Bulletin of Biological and Allied Sciences Research
***ISSN:* 2521-0092**
www.bbasr.org
DOI: https://doi.org/10.54112/bbasr.v2024i1.64
*Bull. Biol. All. Sci. Res., Volume, **9**: 64*
Review Article ***Open Access***

AN OVERVIEW OF HEPATITIS C VIRUS AND LIVER CIRRHOSIS IN PAKISTAN

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(Received, 24th March 2023, Revised 4 February 2024, Published 6th February 2024)

Abstract *Liver cirrhosis is a medical condition characterized by atrophy, fibrosis and physiological malfunctioning of the liver. This ailment may or may not be associated with liver carcinoma, which can be diagnosed via alphafetoprotein (AFP) blood test. The liver is a multi-tasking organ responsible for enzyme synthesis and toxin degradation; the patient with cirrhosis falls prone to various health issues such as jaundice, malaise, nausea, fatigue, swellings, loss of appetite, accumulation of fluid in the abdominal spaces, weight loss etc. This hepatic pathology, in later stages, is fatal. This disease leads to the annual mortality of 4000 lives in the UK and is the 12th major life-threatening disease in the USA. Chronic infection with HCV (hepatitis C virus), HBV (hepatitis B virus), and alcohol consumption are major factors of liver cirrhosis. Due to its slower progression (as it develops over months), liver cirrhosis can be detected earlier via diagnostic tools like CT (Computed Tomography) scan, MRI (Magnetic Resonance Imaging) scan, liver biopsy etc. Liver cirrhosis is the major reason for liver transplants around the world. It is more common in males than females and is prevalent in developing countries. Pakistan has an enormous burden of liver cirrhosis. This article briefly discusses the recent developments in the understanding of the pathogenesis, diagnosis and frequency of liver cirrhosis in the Pakistani population.*

[Citation: Ullah, A., Bibi, A., Ullah, I., Kayani, R.E.Z., Asim, M., Munawar, N., Amjad, M., Siraj, M. , Gohar M., Khan, M.A. (2024). An overview of hepatitis c virus and liver cirrhosis in Pakistan. *Bull. Biol. All. Sci. Res.* **9***: 64. doi:* https://doi.org/10.54112/bbasr.v2024i1.64]
Keywords: *HCV; Inflammation; Liver Cirrhosis; Liver carcinoma; Liver transplant; risk factors*

Introduction

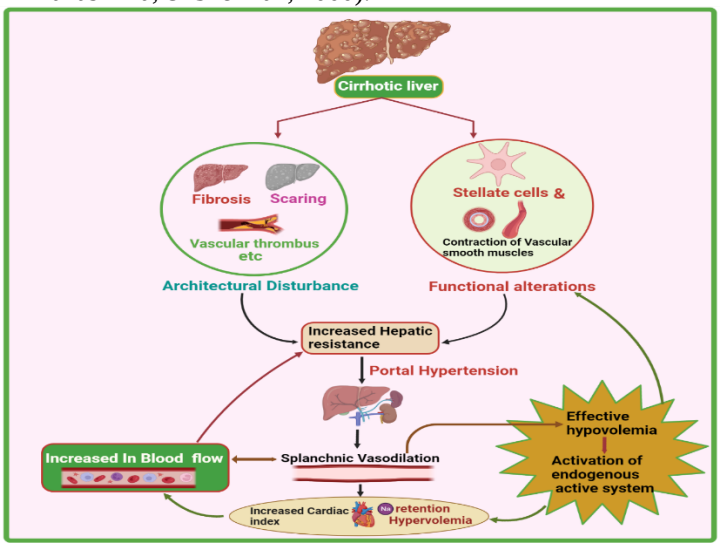
Globally, each year 35 million people succumb to chronic diseases, and the mortality rate is increasing gradually (Williams, 2006). Liver disease is the fifth most common cause of death after stroke, heart disease, chest disease and cancer, as put forth by the Office for National Statistics in the United Kingdom (Munro, Brown, & Manful, 2011). Statistics are reflecting that the instances of liver diseases are escalating. Globally, the exact incidences of cirrhosis, are unknown for several reasons. Compensated cirrhosis usually goes undetected. So, the supposed prevalence may be 1% worldwide instead of the recorded 0.15% in the USA and similar findings worldwide. The figures from Europe are almost the same, while the numbers are even higher in most African and Asian countries where chronic HCV and HBV are more common(Beltrán-Aguilar et al., 2005; Pirovino, Linder, Boss, Köchli, & Mahler, 1988). According to a study, the cirrhosis-caused mortality in Scotland has doubled for males, and increased for females (Smith, 2006). Majority of the cases of liver cirrhosis in Central Asia are due to viral hepatitis (HCV and HBV), which was 57 percent in 1990, plummeting to 54 percent in 2010. Worldwide highest mortality rate due to liver cirrhosis occurred in Kyrgyzstan in 2010 followed by Uzbekistan and Turkmenistan. HBV, HCV are cardinal agents of liver cirrhosis (Fattovich, Stroffolini, Zagni, & Donato, 2004; A. Ullah et al., 2020). In Western Europe and North America HCV is the main cause of cirrhosis. In Italy HBV was attributed 1/3 liver cirrhosis in the early 70s, but since 1989 HCV has been attributing to more than half of cirrhosis cases (De Bac, Stroffolini, Gaeta, Taliani, & Giusti, 1994; Stroffolini et al., 2004).Viral hepatitis is the main cause of liver cirrhosis in developing countries like Pakistan as compared to West, alcohol is the main etiological factor (Huang et al., 2023; I. Hussain, Nasrullah, & Shah, 1998). Evidence of HCV, HBV and co-infection is found in the majority of patients (90%) with chronic liver diseases and cirrhosis in found in 74 % of patients (Bukhtiari et al., 2003; Farooqi &

Khan, 2002; Idrees et al., 2011). In the case of HCV, patient's age and alcohol consumption are the factor involved in the progression to cirrhosis. The chronic HCV develops slowly in young patients in the absence of suitable treatment, while the progression increases from age 40 onward. In this case, if patient drinks, the chances of progression are multiplied by factors. In the case of HBV progression to cirrhosis depends on viral load. When the viral load exceeds 2000 IU/ml the disease progression is rapid.

Liver is a large organ consisting of three lobes and the largest organ in the body after the skin. Between the lobes of liver, there is a gallbladder for storing bile. It is the most vigorous and multitasking organ in the body, often named as the master gland or the 'chemical factory', as it performs more than 500 chemical reactions. It produces bile juice for the digestion of lipids in the small intestine. It is the center of amino acid metabolism. The ammonia from amino acids and nucleic acids metabolism is converted to urea and transported to the kidneys for removal with urine. So, liver is the detoxification center in the body. The digested food goes to the liver through a hepatic portal system to eliminate toxins before entering the heart. The liver is also a storage organ, conserving glycogen, fatty acids and certain vitamins. Hemolysis, the breakdown of old RBCs, also occurs in the liver. The yellow pigment bilirubin and other pigments like urochrome and biliverdin are the products of hemolysis. These pigments are removed with feces or urine, indicating the liver's excretory role (Crawford, 1999; E. R. Schiff, Sorrell, & Maddrey, 2003). The liver also synthesises many important components like cholesterol, vitamin D, fibrinogens, heparin, prostaglandin, etc. (Michalopoulos, 2007). Given the immense physiological importance of liver, it can regenerate itself up to 75%. If 2/3rd of the mice liver is removed, then the remaining 1/3rd liver tissue can regrow within a week to its original form (Higgins, 1931). Similarly, human liver can regenerate within 2 to 3 weeks (Michalopoulos, 2007).

The Liver comprises intrahepatic microvascular units, consisting of several distinct components such as hepatic arterioles, portal venules, central venules, sinusoids, and lymphatics. These subunits comprise smooth muscle cells, endothelial cells and the pericyte-like hepatic stellate cells in the sinusoids. In a healthy liver, integrity of this structural organization is intact (Iwakiri, Shah, & Rockey, 2014). In liver cirrhosis, the liver vasculature is disintegrated, leading to the blockade of the portal and arterial blood supply to the central vein, disturbing the exchange of materials between sinusoids and hepatocytes (Iwakiri, Grisham, & Shah, 2008). The space of Disse (perisinusoidal space) in the liver, has a layer of connective tissues, on which mesh endothelia that line the hepatic sinusoids, rests. The space of Disse also covers hepatic stellate cells, certain mononuclear cells, and lined, on the other side, by hepatocytes. Sinusoidal capillarization is a stage in cirrhosis, in which dead tissues fill the space of Disse (Schaffner & Popper, 1963).

In cirrhosis, hepatocyte islands are separated from the central vein by fibrotic septa (Figure 1). Malfunctioning hepatocytes lead to high pressure buildup in the portal system 'portal hypertension' and liver carcinoma. Cirrhosis is also linked with extra hepatic anomalies like dilation and constriction of splanchnic vessels, increased water and salt reabsorption by kidney, and forceful heart contraction. Cirrhosis and related vascular distortions are traditionally viewed as irreversible, but new data propose that cirrhosis regression or even reversal is possible (Desmet & Roskams, 2004; Wanless, Nakashima, & Sherman, 2000).



Figuer 1. Structural changes in the liver cirrhosis

Inflammation of the liver

Inflamed liver or hepatitis is the beginning of liver disorders. This can be due to viral infections or copper accumulation, due to hereditary diseases like Wilson's disease, or may be due to drug abuse (Brewer, 2000). Associated symptoms are enlargement, liver redness, and pain in some cases. Diagnosis at this stage increases the chances of recovery. If not detected and treated in time, it can become chronic and lead to hepatocellular necrosis, morphological changes and disturbance in blood flow and appearance of scar tissues i.e. fibrosis. Inflammation sets the stage for fibrosis, which evolves into cirrhosis. So, controlling inflammation will likely prevent fibrosis (Markiewski, DeAngelis, & Lambris, 2006).

Liver fibrosis

Liver can heal the scar tissues, through the deposition of collagen fibers. This process also occurs in skin, bone, kidneys, and other organs. But, the fibrogenesis in the skin is harmless because it is not involved in body metabolism and hemostasis, whereas the fibrotic tissue in other organs, including the liver, can hamper their functionalities. This fibrosis process disturbs various metabolic pathways and blood flow. Liver fibrosis is the healing and scaring process to repair the

injury. Blood flow disturbance due to fibrosis results in necrosis and architectural changes in the liver, leading to cirrhosis (Friedman, 2003; GRIFFITHS, 2005).

Liver cirrhosis

Cirrhosis is the necrosis of liver cells and structural deformities due to fibrosis. In cirrhotic liver, nodules appear on the organ surface accompanied by high blood pressure in the portal veins (Anderson & Smith, 2003; A.A.Khan, 1995; Malik & Tariq, 1995; Shamsuddin, 1998). Liver cirrhosis has become the 10th biggest fatal ailment. In Pakistan, HCV (hepatitis C virus) and HBV (hepatitis B virus) are the major causes of cirrhosis (Hamid, Tabbasum, Jafri, Shah, & Khan, 1999).

Hepatocellular carcinoma

Abnormal mitosis and the subsequent appearance of malignant tumors in the liver cause hepatocellular carcinoma or liver cancer. Most primary liver cancers are classified as hepatocellular carcinoma. Liver cancer is 5th among the most prevalent cancers, with more than half a million victims diagnosed annually. In the USA, HCV-cause liver cancer is now the fastest-rising cause of death due to cancer. In the past twenty years, the frequency of liver cancer has increased threefold in the USA (Idrees et al., 2009). The highest incidence rate in the US has been recorded in the Spanish and white Americans aged 45-60 years(Ries et al., 2002). However, about 85% of the patients are reportedly from second-world countries, like Pakistan (El-Serag, Lau, Eschbach, Davila, & Goodwin, 2007; Ferlay et al., 2010). The cause of the liver carcinoma in majority of the cases in these areas has been linked to HBV and HCV infections. Most of the victims are males, almost four-fold higher in number than females.

Cirrhosis irreversible?

Recent findings suggest that in liver cirrhosis patients on antiviral therapy, the reversal rate is 50% (Garcia-Tsao, Friedman, Iredale, & Pinzani, 2010), while in the case of HCV-related cirrhosis the reversal rate is 62%.19 Biopsy based observations are not so reliable, given the fact that biopsy is prone to sampling errors. Hence, these reversal rates may not be that high in reality. The current most accurate method is hepatic venous pressure gradient measurement. So, reversibility rates surveyed through this method would be reliable (Garcia-Tsao et al., 2010; Manne, Akhtar, & Saab, 2014).

Classification of cirrhosis

Cirrhosis has two types: compensated and decompensated stages (Figure 2). The compensated stage cirrhosis is characterized by a heavily-scarred but physiologically-normal liver with almost normal portal pressure. In most cases, the patients are asymptomatic, or may be a bit symptomatic, not developing any worrying and age-shortening complications(Gennaro D'Amico et al., 2001). However, it does not mean that it can be ignored. It can jump to a serious condition suddenly. So, the patients should be on therapy for carcinoma and HCV. Symptoms, if any, can include nausea or abdominal pain, loss of appetite and weight loss, fatigue, and the development of spider angiomas (Sivakrishnan & Pharm, 2019). The decompensated stage cirrhosis is characterized by serious symptoms like high portal pressure, edema and fluid accumulation, hemorrhage, jaundice, and physiological inefficiencies (Bruno et al., 2013; Garcia-Tsao et al., 2006). High portal pressure causes splanchnic and systemic vessel enlargement, developing portosystemic collaterals (G D'amico et al., 2014). The vessels' dilations lead to over-activity of the circulatory system, due to increased blood volume, through the activity of neurohumoral system. Dividing the decompensating stage into sub-stages is not well established. The different suggested prognostic sub-stages based on stratifying factors have been listed in Table 1.

Table 1. Compensated and decompensated stage of liver cirrhosis

	Compensated cirrhosis		Decompensated cirrhosis	
Stage	Stage 1	Stage 2	Stage 3	Stage 4
Clinical	No varices	Varices	Ascites + -	Bleeding +-
	No Ascites	No Ascites	Varices	Ascites
Death (At 1 year)	1%	3%	20%	57%

Agents causing liver cirrhosis

Of all the cirrhosis cases worldwide, 57% are due to HCV and HBV, of which HBV was responsible for 30% while HCV was responsible for 27% of cases. HBV infection is the main cause of cirrhosis in Asia (Di Bisceglie, 2000; Innes et al., 2013; Perz, Armstrong, Farrington, Hutin, & Bell, 2006; Zhou, Zhang, & Qiao, 2014). The viral factors are followed by alcohol consumption as a cause of cirrhosis triggers. Of all instances of cirrhosis, 20% are attributed to alcohol (Ganem & Prince, 2004). In Western countries, the predominant origin is non-alcoholic fatty liver disease (NAFLD) (Correction Naghavi et al., 2015; Liaw et al., 2008). Excessive alcohol intake causes alcoholic liver disease (ALD), by hampering the metabolism of fats, carbohydrates and proteins. Alcohol also converts to acetaldehyde in the liver, damaging the hepatic tissues. These alcohol-based complications account for 20-30% of cases of the cirrhosis (Maddrey, 2000). In 10-20% of individuals who drink heavily for a decade or more,

the risk of developing liver cirrhosis is high (A. Ullah et al., 2020).

Inherited diseases such as hemochromatosis (where body iron level rises) and Wilson's disease (accumulation of copper in liver) are triggers (Camaschella, 2013; Deutsch, Emmanuel, & Koskinas, 2013; Olynyk, Trinder, Ramm, Britton, & Bacon, 2008). Primary biliary cirrhosis and primary sclerosing cholangitis (hardening & scaring of bile ducts) and autoimmune hepatitis (Popov, 2013; Selmi, Bowlus, Gershwin, & Coppel, 2011; van Os et al., 2007). Poorly formed bile ducts (biliary atresia) are other drivers of liver cirrhosis. Metabolic disorders like galactosemia, glycogen storage disorders and alpha-1-antitrypsin deficiency are factors for cirrhosis. Drugs and toxins such as methotrexate, amiodarone and isoniazid and infections like congenital syphilis and schistosomiasis are also causative of liver cirrhosis (Heidelbauch & Bruderly, 2006; Назыров, Байбеков, & Раимов, 2014). Budd-Chiari syndrome is a veno-occlusive disease where blood clots in the hepatic vein lead to liver enlargement and development of collateral vessels (Aydinli & Bayraktar, 2007). Table 2 presents the causes of liver cirrhosis.

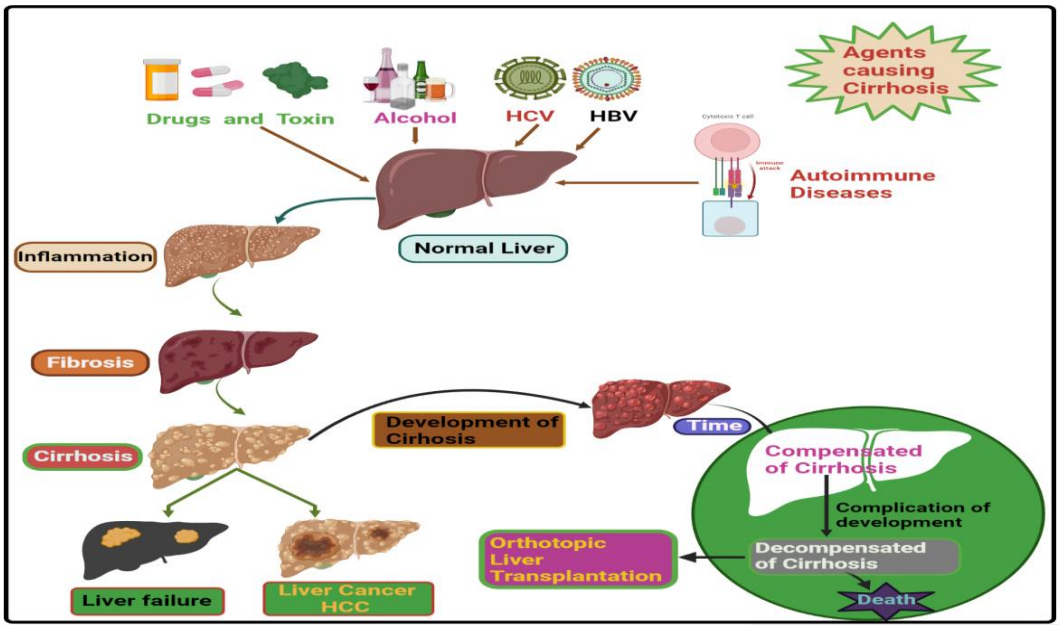


Figure 2. Schematic pathway and development of liver cirrhosis

Table 2. Risk factors for liver cirrhosis

S.No.	Risk factors for cirrhosis
1	HCV and HBV Coinfection with HIV (risk 2–6-fold)
2	Type 2 diabetes
3	Bile duct disorders (e.g., primary biliary cirrhosis, primary sclerosing cholangitis)
4	Old age
5	Male gender
6	Non-alcoholic steatohepatitis
7	Excess alcohol intake
8	Aflatoxin exposure
9	Positive family history of hepatocellular carcinoma
10	Venus outflow obstruction like Budd-Chiari Syndrome

The diagnosis of liver cirrhosis

The diagnosis of liver cirrhosis depends upon the extent or degree of clinical suspicion of etiology. Cirrhosis can be diagnosed from its distinguishing findings on clinical checkups, lab tests and additional studies. Characteristic findings in cirrhosis include the cutaneous sign of liver disease, a firm liver on palpation and the constellation of risks like exposure to hepatotoxic substances, metabolic syndrome and medications, alcohol intaking habits etc(Berg, 2009; Schuppan & Afdhal, 2008). Laboratory and ultrasound base proces-based processes can perform the noninvasive diagnostic evaluation of liver cirrhosis. The different blood tests include liver function tests (LFTs), which assess the amount of aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, alkaline phosphatase (ALP), gamma

glutamyltransferase (GGT) etc. The level of ALT and AST rise due to hepatocyte damage, while the level of GGT rises in chronic alcohol consumption (Berg, 2009). Blood is also checked for creatinine because kidney function declines in the advanced stages of cirrhosis. The viral ABS (full form?) screen is performed for HCV and HBV infection. Platelets count assists as a screen catalog for advanced fibrosis and cirrhosis (Snyder et al., 2006). INR (international normalized ratio) tests blood's ability to clot. PT (prothrombin time) is reduced in cirrhosis. Anti-mitochondrial antibodies are used as an indicator for primary biliary cirrhosis(Jones, James, & Bassendine, 1998), Ferritin levels increase in hemochromatosis, a condition in which the iron load in the body exceeds normal level. Imaging techniques can reveal the abnormalities in the liver. CT, MRI and ultrasound scan of liver are used to diagnose complications of cirrhosis like splenomegaly, ascites or hepatocellular carcinoma. Chest X ray is also used which shows elevated diaphragm due to the passage of ascites fluids (Conder, Rendle, Kidd, & Misra, 2009). Liver biopsy is a gold standard technique in the diagnosis of liver cirrhosis. It can provide the degree of liver injury and determine the histological sorting of inflammation and the fibrosis staging. In all liver diseases, biopsy is prone to sampling variability (Abdi, Millan, & Mezey, 1979; Bedossa, Dargère, & Paradis, 2003; Regev et al., 2002). A biopsy can be done either by a radiographical guide percutaneously or laparoscopically. A greater risk of bleeding has been observed following a biopsy. To avoid tissue fragmentation in suspected cirrhosis, cutting is preferred over a suction needle for biopsy. Chances of Post biopsy liver complications are 60% within two hours of the biopsy and 96% after 24 hours. Mortality due to severe bleeding occurs in 1 out of 10,000 (Bravo, Sheth, & Chopra, 2001). A week before biopsy aspirin and anti-platelets agents should not be used.

Complication of cirrhosis

Cirrhosis is chronic, asymptomatic and unpredicted until complications of the liver appear (L. Schiff, 1969). Cirrhosis is diagnosed when clinical screening is accidentally performed, such as radiological studies, transaminase measurement, or when the patient undergoes liver biopsy. Clinical features of cirrhosis can be known through the patient's history and serological and histological examination **(Table 3).**

Table 3. *Complications related to liver cirrhosis* (Alexander, 2016; Memon et al., 2013; Pedersen, Bendtsen, & Møller, 2015; Wieland, 2016).

Complications related to liver cirrhosis	Description	Causes
Jaundice	Known as icterus; Yellowish skin, sclera, and bio fluid; Excess bilirubin in blood	Hepatocyte excretory dysfunction, bilirubin level in the blood exceeds 2.5-3 mg/dL
Ascites	Fluid builds up in the abdominal cavity and detected when exceeds 25ml	progressive vascular dysfunction and portal hypertension
Nodular liver	Irregular, hard surface on palpation	irregular regeneration
Spider angiomata	Central arteriole with tiny radiating vessels, mainly on trunk and face	Raised estradiol, decreased estradiol degradation in liver
Splenomegaly	normally measures less than 11–12 cm, Enlarged on palpation or in ultrasound	Portal hypertension, splenic congestion
Caput medusa	Prominent veins radiating from umbilicus	Portal hypertension, reopening of umbilical vein that shunts blood from portal vein
White nails	Horizontal white bands or proximal white nail plate	Hypoalbuminemia
Hypertrophic osteoarthropathy/? nger clubbing	Painful proliferative osteoarthropathy of long bones	Hypoxemia due to right-to-left shunting, porto-pulmonary hypertension
Dupuytren's contracture	Fibrosis and contraction of palmar fascia	Enhanced oxidative stress, increased inosine (alcohol exposure or diabetes)
Gynecomastia, loss of male hair pattern	Benign proliferation of glandular male breast tissue	Enhanced conversion of androstenedione to oestrone and estradiol, reduced estradiol degradation in liver Enhanced conversion of androstenedione to oestrone and estradiol, reduced estradiol degradation in liver
Hypogonadism	Mainly in alcoholic cirrhosis and haemochromatosis	Direct toxic e? ect of alcohol or iron
Flapping tremor (asterixis)	Asynchronous ? apping motions of dorsi? exed hands	Hepatic encephalopathy, disinhibition of motor neurons
Foetor hepaticus	Sweet, pungent smell	Volatile dimethyl suphide, especially in portosystemic shunting and liver failure
Anorexia, fatigue, weight loss, muscle wasting	Occurs in >50% of patients with cirrhosis	Catabolic metabolism by diseased liver, secondary to anorexia
Type 2 diabetes	Occurs in 15– 30% of patients with cirrhosis	Disturbed glucose use or decreased insulin removal by the liver

Liver cirrhosis situation in Pakistan

Worldwide, Pakistan has 2nd highest estimated prevalence of hepatitis C, with a very high frequency of cirrhosis. There are additionally ten million people living in Pakistan who suffer from HCV, having great morbidity and death (Aziz et al., 2013). Pakistan Medical Research Council national general population survey 2007-2008 calculated HBV (HBsAg, the Australian antigen) as 2.5% and HCV as 4.8% in the general population, making a combined infection rate of 7.6% (Edwards, Coppens, Prasad, Rook, & Iyer, 2015). Health professionals call these viruses 'The Silent Killer'," as these liver inflaming viruses leave few visible tracks of their presence, but can gradually destroy the liver. In one of its articles, Lancet a reputable international medical journal named Pakistan (K. Ahmad, 2004). However its credibility is lacking without innovative research results to back the claim (K. Ahmad, 2004). Liver cirrhosis-caused mortality rate from the 1990 to 2010 increased in Pakistan and India. The deaths due to liver cirrhosis in India during 2010 were estimated 188,575, which accounts for 1/5th (18.3 %) of worldwide liver cirrhosis death toll(Mokdad et al., 2014). Researches on the disease burden of liver diseases in Pakistan is few and far between, despite this disease showing an increased trend in incidence and prevalence in Pakistan (A. A. Khan, 1995). Several international review articles have discussed this issue (Blachier, Leleu, Peck-Radosavljevic, Valla, & Roudot-Thoraval, 2013). Table 4 presents a list of specific cirrhosis publications pertaining Pakistani population. Majority of patients with chronic liver disease (90%) are infected with either HCV or HBV or have co-infection. Co-infection has been associated with higher severity, and cirrhosis has been recorded in 74% of patients with co-infection (Bukhtiari et al., 2003; Farooqi & Khan, 2002). A reliable study carried out in 2002 showed HBV (46.67%) as the major cause of cirrhosis, trailed by HCV (13.33%), and miscellaneous causes (40%), with male predominance (Wasim et al., 2014). Another study conducted in 2005 showed HCV (52%) as the major cause of cirrhosis (Almani et al., 2008). This change may be due to recent increase in HCV prevalence and decrease in HBV due effective HBV vaccination regimens.

Table 4. List of HCV cirrhosis publications in Pakistani population

Year	Province	No of patients	Male patients	Female patients	Age	CLD*, DCLD*	Ref. No
2001	Punjab	237			20-70	18DCLD	(Bari, Akhtar, Rahbar, & Luby, 2001)
2002	KPK	100			13-40, >40		(A. A. Khan, Haider, & Shafqat, 2002)
2002	Punjab	94			15-65	DCLD	(A. A. Khan et al., 2002)
2002	KPK	100	86	14	18-60	14 DCLD	(Khokhar, 2002)
2002	KPK	82			18-60	82 DCLD	(Arif, Khan, & Khan, 2002)
2003	KPK	654	436	178	Upto 60	CLD	(T. S. Khan, Rizvi, & Rashid, 2003)
2006	KPK	336	228	108	16-96	CLD.DCLD	(Mahsud & Din, 2006)
2007	Punjab	295	226	69	15-80	54 CLD,14 DCLD	(Baig, Siddiqui, Ahmed, Qureshi, & Arif, 2007)
2007	Sindh	174			15-45	55, 11	(Abbas, Batool, Pathan, Muhammad, & Abbas, 2007)
2008	KPK	60			15-65	54 DCLD	(Akhtar, Lutfullah, & Nazli, 2008)
2010	Sindh	5193	3247	1946	21-70	1430 DCLD	(Ahmed, Qureshi, Arif, & Alam, 2010)
2010	Punjab	66	32	34	18-68	CLD. DCLD	(Butt et al., 2010)
2011	Punjab	157	114	43	19-58	21 DCLD	(W. Ahmad et al., 2011)
2012	Punjab	18	11	7	13-47	9 DCLD	(W. Ahmad, Ijaz, & Hassan, 2012)
2012	Sindh	273	155	118	16-48, >48	209 DCLD	(Parkash, Iqbal, Jafri, Azam, & Jafri, 2012)
2014	Sindh	74	59	15	15-45, >45		(I. Hussain et al., 1998)
2014	Sindh	56				52,	(Mokdad et al., 2014)

2014	Sindh	150			15-60		(Naheed, 1998)
2016	Sindh	177	70	107	20-80	CLD	(Achakzai et al., 2016)
2016	KPK	171	110	61	26-54	24, DCLD	(A. Khan, Ayub, & Khan, 2016)
2017	Punjab	178	116	62	20-79	CLD, DCLD	(H. Ullah, Rehman, & Zafar, 2017)
2017	Sindh	1089	409	675	18-65	CLD	(Capileno et al., 2017)
2017	Punjab	100	47	53		CLD, DCLD	(Saeed, Ahmad, Idrees, & Sabir, 2017)
2017	Pakistani population	573	290	283	19-80	CLD, DCLD	(Azam et al., 2017)
2018	Punjab	259	148	111		CLD	(Azam et al., 2017)
2018	Sindh	45			25-75	CLD, DCLD	(Kamani & Shaikh, 2018)
2018	Sindh	200	76	124		CLD	(Parkash, Jafri, Munir, & Iqbal, 2018)
2019	Punjab	672	370	302	23-89	CLD	(Parkash et al., 2018)
2019	Sindh	473	279			CLD, DCLD	(Mahmood, Haider, Adil, Ubaid, & Talib, 2019)
2019	Punjab	115				CLD	(Farooq et al., 2019)
2019	Sindh	300	205	95	<59	CLD	(Bilal, Arain, Dayo, Ghoto, & Bilal, 2019)
2020	KPK	267	159	108	19-87	CLD, DCLD	(A. Ullah et al., 2020)
2020	Punjab	192	36	156	20-50	CLD	(Wagan, Bhutoo, Khan, & Raheem, 2020)
2020	Sindh	196	123	73	12-71	CLD	(Qureshi et al., 2020)
2021	KPK	44	25	19	23-81	CLD, DCLD	(A. Ullah et al., 2021)
2021	KPK	1260			20-70	CLD	(Biland, Gardezi, Haq, & Tehami[4], 2021)
2021	Sindh	120			>60	CLD	(K. HUSSAIN et al.)
2022	Sindh	88	58	30		CLD, DCLD	(Kamran, Khalid, Siddiqui, Aftab, & Azmat, 2022)
2022	KPK	278	145	133		CLD	(Muhammad, Afridi, Ali, Mehmood, & Shoaib, 2022)
2022	KPK	525	232	301		CLD	(S. Ullah et al., 2022)

*Compensated liver disease (CLD): the liver is heavily scarred but still usually asymptomatic or minute symptomatic. Patients with compensated liver disease do not have symptoms related to their cirrhosis but may have asymptomatic esophageal or gastric varices. Some symptoms are weight loss, Loss of appetite, Nausea or abdominal pain, fatigue, loss of energy etc. *Decompensated liver disease (DCLD); the liver function is lost. Patients with decompensated liver disease have symptomatic complications related to cirrhosis, including those related to hepatic insufficiency (jaundice), portal hypertension (ascites, variceal haemorrhage, or hepatic encephalopathy) and Hepatocellular carcinoma etc.

In Asia, more than half of the liver cirrhosis burden is attributable to hepatitis B and hepatitis C. Hepatitis B accounted for 44% and 42% of DALYs from liver cirrhosis estimated for East Asia and Central Asia, respectively, in 2010. The increases in mortality occurred in Pakistan between 1980 and 2010. In 1980, the numbers of deaths due to cirrhosis was 10,324 while in 1990 deaths were 14,453 **(Table 5).** The number of deaths in 2000 are 24,542, and in 2010, there were an estimated 31,373 (16,325-61,028) liver cirrhosis deaths in Pakistan, accounting for almost one-fifth (18.3%) of the global liver cirrhosis death toll (Table 6). A particularly alarming finding of our study pertains to iatrogenic causes, particularly the reuse of syringes in health facilities, in the transmission and creation of large population reservoirs of hepatitis C in low-income countries. In Pakistan, the reuse of syringes in health facilities has been common practice (K. Ahmad, 2004; E Tsega, Nordenfeit, & Hansson, 1995; Edemariam Tsega, Nordenfelt, Hansson, Mengesha, & Lindberg, 1992).

Table 5. Mortality rate (95% uncertainty intervals) in Pakistani Population due to Liver Cirrhosis for 1980 to 2010

Country	1980	1990	2000	2010
Pakistan	10,324 (6,129-16,651)	14,453 (8,249-24,503)	24,542 (13,529-44,344)	31,373 (16,325-61,028)

Table 6. Country-level age-standardized mortality rate (per 100,000) for both sexes and percent change(Δ)

Country	1980	1990	2000	2010	% Δ 1980 to 2010	% Δ 1990 to 2010
Pakistan	21.7	22.4	29.3	28.5	31.3	27.5

Age-standardized liver cirrhosis mortality rates in Pakistan for both sexes increased from 1980-2010, and mortality rates of cirrhosis in 2000 were among the upper 30th percentile globally. In 1980, the percentage was 21.7 for both sexes, increasing to 22.4 %. Age-standardized liver cirrhosis mortality rate in Pakistan in 2000 was the highest, which is 29.3 %. In 2010, the death percentage was 28.5 %. The percentage change (Δ) between 1980 to 2010 is 31.3 %, while in 1990 to 2010 is 27.5 % (Mokdad et al., 2014).

Future directions in tackling liver cirrhosis

Liver cirrhosis research has garnered immense insights and therapeutic possibilities in recent years. Some of these have been outlined below. Blood lysosomal acid lipase activity drops drastically in cryptogenic cirrhosis, the end stage of a chronic liver disease. It has emerged that pro-brain natriuretic peptide and troponin T-hypersensitivity levels are linked to the severity of liver malfunction in liver cirrhosis. Beta adrenergic blockade by non-selective β-blockers (NSBBs) can alleviate portal hypertension, a major complication of liver cirrhosis. Based on a study, Nuclear Factor-E2-related factor 2 (Nrf2) /Heme Oxygenase 1 (HO-1) can potentially be a therapeutic target in portal hypertension in cirrhosis. A study found that arginine vasopressin promotes liver fibrosis in several organs, including the liver. A subsequent lobotomy-based study in the hamster revealed that a deficiency of this neuropeptide hormone led to the reversal of liver cirrhosis(Quintanar-Stephano et al., 2017). The reversion mechanism was via the decreased levels of alkaline phosphatase in serum and the expression of type I collagen and TIMP-2 (tissue inhibitor of metalloproteinase), and increased type III collagen deposition, MMP-13 (matrix metalloproteinase) (Quintanar-Stephano et al., 2017). Human serum albumin (HAS), the ubiquitous plasma protein undergoes conformational and post-translational modifications-driven functional alterations in liver diseases, as in other inflammatory diseases(Naldi, Baldassarre, Domenicali, Bartolini, & Caraceni, 2017). Circulating pro-inflammatory cytokine levels is higher in cirrhosis patients as compared to controls. The study found elevated IL-6 levels in acute-on-chronic liver failure patients and IL-10 in subjects with infection-related acute-on-chronic liver failure. Increased IL-10 and IL-17 levels were found as markers of progression to death in acute-on-chronic liver failure cases(Fischer et al., 2017).

HCV clearance using direct-acting antivirals (DAA) ameliorated advanced cirrhosis(Ippolito et al., 2017). Plasma transfusion to manage cirrhosis is under investigation, though it suffers from the issue of blood coagulation. Liver regenerative therapy for cirrhosis by intrahepatic arterial infusion of adipose tissue-derived stromal/stem cell is promising (Sakai et al., 2017). Statin has shown some beneficial effects on cirrhosis conditions, which should be investigated further(Kim, Loomba, Prokop, & Singh, 2017). Profiling the gut metagenomes of patients with liver cirrhosis can be insightful. HCV infection affects the extrahepatic system and leads to non-liver-related mortality as well. So, removing this persistent, inflaming virus using interferon (IFN)-based antiviral therapy and DAA should be a priority. Though current understanding emphasizes the risk of these viruses, almost all chronic infectious agents inflame the liver, potentially inducing fibrosis and cirrhosis(Lee, Divens, & Fowler, 2017). Awareness can prevent infections, which can go a long way in reducing the rate of liver cirrhosis-related morbidities and mortalities. Liver disease can evolve into any pathological form, from cardiac arrest to renal failure or cancer. The general public should be educated about the offending factors.

Conclusion

Like other ailments, liver disease is a multifactorial, inflammatory pathological condition, developing to a large extent due to lifestyle assaults. Currently, the awareness regarding liver cirrhosis is poor in most of the developing countries. Nationwide multi-center cohort studies can give a clear picture of instances, therapy and prevention of liver cirrhosis. Inexpensive diagnostic protocols can detect cirrhosis risks in patients. This review is expected to contribute to raising awareness and research on liver cirrhosis in Pakistan.

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Declarations

Acknowledgments

Not applicable

Funding

Not applicable

Author's contributions

Aam AB, IU, REZK, wrote the initial draft of manuscript. MA, NM, MA, MG, MS, and MJK edit the manuscript for final submission. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for Publication

Not applicable

Competing interests

The authors declare that they have no competing interests.