REVIEW ARTICLE

Changing epidemiology (etiology, complications) and projections of liver cirrhosis in Pakistan and beyond – A Review

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Abstract

Liver Cirrhosis is a significant cause of morbidity and mortality worldwide among patients suffering from chronic liver disease. Liver cirrhosis was responsible for more than 2.4% of global deaths in 2019, with Asia-Pacific accounting for 62.6% of deaths due to liver diseases. Multiple causes are associated with the development of liver cirrhosis, but hepatitis B and C, and metabolic dysfunction-associated fatty liver disease are among the most common risk factors. However, the epidemiological trends of liver cirrhosis in terms of aetiology and complications are changing in different regions of the world. The current narrative review was planned to highlight aetiological trends, complications and future projections associated with liver cirrhosis at the global, regional (South Asia) and national (Pakistan) levels. While viral infections, like hepatitis B and C, continue to be the primary causes of liver cirrhosis, there is a noticeable increase in metabolic dysfunction-associated fatty liver disease, particularly in developed countries. It is anticipated that viral-related cirrhosis cases may decline, while those due to metabolic dysfunction-associated fatty liver disease are expected to rise.

Keywords: Liver cirrhosis, Chronic liver diseases, MAFLD, Hepatitis, Public health.

DOI: https://doi.org/10.47391/JPMA.22515

Introduction

Liver cirrhosis is a condition characterised by irreversible, diffuse hepatic fibrosis, nodular regeneration, and distortion of the parenchyma of the liver. Early-stage cirrhosis is frequently asymptomatic, making early identification difficult. Symptoms worsen as the condition advances. Clinical manifestations vary by disease stage, ranging from asymptomatic early cirrhosis to symptoms like fatigue, jaundice and ascites, and potentially life-threatening complications, such as variceal bleeding and hepatic encephalopathy.[1] It poses a significant global public health challenge, contributing to substantial morbidity and mortality among patients with chronic liver disease (CLD).

Liver cirrhosis is one of the leading causes of death worldwide, accounting for approximately 2.4% of global mortality.[2] The major causes of cirrhosis include hepatitis B virus (HBV), hepatitis C Virus (HCV), metabolic dysfunction-associated fatty liver disease (MAFLD), which was previously known as non-alcoholic fatty liver disease (NAFLD), and alcohol-associated liver cirrhosis.[3] Advances in medical treatments, such as HBV vaccination, and direct-acting antivirals for HBV and HCV, have shifted the landscape of cirrhosis aetiology. However, the rising global burden of alcohol-related cirrhosis, with an annual mortality rate of 8%, and the increasing prevalence of MAFLD due to obesity and diabetes underscore ongoing challenges.[4] Notably, obesity and diabetes are two important causes adding to the rising prevalence of MAFLD, which, in turn, increases the burden of MAFLD-associated liver cirrhosis.[5]

In the course of continued hepatic fibrosis, architectural distortion is observed along with blood vessels of the liver. Fibrosis and deposition of extracellular matrix (ECM) lead to compression of the liver sinusoids and small hepatic veins, which leads to increased resistance against blood flow to the liver. This eventually leads to portal hypertension, one of the complications of liver cirrhosis, characterised by the formation of collateral blood vessels, especially in the oesophageal and gastric regions.[6] Other complications of liver cirrhosis include ascites, hepatic encephalopathy, and the potential progression to hepatocellular carcinoma (HCC).

Managing liver cirrhosis necessitates a multifaceted strategy that includes lifestyle modifications, pharmacological treatments, and, in some cases, surgical procedures. It is critical to make an accurate diagnosis based on the patient's history, physical exam, blood test and imaging. Treatment is guided by staging using Child-Pugh and model for end-stage liver disease (MELD) scores. Lifestyle changes, such as abstaining from alcohol and

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Submission completed: 06-01-2025 **1st Revision received:** 24-06-2025
Acceptance: 15-11-2025 **Last Revision received:** 14-11-2025

eating a nutritious diet, are critical, particularly in alcohol-related and MAFLD cases. Antiviral medications for hepatitis, diuretics, beta-blockers, lactulose and rifaximin are used to treat a variety of symptoms and consequences. In extreme situations, liver transplantation is explored, which is aided by new therapies, such as anti-fibrotic medicines and stem cell therapy. Regular monitoring and patient education are essential for efficient treatment and a higher quality of life.

Considering the rising burden of liver cirrhosis globally, it is of paramount importance to evaluate the relevant trends by epidemiologists and public health specialists to provide crucial data for clinicians to treat their patients. Moreover, such data helps and guides policymakers in identifying high-risk areas and groups of individuals to direct targetted interventions, especially treating the aetiologies of cirrhosis, such as HBV and HCV infections. Hence, the current narrative review was planned to explore the global, regional (South Asia) and national (Pakistan) trends of liver cirrhosis in terms of aetiology, complications and future projections.

Global Aetiological Trends

The underlying causes of liver cirrhosis have been shifting over the last 10 years. A study examining the evolving epidemiology of cirrhosis between 2010 and 2019, utilising data from the Global Burden of Disease (GBD) 2019 study[7] across 204 countries,[7] revealed significant global figures (Figure 1).

In 2019, there were 2.05 million new cases and 1.47 million deaths attributed to liver cirrhosis. HCV remained the leading cause, accounting for the largest proportion of cirrhosis-related incidence (26.9%), mortality (26.8%), and disability-adjusted life years (DALYs) (26.3%). However, MAFLD emerged as a rapidly growing contributor to incident cirrhosis (+26.7%), cirrhosis-related mortality (+25.1%) and DALYs (+21.0%) worldwide during the specified timeframe.[8]

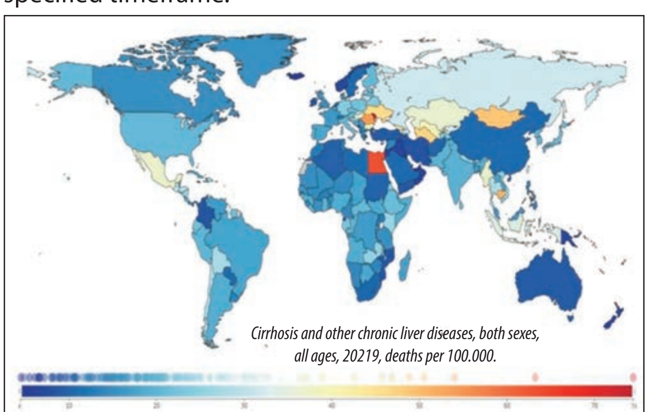

Figure-1: Global trends of mortality rates associated with liver cirrhosis.[7]

Another study examining the epidemiology of CLD in the United States, analysed data from 58,731 patients gathered through the National Health and Nutrition Examination Surveys, spanning from 1998 to 2016. The findings revealed that the prevalence of chronic HBV and alcoholic liver disease (ALD) remained steady, while chronic HCV decreased by almost half, from 1.6% in 1988-94 to 0.9% in 2013-16. Conversely, there was a notable rise in the prevalence of MAFLD, increasing from 20% to 31.9% from 2013 to 2016.[9]

A population-based study on 9261 patients in Indiana, USA, examined incident cases of cirrhosis from 2004 to 2014, and revealed rising proportions of patients diagnosed with alcohol-associated cirrhosis (increasing by 0.8% annually) and cirrhosis associated with MAFLD (increasing by 0.6% annually). Conversely, the proportion of cases linked to viral hepatitis decreased by 1.4% each year.[10]

A review examining the burden of liver disease in Europe revealed that liver cirrhosis caused 1.8% of all deaths in Europe, with the highest rates in south-eastern and north-eastern regions. Since the 1970s, countries like Hungary have seen dramatic increases in cirrhosis mortality, but there has been a recent decline in liver disease-related mortality. particularly among Mediterranean countries, due to HBV vaccination, reduced alcohol intake, and lower HCV transmission. However, in western Europe, particularly the United Kingdom and Ireland, cirrhosis mortality has risen over the past decade. In France, the causes of cirrhosis have been found to be alcohol and MAFLD (66%), MAFLD only (13%), alcohol only (9%), HCV (6%), and other factors (6%).[11]

A commentary on CLD in Africa revealed that it poses a significant health burden, accounting for 2.5% of deaths and 1.3% of total DALYs in 2019. The primary causes of cirrhosis and HCC in the region include chronic viral hepatitis (hepatitis B, C and D), heavy alcohol consumption, aflatoxin B1 exposure, and, increasingly, metabolic risk factors linked to MAFLD.[12]

Even though sparse data is available from the Middle East, literature states that liver cirrhosis remains one of the top four causes of mortality in the region. Egypt, which has the highest prevalence of HCV in the world, experiences a high prevalence of cirrhosis complications and deaths. Besides, MAFLD also appears to be a significant contributor to cirrhosis in the region.[13]

Complications

Several studies have reported the overall prevalence of various complications resulting from liver cirrhosis. One study, which included about 13% of hospitalised patients in South Korea each year, found that among 14,601 patients with decompensated cirrhosis, 11,201 (76.7%) experienced at least one decompensation-related complication, with roughly three-quarters of these patients requiring hospitalisation. The most common complications were ascites (54.8%), gastroesophageal variceal bleeding (33.2%), hepatic encephalopathy (27.4%), and hepatorenal syndrome (3.6%).[14]

Additionally, when examining the trends of individual common complications, it was found that the most prevalent infections in liver cirrhosis patients include spontaneous bacterial peritonitis (SBP), urinary tract infections, pneumonia and cellulitis. These infections account for approximately 30-50% of deaths in patients with cirrhosis and occur in 32-34% of hospitalised cirrhotic patients, a rate that is 4-5 times higher than that of the general hospitalised population.[15]

In a prospective study involving 63,364 individuals with cirrhosis, the cumulative incidence rates of ascites were 5.1% at one year, 9.5% at three years, and 10.7% at five years.[16] Another complication of cirrhosis is variceal bleeding. In patients with cirrhosis, varices form at an annual rate of 9%. It occurs in 1.2% to 4% of patients within three years, and the six-week mortality rate after variceal bleeding is 17.7%. In the US, variceal bleeding affects up to 70.6 per 100,000 hospitalisations and constitutes 10.5% of hospital admissions for cirrhosis.[17]

Hepatic encephalopathy is a neuropsychiatric disorder closely related to prognosis. An American study revealed that among 49,164 individuals with HE, the median survival for patients aged >65 years was significantly shorter, averaging only 0.95 years after the diagnosis of HE was established.[18] A meta-analysis combining data from 30 selected studies involving 18,474 patients with cirrhosis found that 5,648 of the patients developed acute kidney injury (AKI), resulting in a pooled incidence rate of 29% whereas, in-hospital mortality, evaluated in eight of the studies, was six times higher in patients with AKI compared to those without AKI.[19]

Liver cirrhosis is the primary risk factor for the development of HCC. A Swedish nationwide population-based cohort study examined 15,215 individuals diagnosed with cirrhosis, and found that the incidence rate of HCC was 23 per 1,000 person-years.[20]

Projected Morbidities and Moralities

Wang et al. analysed data on the incidence and mortality of liver cirrhosis from 1990 to 2019 from the GBD study. The results, according to the Nordpred model analysis, indicated that the incidence of liver cirrhosis is expected to rise from 1,317,848.92 cases in 1990-1994 to a projected 2,409,435.31 cases in 2035-2039.[21] Another study modelled the MAFLD disease burden by 2030, and predicted that by 2030, the MAFLD population in the US is projected to grow by 18.3% to 100.9 million cases, with a prevalence of 28.4%, while the UK is expected to see the largest increase, rising 20.2% from 14.08 million cases in 2016 to 16.92 million cases in 2030.[22] Germany will have the smallest increase at 13.5%, from 18.45 million to 20.95 million cases. China is expected to experience the greatest overall and relative increase in MAFLD prevalence, with cases rising 29.1% from 246.33 million in 2016 to 314.58 million in 2030.[22]

Another review highlighted how the global burden of cirrhosis is expected to increase significantly in the coming years across various aetiologies. For HCV-associated cirrhosis, the number of incident decompensated cases is projected to rise from 148,000 in 2020 to 174,000 in 2030, with the rate per 100,000 population remaining stable. HBV-associated cirrhosis is anticipated to see a 39% increase in related deaths between 2015 and 2030, despite a decline in infection incidence. Alcohol-associated cirrhosis is projected to experience a 77% rise in the age-standardised incidence of decompensated cases, growing from 9.9 per 100,000 patient-years in 2019 to 17.5 per 100,000 patient-years by 2040.[23]

Aetiological Trends in South Asia

The aetiological trends of liver cirrhosis vary widely owing to diverse risk factors, individual health statuses, socioeconomic conditions, and healthcare infrastructure. In Asia, liver cirrhosis is predominantly caused by chronic HBV and HCV infections.[24] According to the World Health Organisation (WHO) Global Health Estimates (GHE) of 2015, liver pathologies contributed to the highest number of deaths (4.7%) compared to other regions.[25] In 2015, the Asia-Pacific region experienced 54.3% of the 1,161,914 global deaths from cirrhosis. The region was responsible for nearly 70% of worldwide cirrhosis-related deaths caused by HBV, approximately 40% due to HCV, almost half resulting from alcohol consumption, and slightly more than half from MAFLD or other reasons, such as autoimmune, cholestatic, metabolic, or drug-induced liver diseases. In the Asia-Pacific region, 51.3% of cirrhosis-related deaths were attributed to HBV compared to 18.4% in the US and 24.3% in Europe.[26] HCV was responsible for 15.7% of these deaths in the Asia-Pacific region compared to 37.5% in the US and 32.6% in Europe. Alcohol consumption led to 20.8% of cirrhosis deaths in the Asia-Pacific, whereas it accounted for 31.2% in the US and 30.9% in Europe. MAFLD and other diseases caused 12.1% of cirrhosis deaths in both the Asia-Pacific region and Europe, while in the US, the figure was 12.8% .[24]

Pakistan: In South Asia, Pakistan bears one of the highest burdens of CLD. A systematic review in 2018 estimated overall HCV seroprevalence at 4.8% nationally, with regional variations up to 7% in the Punjab province.[27] Meanwhile, in Khyber Pakhtunkhwa (KP) and Sindh, HBV prevalence in adults ranges 2-4% showing the highest rates.[28] NAFLD, now reclassified as MAFLD, affects roughly 18-25% of urban Pakistani adults.[29] Consequently, viral hepatitis (both B and C) continues to be the primary driver of cirrhosis in Pakistan, but MAFLD-related cirrhosis is rapidly ascending, particularly in tertiary-care centres in Karachi and Lahore.[29,30]

India: In South Asia, HCV is particularly predominant, with India and Pakistan reporting higher cases than the rest of the Asian continent.[31] Similar to China, India is a large contributor to liver diseases, particularly HBV. Liver cirrhosis is a significant public health challenge in India. According to the GBD study, >33% of all the mortalities from liver cirrhosis resulted from HBV, whereas HCV accounted for 22%.[32] In India, it is known that >40 million people are chronically infected with HBV.[33] In terms of route of transmission, vertical transmission from mother to child, and horizontal transmission due to blood products and substance abuse are major routes. Despite the availability of an effective vaccine, vaccination coverage remains low, especially in rural areas. HCV contributes significantly to liver cirrhosis.[34] The incidence of HCV in India is estimated to be 1-2%, resulting in around 12-24 million infected persons.[25] HCV is usually transmitted by blood-to-blood contact, and intravenous (IV) drug use is a significant risk factor. The WHO estimates that 3.7% of the Indian population is infected with HBV, and 1.2% with HCV.[35] HBV and HCV combined account for around 60-70% of all liver cirrhosis cases in India.[35]

ALD is another leading cause of liver cirrhosis in India. The pattern of alcohol use in India has shifted significantly, with per capita alcohol consumption increasing over the last several decades. According to the WHO, India's per capita alcohol consumption rose from 2.4 litres in 2005 to 5.7 litres in 2016.[35] Men are more likely than women to consume alcohol, with 27% of men and 1.6% of women reporting it. Alcohol-related liver damage most commonly affects those aged 30-50 years. ALD accounts for around 10-15% of all liver cirrhosis cases in India, and alcohol consumption is responsible for up to 20% of liver cirrhosis fatalities.[35]

MAFLD is becoming a major cause of liver cirrhosis in India, owing to increased obesity, diabetes and metabolic syndrome rates.[36] Obesity is becoming more common in India, accounting for around 12.6% of the adult population. India has the second-highest population of diabetics in the world, with an estimated 77 million individuals afflicted. MAFLD affects 9-32% of the Indian population, with metropolitan regions having a greater incidence.[36] This increase in lifestyle-related disorders is leading to the rise in cases of liver cirrhosis caused by MAFLD.

Afghanistan: Chronic viral hepatitis and alcohol usage are the leading causes of liver cirrhosis in Afghanistan. Chronic HBV and HCV infections are common due to insufficient healthcare infrastructure and a lack of extensive immunisation programmes. HBV and HCV are transferred by contaminated blood and bodily fluids, with poor medical practices and hazardous blood transfusions playing a crucial role in their spread. The prevalence of HBV in Afghanistan is believed to be 3-5%, whereas HCV prevalence is approximately 1-2%. Alcohol drinking, while not universally popular due to cultural and religious standards, is a significant cause of liver disease in several demographic groups. ALD accounts for around 10-15% of liver cirrhosis patients.[37]

Bangladesh: Chronic viral hepatitis and the increasing prevalence of MAFLD are major causes of liver cirrhosis in Bangladesh. The country has a high prevalence of HBV, with around 5-7% of the population chronically infected, while HCV prevalence is estimated to be 1-2%. Unsafe medical practices and a lack of sufficient screening expedite the spread of these illnesses. MAFLD is becoming more of an issue as a result of lifestyle changes, including increased obesity rates and a large number of diabetics. Alcohol intake is generally low due to cultural and religious considerations, and it accounts for a lesser fraction of liver cirrhosis instances.[38]

Bhutan: Liver cirrhosis in Bhutan is mostly caused by persistent viral hepatitis, specifically HBV, and alcohol usage. The prevalence of HBV is considerable, with estimates indicating that around 5% of the population is chronically infected. HBV spreads mostly through vertical transmission from mother to child, and risky medical practices. HCV is less common, but it remains a worry. Alcoholism is a serious public health concern in Bhutan, with high rates of alcohol use contributing significantly to liver cirrhosis. ALD accounts for around 20-25% of all liver cirrhosis cases in Bhutan.[39]

Maldives: In the Maldives, chronic viral hepatitis and MAFLD are the leading causes of liver cirrhosis. Compared to other South Asian nations, the prevalence of HBV and HCV is quite low, with HBV affecting around 2-3% of the population, and HCV prevalence being around 1%. However, rising rates of obesity and diabetes are contributing to an increase in MAFLD instances, which is now a leading cause of liver cirrhosis. Alcohol use is generally low due to cultural and religious standards, although it remains a dangerous issue for a tiny percentage of the population.[40]

Nepal: Liver cirrhosis in Nepal is mostly caused by persistent viral hepatitis, alcohol usage and MAFLD. HBV and HCV infections are common, with HBV affecting around 4-6% of the population, and HCV impacting approximately 1-2%. Unsafe medical practices, low immunisation coverage, and vertical transmission contribute significantly to the spread of these illnesses. Alcohol intake is a major cause of liver disease in Nepal, accounting for around 15-20% of all liver cirrhosis cases. The increased incidence of obesity and diabetes is contributing to a rise in MAFLD instances.[41]

Sri Lanka: Cirrhosis of the liver in Sri Lanka is mostly caused by chronic viral hepatitis, alcohol usage, and MAFLD. HBV and HCV are common, with HBV afflicting around 3-5% of the population, and HCV affecting approximately 1-2%. Unsafe medical practices and low immunisation coverage add to the spread of these illnesses. Alcohol use is a major public health concern, with high rates of alcohol use accounting for a considerable share of liver cirrhosis diagnoses. ALD accounts for around 20-25% of all liver cirrhosis patients in Sri Lanka. Obesity and diabetes rates are also increasing, resulting in a rise in MAFLD instances.[42]

Complications

Liver cirrhosis is a chronic and irreversible condition that presents with many complications, especially in patients where the condition is not well-managed. Common complications include ascites, hepatic encephalopathy, and variceal bleeding.

One of the most frequent and critical symptoms of liver cirrhosis is hepatic encephalopathy. In South Asia, the prevalence of hepatic encephalopathy among liver cirrhosis patients is believed to be 30-45%. Hepatic encephalopathy has a substantial influence on patients' quality of life, and increases death rates. In countries like India and Pakistan, where healthcare resources are generally low, controlling this illness is a significant problem.

Variceal haemorrhage is the leading cause of death among cirrhosis patients in South Asia.[43] According to reports, the prevalence of variceal bleeding in cirrhotic individuals is 30-40% in countries, such as India and Pakistan.[44,45] The problem is aggravated by individuals presenting late and having restricted access to endoscopic therapies and specialised care. Endoscopic variceal ligation (EVL) and sclerotherapy are frequently used in emergency situations, although they are not widely available, especially in rural communities.[1,24] The mortality rate from variceal haemorrhage remains high, highlighting the need for enhanced hospital infrastructure.

HCC, a primary liver cancer, is a serious consequence of liver cirrhosis with a high incidence rate in South Asia.[46] Chronic HBV and HCV infections are the primary culprits, with research showing that these viral infections account for 60-80% of HCC cases in countries, such as India and Bangladesh.[47] The yearly incidence of HCC among cirrhotic individuals is 2-8%.[48] Screening and early detection are frequently insufficient, resulting in late diagnosis and poor prognosis. Efforts to enhance HBV vaccination and access to antiviral therapies are critical for lowering the incidence of HCC. HCC is the most feared complication of cirrhosis in Pakistan, with an estimated annual incidence of 4-5 per 100,000.[31] Chronic HCV accounts for 50-60% of HCC cases, followed by HBV (25-30%) and MAFLD (10-15%).[49] Despite increasing availability of ultrasound and alpha-fetoprotein screening, >70% of Pakistani HCC patients present at an advanced stage, contributing to one-year survival rates <30%.[28,50]

SBP is an abrupt bacterial infection of the ascitic fluid that poses a serious risk to cirrhotic patients in South Asia. The prevalence of SBP in ascites patients ranges 10-30%.[51] Poor sanitation, delayed diagnosis, and a lack of preventive antibiotics contribute to SBP's high incidence and fatality rates. Management normally includes empirical antibiotic therapy, but the rise of drug-resistant bacteria is a growing issue. SBP occurs in 15-25% of cirrhotic patients with ascites in Pakistani cohorts.[51,52] Culture-positive SBP accounts for 40-50% of cases, with the remainder classified as culture-negative neutrocytic ascites. In tertiary hospitals in Karachi, in-hospital mortality for SBP remains 20-25%, often due to delayed paracentesis and rising antimicrobial resistance.[51,52]

Projected Morbidities and Mortalities

Understanding projected morbidities and mortalities associated with liver cirrhosis can help develop tailored interventions across different regions. In Asia, morbidities and mortalities are projected to increase due to the public health crisis of rising HBC and HCV infections, which are primary causes of liver cirrhosis.[53] In China, it has been estimated that >120 million individuals are chronic HBV carriers, and the number is expected to increase as the population ages.[54] A similar situation is observed in Pakistan where an estimated >15 million individuals are infected with HCV, but this is an underestimation because of the low level of screening and management.[27] Hence, Pakistan is facing a growing burden of liver cirrhosis and its associated complications.

MAFLD is another growing concern, being responsible for liver cirrhosis primarily due to unhealthy dietary habits, obesity and metabolic syndrome (including diabetes). In countries like Japan, it has been estimated that 20-30% of the population suffers from MAFLD, and the cases and complications associated with liver cirrhosis are expected to increase in the coming years.[55] If this trend continues, a significant toll is expected on the healthcare infrastructure, especially in the low- and middle-income countries (LMICs) of Asia.

Mortalities may remain high in the coming years in Asia primarily due to a lack of proper healthcare infrastructure and funding available to treat patients suffering from liver cirrhosis. The WHO has been advocating vaccination against HBV infections globally, but in many parts of the world, this has been unsuccessful mainly due to cultural practices.[56]

Aetiological Trends in Pakistan

Pakistan, like other LMICs, faces challenges in terms of rising cases of liver cirrhosis and its associated complications (Figures 2-3). Liver cirrhosis is the leading cause of CLD in Pakistan, which is among the 10 countries with the highest prevalence of liver diseases. The aetiology of liver cirrhosis in Pakistan has changed dramatically in recent decades, owing to developments in public health dynamics, socioeconomic variables, and healthcare access. Historically, HBV and HCV infections were the leading cause of liver cirrhosis in the country.[28] Since the introduction of large-scale vaccination programmes against HBV, a shift from HBV as the primary cause of cirrhosis has been observed.[28] Over the years, the number of HCV-related liver cirrhosis case has been on the rise, which is now the most common cause of liver cirrhosis in Pakistan.[57]

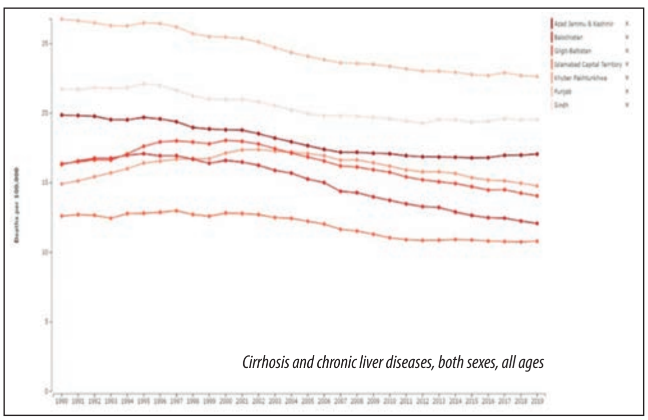

Figure-2: Trends of liver cirrhosis across various regions in Pakistan.[7]

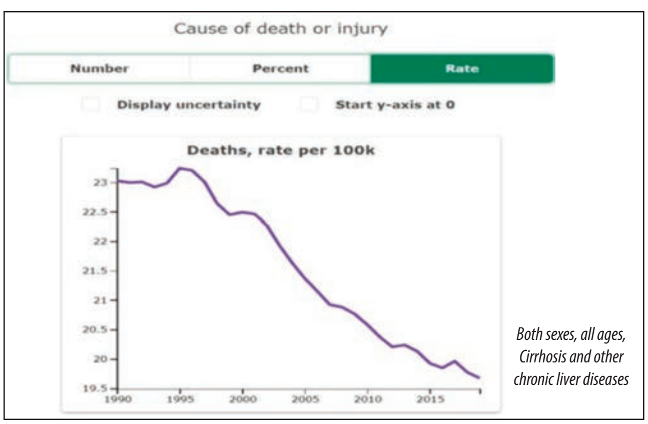

Figure-2: Liver cirrhosis Mortality rate per 100,000 from 1990 to 2015 in Pakistan.[7]

In a 2016 study at three tertiary care hospitals in Karachi, the aetiology of cirrhosis was investigated among a cohort comprising 211 male and 166 female patients.[58] The study identified multiple aetiological factors contributing to cirrhosis, including HBV, HCV, HDV, chronic alcohol consumption, and MAFLD.[58] However, it was found that HCV was the leading cause of liver cirrhosis, followed by HBV infections. Such conclusions signify the changing aetiology of liver cirrhosis in Pakistan. Another study observed that just about half of the liver cirrhosis cases were caused by HCV infection.[59] Similarly, another study carried at a tertiary hospital found that approximately 70% of the liver cirrhosis cases were associated with HCV infections.[60]

The changing trends in the aetiology of liver cirrhosis have been observed in different provinces of Pakistan. A study in the KP province explored the frequency of HCV-related liver cirrhosis patients and investigated the prevalence of different HCV genotypes. The study found a high frequency of HCV cirrhosis in Peshawar (33.3%), followed by Mardan and Kohat (10.5% and 5.2%, respectively).[49] The HCV genotype 3a was the major prevalent genotype, and the prevalence of different HCV genotypes reported was as follows: 3a (48.3%), 3b (10.5%), 2a (11.2%), 1a (6%) and 1b (1.1%).[49]

A descriptive cross-sectional study conducted in 2022 in Islamabad and Rawalpindi included 586 patients with hepatitis B surface antigen (HBsAg) positivity. The study found that most patients (52.04%) had HBV mono-infection, while a smaller proportion (11.77%) were co-infected with HDV.[61] Liver cirrhosis was present in 23.72% of the patients, while the remaining 76.27% did not have cirrhosis. Patients with HDV co-infection had a higher likelihood of developing liver cirrhosis compared to those with HBV mono-infection.[61] Moreover, another study conducted in a tertiary hospital in Punjab reported that >80% of liver cirrhosis cases were caused by an underlying HCV infection.[50]

A study in Karachi, involving 273 adult patients with cirrhosis, discovered that 247(90.5%) patients had cirrhosis related to viral infections.[62] Among these cases, cirrhosis caused by HCV was the most prevalent, affecting 198(72.5%) participants, while HBV-related cirrhosis was observed in only 49 patients. Specifically, 39(14.3%) individuals had isolated HBV-related cirrhosis, and 10(3.7%) had cirrhosis caused by both HBV and HDV[1] Non-B non-C-related cirrhosis was found in only 26(9.5%) patients.[62] Moreover, unpublished data from the Aga Khan University in Karachi has concluded that the prevalence of liver cirrhosis was 20% between 2008 and 2021, with the primary aetiology being HCV. Findings from these studies agree that the trends of aetiology of liver cirrhosis are now shifting towards HCV from HBV infections.

In the Western world, MAFLD is now emerging as the leading cause of CLD. Similarly, in Pakistan, there has been a notable rise in cases of MAFLD leading to liver cirrhosis.[29] Such a shift in Pakistan is in line with the globally recognised trends that are largely attributed to obesity, diabetes, metabolic disorders, and changes in lifestyle.[63] Such factors directly lead to the possible development of MAFLD, which may eventually lead to cirrhosis. A recent study determining the frequency at a tertiary hospital among non-obese patients found that a significant number of patients had fatty liver.[30] Moreover, various studies have reported that the prevalence of MAFLD has increased from 14% to 47% .[64] Such findings suggest possible future development of cirrhosis in case the necessary interventions are not put in place. However, further studies are required to explore the burden of MAFLD-related liver cirrhosis cases in Pakistan.

Complications

A study conducted in Peshawar from 2015 to 2018, comprising 267 HCV cirrhotic patients, reported that ascites was high in 157(59%) patients; 38.6% males and 20.6% females. It was moderate in 71, and mild in 29 patients.[49] Albumin level was abnormal in 174 patients and spleen enlargement was reported in 171. The respiratory process was abnormal in 16 patients. The majority of the HCV cirrhotic patients had gastrointestinal problems. Swollen abdomen was observed in 89 patients, and non-tenderness in 175. Besides, different complications, such as fever, vomiting, diarrhoea, constipation, jaundice and anaemia were found during the treatment of these patients.[49]

In a study Karachi study involving 273 adult patients with cirrhosis, a history of decompensation was noted in 93(34%), with ascites (14%), upper gastrointestinal bleeding (16.5%) and hepatic encephalopathy (3%) being the most common occurrences.[62] The majority of the participants 180(66%) had no prior episode of cirrhosis-related decompensation. Moreover, laboratory analysis revealed low levels of haemoglobin, platelets, protein and albumin in the patient cohort.[62]

A study was conducted to identify common coagulation disorders in patients with CLD from January to October 2019, involving 278 patients from KP's Buner district.[50] Of these patients, 23(8.3%) had a normal prothrombin time (PT) of <15 seconds, while 255(91.7%) exhibited a prolonged PT. Additionally, 245(88%) patients had a prolonged activated partial thromboplastin time (aPTT).[2] Both PT and aPTT were prolonged in 236(84.89%) patients. Furthermore, 164(64%) patients had a low platelet count. The study found that most cirrhotic patients (>90%) had an abnormal coagulation profile and a reduced platelet count.[52]

A cross-sectional study in Karachi from May 9 to October 5, 2019, included 167 patients with HCV-induced liver cirrhosis.[65] Thrombocytopenia was present in most patients 130(77.8%) and oesophageal varices were found in 141(84.4%).[65] A significantly higher occurrence of oesophageal varices was observed among patients with thrombocytopenia, ascites and a Child-Pugh score of "C".[65]

Projected Morbidities and Moralities

Gazder et al. assessed the impact of cirrhosis on health-related quality of life in 115 patients at a private tertiary care hospital in Karachi. Variables, such as advancing age, gender, residence status, duration of liver sickness, Child-Turcotte-Pugh class, hypertension, diabetes, tobacco use, income per month and level of education, exhibited significant relationships with physical role, bodily pain, general health, social functioning, role emotional, vitality and mental health.[66] The study reported moderate disability in physical functioning and notable impacts on mental health, emotional wellbeing and body pain.[66] In a 2012 cross-sectional study in Karachi, comprising 273 adult patients with cirrhosis, 187(69%) showed poor health-related quality of life.[62] Within the various domains assessed, the fatigue domain exhibited the lowest CLD Questionnaire (CLDQ) score. Haemoglobin, albumin levels, diastolic blood pressure, and prior history of decompensation were identified as significant factors linked to health-related quality of life in patients with liver cirrhosis.[62]

To determine the frequency of MAFLD in patients with rheumatoid arthritis, a study was conducted in 2019 in Lahore with 192 seropositive rheumatoid arthritis patients. Among them, 39(20.3%) female patients had fatty liver.[67]

Discussion

Liver cirrhosis is turning out to be a serious global public health challenge with the rise in associated morbidities and mortalities. Liver cirrhosis is caused by a variety of factors, most significant of which are HBV, HCV and MAFLD pathologies. Considering the rising incidence of this pathology, there is an urgent need to address the risk factors of liver cirrhosis to curb its rise globally.

The trends in terms of aetiologies and complications show a global variation, with some regions reporting higher cases than others. Regions, especially Asia and Africa, tend to report a higher number of liver cirrhosis cases than other regions due to various reasons. Sharing needles, contaminated blood transfusions, and vertical transmission are the most common reasons for the high burden of liver cirrhosis in these regions.[68] Moreover, the cases of liver cirrhosis are diagnosed at a late stage due to lack of adequate screening of individuals, especially those at high risk, hence facing high morbidities and mortalities.

On the other hand, the incidence of liver cirrhosis in the West is on the decline primarily due to effective vaccination programmes against HBV and early detection and treatment of the patients.[69] However, a shift in the aetiological trend of liver cirrhosis is now noted in the Western world due to a rise in MAFLD cases. Unhealthy dietary habits and lack of physical activity predispose individuals to obesity, metabolic syndrome, and diabetes. Hence, public awareness campaigns have been initiated to educate the general population regarding healthy dietary habits and significance of physical activity.

Further, variations in terms of aetiology and complications have also been noted, underlining the need for tailored approaches in different regions of the world to help address and mitigate the rising incidence of liver cirrhosis and its complications. Screening programmes should be initiated, especially targetting high-risk populations, such as those involved in substance abuse, and sharing of needles, as well as those who have undergone blood transfusion.

Conclusion

Liver cirrhosis is a growing public health challenge that shows variations in terms of aetiology and complications globally. The increasing number of cases places a high burden on the healthcare systems, especially in LMICs. Western regions are able to cope better with liver cirrhosis and its complications, but the other regions are still facing a crisis owing to the rising number of liver cirrhosis cases.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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Author Contribution:

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