WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Diseases accompanied by hepatomegaly and hepatosplenomegaly

***Turdaliev S.O.*[*1], *Saurabh Gavit*[*2], *Sudarshan Chothe*[*3]**

[*1] Professor, [*2*3] IMF OSHSU (Student)
Department of Hospital Therapy

ABSTRACT :

Hepatomegaly and hepatosplenomegaly are significant clinical findings that are indicative of an underlying pathology, from benign, self-limited disorders to threatening, life-threatening disease. This overview presents a comprehensive account of the significant diseases accompaniment of liver and spleen enlargement. The conditions included are steatohepatosis, hepatitis of various types (viral, toxic, alcoholic, drug-induced, and autoimmune), storage diseases such as hemochromatosis, amyloidosis, and Wilson-Konovalov disease, and Budd-Chiari syndrome. The review addresses the pathophysiology, classification, etiology, risk factors, diagnostic approach, and treatment in all these diseases. Exhaustive literature review is the review method adopted here. The goal is to provide a systematic and thorough reference for clinicians and students to help in differential diagnosis and patient management of hepatomegaly and hepatosplenomegaly.

Introduction

Hepatomegaly, hepatomegaly, and hepatosplenomegaly (HSM), liver enlargement with or without spleen enlargement, are important clinical observations that necessitate thorough diagnostic evaluation . They are not disease states but manifestations of a wide variety of underlying disorders, including infectious, metabolic, inflammatory, toxic, neoplastic, and congestive etiologies . Systematic and systematic approach is necessary to identify the underlying cause, to prevent invasive diagnostic procedures, and to enable early diagnosis and treatment .

Pathophysiology

The pathogenesis of hepatomegaly and hepatosplenomegaly is varied and depends on the underlying disease . Most commonly, the enlargement is due to

Inflammation

Infiltration of inflammatory cells in the liver and spleen, such as in hepatitis .

Congestion: Blocked venous blood flow out of the liver (obstruction of outflow), leading to enlargement and congestion with blood of the organs, as with Budd-Chiari syndrome or right-sided heart failure .

Infiltration: Deposition of abnormal material within the liver and spleen. This can be fat (steatosis), iron (hemochromatosis), copper (Wilson's disease), amyloid proteins (amyloidosis), or cancer cells (leukemia, lymphoma) .

Storage: Metabolite build-up in lysosomal storage diseases (LSDs) due to inherited enzyme deficiencies .

Classification

The causes of hepatomegaly and hepatosplenomegaly can be classified into several types:

Infectious Diseases:Acute viral hepatitis (Hepatitis A, B, C, D, E) Infectious mononucleosis (Epstein-Barr virus) Cytomegalovirus (CMV) Malaria, Leishmaniasis,

Schistosomiasis Metabolic Diseases:Steatohepatosis (alcoholic and non-alcoholic) Lysosomal storage diseases (e.g., Gaucher disease, Niemann-Pick disease) Hereditary hemochromatosis Wilson-Konovalov disease Amyloidosis Hematologic Diseases:Myeloproliferative and lymphoproliferative diseases (e.g., leukemia, lymphoma) Hemolytic anemias (e.g., sickle cell anemia, thalassemia)

Congestive Causes:Budd-Chiari syndrome Right-sided heart failure Veno-occlusive disease Inflammatory/Autoimmune Diseases:Autoimmune hepatitis Systemic lupus erythematosus, Sarcoidosis Toxic Causes:Alcoholic hepatitis Drug-induced liver injury (DILI) Neoplastic Diseases:Primary liver tumors (hepatocellular carcinoma, hepatoblastoma) Metastatic tumors to the liver

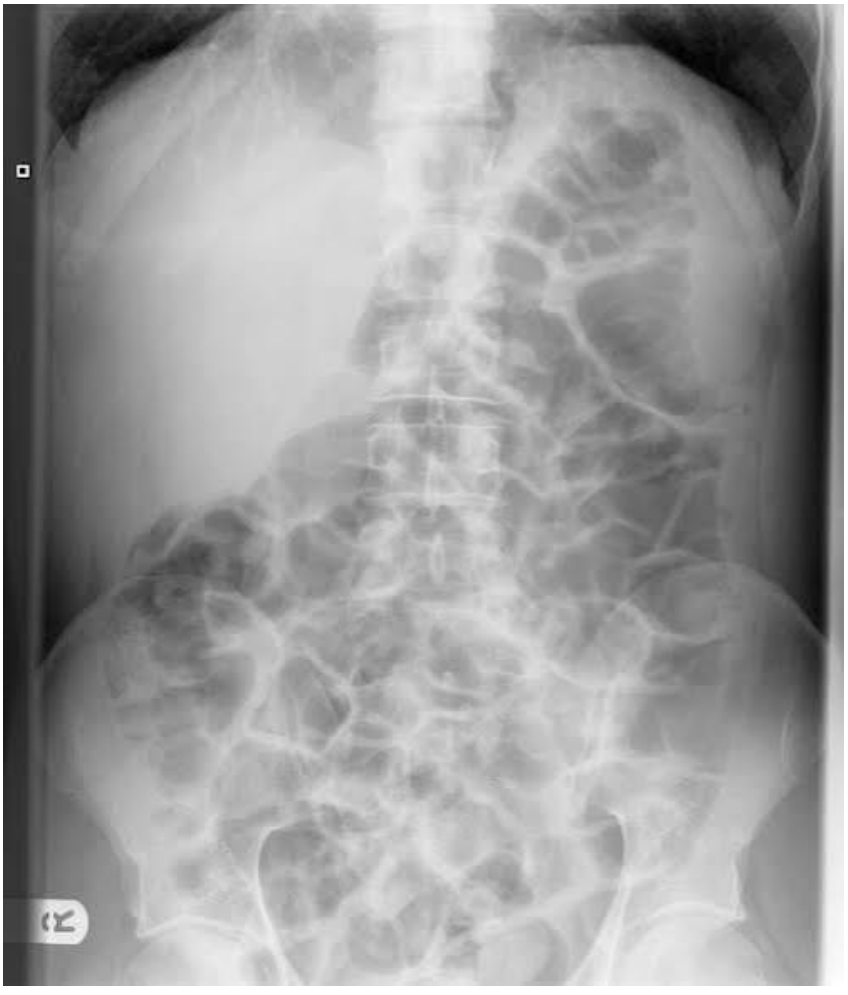
Vaso-Occlusive Crisis:	***P* = 0.501**		
Frequency of crisis	No. of patients	Hepatomegaly Number (%)	No hepatomegaly Number (%)
1 in 5 years	1	0 (0)	1 (5.5)
1 per year	19	14 (43.8)	5 (27.8)
2 per year	15	10 (31.2)	5 (27.8)
3 per year	13	7 (21.9)	6 (33.3)
4 per year	2	1 (3.1)	1 (5.5)
TOTAL	50	32 (100)	18 (100)
Hemolytic Crisis:	***P* = 0.029**		
Frequency of crisis	No. of patients	Hepatomegaly Number (%)	No hepatomegaly Number (%)
None	25	13 (40.6)	12 (66.7)
Once Only	2	0 (0)	2 (11.1)
1 per year	20	16 (50)	4 (22.2)
2 per year	3	3 (9.4)	0 (0)
TOTAL	50	32 (100)	18 (100)

Steatohepatosis

Steatohepatosis, or fatty liver disease, is characterized by build-up of fat (steatosis) in hepatocytes . When inflammation and hepatocyte damage are present, it is termed steatohepatitis .

Pathophysiology

The "two-hit" hypothesis has traditionally been used to describe the pathogenesis of development of steatohepatitis from basic steatosis, but a "multiple-parallel hits" model is now accepted more widely. Insulin resistance is a key pathogenic process, which leads to increased delivery of fatty acids to the liver and de novo lipogenesis . This lipid accumulation (initial hit) sets the stage for additional insults (second hits), e.g., oxidative damage, mitochondrial injury, and inflammatory cytokine production, leading to inflammation, hepatocyte injury, apoptosis, and fibrosis .



Causes and Risk Factors

Metabolic
dysfunction-associated steatotic liver disease (MASLD), formerly NAFLD: Associated with metabolic syndrome, obesity, type 2 diabetes mellitus, and dyslipidemia .
Alcohol-
related liver disease (ALD): Caused by chronic excessive alcohol consumption .

Hepatitis
Hepatitis is inflammation of liver tissue . It can be either acute or chronic.

Viral Hepatitis
Viral hepatitis is due to infection with any one of the five major hepatitis viruses: A, B, C, D, or E .

Pathophysiology: Viral hepatitis liver injury is not due to direct viral action but to the host immune response directed against the infected hepatocytes. Inflammation leads to hepatocyte damage and necrosis . Chronic infection (by HBV, HCV, HDV) can lead to progressive liver fibrosis, cirrhosis, and hepatocellular carcinoma .

Causes and Risk Factors:

Hepatitis A (HAV) and E (HEV): Transmitted through the fecal-oral route, through contaminated food or water .

Hepatitis B (HBV), C (HCV), and D (HDV): Transmitted through contact with infected blood or body fluids (e.g., unsafe injection, sexual contact, mother-to-child transmission) .
Toxic Hepatitis:Toxic hepatitis is liver inflammation caused by exposure to a toxin or chemical.

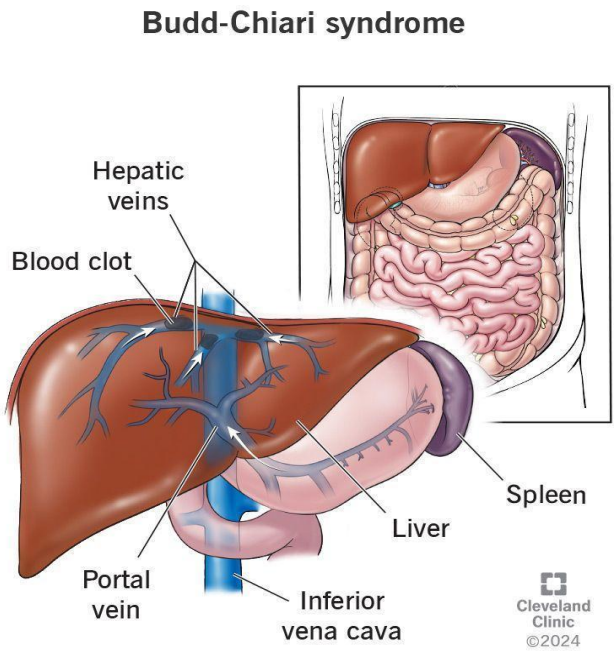
Alcoholic Hepatitis:A form of toxic hepatitis caused by alcohol abuse . The pathogenesis mechanism is complex, involving direct hepatotoxicity of alcohol metabolites (e.g., acetaldehyde), oxidative stress, and induction of inflammatory response .

Drug-Induced Liver Injury (DILI): Liver damage caused by prescription medications, over-the-counter drugs, or herbal preparations . Mechanisms are dose-dependent and predictable (e.g., acetaminophen overdose) or idiosyncratic and unpredictable . Several drugs can induce DILI, such as some antibiotics, NSAIDs, and statins .

Autoimmune Hepatitis (AIH)AIH is a chronic liver inflammation that results from an immune attack on the body's own liver cells .

Pathophysiology: Cause not clearly defined, but postulated to be the result of the interplay of genetic susceptibility and environmental factors in an individual who is susceptible. This leads to a T-cell mediated autoimmune destruction of hepatocytes .

Risk Factors: It is more common in females and is typically associated with other autoimmune diseases .



Storage Diseases

Hereditary Hemochromatosis

Hereditary hemochromatosis is an inherited condition because of which there is increased intestinal absorption of dietary iron, leading to its accumulation in organs, primarily the liver, heart, and pancreas .

Pathophysiology: In most of the cases, it is caused by mutations of the HFE gene, which plays a role in regulation of hepcidin production, which is the key hormone controlling iron absorption. Defective HFE function is characterized by reduced hepcidin levels, causing dysregulated iron uptake and progressive iron accumulation . Excess iron is toxic to tissue, generating reactive oxygen species that lead to cellular damage and fibrosis .

Genetic Factors: It is an autosomal recessive disorder, most commonly associated with the C282Y mutation in the HFE gene .

Amyloidosis

Amyloidosis is a group of diseases resulting from deposition of abnormal, misfolded proteins (amyloid fibrils) in organs and tissues, and the liver can be included .

Pathophysiology: In hepatic amyloidosis, protein deposits are deposited in the space of Disse and sinusoids, hepatocytes being compressed and the liver cell undergoing atrophy and pressure-induced damage. This occupation may lead to hepatomegaly and impair liver function . The most common types to affect the liver are AL (light-chain) amyloidosis and AA (secondary) amyloidosis .

Causes: AL amyloidosis is a plasma cell dyscrasia, while AA amyloidosis is in the setting of chronic inflammatory conditions like rheumatoid arthritis or chronic infections .

Wilson-Konovalov Disease

Wilson-Konovalov disease, or Wilson disease, is an unusual autosomal recessive inheritance disorder of copper metabolism .

Pathophysiology:It is caused by mutations in the ATP7B gene that encodes for the incorporation of copper into ceruloplasmin and for the excretion of excess copper into bile. The biliary excretion of copper is impaired by the genetic defect, leading to the buildup of toxic copper in the corneas, brain, and liver . Copper excess in the liver causes oxidative stress and hepatocyte damage, leading to a spectrum of liver disease ranging from steatosis to acute hepatitis, chronic hepatitis, cirrhosis, and acute liver failure *.

Genetic Factors: An autosomal recessive disorder caused by mutations in the ATP7B gene .

Budd-Chiari Syndrome (BCS)

BCS is a rare condition secondary to hepatic venous outflow obstruction, from the small hepatic venules to the inferior vena cava .

Pathophysiology:Obstruction, more often thrombosis, leads to an extreme increase in sinusoidal pressure and hepatic congestion. This leads to backup of blood in the liver and causes painful hepatomegaly, ascites, and ischemic hepatocyte injury (centrilobular necrosis). In the long term, this can lead to fibrosis and cirrhosis .

Causes and Risk Factors: Most are due to an underlying prothrombotic disorder, such as myeloproliferative disorders (e.g., polycythemia vera), hereditary thrombophilias (e.g., Factor V Leiden mutation), pregnancy, oral contraceptives, or abdominal malignancies compressing the veins .

Diagnostic Techniques A complete work-up for a patient with hepatomegaly or hepatosplenomegaly is:

Physical Examination: To establish the hepatomegaly and/or splenomegaly, check for tenderness, and inspect for stigmata of chronic liver disease (e.g., jaundice, ascites, spider angiomata) .

Blood Tests:

Complete Blood Count (CBC): May show anemia, thrombocytopenia, or findings of infection or hematologic malignancy .

Liver Function Tests (LFTs): Such as ALT, AST, alkaline phosphatase, bilirubin, and albumin, to detect liver injury, cholestasis, and synthetic failure .Coagulation Studies: Prothrombin time (PT/INR) to assess liver synthetic function .

Imaging:

Abdominal Ultrasound: The initial imaging modality of choice. It is non-invasive, easily obtained, and can check for organ size, inspect liver texture (e.g., fatty infiltration), and demonstrate ascites, portal hypertension, or thrombosis of the portal or hepatic veins .

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI): Are more accurate regarding anatomy and can be helpful to detect tumors, cysts, or signs indicative of particular diseases (e.g., hypertrophy of the caudate lobe in Budd-Chiari syndrome) .

Specific Diagnostic Tests:

Viral Hepatitis: Serology for antigens and antibodies to hepatitis A, B, and C .

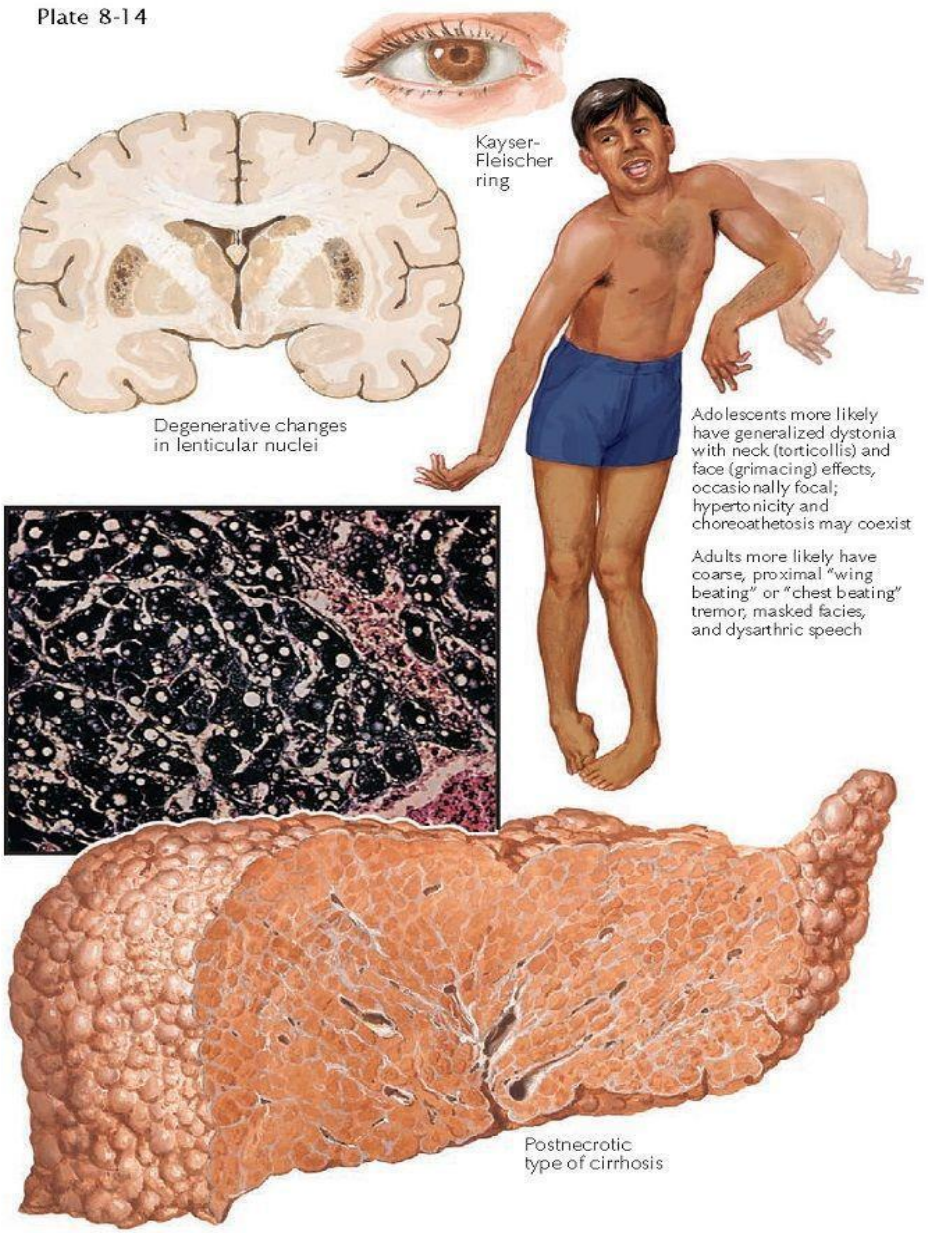
Autoimmune Hepatitis: Autoantibody (e.g., ANA, anti-SMA) and immunoglobulin G (IgG) determinations .

Hemochromatosis: Iron studies (serum ferritin, transferrin saturation) and genetic testing for HFE mutations .

Wilson-Konovalov Disease: Serum ceruloplasmin levels (usually low), 24-hour urine copper excretion (increased), and slit-lamp examination for Kayser-Fleischer rings .

Amyloidosis: Tissue biopsy (e.g., from abdominal fat pad or involved organ) with Congo red stain, which causes characteristic apple-green birefringence on polarized light microscopy .

Budd-Chiari Syndrome:Doppler ultrasound, CT, or MRI venography for visualization of the hepatic veins and IVC and demonstration of obstruction .



Liver Biopsy: An invasive procedure that may have to be performed to establish a diagnosis, assess the inflammatory grade, and stage the extent of fibrosis or cirrhosis. It is often necessary for the diagnosis of steatohepatitis, autoimmune hepatitis, drug-induced liver injury, and amyloidosis .

Management Strategies Management is directed against the etiology of hepatomegaly or hepatosplenomegaly.

Steatohepatosis

MASLD/MASH: Lifestyle modification is the cornerstone of management, like weight reduction by diet and exercise . Weight reduction by 7–10% can improve steatosis, inflammation, and even fibrosis . In March 2024, the FDA granted approval for resmetirom (Rezdiffra™) for MASH in moderate to advanced fibrosis .

Alcoholic Steatohepatitis: Abstinence from alcohol is required. Nutritional support is crucial. In severe cases, corticosteroids may be given .

Hepatitis

Viral Hepatitis: Hepatitis A and E:
Typically self-limiting and require supportive treatment .

Chronic Hepatitis B: Long-term therapy with oral antiviral medication (e.g., tenofovir, entecavir) to suppress virus replication and prevent disease progression .

Chronic Hepatitis C: Curable in most patients with short courses (8-12 weeks) of highly effective direct-acting antiviral (DAA) medications .

Autoimmune Hepatitis: Therapy with immunosuppression, typically with corticosteroids (e.g., prednisone) with or without azathioprine, to suppress inflammation and prevent progression of cirrhosis .
Toxic Hepatitis (DILI): Treatment is primarily identification and withdrawal of the offending drug or toxin. In acetaminophen overdose, N-acetylcysteine is a specific antidote .

Storage Diseases

Hemochromatosis: Therapeutic phlebotomy (regular removal of blood) to eliminate excess iron stores is the typical treatment . If phlebotomy is not available, iron chelation therapy can be used .

Amyloidosis: Treatment depends on the type. In AL amyloidosis, chemotherapy or autologous stem cell transplant is used to treat the underlying plasma cell disorder . For ATTR amyloidosis, drugs like tafamidis might stabilize the TTR protein, while gene-silencing therapies (patisiran, vutrisiran) might reduce its production .

Wilson-Konovalov Disease: Chronic therapy with copper-chelating drugs like penicillamine or trientine, or zinc salts which interfere with intestinal copper absorption .

Budd-Chiari Syndrome

Treatment is stepwise in strategy :

Medical Therapy: Anticoagulation to prevent extension and recurrence of thrombus and ascites management with diuretics.

Interventional Procedures: Upon failure of medical therapy, measures to re-establish hepatic outflow are considered. This may include angioplasty with vein stenting of occluded veins or a transjugular intrahepatic portosystemic shunt (TIPS) to decompress congested liver.

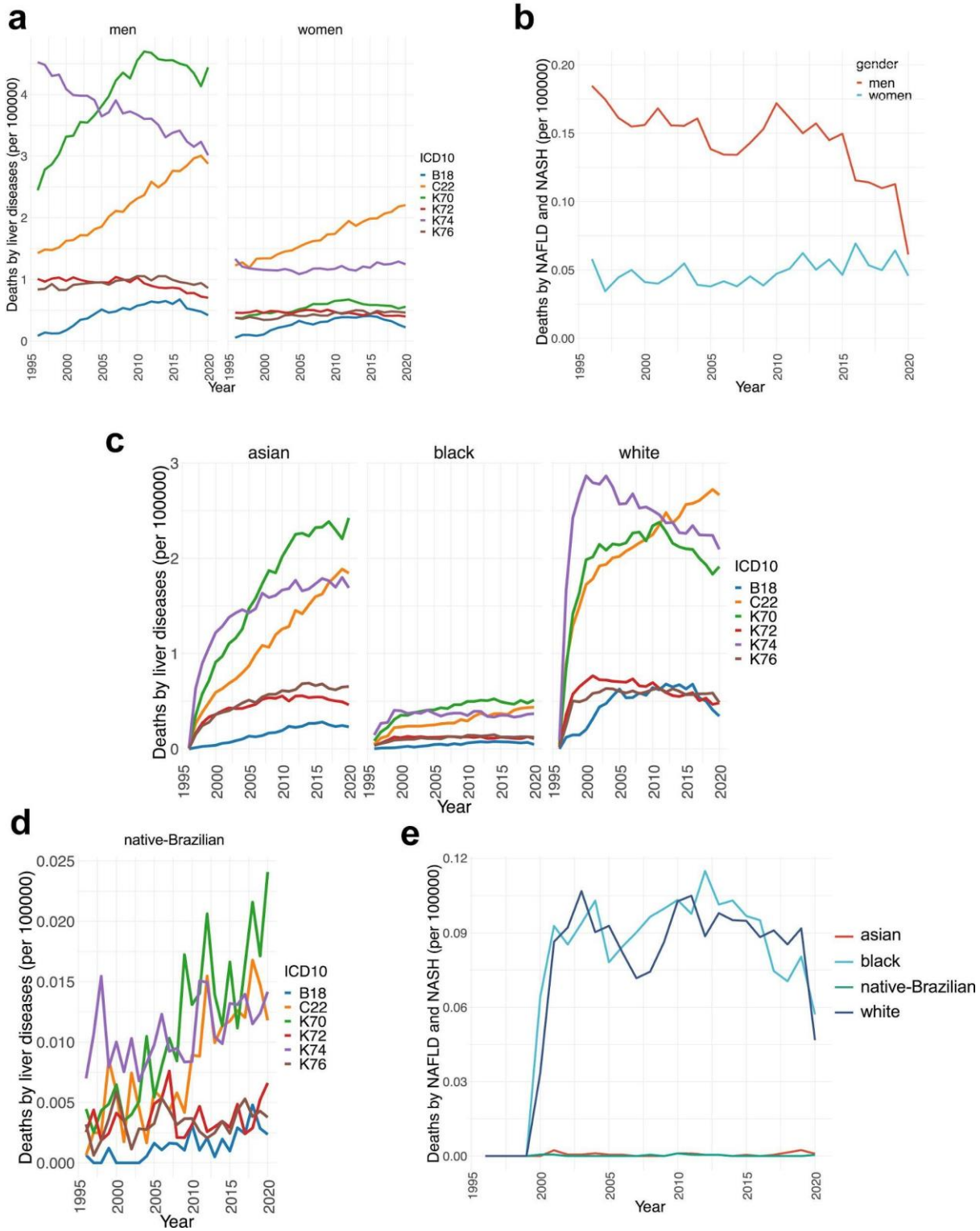
Liver Transplantation: In those with fulminant hepatic failure or end-stage liver disease and have not responded with other therapies .

Lifelong Follow-Up :For most of the chronic conditions outlined, specialist follow-up throughout a patient's lifetime is required. This includes regular assessment of disease activity, screening for complications (notably hepatocellular carcinoma in cirrhotic patients of any etiology), and the handling of treatment side effects .

Methodology:

This is a systematic review of the literature. Data were drawn from a broad range of sources, including peer-reviewed scientific literature, medical textbooks, clinical guidelines published by professional associations, and reputable medical websites. The search was conducted by employing keywords related to each of the provided diseases and clinical presentations. While this review synthesizes evidence from literature-based case reports and expert

opinion, neither original data analysis nor explicit expert consultation is included. The aim is to provide a systematic synthesis of current knowledge on the conditions. Ethical considerations to disease management such as patient autonomy and informed consent are of utmost significance in clinical practice but outside the scope of this review to detail.



The Modeling and Analysis

This article does not engage primary modeling or statistical analysis as it is a literature review. Comparative analysis is used to differentiate between the various etiologies of hepatomegaly and hepatosplenomegaly. The following table gives a simplified model for comparing major features of the under consideration diseases.

Results and Discussion

Evaluation of hepatomegaly and hepatosplenomegaly reveals a complex interaction of heterogeneous pathological processes. Etiologies are heterogeneous, varying from benign states like steatohepatosis, rising prevalence with the obesity epidemic , to the extremely rare inheritable diseases like Wilson's disease and Budd-Chiari syndrome . The first evaluation, with a focus on thorough history, physical examination, standard laboratory investigations, and abdominal ultrasonography, is crucial in narrowing down the differential diagnosis .

The above conditions demonstrate various pathophysiologic mechanisms leading to hepatosplenomegaly. For instance, in alcoholic liver disease and steatohepatosis, the first insult is metabolic, leading to resulting fat accumulation and oxidative stress . On the other hand, viral and autoimmune hepatitis result from an inflammatory immune response against liver cells . Hemochromatosis and Wilson's disease are caused by the toxic storage of some substances (iron and copper, respectively) due to genetic disorders in their metabolism . Finally, Budd-Chiari syndrome is a hemodynamic cause, where mechanical obstruction to blood flow results in congestion and ischemic damage .

Improvements in diagnostic and treatment modalities have significantly improved outcomes for the majority of these diseases. Development of direct-acting antivirals has revolutionized treatment of hepatitis C, so that it is now a curable illness . In genetic illness, increased insight into their molecular basis has led to targeted treatments, as in chelation in Wilson's disease and phlebotomy in hemochromatosis . For Budd-Chiari syndrome, interventional radiology interventions such as TIPS have provided a safer alternative to surgery for the majority of patients . However, in the case of the majority of these conditions, especially the ones leading to cirrhosis, liver transplantation remains the sole treatment of end-stage disease .One of the important issues for clinical practice is the frequently-asymptomatic presentation of a large number of these diseases in the initial phase. Patients present late with complications of portal hypertension and cirrhosis. This emphasizes the importance of screening high-risk populations, i.e., metabolic syndrome patients for MASH, or first-degree relatives of genetic disease patients such as hemochromatosis or Wilson's disease.

Conclusion

Hepatomegaly and hepatosplenomegaly are important clinical presentations that require complete and systematic evaluation. The differential diagnosis is very broad, encompassing a variety of infectious, metabolic, toxic, inflammatory, congestive, and neoplastic conditions. Such precise diagnosis and proper treatment necessitate clear understanding of the pathophysiology of diseases such as steatohepatosis, hepatitis, storage diseases, and Budd-Chiari syndrome. The establishment of sophisticated diagnostic modalities and specific treatments has changed the prognosis of the majority of these diseases. Early detection and treatment are, however, necessary to prevent progression to inevitable liver fibrosis, cirrhosis, and its fatal complications. Multi-disciplinary management and long-term follow-up are often needed to manage these challenging chronic conditions optimally.

Acknowledgements

I would like to express my sincere gratitude to the Department of Hospital Therapy for their valuable guidance, support, and encouragement throughout the preparation of this article.
I am especially thankful to Dr.Turdaliev S.O. , Head of the Department, for their expert advice and constructive feedback.
I also extend my appreciation to all the faculty members and hospital staff who provided insightful information and practical experience, which greatly enriched the content of this work.

REFERENCE

General and Pathophysiology

*** Karlsen, T. H., Folseraas, T., Thorburn, D., & Vesterhus, M. (2017). Primary sclerosing cholangitis—A comprehensive review. Journal of Hepatology, 67(6), 1298–1323.**

*** Bowlus, C. L., & Gershwin, M. E. (2014). The genetics of primary biliary cirrhosis. Seminars in Liver Disease, 34(3), 329–338.**

*** Sirica, A. E., Gores, G. J., Groopman, J. D., Selaru, F. M., Strazzabosco, M., Butel, J. S., & Marrero, J. A. (2019). Cholangiocarcinoma: From pathogenesis to therapy. Hepatology, 69(3), 1361–1379.**

*** Jindal, V., & Thuluvath, P. J. (2017). Primary Biliary Cholangitis and Primary Sclerosing Cholangitis: Current Knowledge of Pathogenesis and Therapeutics. Clinical and Molecular Hepatology, 23(2), 119–130.**

II. Acute Cholangitis (Bacterial Cholangitis)

*** Kiriyama, S., Takada, T., Hwang, T. L., Akazawa, K., King, H. K., Mirza, B. I., ... & Gomi, H. (2018). Tokyo Guidelines 2018: initial management of acute biliary infection and flowchart for acute cholangitis. Journal of Hepato-Biliary-Pancreatic Sciences, 25(1), 71–80.**

*** Gomi, H., Solomkin, J. S., Schlossberg, D., Okamoto, K., Takada, T., Strasberg, S. M., ... & Windsor, J. A. (2018). Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. Journal of Hepato-Biliary-Pancreatic Sciences, 25(1), 3–21.**

III. Primary Biliary Cholangitis (PBC)

*** Lindor, K. D., Bowlus, C. L., Boyer, T., Rockey, D. C., & Hoofnagle, J. H. (2019). Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology, 69(1), 394–419.**

*** European Association for the Study of the Liver. (2017). EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. Journal of Hepatology, 67(1), 145–172.**

*** Beuers, U., & Gershwin, M. E. (2018). Obeticholic acid for primary biliary cholangitis. New England Journal of Medicine, 378(15), 1421–1431.**

IV. Primary Sclerosing Cholangitis (PSC) & Cholangiocarcinoma (CCA)