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LIVER CIRRHOSIS: A REVIEW

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Abstract:

Liver cirrhosis (LC), is the end-stage of chronic Liver disease, is the major risk factor contributing in the development of the Hepatocellular Carcinoma (HCC). It is the leading cause of deaths worldwide being the 14th most common death cause globally. According to previous studies, 1%-57% mortalities with 1-year has been reported on the sub classification of LC mortality. The Emerging trends in the management of LC patients is prevention, intervention, avoiding the clinical decompensating and liver transplantation. In this review we summarized the impact of LC on the management and prognosis of patients with primary Liver carcinoma or non-hepatic malignancies.

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INTRODUCTION:

The liver is the largest organ occupying 2.5% of total Body weight and providing a functions for maintaining biological functions. [1] It is involve in metabolizing the macromolecules like carbohydrates, lipids and protein, regulating the blood volume, involve in the support mechanism of immune system and endocrine pathways control. Mainly it is also involve in the breakdown of xenobiotic compounds. [1,2] Globally, approximately170 million individuals are being effected of Hepatitis C virus (HCV) that is the leading cause of Chronic Liver Disease (CLD).Out of these HCV infected patients 20-30% will develop LC or Hepatocellular Carcinoma (HCC).As being the most prevalent carcinoma HCC can grow at any stage of LC. In our population, approximately 30,000 individuals die annually due to HCC and HCV is the major contributing factor in 70-80% of the mortalities.[3,4]

As LC is the most advance stage of liver fibrosis that result in the distortion of liver parenchyma prospective growth of liver failure. In the last few years the progress has been done in the field of Hepatic Fibrosis (HF) focusing on the regulatory pathways, cellular potentials, genetic causes and new models for therapeutic directions. [4,5] The Study conducted in Japan observed that the decrease in the incidence of HCV and HBV infection showed the significant decline in the cirrhosis cases. [6] Liver transplantation has been the suggestive cure for the LC and it can help in the survival of patients and improve the quality of life of patients with last stage Liver Disease. [7]

In this review, we provide a concise overview about the impact of liver cirrhosis on the management and prognosis of patients with primary liver cancer.

TYPES AND STAGES OF LIVER CIRRHOSIS:

Many classification systems and models have proposed in last few years. But the most commonly used staging systems in the classification of LC are Child-Pugh Classification, Model for End-Stage Liver Disease (MELD). [8] The most commonly used classification is Child-Pugh Classification (CPC) 16. The CPC was introduced approximately 50 years ago to access the postoperative prognosis of the portal hypertension in patients suffering from LC. According to CPC 1-3 points are allocated to all the variables and their sum is split into three equal subgroups: Class A comprises of 5-6 points, class B comprises of 7-9 points and C as 10-15 points (Table 1). [8,9]

	Points		
Variable	**1**	**2**	**3**
Encephalopathy	**None**	**Stage I-II**	**Stage III-IV**
Ascites	**Absent**	**Controlled**	**Refractory**
Bilirubin (mg/dL)	**>2**	**2-3**	**>3**
Albumin (g/L)	**>35**	**28-35**	**<28**
Prothrombin time (seconds)	**<4**	**4-6**	**>6**
Sum of Points	**5-6**	**7-9**	**10-15**
Stage	**A**	**B**	**C**
1 Year survival Rate %	**95**	**80**	**44**

Table 1: Child-Pugh score

For the final predication of patients reported with compensated and decompensated LC the Four Phase Clinical Classification was introduced that is further sub classified into five phases. [10] In this classification system compensated Cirrhosis (CC) comprises of two stages whereas decompensated cirrhosis (DC) of three stages (Table 2). [11,12] Patients having compensated Cirrhosis without varices are included in stage 1 having mortality rate of 1.5% annually, Stage 2 comprise of patients with varices with 2% mortality yearly, Patients reporting with bleeding without other diseases complications are at stage 3 and have approximately 21% mortality reported per annum where as non-bleeding decompensation such as ascites and encephalopathy are in stage 4 and 27% is the mortality rate and stage 5 involves > 1 decompensating events and having 88% highest mortality rate reported annually. [11,12] Recently, Clinical stage 5 that involve the patients with bacterial spontaneous infectious having 66% mortality in one year and Clinical Stage 6 involving patients with Kidney failure as 70% mortality rate has been suggested to add in the classification system. According to one-year survival report, stage A, B, C is 95%, 80% and 44%. [12]

Stage	Definition	5-Year mortality rate (%)
Compensated Stage		
1	No Varices	**15**
2	Varices	**10**
Compensated Stage		
3	Bleeding no other decompensating event	**20**
4	Ascites, jaundice or encephalopathy	**30**
5	>1 decompensating	**88**

Table 2: Clinical Stages of Liver Cirrhosis

The End Stage Liver Disease Model (MELD) is useful in the liver transplantation according to the studies reported in 2002 and 2006 in America and Europe. [13-17] The major benefit of the MELD paralleled to the CPC is only that the objective variables are used for its calculation and the lack of an upper limit for disease severity. [8]

CLINICAL PRESENTATION:

Patients history in combination with serological and histological investigations was very useful for the identification of causes of cirrhosis. [18] Majority of the patients have never expected clinical consideration and in autopsies majority of undiagnosed cirrhosis is usually determined. Asymptomatic cirrhosis is usually identified by conducting screening tests like Liver Function tests and radiography findings (Figure 1). [19]

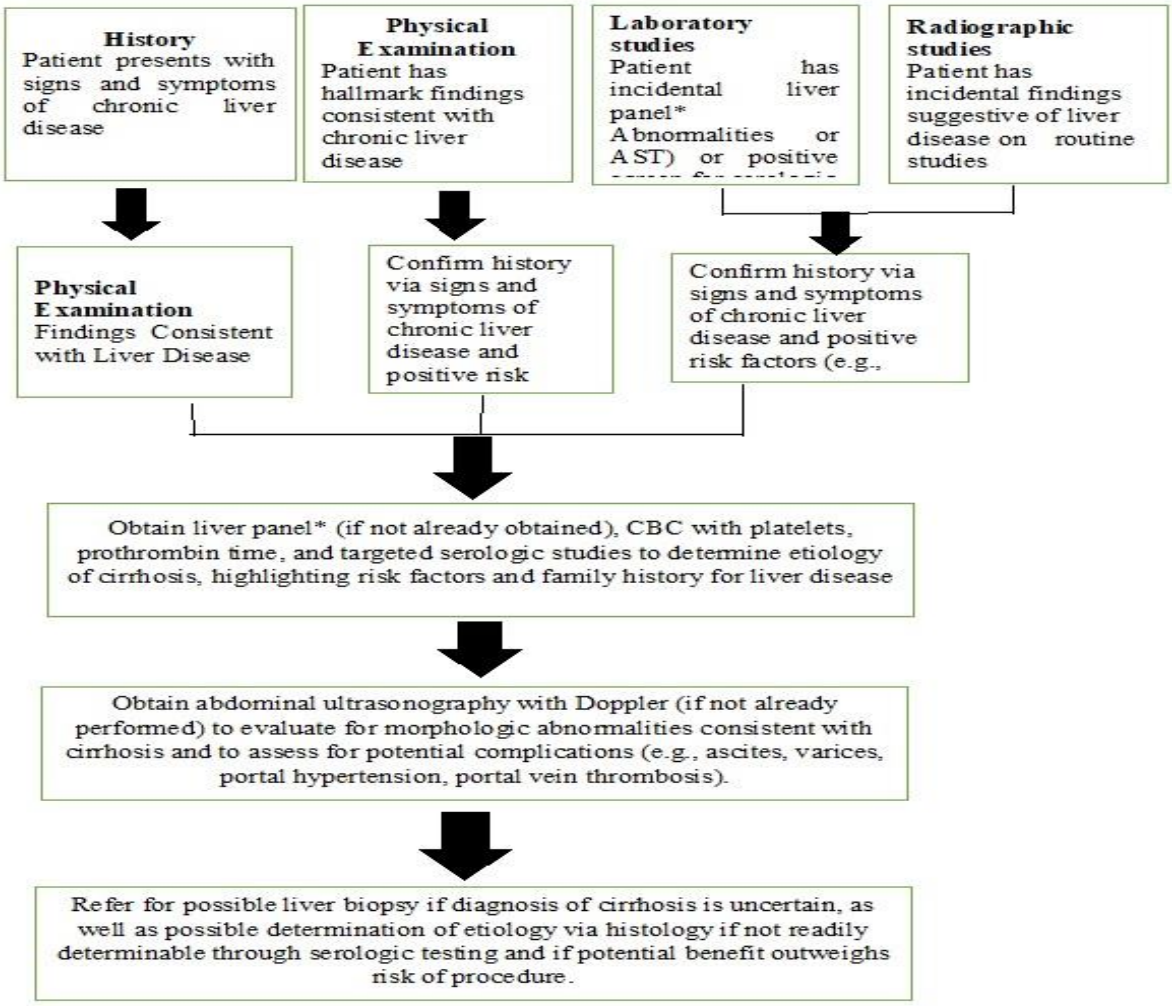

Figure 1: Pathway of Liver Cirrhosis Patients

However, the clinical introduction of patients with Liver Failure/Cirrhosis is as yet predominant and is described by terrifying complications, for example, variceal hemorrhages, ascites, unconstrained bacterial peritonitis, or hepatic encephalopathy of metabolic disorder in non-alcoholic steatohepatitis (Figure 2). [20]

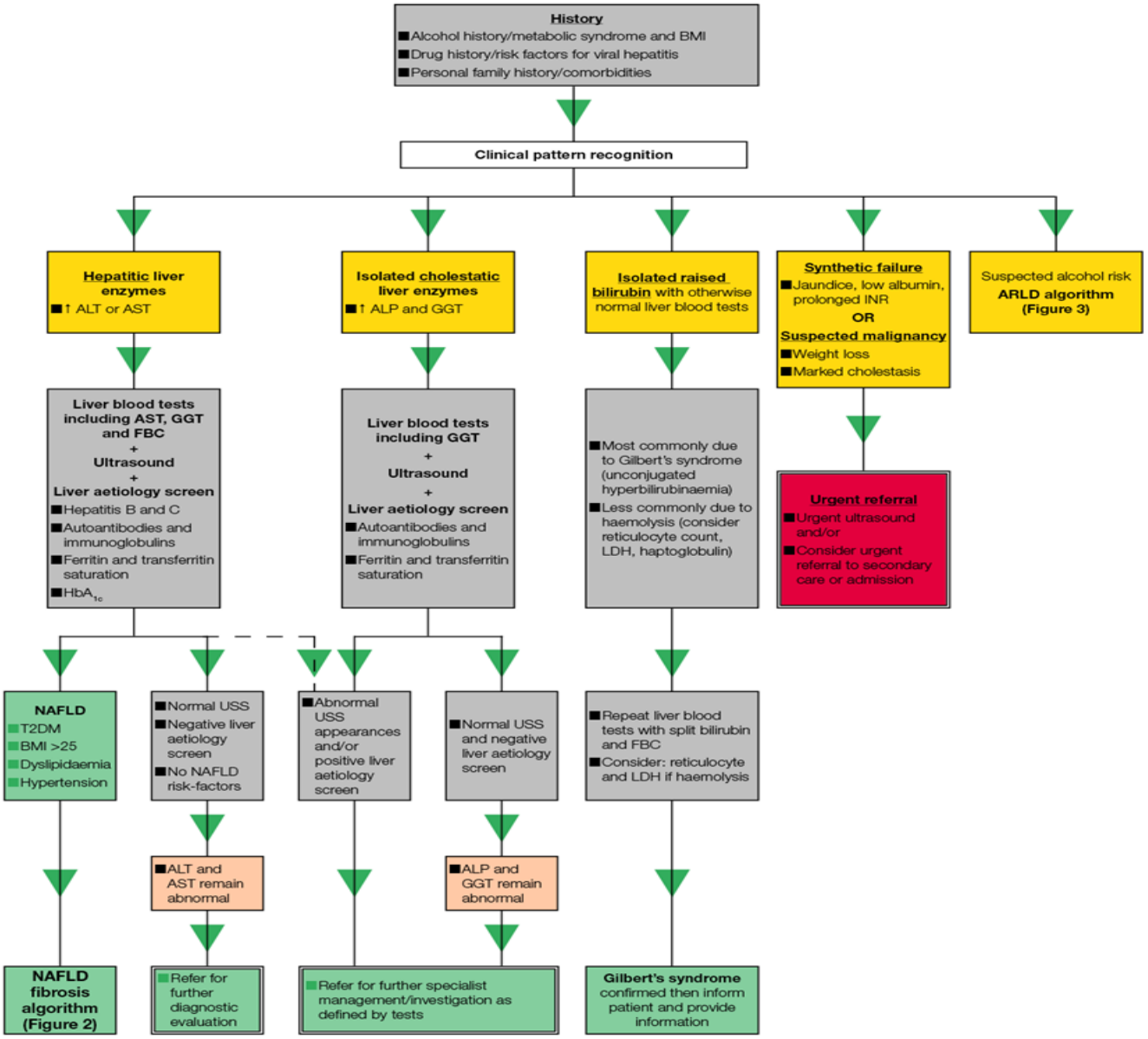

Figure 2: Clinical Presentation (This figure details the initial response to abnormal liver blood tests. Boxes in yellow indicate the initial evaluation of the clinical presentation. Patients with marked derangements of liver blood tests, synthetic failure and or suspicious clinical symptoms should be considered for urgent referral to secondary care (red box). For the remainder the clinical history alongside evaluation of the pattern of liver blood test derangements will determine choice of pathway and is shown in the blue box. A blue box indicates that all the test that should be request at the stage rather than a heredity within it. The presence of metabolic syndrome criteria should be sought to support the diagnosis of NAFLD for the children test should be consulted for modification of recommendations. Area of diagnostic uncertainty are indicated in orange boxes and the decision for repeat testing or referral to secondary care will be influenced by the magnitude of enzymes elevation and clinical context. Green boxes indicate the final outcomes for users).

ETIOLOGY OF CIRRHOSIS:

Patients History generally described the etiology of cirrhosis. It is also associated with serological and histological assessment. In Western world HCV and Alcoholic fatty liver disease (ALD are frequent occurring diseases. In many regions of Asia and sub-Saharan Africa along with HCV and ALD, HBV is also prevalent. Multiple etiological variables often lead to the growth of cirrhosis, as illustrated: frequent (mild) alcohol intake, age >50 years, and sex are the variables for HCV, [21.22] elder age obesity, type II diabetes, hypertension and hyperlipidemia in NASH (Table 3). [20,23]

GENERAL FINDINGS	DESCRIPTION	ETIOLOGY
Jaundice	Yellow discoloration of skin, cornea and mucous membranes	Compromised hepatocyte excretory function, occurs when serum bilirubin >2mg/dl
Spider Angiomata	Central arteriole with tiny radiating vessels, mainly on trunk and face	Elevated estradiol, decreased estradiol degradation in liver
Nodular liver	Irregular, hard surface on palpation	Fibrosis, irregular regeneration
Splenomegaly	Enlarged on palpation or in ultrasound	Portal hypertension, splenic congestion
Ascites	Proteinaceous fluid in abdominal cavity, clinically detected when ≥ 1.5L	Portal hypertension
Caput medusae	Prominent veins radiating from umbilicus	Portal hypertension, reopening of the umbilical vein that shunts blood from the portal vein
Cruveilhier baumgarten syndrome	Epigastrtic vascular murmur	Shunts from portal vein to umbilical vein branches, can be present without caput medusae
Spider angiomata	Central arteriole with tiny radiating vessels, mainly on trunk and face	Elevated estradiol, decreased estradiol degradation in liver
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Caput medusae	Prominent veins radiating from umbilicus	Portal hypertension, reopening of the umbilical vein that shunts blood from the portal vein
Cruveilhier Baumgarten syndrome	Epigastric vascular murmur	Shunts from portal vein to umbilical vein branches, can be present without Caput medusae
Palmar erythema	Erythema sparing the central portion of the palm	Elevated estradiol, decreased estradiol degradation in liver
White nails	Horizontal white bands and or proximal white nail plate	hypoalbuminemia
Hypertrophic osteoarthropathy/finger clubbing	Painful proliferative osteoarthropathy of long bones	Hypoxemia due to right-to-left shunting, porto-pulmonary hypertension
Dupuytren's contracture	Fibrosis and contraction of the palmar fadcia	Enhanced oxidative stress, elevated hypoxanthine (alcohol exposure or diabetes)
Gynecomastia, loss of hair male pattern	Benign proliferation of glandular male breast tissue	Enhanced conversion of androstenedione to estrone and estradiol, decreased estradiol degradation in liver

Hypogonadism	Mainly in alcoholic cirrhosis and hemochromatosis	Direct toxic effect of alcohol or iron
Flapping tremor (asterixis)	Asynchronous flapping motions of dorsiflexed hands	Hepatic encephalopathy, disinhibition of motor neurons
Foetor hepaticus	Sweet, pungent smell	Volatile dimethylsulfide, especially in portosystemic shunting and liver failure
Anorexia, fatigue, weight loss, muscle wasting	Occurs in >50% of cirrhotics	Catabolic metabolism by diseased liver, secondary to anorexia
Type 2 diabetes	Occurs in 15-30% of cirrhotics	Disturbed glucose utilization and/or decreased insulin removal by the liver

Table 3: Clinical Features of Cirrhosis

Worldwide, in 2017 almost 57% of cirrhosis was reported. It was observed that cirrhosis is caused 30% by HBV and 27% by HCV. [24] Several studies indicated that the principal cause of LC is consumption of Alcohol. LC caused by HCV is mostly common in United States of America (USA) and the United Kingdom (UK), similar findings was also reported in Italy in which they described the major foundation of LC is HCV. [25-27]

Into the certain extent, in prevalent regions HBV is the main reason of LC. HCV continues the significant diagnosis of LC in Japan. [28] The main causes of liver cirrhosis in Mexico are alcohol and HCV. [29] LC of unidentified causes has been identified as cryptogenic cirrhosis, and non-alcoholic steatohepatitis (NASH) is accepted as a major cause of cryptogenic LC and/or HCC. Although, precise incidence of NASH-related LC is not known. The etiological findings the study accompanied in japan in 2008 reported the clinical symptoms of 33,379 patients with LC from 58 hospitals and identified the exact etiological proportions for liver cirrhosis. [28]

EPIDEMIOLOGY:

In 2001, Liver cirrhosis was the 10th major reason of mortality for males and the 12th reason of mortality for females in the United States, resulting in approximately twenty seven thousand fatalities. In developing countries such as Pakistan, LC is more common than in developed countries. Universal, 11th most common reason of mortality was Cirrhosis and cancer of liver is the 16th major reason of mortality; if it is combined the mortality due to LC and cancer in liver, all globally fatalities appears as 3.5%, accounting for 1.6% and 2.1% of the global burden. [30] The accurate occurrence of cirrhosis around the world is unidentified. The precise incidence of cirrhosis globally is not known. It was expected at 0.15% or 400,000 victims in the USA, which accounted for more than 25,000 victims. Similar figures were recorded from Europe and are still greater in mainly Asian and African nations where persistent viral hepatitis B or C is common. Since liver failure is often unidentified for the long period of time. It was determined that almost 1% of the population might have histological cirrhosis. [10] Over the previous two decades, there has been rising proof supporting the very high incidence of NAFLD and NASH in the common population. In a latest meta-analysis, the worldwide incidence of NAFLD was estimated to be 25.2% with the largest incidence in the Middle East and South America (31.8% and 30.4%, respectively) and the smallest recorded levels in Africa (13.5%). In addition, NAFLD prevalence levels in North America, Europe and Asia have been recorded to be 24.1 percent, 23.7 percent and 27.4 percent respectively. [31] In addition, NASH incidence in the general population is estimated to be between 1.5 percent and 6.45 percent. [31] These high occurrence rates for NAFLD and NASH are being determined by the worldwide epidemic. [32,33]

PATHOPHYSIOLOGICAL CHANGES:

In the pathogenesis of cirrhosis complications the Gut microbiota and bacterial translocation (BT) plays a vital role. The preferable BT site for cirrhosis is the small intestine. [34] For the promotion of BT the small intestinal bacterial overgrowth (SIBO) is more suitable. [11,35] The environmental and host factors can progress the liver fibrosis progresses based on the cause of liver disease. [36] Cirrhosis is followed by a deformation of the hepatic vasculature. This prompts an exchanging of the blood supply straight into the hepatic outpouring, trading off the trade between the hepatic sinusoid and liver parenchyma, for example hepatocyte. [37] Histologically, cirrhosis is a vascularized fibrotic septa linking to portal tracts, prompting to hepatocytes. Major clinical impact of cirrhosis incorporate impaired hepatocyte function,

improved intrahepatic obstruction and development of hepatocellular carcinoma (HCC).Cirrhosis and its related vascular distortion are to be irreversible. [38]

GENETIC MUTATIONS EFFECTING LIVER CHIROSIS:

Recently, the genetic polymorphisms have been described as the that increased risk of developing fibrosis. Cytokines and chemokines Genes encodes and their receptors molecules containing fibrogenesis , blood coagulation, antigen, iron uptake, antioxidant metabolism, and antibacterial are associated. [39] In a recent study, 1,609 of the 24,882 single nucleotide polymorphisms (SNPs) were found to be associated with chronic fibrosis proliferation having the involvement of DDX5 gene, which has a high positive predictive value. [40] Together with excessive use of Alcohol, obesity is also the risk factors. SNPs will allow the establishment of risk profiles for individual patient. [41]

MANAGEMENT OF LIVER CHIROSIS:

Preventive diagnosis and treatments are essential for the initiation of therapy. Physiological changes such as leading hepatotoxicity, including diabetes medications should be prescribed to prevent liver disease. In addition, patients should examine the complications and undergo appropriate management if they are present, especially as the diagnosis of patients is primarily determined by liver disease. [42,43]

Recommendations:

There have been many advances in the complications of cirrhosis patients' medical care and end-stage liver disease. In future, the primary prevention and therapy of cirrhosis will be emphasized, while using the non-invasive techniques to screen for the early stages, to monitor the effects of antibiotic drugs and pharmacological targets of fibrogenic pathways. Continuing basic and clinical research to eliminate cirrhosis as it will be the great contributor to patient's survival.

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