non-response of hypovolemia (rising haematocrit, blood urea, creatinine).5

MANAGEMENT

During the evolution of acute pancreatitis, two peaks of mortality have been identified. The first is during the first week of the disease when there is sterile inflammation of the pancreas.

This inflammation can subsequently progress to a systemic level (SIRS) and result in organ failure. The secondpeak occurs after the first week and is due to infection of the necrotic pancreatic tissue6. To prevent mortality these 2 phases of disease must be managed properly.

FLUID MANAGEMENT

Hypovolemia may occur from multiple factors affecting patients with AP, including vomiting, reduced oral intake, third spacing of fluids, increased respiratory losses and diaphoresis. Pancreatic hypoperfusion leads to increased pancreatic necrosis and ongoing release of pancreatic enzymes activating numerous cascades. Correct fluid management is the most important aspect of management during the early phase of the disease.

To prevent future complications, all patients should receive aggressive hydration during the first 24 hours of the disease. The recommended rate of flu- id administration is 5-10ml/kg/h (250-500 ml/h in a 50kg patient)6. A patient in shock may need more rapid repletion as boluses, while the rate of administration may have to be reduced in those with co- existing cardiovascular or renal disease.

Replacement should be with an isotonic crystalloid fluid but there is still no consensus as to which fluid is best, with some guidelines recommending Lactated Ringer's solution5 while others see no difference between normal saline and Ringer's lactate.7

However, overly aggressive fluid therapy also increases morbidity and mortality due to pulmonary oedema and abdominal compartment syndrome.

Therefore, the patient should be closely monitored and the fluid administration reassessed at frequent intervals to achieve goals of heart rate <120, mean arterial pressure (MAP) >65 mmHg, urinary output>0.5 ml/kg/h and haematocrit 35–44%.After the resuscitation goals are met, the rate of fluid administration can usually be reduced to 2–3 ml/kg/h.6

During the early critical phase, vasopressors might be administered as an adjunct to fluid administration to temporarily increase a low MAP.6Patients undergoing volume resuscitation should have the head of the bed elevated, undergo continuous pulse oximetry, and receive supplemental oxygen.

ANTIBIOTICS

Routine administration of antibiotics in acute pancreatitis is discouraged in international guidelines5-7. This is because prophylactic antibiotics have not been found to have any impact on therates of organ failure and length of hospital stay.7

Antibiotics are indicated if infected pancreatic necrosis is suspected based on failure to clinically improve after 7–10 days of hospitalization, imaging signs of infection (i.e. gas in peripancreatic collections) and if organisms are found in percutaneous fine needle inspiration (FNA) of peripancreatic collections.

When infected necrosis is suspected, anti- biotics are started empirically after obtaining blood cultures and discontinued if cultures are found to be negative. The choice of empirical antibiotics should be based on local sensitivity patterns as well as the antibiotic's ability to penetrate pancreatic necrosis. Carbapenems, quinolones, cephalosporins in high doses and metronidazole have good pancreatic tis- sue penetration.8

ANALGESIA

Opiates are often necessary to achieve effective analgesia in these patients. There is no evidence from human studies to indicate which specific opiates are best.9

NUTRITION

There is a longstanding misconception that the inflamed pancreas requires prolonged rest by fasting. Bowel rest is associated with disturbed intestinal motility, bacterial overgrowth and intestinal mucosal atrophy, which leads to bacterial translocation from the gut that can result in infection of the necrotic pancreatic tissue. Therefore, early oral feeding is recommended if the patient is clinically improving with a reduction in nausea & vomiting and abdominal pain.

If the patient cannot take orally, enteral feeding by nasogastric tube is recommended. If the patient does not tolerate nasogastric feeding due to delayed gastric emptying, naso-jejunal feeding is an option. Parenteral nutrition should be the last option if the patient does not tolerate any of the enteral feeding methods even by 5th day after admission.5,9

INTERVENTIONS FOR LOCAL COMPLICATIONS

The most common local complication that can occur with acute pancreatitis is peripancreatic fluid collections. The vast majority of patients with fluid collections can be managed without interventions and unnecessary invasive procedures can increase morbidity and mortality. Indications for drainage of collections are suspicion of infection, obstruction of surrounding structuresby the collection (e.g. biliary obstruction, gastric outlet obstruction, intestinal obstruction), persistent symptoms such as pain, loss of appetite and loss of weight (persisting >8 weeks after the onset of acute pancreatitis)5.

In the absence of these indications, collections do not warrant intervention regardless of their size or location.

Interventions should preferably be delayed for >4 weeks from the onset to allow for the development of walling-off of the collection but in unstable patients, interventions may have to be performed earlier.5

It is preferable to use the least invasive means to drain the collection as this reduces pro-inflammatory activity and reduces mortality and hospital stay. Endoscopic drainage or percutaneous image-guided drainage are therefore the preferred methods while surgical drainage is restricted to patients in whom the less invasive methods are not possible. 5

GALLSTONE PANCREATITIS

Endoscopic retrograde cholangiopancreatography (ERCP) should not be used routinely for patients with gallstone pancreatitis because it can increase complications. There are only two instances when urgent ERCP (within 24 hours) is warranted in gallstone pancreatitis – concurrent acute cholangitis and the presence of ongoing biliary obstruction.5

To prevent the recurrence of gallstone pancreatitis, cholecystectomy is recommended during the index admission rather than a more delayed approach7.

CONCLUSION

Acute pancreatitis is a condition that can lead to much morbidity and mortality if there is mismanagement in the initial 1-2 days of the disease.

The best marker for predicting acute severe pancreatitis is considered as the fulfilment of SIRS criteria on admission. The most important aspect of the initial management is adequate fluid resuscitation. The recommended rate of fluid administration is 5-10ml/kg/h. Routine administration of antibiotics is not recommended and antibiotics are indicated only if infected pancreatic necrosis is suspected.

Opiates are often necessary to achieve effective analgesia. Prolonged bowel rest by fasting is not recommended and enteral feeding is recommended if the patient is clinically improving. The vast majority of patients with peripancreatic fluid collections can be managed without interventions. Indications for drainage of collections are suspicion of infection, obstruction of surrounding structures by the collection and persistent symptoms.

Interventions shouldpreferably be delayed for >4 weeks from the onset of the disease. ERCP should not be used routinely for patients with gallstone pancreatitis and is warranted only if there is concurrent acute cholangitis or on- going biliary obstruction. To prevent the recurrence of gallstone pancreatitis, cholecystectomy is recommended during the index admission rather than a more delayed approach.

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Splenic Pseudocyst: A Case Report

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ABSTRACT:

Splenic pseudocysts are rare and found in <1% splenectomies. Most are asymptomatic and require intervention only when symptoms develop. Splenic pseudocysts usually develop secondary to trauma and rarely grow to be large. Pseudocysts have also been reported to occur following splenic infarction and infection. Symptoms appear to be present in only 30-60% patients.We report a case of splenic pseudocyst in a patient with past penetrating trauma to the abdomen.

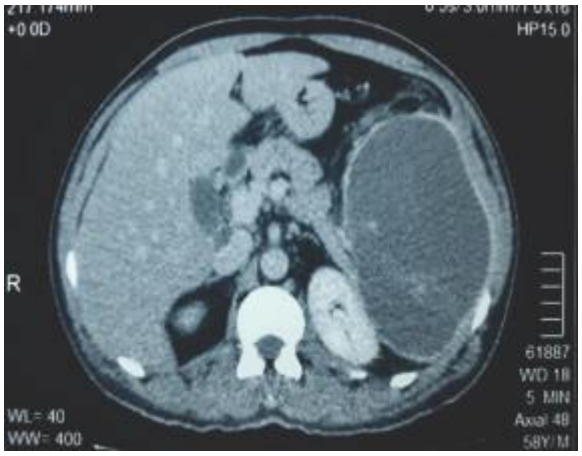
A 58-year-old male presented with severe left upper-quadrant abdominal pain for 2 months, with abdominal fullness and early satiety for 2 years. He had suffered a laceration of the right kidney with hemoperitoneum following a blast injury 26 years ago requiring midline laparotomy. CECT abdomen confirmed a large splenic pseudocyst of 11.8x14.2x 17 cm. He underwent elective open splenectomy and was discharged upon recovery on postoperative day 8.Although minimally invasive procedures including cyst aspirationhas recently gained popularity, disease recurrence remains a concern. Thus, laparoscopic partial or total splenectomy appears to be the best form of management with low recurrence rates.

INTRODUCTION

Pseudocysts of the spleen are rareand found in <1% splenectomies (1,2). They usually develop secondary to trauma (1-3) and rarely grow to be large. Most remain asymptomatic and require exploration only when symptoms develop.We report a case of splenic pseudocyst occurring in a patient with past trauma to the abdomen.

CASE REPORT

A 58-year-oldSri Lankan Sinhalese male with a history of diabetes for 5 years presented with severe left upper-quadrant abdominal pain associated with abdominal fullness and early satiety for more than 2 years.



He had suffered a laceration of the right kidney with hemoperitoneum following a blast injury 26 years agorequiring midline laparotomy. No other intra-abdominal injuries had been noted during the laparotomy. The renal laceration had been repaired with catgut with a non-corrugated peritoneal drain in place.

The abdomen was packed with haemostatic gel to achieve haemostasis. Onexamination he had mild tenderness over the left upper quadrant with notable splenomegaly.In the presence of splenomegaly with thrombocytosis, leucocytosis, and anaemia with rouleaux formation(ESR 130/hour), a myeloproliferative disorder was suspected– butwas subsequently excluded. His LDH levels were elevated(509U/L).

An ultra sound scan of the abdomen showed, an enlarged spleen with multiple, irregular, and avascular hypoechoic areas raising the initial suspicion of a splenic infarct. However, CECT abdomen confirmed a large splenic pseudocyst of 17 x 11.8 x 14.2 cm size with evidence of splenic atrophy/rupture within.

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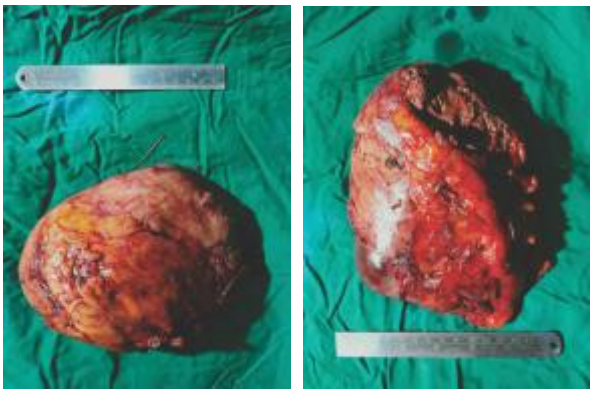
He was vaccinated for pneumococcus, meningococcus and haemophilusto be later followed by elective open splenectomy.

Surgery was performed via midline laparotomy where dense adhesions were encountered around the spleen, transverse colon, greater curvature of stomach and small bowel. Owing to the dense adherent nature of the cyst to the stomach, part of the cyst was left on the greater curvature during splenectomy. His post-operative course was complicated with grade A pancreatic fistula which settled spontaneously. He was discharged on postoperative day 8.Histopathological analysis of the specimen showed splenic infarction.



DISCUSSION

Splenic pseudocysts are encountered rarely which occur mostly following traumatic injuries.

Many publications rely on the presence of a lining epithelium in differentiating true/primary cysts from false/pseudo/secondarycysts of the spleen (4–9).This classification has been challenged however owing to the difficulty encountered in identifying this lining epithelium (3). Furthermore, Leon Morgenstern and Christos et al argue that pseudocysts of the spleen are more likely to becongenitalthan due to trauma (3-6). In comparison Arkuszewski et al reports, that injuries leading to pseudocysts of the spleen can be trivial and come to pass without the patient noticing (2). Pseudocysts have also been reported to occur following splenic infarction and infection (e.g. tuberculosis, mononucleosis)'(4).

Symptoms appear to be present in only 30-60% patients. Pain in the left upper abdominal quadrant, nausea, vomiting, symptoms of gastric compression and splenomegaly are common presentations of the disease. Features such as radiating shoulder pain, hypersplenism and pleural effusion have also been reported.Of these symptoms, index patient hadleft sided abdominal painand fullness with early satiety.

The diagnosis can beestablished via cross sectional imaging – eitherCT or MRI. Typical features on CT imaging include a regular wall with or without calcification, and absence of any solid components on the wall or within the cyst (3). Symptomatic cysts and those exceeding 5 cm in size ' are usually intervened due to their risk of rupture, despite the actual risk of this complication being largely unknown with only a few cases reported in the literature (2-4,6).

Although minimally invasive surgery can be done through many approaches with good efficacy and safety (marsupialization, fenestration, cystectomy, percutaneous drainage with or without sclerosant injection), the evidence base is conflicting and disease recurrence remains a concern (1-4,7,10). Overall, laparoscopic partial or total splenectomy appears the best means of management – given its efficacy the low recurrence risk. Post operative complications including pain and other wound related complications of laparoscopy are comparable to minimally invasive procedures (1-4,10). Regardless of the approach a total splenectomy is appears to be the best option in relation to overall safety of the procedure and low risk of recurrence especially for multiple, hilar or large cysts involving a significant portion of splenic parenchyma '(1,2,4,6,11).

CONCLUSION

Splenic pseudocysts appear to be a rare and less well understoodoccurrence. Partial or total splenectomy via the laparoscopic approach appears to be the best form of management with only a low risk of recurrence.

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