

# Etiologies of Liver Cirrhosis and Their Clinical Presentation among Inpatients in Medical City Complex - Baghdad Teaching Hospital

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## Abstract

**Background:** Liver cirrhosis is one of common diseases that doctors deal with during working days, so it is important for all doctors to have a basic knowledge about its etiologies, clinical presentations, complications and prognosis.

**Aim of the study:** 1) To detect the most common causes of liver cirrhosis among Iraqi patients. 2) To Find the most common clinical presentations and look for any association between them and a particular etiology. 3) To make recommendations regarding screening for the most common etiology among population and deal with it and treat it early prior to development of liver fibrosis and cirrhosis.

**Patient and methods:** A cross-sectional study was conducted from January 2016 to January 2019. 1000 patients were enrolled in the current study and followed at medical wards at Baghdad teaching hospital, taking detailed history from them including history of alcohol intake, drug history, etc... and sending them for complete work up including Abdominal US, virology screening, autoimmune, Wilson, iron study etc... and calculating Child - Pugh score for each patient.

**Results:** 1) The most common causes of liver cirrhosis are alcoholic liver disease (20%) and HCV (20%) followed by HBV (18%), NAFLD (14%), cryptogenic (14%), AIH (6%), Wilson (4%), PBC (4%). 2) the most common presentation of liver cirrhosis from all causes are ascites (38%) and encephalopathy (38%). followed by bleeding varices (21%), jaundice (11%). 3) HCV was associated significantly with Encephalopathy, NAFLD significantly associated with bleeding varices, Cryptogenic significantly associated with ascites, Wilson disease and PBC significantly associated with jaundice.

**Conclusions:** HCV and alcoholism are so common among Iraqi patients with liver cirrhosis, while NAFLD cases are commonly related to diabetes mellitus and obesity. Ascites and encephalopathy are the most common presentation at medical wards from all causes of liver cirrhosis. Most cases of liver cirrhosis due to HCV are within middle and elderly. While Wilson disease should be kept at the top of differential diagnosis of liver cirrhosis among young individuals as it is significantly related to young age group. Cryptogenic cases of liver cirrhosis need aggressive work up and screening for uncommon causes.

**Keywords:** hepatic cirrhosis, etiology, presentation

## 1. Introduction

### 1.1 Definition of Liver Cirrhosis

Cirrhosis, which can be the final stage of any chronic liver disease, is a diffuse process characterized by fibrosis and conversion of normal architecture to structurally abnormal nodules. These “regenerative” nodules lack normal

lobular organization and are surrounded by fibrous tissue. The process involves the whole liver and generally is considered irreversible. Although cirrhosis is histologically an “all-or-nothing” diagnosis, clinically it can be classified by its status as compensated or decompensated. Decompensated cirrhosis is defined by the presence of ascites, variceal bleeding, encephalopathy, or jaundice, which are complications that result from the main consequences of cirrhosis: portal hypertension and liver insufficiency (Lee Goldman, Andrew I. Schafer. 2016).

### *1.2 Diagnosis of Liver Cirrhosis*

Although cirrhosis is strictly speaking a histologic diagnosis, a combination of clinical, laboratory, and imaging features can help confirm a diagnosis of cirrhosis.

A clinical stigmata of liver cirrhosis includes palmar erythema, Terry’s nails, Clubbing of the fingernails, Gynecomastia, Spider telangiectasias (or angiomas), Dilated abdominal veins (caput medusae) with flow away from the umbilicus, toward the inferior vena cava in the infraumbilical area and toward the superior vena cava in the supraumbilical area, suggest intrahepatic portal hypertension. On the other hand, dilatation of veins in the flank with blood draining toward the superior vena cava suggests inferior vena caval obstruction. Parotid enlargement is also a feature of cirrhosis, especially alcoholic cirrhosis.

Patients with a history of chronic liver disease with gastroesophageal varices, ascites, or hepatic encephalopathy are likely to have cirrhosis, and liver biopsy is not essential in such cases for confirming cirrhosis. In patients with a diagnosis of chronic liver disease without these complications, physical findings of an enlarged left hepatic lobe with splenomegaly, along with the cutaneous stigmata of liver disease described earlier, suggest cirrhosis, especially in the setting of thrombocytopenia and impaired hepatic synthetic function (e.g., hypoalbuminemia, prolongation of the prothrombin time). If physical and laboratory findings are not suggestive of cirrhosis, imaging studies can help make a diagnosis of cirrhosis. A small nodular liver with splenomegaly and intra-abdominal collaterals and the presence of ascites on abdominal US (or other cross-sectional imaging study) suggests cirrhosis.

Liver biopsy has long been the gold standard for diagnosing cirrhosis but may be associated with costs and procedure related risks, albeit infrequently the major concerns regarding the use of a liver biopsy to diagnose cirrhosis includes sampling error and interobserver disagreement in the estimation of the extent of fibrosis. The ideal combination of clinical findings and routine laboratory tests to determine whether a patient has cirrhosis without the need for a liver biopsy has been addressed in a systematic fashion (Mark Feldman, Lawrence S. Friedman, Lawrence J. Brandt. 2016).

### *1.3 Etiologies of Liver Cirrhosis and Their Epidemiological Studies Worldwide*

- 1) Alcoholism
- 2) Chronic viral hepatitis: hepatitis B, Hepatitis C
- 3) Autoimmune hepatitis
- 4) Nonalcoholic steatohepatitis
- 5) Biliary cirrhosis: Primary biliary cirrhosis, Primary sclerosing cholangitis. Autoimmune cholangiopathy
- 6) Cardiac cirrhosis
- 7) Inherited metabolic liver disease: Hemochromatosis, Wilson's disease, Alpha 1 antitrypsin deficiency, Cystic fibrosis
- 8) Cryptogenic cirrhosis

#### **HCV infection:**

The worldwide seroprevalence of HCV infection, based on detection of antibody to HCV (anti-HCV), is estimated to be 3%, with more than 170 million people infected chronically. The overall worldwide prevalence increased from 1990 to 2010.1 marked geographic variation exists, with infection rates ranging from 1.3% to 1.6% in the United States to 15% in Egypt. In 2002, between 3.2 and 5 million persons were infected with HCV in the United States, <sup>(3)</sup> but the incidence of HCV has declined continually since 1994. The highest prevalence in different age groups shifted from 35 to 44 years (2.5%) to 55 to 64 years in 2005 (2.7%). It has therefore been recommended that all persons born between 1945 and 1965 be tested for anti-HCV (Smith BD, Morgan RL, Beckett GA, et al. 2012).

#### **HBV infection:**

The sequelae of chronic HBV infection vary from an inactive carrier state to the development of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), extrahepatic manifestations, and death. The prognosis appears to vary with the clinical setting. Long-term follow-up studies of HBsAg positive blood donors have shown that the

majority remain asymptomatic with a very low risk of cirrhosis or HCC (Villeneuve JP, Desrochers M, Infante-Rivard C, et al. 1994), (Manno M, Cammà C, Schepis F, et al. 2004).

The prognosis is worse in HBV-infected patients from endemic areas and in patients with chronic hepatitis B (Fattovich G, Brollo L, Giustina G, et al. ), (Liaw YF, Lin DY, Chen TJ, Chu CM. 1989).

#### **Alcoholic liver disease:**

Excessive alcohol consumption is associated with a range of hepatic manifestations, including alcoholic fatty liver disease (with or without steatohepatitis), alcoholic hepatitis, and cirrhosis. Patients with an alcohol intake of 30 or more grams per day are at increased risk of cirrhosis, although the majority of patients will not develop cirrhosis despite heavy alcohol intake (point prevalence of 1 percent for those who drink 30 to 60 g/day and 6 percent for those who drink 120 g/day). Unfortunately, among those who do develop liver disease, symptoms often develop only after severe, life-threatening liver disease has already developed (Bellentani S, Saccoccio G, Costa G, et al. 1997)

#### **NAFLD:**

Nonalcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis when no other causes for secondary hepatic fat accumulation (eg, heavy alcohol consumption) are present. NAFLD may progress to cirrhosis and is likely an important cause of cryptogenic cirrhosis (Caldwell SH, Oelsner DH, Iezzoni JC, et al. 1999), (Poonawala A, Nair SP, Thuluvath PJ. 2000 ).

Nonalcoholic fatty liver disease (NAFLD) is subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). In NAFL, hepatic steatosis is present without evidence of inflammation, whereas in NASH, hepatic steatosis is associated with hepatic inflammation that histologically is indistinguishable from alcoholic steatohepatitis (Ludwig J, Viggiano TR, McGill DB, Oh BJ. 1980), (Sheth SG, Gordon FD, Chopra S. 1997).

#### **Autoimmune hepatitis:**

Autoimmune hepatitis is a chronic hepatitis that occurs in children and adults of all ages. It is characterized by immunologic and autoimmunologic features, generally including the presence of circulating autoantibodies and high serum globulin concentrations (Krawitt EL. 2006).

Autoimmune hepatitis has a heterogeneous and fluctuating nature, leading to marked variability in its clinical manifestations. The spectrum includes asymptomatic patients, those with considerable and sometimes debilitating symptoms, and those with acute liver failure. Furthermore, long periods of subclinical disease may occur before or after presentation. Physical findings range from a normal physical examination to the presence of hepatomegaly, splenomegaly, stigmata of chronic liver disease, and jaundice (Muratori P, Granito A, Quarneti C, et al. 2009).

#### **Primary biliary cirrhosis:**

Primary biliary cirrhosis (PBC) is characterized by a T-lymphocyte-mediated attack on small intralobular bile ducts. A continuous assault on the bile duct epithelial cells leads to their gradual destruction and eventual disappearance. The sustained loss of intralobular bile ducts causes the signs and symptoms of cholestasis and eventually results in cirrhosis and liver failure (Kaplan MM. 1996), (Moebius U, Manns M, Hess G, et al. 1990).

PBC occurs worldwide and predominantly in women, with a female-to-male ratio of 9: 1.

The diagnosis of PBC usually is made between the ages of 30 and 60 years, with a range of 21 to 93 years. The disease has been documented in even younger patients-2 teenagers 15 and 16 years of age, respectively (Dahlan Y, Smith L, Simmonds D, et al. 2003).

#### **Hemochromatosis:**

Hereditary hemochromatosis is an autosomal recessive disorder in which mutations in the HFE gene cause increased intestinal iron absorption. The clinical manifestations of this disorder, and of other forms of iron overload, are related to excessive iron deposition in tissues, especially the liver, heart, pancreas, and pituitary (Bacon BR, Adams PC, Kowdley KV, et al. 2011).

Progressive iron deposition is associated with hepatomegaly, elevated liver enzymes, and the eventual development of increasing fibrosis and cirrhosis (Adams PC, Deugnier Y, Moirand R, Brissot P. 1997), (Fracanzani AL, Fargion S, Romano R, et al. 1995).

#### **Wilson disease:**

Wilson disease (hepatolenticular degeneration) is due to a genetic abnormality inherited in an autosomal recessive

manner that leads to impairment of cellular copper transport. Impaired biliary copper excretion leads to accumulation of copper in several organs, most notably the liver, brain, and cornea. Over time, the liver is progressively damaged and eventually becomes cirrhotic. In addition, patients may develop neurologic complications, which can be severe (J Hepatol. 2012).

#### **Budd – Chiari syndrome:**

The Budd-Chiari syndrome can be defined as any pathophysiologic process that results in an interruption or diminution of the normal flow of blood out of the liver. However, as commonly used, the Budd-Chiari syndrome implies thrombosis of the hepatic veins and/or the intrahepatic or suprahepatic inferior vena cava (Valla DC. 2008). (Menon KV, Shah V, Kamath PS. 2004).

BCS is a rare disease. In Sweden, prevalence rates in 1990 to 2001 were estimated to be 1.4 per million population (Rajani R, Melin T, Bjornsson E, et al. 2009).

There is a slight female predominance. The median age at diagnosis was 37 in one case series (Darwish Murad S, Plessier A, Hernandez-Guerra M, et al. 2009).

The incidence of BCS in Asia may be higher. BCS accounted for 17% of hospital admissions for liver-related disease in Kathmandu, Nepal, from 1990 to 1992 (Shrestha SM, Okuda K, Uchida T, et al. 1996).

#### **Cardiac cirrhosis:**

Patients with long-standing right-sided congestive heart failure may develop chronic liver injury and cardiac cirrhosis. This is an increasingly uncommon, if not rare, cause of chronic liver disease given the advances made in the care of patients with heart failure. Patients typically have signs of congestive heart failure and will manifest an enlarged firm liver on physical examination.

#### **Primary sclerosing cholangitis:**

As in PBC, the cause of PSC remains unknown. PSC is a chronic cholestatic syndrome that is characterized by diffuse inflammation and fibrosis involving the entire biliary tree, resulting in chronic cholestasis. This pathologic process ultimately results in obliteration of both the intra- and extrahepatic biliary tree, leading to biliary cirrhosis, portal hypertension, and liver failure.

#### **Other types of cirrhosis:**

**$\alpha$ 1AT deficiency** results from an inherited disorder that causes abnormal folding of the  $\alpha$ 1AT protein, resulting in failure of secretion of that protein from the liver. It is unknown how the retained protein leads to liver disease. Patients with  $\alpha$ 1AT deficiency at greatest risk for developing chronic liver disease have the ZZ phenotype, but only about 10–20% of such individuals will develop chronic liver disease. Diagnosis is made by determining  $\alpha$ 1AT levels and phenotype. Characteristic periodic acid–Schiff (PAS)-positive, diastase-resistant globules are seen on liver biopsy.

#### **Cryptogenic cirrhosis:**

Cryptogenic cirrhosis (CC) is the end stage of a chronic liver disease in which its underlying etiology remains unknown after extensive clinical, serological, and pathological evaluations have been performed.

##### *1.4 Types of Decompensation*

At this stage, there are signs of decompensation: **ascites, variceal hemorrhage, jaundice, hepatic encephalopathy**, or any combination of these findings. Ascites, which is the most frequent sign of decompensation, is present in 80% of patients with decompensated cirrhosis (Lee Goldman, Andrew I. Shafer. 2012).

##### ***Variceal Hemorrhage***

Gastroesophageal varices are present in approximately 50% of patients with newly diagnosed cirrhosis. Large varices, severe liver disease, and red wale markings on varices are independent predictors of variceal hemorrhage. Bleeding from gastroesophageal varices can be manifested as overt hematemesis or melena, or both (Dennis L. Kasper, Anthony S. Fauci, Stephen L. Hauser, Dan L. Longo, J. Larry Jameson, Joseph Loscalzo. 2015).

##### ***Ascites:***

Ascites is the most common cause of decompensation in cirrhosis and occurs at a rate of 7 to 10% per year. The most frequent symptoms associated with ascites are increased abdominal girth, which is often described by the patient as tightness of the belt or garments around the waist, and recent weight gain. When present in small to moderate amounts, ascites can be identified on examination by bulging flanks, flank dullness, and shifting dullness

(Lee Goldman, Andrew I. Shafer. 2012).

### **Hepatic Encephalopathy**

Hepatic encephalopathy, which is the neuropsychiatric manifestation of cirrhosis, occurs at a rate of approximately 2 to 3% per year. On physical examination, early stages may demonstrate only a distal tremor, but the hallmark of hepatic encephalopathy is the presence of asterixis. Additionally, patients with hepatic encephalopathy may have sweet-smelling breath, a characteristic termed fetor hepaticus ((Lee Goldman, Andrew I. Shafer. 2012).

### **Jaundice**

In cirrhosis is a reflection of the inability of the liver to excrete bilirubin and is therefore the result of liver insufficiency. However, in cholestatic diseases leading to cirrhosis (e.g., primary biliary cirrhosis, primary sclerosing cholangitis, vanishing bile duct syndrome), jaundice is more likely due to biliary damage than liver insufficiency ((Lee Goldman, Andrew I. Shafer. 2012).

**Child-pugh score** (Dennis L.Kasper, Anthony S.Fauci, Stephen L.Hauser, Dan L.Longo, J, Larry Jameson, Joseph Loscalzo. 2015):

Factor	Units	Points Toward Total Score		
		1	2	3
Serum bilirubin	μmol/L	<34	34–51	>51
	mg/dL	<2.0	2.0–3.0	>3.0
Serum albumin	g/L	>35	30–35	<30
	g/dL	>3.5	3.0–3.5	<3.0
Prothrombin time	seconds prolonged	<4	4–6	>6
	INR <sup>a</sup>	<1.7	1.7–2.3	>2.3
Ascites		None	Easily controlled	Poorly controlled
Hepatic encephalopathy		None	Minimal	Advanced

<sup>a</sup>International normalized ratio.

**Note:** The Child-Pugh score is calculated by adding the scores for the five factors and can range from 5 to 15. The resulting Child-Pugh class can be A (a score of 5–6), B (7–9), or C (≥10). Decompensation indicates cirrhosis, with a Child-Pugh score of ≥7 (class B). This level has been the accepted criterion for listing a patient for liver transplantation.

## **2. Patients and Methods**

The current study is a cross sectional study, which was conducted from January 2016 to January 2019, 1000 patients were enrolled in the study from Medical wards at Baghdad teaching hospital.

### **2.1 Selection Criteria**

- 1) Inpatient, admitted with a previous or new diagnosis of Liver cirrhosis.
- 2) All cases of Liver cirrhosis were taken, including known and unknown cause of cirrhosis
- 3) All cases that were selected having decompensated liver cirrhosis with different types of decompensation (Encephalopathy, jaundice, Ascites, Bleeding varices)
- 4) All patients were above 14 years old, with both sexes males and females.
- 5) Patients that are selected previously diagnosed as liver cirrhosis with or without liver biopsy depending upon clinical and radiological evidence.

The study was approved by Research Ethics Committee at Baghdad teaching hospital, all patients included signed an informed consent form after receiving information about the study. After that the following data were collected from each patient:

- 1) Age
- 2) Sex
- 3) Date of Diagnosis of cirrhosis
- 4) Clinical presentation (decompensation)
- 5) Etiology of liver cirrhosis
- 6) Calculate child – Pugh score for each patient. (Based upon Clinical and Lab data obtained from patient's file).
- 7) Regarding the diagnosis of NAFLD (without biopsy ) depending on:
  - a. Exclusion of other causes of liver cirrhosis

Patient fulfill the criteria of diagnosis of metabolic syndrome (BMI>30, waist circumference >102 cm for male

and >88 cm for females, Triglyceride >150 mg/dl, HDL<40 mg/dl for male and <50 mg/dl for female, and all patients were Diabetic) as a NAFLD is significantly associated with obesity DM type 2 and metabolic syndrome.(Ruhl & Everhart, 2003; Miyazaki, Glass, Triplitt, Wajcberg, Mandarino, & DeFronzo, 2002; Clark, Brancati, & Diehl, 2003; Williams et al., 2011).

- 8) Considering the diagnosis of cryptogenic cirrhosis (without biopsy ) depending on:
  - a. Exclusion of all other causes
  - b. All patients were not diabetic, not obese (normal BMI), no dyslipidemia.
  - c. Biopsy was not taken, because all patients taken were in decompensated state, with coagulopathy, small liver. Or uncooperative patient or his relatives.

2.2 Statistical Study

Anderson darling test was done to asses if continuous variables follow normal distribution, if follow normal distribution than mean and standard deviation used, if did not follow normal distribution than median and interquartile range (25% to 75% percentile range) will be used to present the data.

Discrete variables presented using there number and percentage used to present the data, chi square test used to analyze the discrete variable or Fisher exact test used to analyze the distribution between 2 groups (used instead of chi square for 2x2 table, if total sample <20 and if 2 or more with expected frequency less than 5). One way ANOVA used to analyze the differences between more than two groups (if they follow normal distribution with no significant outlier).

Linear regression analysis performed to assess the relationship between different variables, if one or both of them follow normal distribution person regression used but if both did not follow normal distribution spearman correlation will used. Scatter plot used to present the regression analysis, r (correlation coefficient or standardized beta is a representative of magnitude and direction of the relationship), r<0.25 weak, 0.25 – 0.5 mild, 0.5 – 0.75 moderate, >0.75 strong correlation. Negative sign indicate inverse relationship, but positive sign represent direct relationship.

SPSS 20.0.0, Minitab 17.1.0 software package used to make the statistical analysis, p value considered when appropriate to be significant if less than 0.05.

3. Results

1000 Patients were selected, Mean age of patients is 55.6 ± 15.6 years, about 57% of them were males and 43% were females (male to female ratio was 1.3:1) median duration of cirrhosis since diagnosis 15 months (with interquartile range 2.25 – 48 months) as illustrated in Table 1.

Table 1. Demographic data

Variables	Value
Age (years), mean ± SD	55.6 ± 15.6
Sex	
Female	43 (43.0%)
Male	57 (57.0%)
Cirrhosis duration (months), median (IQR)	15 (2.25 – 48)

The most common initial presentation was ascites and encephalopathy followed by bleeding varices and jaundice, while during the course of decompensation 65% had ascites, 57% had jaundice, 38% had encephalopathy and 24% had bleeding varices. The majority of patients presented with two of these symptoms 58% followed by 30% had only one and 10% had three and only 2% presented with all of them, as illustrated in Table 2

Table 2. Signs of liver cirrhosis

Variables	Values
<b>Initial presentation, number (%)</b>	
Ascites	340 (34.0%)
Bleeding varices	210 (21.0%)
Encephalopathy	340 (34.0%)
Jaundice	110 (11.0%)
<b>Clinical signs of cirrhosis during admission</b>	
Ascites	650 (65.0%)
Jaundice	570 (57.0%)
Encephalopathy	380 (38.0%)
Bleeding varices	240 (24.0%)
<b>Number of clinical signs in each patient</b>	
Single	30 (30.0%)
Two	58 (58.0%)
Three	10 (10.0%)
Four	2 (2.0%)

There was no significant difference in child – Pugh score for patients according to their initial presentation, as illustrated in Table 3.

Table 3. Child - Pugh score in each initial presentation

Bleeding varices	Jaundice	Ascites	Encephalopathy	All	p value
10.8 ± 2.0	10.1 ± 2.3	11.2 ± 1.6	9.9 ± 2.4	10.7 ± 2.0	0.108

The most common causes of liver cirrhosis are illustrated in Table 4.

Table 4. Etiology of cirrhosis

Variables	Value
HCV	200 (20.0%)
Alcoholic	200 (20.0%)
HBV	173 (17.3%)
NAFLD	140 (14.0%)
Cryptogenic	130 (13.0%)
Autoimmune	55 (5.5%)
Wilson disease	37 (3.7%)
PBC	35 (3.5%)
Hemochromatosis	30 (3.0%)

HCV associated significantly with encephalopathy and bleeding varices, NASH associated significantly with bleeding varices, cryptogenic associated significantly ascites, Wilson disease associated significantly with jaundice, PBC associated significantly with jaundice Table 5.

Table 5. Association between clinical presentation and etiology of cirrhosis

	Ascites	Bleeding varices	Encephalopathy	Jaundice	P value
<b>HCV</b>					
No HCV	310 (91.2%)	150 (71.4%)	230 (67.6%)	110 (100.0%)	0.022 [Sig.]
HCV	30 (8.8%)	60 (28.6%)	110 (32.4%)	0 (0.0%)	
<b>HBV</b>					
No HBV	260 (76.5%)	190 (91%)	280 (83%)	90 (82%)	0.630
HBV	80 (23.5%)	20 (9%)	570 (17%)	20 (18%)	
<b>Alcoholic</b>					
Not	260 (76.5%)	170 (81.0%)	280 (82.4%)	90 (81.8%)	0.937
Alcoholic	80 (23.5%)	40 (19.0%)	60 (17.6%)	20 (18.2%)	
<b>NAFLD</b>					
Not	300 (88.2%)	140 (66.7%)	330 (97.1%)	90 (81.8%)	0.016 [Sig.]
NAFLD	40 (11.8%)	70 (33.3%)	100 (2.9%)	20 (18.2%)	
<b>Cryptogenic</b>					
Not	240 (70.6%)	210 (100.0%)	300 (88.2%)	110 (100.0%)	0.007 [Sig.]
Cryptogenic	100 (29.4%)	0 (0.0%)	40 (11.8%)	0 (0.0%)	
<b>Wilson disease</b>					
Not	340 (100.0%)	210 (100.0%)	320 (94.1%)	90 (83%)	0.039 [Sig.]
WD	0 (0.0%)	0 (0.0%)	20 (5.9%)	20 (17%)	
<b>Autoimmune</b>					
Not	340 (100.0%)	190 (90.5%)	300 (88.2%)	110 (100.0%)	0.149
Autoimmune	0 (0.0%)	20 (9.5%)	350 (14.8%)	0 (0.0%)	
<b>PBC</b>					
Not	330 (97.1%)	210 (100.0%)	340 (100.0%)	80 (72.7%)	<0.001 [Sig.]
PBC	10 (2.9%)	0 (0.0%)	0 (0.0%)	30 (27.3%)	

HCV positive was more with age group > 45 years compared HCV negative as illustrate in Table 6.

Table 6. HCV

Variables	HCV		P value	
	Negative	Positive		
Age	≤45 years	220 (27.5%)	0 (0.0%)	0.002 [Sig.]
	46 – 65	410 (51.3%)	90 (45.0%)	
	>65	170 (21.3%)	110 (55.0%)	
Sex	Female	370 (46.3%)	60 (30.0%)	0.189
	Male	430 (53.8%)	140 (70.0%)	
Child – Pugh score	A	10 (1.3%)	10 (5.0%)	0.052
	B	220 (27.5%)	10 (5.0%)	
	C	570 (71.3%)	180 (90.0%)	
Duration since Diagnosis	<1 year	310 (38.8%)	100 (50.0%)	0.613
	1 – 3 year	260 (32.5%)	60 (30.0%)	
	>3 year	230 (28.8%)	40 (20.0%)	

HBV positive associated more with male than female as illustrated in Table 7.

Table 7. HBV

Variables	HBV		P value	
	Negative	Positive		
Age	≤45 years	160 (19.5%)	60 (33.3%)	0.432
	46 – 65	420 (51.2%)	80 (44.4%)	
	>65	240 (29.3%)	40 (22.2%)	
Sex	Female	390 (47.6%)	40 (22.2%)	0.049 [Sig.]
	Male	430 (52.4%)	140 (77.8%)	
Child – Pugh score	A	20 (2.4%)	0 (0.0%)	0.414
	B	210 (25.6%)	20 (11.1%)	
	C	590 (72.0%)	160 (88.9%)	
Duration since Diagnosis	<1 year	320 (39.0%)	90(50.0%)	0.518
	1 – 3 year	260 (31.7%)	60 (33.3%)	
	>3 year	240 (29.3%)	30 (16.7%)	

Alcoholic etiology associated more with male compared with female, also alcoholic associated less with child – Pugh group A and more with group B then Group C on comparison with non – alcoholic group as illustrated in Table 8.

Table 8. Alcoholic

Variables	Alcoholic		P value	
	Negative	Positive		
Age	≤45 years	180 (22.5%)	40 (20.0%)	0.572
	46 – 65	380 (47.5%)	120 (60.0%)	
	>65	240 (30.0%)	40 (20.0%)	
Sex	Female	430 (53.8%)	0 (0.0%)	<0.001 [Sig.]
	Male	370 (46.3%)	20 (100.0%)	
Child – Pugh score	A	20 (2.5%)	0 (0.0%)	0.008 [Sig.]
	B	130 (16.3%)	100 (50.0%)	
	C	650 (81.3%)	100 (50.0%)	
Duration since Diagnosis	<1 year	340 (42.5%)	70 (35.0%)	0.685
	1 – 3 year	240 (30.0%)	80 (40.0%)	
	>3 year	220 (27.5%)	50 (25.0%)	

NASH significantly associated more with female compared to male as illustrated in Table 9

Table 9. NAFLD

Variables	NAFLD		P value	
	Negative	Positive		
Age	≤45 years	200 (23.3%)	20 (14.3%)	0.654
	46 – 65	430 (50.0%)	70(50.0%)	
	>65	230 (26.7%)	50 (35.7%)	
Sex	Female	300 (34.9%)	130 (92.9%)	<0.001 [Sig.]
	Male	560 (65.1%)	10 (7.1%)	
Child – Pugh score	A	20 (2.3%)	0 (0.0%)	0.493
	B	180 (20.9%)	50 (35.7%)	
	C	660 (76.7%)	90 (64.3%)	
Duration since Diagnosis	<1 year	370 (43.0%)	40 (28.6%)	0.335
	1 – 3 year	280 (32.6%)	40 (28.6%)	
	>3 year	210 (24.4%)	60 (42.9%)	

Cryptogenic associated significantly with duration of cirrhosis less than 1 year compared to non – cryptogenic as illustrated in Table 10.

Table 10. cryptogenic

Variables	Cryptogenic		P value	
	Negative	Positive		
Age	≤45 years	180 (20.9%)	40 (28.6%)	0.709
	46 – 65	440 (51.2%)	60 (42.9%)	
	>65	240 (27.9%)	40 (28.6%)	
Sex	Female	350 (40.7%)	80 (57.1%)	0.249
	Male	510 (59.3%)	60 (42.9%)	
Child – Pugh score	A	10 (1.2%)	10 (7.1%)	0.114
	B	220 (25.6%)	10 (7.1%)	
	C	630 (73.3%)	110 (84%)	
Duration since Diagnosis	<1 year	310 (36.0%)	100 (71.4%)	0.012 [Sig.]
	1 – 3 year	320 (37.2%)	0 (0.0%)	
	>3 year	230 (26.7%)	30 (27%)	

Wilson disease associated significantly with age group less than 45 years as illustrated in Table 11.

Table 11. Wilson disease

Variables	Wilson disease		P value	
	Negative	Positive		
Age	≤45 years	180 (18.8%)	37 (100.0%)	0.003
	46 – 65	500 (52.1%)	0 (0.0%)	
	>65	280 (29.2%)	0 (0.0%)	
Sex	Female	410 (42.7%)	20 (50.0%)	1.0
	Male	550 (57.3%)	20 (50.0%)	
Child – Pugh score	A	200 (2.1%)	0 (0.0%)	NA
	B	210 (21.9%)	20 (52.0%)	
	C	730 (76.0%)	20 (50.0%)	
Duration since Diagnosis	<1 year	410 (42.7%)	0 (0.0%)	NA
	1 – 3 year	300 (31.3%)	20 (52.0%)	
	>3 year	250 (26.0%)	17 (48.0%)	

Autoimmune hepatitis associated significantly with age group 46 – 65 years, and also with female sex as illustrated in Table 12.

Table 12. Autoimmune

Variables	Autoimmune		P value	
	Negative	Positive		
Age	≤45 years	220 (23.4%)	0 (0.0%)	0.046 [Sig.]
	46 – 65	440 (46.8%)	60 (100.0%)	
	>65	280 (29.8%)	0 (0.0%)	
Sex	Female	370 (39.4%)	60 (55.0%)	0.005 [Sig.]
	Male	570 (60.6%)	0 (0.0%)	
Child – Pugh score	A	20 (2.1%)	0 (0.0%)	NA
	B	230 (24.5%)	0 (0.0%)	
	C	690 (73.4%)	60 (55.0%)	
Duration since Diagnosis	<1 year	400 (42.6%)	10 (16.7%)	0.337
	1 – 3 year	30 (31.9%)	20 (33.3%)	
	>3 year	24 (25.5%)	15 (49.0%)	

PBC associated significantly with female, and with duration of cirrhosis of 1 – 3 years as illustrated in Table 13.

Table 13. Primary biliary cirrhosis

Variables		PBS		P value
		Negative	Positive	
Age	≤45 years	20 (20.8%)	2 (50.0%)	0.251
	46 – 65	48 (50.0%)	2 (50.0%)	
	>65	28 (29.2%)	0 (0.0%)	
Sex	Female	39 (40.6%)	4 (100.0%)	0.031 [Sig.]
	Male	57 (59.4%)	0 (0.0%)	
Child – Pugh score	A	2 (2.1%)	0 (0.0%)	NA
	B	21 (21.9%)	2 (50.0%)	
	C	73 (76.0%)	2 (50.0%)	
Duration since Diagnosis	<1 year	41 (42.7%)	0 (0.0%)	0.012 [Sig.]

#### 4. Discussion

In this current study, The most common causes of liver cirrhosis are alcoholic liver disease (20%) and HCV (20%) followed by HBV (18%), NAFLD (14%), cryptogenic (14%), AIH (6%), wilson (4%), PBC (4%).

The most common presentation of liver cirrhosis from all causes are ascites (38%) and encephalopathy (38%). followed by bleeding varices (21%), jaundice (11%). Comparing with results from national studies and international studies, Dr. Ashraf et al, in his study published in December 2015, taking 41 patients, showed that the most common cause of liver cirrhosis is alcoholic liver disease and cryptogenic, followed by Wilson, HCV, HBV respectively.

Internationally, Michitaka, K., Nishiguchi, S., Aoyagi, Y. et al published at 2009, National survey study in Japan taking 33,379 patients with liver cirrhosis, showed HCV (60.9%), HBV (13.9%), Alcoholism (13.6%), PBC (2.4%), AIH (1.9%), NASH (2.1%) (Michitaka et al., 2010).

Sang Soo Lee, Young-Sang Byoun et al, At 2010, published a study in Korea showed most common cause of liver cirrhosis is Viral (73.4%)(among them HBV 83.7%, HCV 15.5%, HBV+HCV 0.9%) followed by alcoholism (18.1%), Cryptogenic (6.6%), Budd chiari (1%), AIH (0.9%).(Sang Soo Lee, Young-Sang Byoun, Sook-Hyang Jeong, Yeo Myung Kim, Ho Gil, Bo-Young Min. 2012)

GONCALVES, Patricia Lofego et al., At 2011, published a study in Brazil, taking 1,516 patients with liver cirrhosis, showed that the most common causes of liver cirrhosis are alcoholism (39.7%), Alcoholism with HBV or HCV (16.1%), HCV alone (14.5%), HBV alone (13.1%), cryptogenic (9.8%).(GONCALVES, Patricia Lofego et al. 2013)

Nwokediuko S C, Osuala P C et al. At 2013, published a study in Nigeria, showed the most common causes of liver cirrhosis are Alcoholism followed by HBV, Herbs and lastly HCV (Nwokediuko et al., 2013).

The most common presentation of liver cirrhosis for all causes is Ascites (38%) and Encephalopathy (38%), followed by bleeding varices (21%) and jaundice (11%) respectively. **That means:**

- 1) Chronic liver disease should be kept at the top of differential diagnosis of Ascites.
- 2) Decompensated liver cirrhosis should be kept in mind in differential diagnosis of encephalopathy.

For each individual cause of liver cirrhosis and clinical presentation, It was found the HCV was significantly associated with encephalopathy and bleeding varices, comparing with international studies, Benvegnù L, Gios M, Boccato S, et al published a study at 2004 in Italy showed that Hepatocellular carcinoma was the most frequent complication in untreated cases of HCV (24.5%), followed by ascites (20.1%), bleeding (5.7%), and encephalopathy (2.9%). In contrast, treated patients had the same incidence of HCC and ascites (15.6%), followed by bleeding (3.4%) and encephalopathy (0.9%).(Benvegnù et al., 2004) Planas, Ramon et al. Published a study at 2004 in Journal of hepatology showed Ascites was the most frequent first decompensation in HCV(48%), followed by portal hypertensive gastrointestinal bleeding (PHGB) (32.5%), severe bacterial infection (BI) (14.5%) and hepatic encephalopathy (HE) (5%).(Planas, Ramon et al. 2002). Such difference in these results from current study may occur because Our patients usually come late with life threatening situations, they don't pay attention to

abdominal distension that could developed earlier than encephalopathy or bleeding varices.

NAFLD associated significantly with bleeding varices, cryptogenic cirrhosis was associated significantly with Ascites, while Wilson and PBC were significantly associated with Jaundice. No previous international study was found studying specifically which signs of decompensation most likely to develop in these etiologies of liver cirrhosis.

Regarding Age group the study found that HCV was significantly presented in middle age and elderly. That mean still, we can screen for HCV and treat it prior to development of fibrosis and cirrhosis. Same results obtained from other study, in which Pradat et al., noted in a study published at 2007, taking 247 patient with HCV, that most HCV patients, if untreated, are expected to develop cirrhosis at about 65 years, irrespective of the age at infection. (Pradat, Voirin, Tillmann, & Chevallerier, 2007). Wilson disease significantly present in Young aged patients. Comparing with other study, Merle, Schaefer, Ferenci, and Stremmel in a study published at 2005, showed that most common age of diagnosis of Wilson is about 15 year old with no treatment developed cirrhosis within young age group (Merle et al., 2007). Autoimmune hepatitis significantly present in middle aged patients. In comparison with an international study, Feld, Dinh et al, published a study at 2005, taking 139 patients with AIH, mean age of diagnosis  $43.5 \pm 16.6$  years (Feld et al., 2005). All other etiologies had no significant relationship to specific age group.

Regarding Sex group Current study shows that HBV significantly present in males Different international studies showed that male gender is predominant in HBV cirrhosis worldwide. There was no substantial difference in the percentage of male gender among different series from different parts of the world, ranging from 86 to 95% (Realdi et al., 1994; de Jongh et al. 1992).

Previous cross-sectional studies have shown that the male-to-female ratio increased proportionally during the course of chronic HBV infection: the ratio was 1.2:1 in the immune-tolerant phase (HBeAg-positive patients with normal aminotransferase), 5-6:1 in chronic hepatitis, and 6-8:1 in cirrhosis (Chu, Liaw, Sheen, Lin, & Huang, 1983). These data suggest that male HBsAg carriers are more likely to have progressive liver disease than carriers of female gender. One recent longitudinal study from Taiwan has confirmed that male patients are significantly more likely to have high aminotransferase activities during the immune clearance phase and more relapse of hepatitis B after HBeAg seroconversion than females (Chu, Hung, Lin, Tai, & Liaw, 2004). These findings may explain the predominance of male gender in HBV cirrhosis.

- 1) The study also shows significant association between alcoholic cirrhosis and male gender. Comparing with international studies, women are more susceptible than men to the toxic effects of alcohol on the liver for any given dose of alcohol, even though men abuse or depend on alcohol more than women, at A 12-year prospective study of alcohol use in over 13,000 participants in Denmark showed that the risk of development of alcohol-related liver disease increased in women who consumed 7 to 13 beverages per week (84-156 g) compared with men who consumed 14 to 27 beverages per week. (Becker, Deis, Sorensen et al., 1996), Compared with their male counterparts, women with alcoholic liver disease have a more rapid progression to fibrosis that persists even after abstinence from alcohol. (Pares et al., 1986; Poynard et al., 2003). However among Iraqi patients no female cases were reported with alcoholic cirrhosis, most likely related to social and religious reasons prevent women from drinking.
- 2) In the current study, NAFLD were significantly present in females. Comparing with other international studies, most of the studies reported that NAFLD is significantly more prevalent in men than in women, Ruhl et al. (Ruhl & Everhart, 2003). Reported that NAFLD was more prevalent in men than in women (4.3% vs 1.6%, respectively), a finding essentially explained by the higher waist-to-hip circumference (WHR) ratio in men. WHR is correlated with visceral adipose tissue (VAT) and visceral adiposity is associated with both peripheral and hepatic Insulin resistance. (Falck-Ytter, Younossi, Marchesini, & McCullough, 2001; Miyazaki et al., 2002). In another study using the same database but different cohort size, Clark et al. (Clark, Brancati, & Diehl, 2003), also reported that men have higher prevalence of NAFLD than women (5.7% vs 4.6%, respectively), Moreover, in the Dallas Heart Study, non-Hispanic white men had an approximately 2-fold higher prevalence of hepatic steatosis than white women. Factors, including lifestyle and sex hormone may also influence the gender difference in the prevalence of NAFLD. In one study, individuals with NAFLD had similar degrees of Insulin resistance and obesity to those without, but males with NAFLD consumed more non-diet soda on a weekly basis (54.4% vs 34%,  $P = 0.037$ ) (Williams et al., 2011).

Difference between these results and current study, may have many causes, could be related to obesity variations, or due to small sample size. More studies are needed concerning this subject with larger sample and more details to work on.

The study also shows a significant association between AIH and female gender, resembling results from other international studies, Feld et al., published a study at 2005, taking 135 patients with AIH, showed a female predominance (75.4%). (Feld et al., 2005), Verma et al. published a study at 2007, taking 157 patient with AIH, also showed female predominance (77.2%) (Verma, Torbenson, & Thuluvath, 2007).

Also the study shows significant association between PBC and female gender, comparing with international studies, Fumio Sakauchi et al, published a study at 2005 in Japan, taking 5,805 patients, showed that PBC most common in females (89%) while in males (11%). (Fumio et al., 2005).

Other etiologies had no significant relationship to specific sex.

Regarding the duration since diagnosis, All cases of different etiologies were presented with different durations since diagnosis of liver cirrhosis ranging from below than 1 year, from 1 to 3 years and more than 3 years with no significant association to specific etiology apart from cryptogenic cases that were significantly associated with less than 1 year group, this can give an idea about rapidity of developing decompensation with cryptogenic liver cirrhosis, and focuses on the importance of aggressive work up to diagnose unknown causes and proper management of compensated cases. No previous study was found to compare with regarding this entity.

## 5. Conclusions

- 1) HCV and Alcoholic liver disease are the most common causes of liver cirrhosis.
- 2) Ascites and encephalopathy are the most common presentation at medical wards from all causes of liver cirrhosis.
- 3) Most cases of liver cirrhosis due to HCV are within middle and elderly. While Wilson disease should be kept at the top of differential diagnosis of liver cirrhosis among young individuals as it is significantly related to young age group.
- 4) Alcoholic liver disease should be kept in mind at the top of differential diagnosis of liver cirrhosis in males. While a differential diagnosis of NAFLD, AIH, PBC are significantly among females

## Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

## References

- Adams, P. C., Deugnier, Y., Moirand, R., & Brissot, P. (1997). The relationship between iron overload, clinical symptoms, and age in 410 patients with genetic hemochromatosis. *Hepatology*, 25(1), 162-166. <https://doi.org/10.1002/hep.510250130>
- Armstrong, G. L., Wasley, A., Simard, E. P., McQuillan, G. M., Kuhnert, W. L., & Alter, M. J. (2006). The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Annals of internal medicine*, 144(10), 705-714. <https://doi.org/10.7326/0003-4819-144-10-200605160-00004>
- Bacon, B. R., Adams, P. C., Kowdley, K. V., Powell, L. W., & Tavill, A. S. (2011). Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*, 54(1), 328-343. <https://doi.org/10.1002/hep.24330>
- Becker, U., Deis, A., Sorensen, T. I., Gronbaek, M., Borch-Johnsen, K., Muller, C. F., ... & Jensen, G. (1996). Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology*, 23(5), 1025-1029. <https://doi.org/10.1002/hep.510230513>
- Bellentani, S., Saccoccio, G., Costa, G., Tiribelli, C., Manenti, F., Sodde, M., ... & Dionysos Study Group. (1997). Drinking habits as cofactors of risk for alcohol induced liver damage. *Gut*, 41(6), 845-850. <https://doi.org/10.1136/gut.41.6.845>
- Benvegnu, L., Gios, M., Boccato, S., & Alberti, A. (2004). Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut*, 53(5), 744-749. <https://doi.org/10.1136/gut.2003.020263>
- Caldwell, S. H., Oelsner, D. H., Iezzoni, J. C., Hespeneide, E. E., Battle, E. H., & Driscoll, C. J. (1999). Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology*, 29(3), 664-669. <https://doi.org/10.1002/hep.510290347>
- Chu, C. M., Hung, S. J., Lin, J., Tai, D. I., & Liaw, Y. F. (2004). Natural history of hepatitis be antigen to antibody seroconversion in patients with normal serum aminotransferase levels. *The American journal of medicine*, 116(12), 829-834. <https://doi.org/10.1016/j.amjmed.2003.12.040>

- Chu, C. M., Liaw, Y. F., Sheen, I. S., Lin, D. Y., & Huang, M. J. (1983). Sex difference in chronic hepatitis B virus infection: an appraisal based on the status of hepatitis B e antigen and antibody. *Hepatology*, 3(6), 947-950. <https://doi.org/10.1002/hep.1840030611>
- Clark, J. M., Brancati, F. L., & Diehl, A. M. (2003). The prevalence and etiology of elevated aminotransferase levels in the United States. *The American journal of gastroenterology*, 98(5), 960-967. <https://doi.org/10.1111/j.1572-0241.2003.07486.x>
- Dahlan, Y., Smith, L., Simmonds, D., Jewell, L. D., Wanless, I., Heathcote, E. J., & Bain, V. G. (2003). Pediatric-onset primary biliary cirrhosis. *Gastroenterology*, 125(5), 1476-1479. <https://doi.org/10.1016/j.gastro.2003.08.022>
- De Jongh, F. E., Janssen, H. L., Robert, A., Hop, W. C., Schalm, S. W., & Van Blankenstein, M. (1992). Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. *Gastroenterology*, 103(5), 1630-1635. [https://doi.org/10.1016/0016-5085\(92\)91188-A](https://doi.org/10.1016/0016-5085(92)91188-A)
- European Association For The Study Of The Liver. (2012). EASL clinical practice guidelines: Wilson's disease. *Journal of hepatology*, 56(3), 671-685. <https://doi.org/10.1016/j.jhep.2011.11.007>
- Falck-Ytter, Y., Younossi, Z. M., Marchesini, G., & McCullough, A. J. (2001, January). Clinical features and natural history of nonalcoholic steatosis syndromes. In *Seminars in liver disease* (Vol. 21, No. 1, pp. 15-22). <https://doi.org/10.1055/s-2001-12926>
- Fattovich, G., Brollo, L., Giustina, G., Noventa, F., Pontisso, P., Alberti, A., ... & Ruol, A. (1991). Natural history and prognostic factors for chronic hepatitis type B. *Gut*, 32(3), 294-298. <https://doi.org/10.1136/gut.32.3.294>
- Feld, J. J., Dinh, H., Arenovich, T., Marcus, V. A., Wanless, I. R., & Heathcote, E. J. (2005). Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. *Hepatology*, 42(1), 53-62. <https://doi.org/10.1002/hep.20732>
- Feld, J. J., Dinh, H., Arenovich, T., Marcus, V. A., Wanless, I. R., & Heathcote, E. J. (2005). Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. *Hepatology*, 42(1), 53-62. <https://doi.org/10.1002/hep.20732>
- Fracanzani, A. L., Fargion, S., Romano, R., Conte, D., Piperno, A., D'Alba, R., ... & Fiorelli, G. (1995). Portal hypertension and iron depletion in patients with genetic hemochromatosis. *Hepatology*, 22(4), 1127-1131. <https://doi.org/10.1002/hep.1840220417>
- Goldman, L., & Schafer, A. I. (2011). *Goldman's Cecil medicine E-book* (24th ed., pp. 1001-1003). Elsevier Health Sciences.
- Gonçalves, P. L., Zago-Gomes, M. D. P., Marques, C. C., Mendonça, A. T., Gonçalves, C. S., & Pereira, F. E. L. (2013). Etiology of liver cirrhosis in Brazil: chronic alcoholism and hepatitis viruses in liver cirrhosis diagnosed in the state of Espirito Santo. *Clinics*, 68(3), 291-295. [https://doi.org/10.6061/clinics/2013\(03\)OA02](https://doi.org/10.6061/clinics/2013(03)OA02)
- Kaplan, M. M. (1996). Primary biliary cirrhosis. *New England Journal of Medicine*, 335(21), 1570-1580. <https://doi.org/10.1056/NEJM199611213352107>
- Kasper, D., Fauci, A., Hauser, S., Longo, D., Jameson, J., & Loscalzo, J. (2015). *Harrison's principles of internal medicine, 19e* (Vol. 1, No. 2). McGraw-hill.
- Krawitt, E. L. (2006). Autoimmune hepatitis. *New England Journal of Medicine*, 354(1), 54-66. <https://doi.org/10.1056/NEJMra050408>
- Lee, G., Andrew, I. S. (2016). *Goldman-Cecil Medicine* (25th ed.). Philadelphia: Elsevier Saunders.
- Lee, S. S., Byoun, Y. S., Jeong, S. H., Kim, Y. M., Gil, H., Min, B. Y., ... & Kim, J. W. (2012). Type and cause of liver disease in Korea: single-center experience, 2005-2010. *Clinical and molecular hepatology*, 18(3), 309. <https://doi.org/10.3350/cmh.2012.18.3.309>
- Liaw, Y. F., Lin, D. Y., Chen, T. J., & Chu, C. M. (1989). Natural course after the development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *Liver*, 9(4), 235-241. <https://doi.org/10.1111/j.1600-0676.1989.tb00405.x>
- Ludwig, J., Viggiano, T. R., McGill, D. B., & Oh, B. J. (1980, July). Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. In *Mayo Clinic Proceedings* (Vol. 55, No. 7, pp. 434-438).
- Manno, M., Cammà, C., Schepis, F., Bassi, F., Gelmini, R., Giannini, F., ... & Villa, E. (2004). Natural history of

- chronic HBV carriers in northern Italy: morbidity and mortality after 30 years. *Gastroenterology*, 127(3), 756-763. <https://doi.org/10.1053/j.gastro.2004.06.021>
- Mark, F., Lawrence, S. F., Lawrence, J. B. (2016). *Sleisenger and Fordtran's Gastrointestinal and Liver Disease* (10th ed., pp. 1254-1257). Philadelphia: Elsevier Saunders.
- Menon, K. N., Shah, V., & Kamath, P. S. (2004). The Budd–Chiari syndrome. *New England Journal of Medicine*, 350(6), 578-585. <https://doi.org/10.1056/NEJMra020282>
- Merle, U., Schaefer, M., Ferenci, P., & Stremmel, W. (2007). Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. *Gut*, 56(1), 115-120. <https://doi.org/10.1136/gut.2005.087262>
- Michitaka, K., Nishiguchi, S., Aoyagi, Y., Hiasa, Y., Tokumoto, Y., & Onji, M. (2010). Etiology of liver cirrhosis in Japan: a nationwide survey. *Journal of gastroenterology*, 45(1), 86-94. <https://doi.org/10.1007/s00535-009-0128-5>
- Miyazaki, Y., Glass, L., Triplitt, C., Wajeberg, E., Mandarino, L. J., & DeFronzo, R. A. (2002). Abdominal fat distribution and peripheral and hepatic insulin resistance in type 2 diabetes mellitus. *American Journal of Physiology-Endocrinology and Metabolism*, 283(6), E1135-E1143. <https://doi.org/10.1152/ajpendo.0327.2001>
- Moebius, U., Manns, M., Hess, G., Kober, G., zum Büschenfelde, K. H. M., & Meuer, S. C. (1990). T cell receptor gene rearrangements of T lymphocytes infiltrating the liver in chronic active hepatitis B and primary biliary cirrhosis (PBC): oligoclonality of PBC-derived T cell clones. *European journal of immunology*, 20(4), 889-896. <https://doi.org/10.1002/eji.1830200426>
- Murad, S. D., Plessier, A., Hernandez-Guerra, M., Fabris, F., Eapen, C. E., Bahr, M. J., ... & Janssen, H. L. (2009). Etiology, management, and outcome of the Budd-Chiari syndrome. *Annals of internal medicine*, 151(3), 167-175. <https://doi.org/10.7326/0003-4819-151-3-200908040-00004>
- Muratori, P., Granito, A., Quarneti, C., Ferri, S., Menichella, R., Cassani, F., ... & Muratori, L. (2009). Autoimmune hepatitis in Italy: the Bologna experience. *Journal of hepatology*, 50(6), 1210-1218. <https://doi.org/10.1016/j.jhep.2009.01.020>
- Nwokediuko, S. C., Osuala, P. C., Uduma, U. V., Alaneme, A. K., Onwuka, C. C., & Mesigo, C. (2013). Pattern of liver disease admissions in a Nigerian tertiary hospital. *Nigerian Journal of Clinical Practice*, 16(3), 339-342. <https://doi.org/10.4103/1119-3077.113458>
- Parés, A., Caballería, J., Bruguera, M., Torres, M., & Rodés, J. (1986). Histological course of alcoholic hepatitis: influence of abstinence, sex and extent of hepatic damage. *Journal of hepatology*, 2(1), 33-42. [https://doi.org/10.1016/S0168-8278\(86\)80006-X](https://doi.org/10.1016/S0168-8278(86)80006-X)
- Planas, R., Montoliu, S., Ballesté, B., Rivera, M., Miquel, M., Masnou, H., ... & Solà, R. (2006). Natural history of patients hospitalized for management of cirrhotic ascites. *Clinical Gastroenterology and Hepatology*, 4(11), 1385-1394.
- Poonawala, A., Nair, S. P., & Thuluvath, P. J. (2000). Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: a case-control study. *Hepatology*, 32(4), 689-692. <https://doi.org/10.1053/jhep.2000.17894>
- Poynard, T., Mathurin, P., Lai, C. L., Guyader, D., Poupon, R., Tainturier, M. H., ... & Panfibrosis Group. (2003). A comparison of fibrosis progression in chronic liver diseases. *Journal of hepatology*, 38(3), 257-265. [https://doi.org/10.1016/S0168-8278\(02\)00413-0](https://doi.org/10.1016/S0168-8278(02)00413-0)
- Pradat, P., Voirin, N., Tillmann, H. L., Chevallier, M., & Trépo, C. (2007). Progression to cirrhosis in hepatitis C patients: an age-dependent process. *Liver International*, 27(3), 335-339. <https://doi.org/10.1111/j.1478-3231.2006.01430.x>
- Rajani, R., Melin, T., Björnsson, E., Broomé, U., Sangfelt, P., Danielsson, Å., ... & Almer, S. H. (2009). Budd-Chiari syndrome in Sweden: epidemiology, clinical characteristics and survival—an 18-year experience. *Liver International*, 29(2), 253-259. <https://doi.org/10.1111/j.1478-3231.2008.01838.x>
- Realdi, G., Fattovich, G., Hadziyannis, S., Schalm, S. W., Almasio, P., Sanchez-Tapias, J., ... & Noventa, F. (1994). Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. *Journal of hepatology*, 21(4), 656-666. [https://doi.org/10.1016/S0168-8278\(94\)80115-0](https://doi.org/10.1016/S0168-8278(94)80115-0)
- Ruhl, C. E., & Everhart, J. E. (2003). Determinants of the association of overweight with elevated serum alanine

- aminotransferase activity in the United States. *Gastroenterology*, 124(1), 71-79. <https://doi.org/10.1053/gast.2003.50004>
- Sakauchi, F., Mori, M., Zeniya, M., & Toda, G. (2005). A cross-sectional study of primary biliary cirrhosis in Japan: utilization of clinical data when patients applied to receive public financial aid. *Journal of epidemiology*, 15(1), 24-28. <https://doi.org/10.2188/jea.15.24>
- Sheth, S. G., Gordon, F. D., & Chopra, S. (1997). Nonalcoholic steatohepatitis. *Annals of internal medicine*, 126(2), 137-145. <https://doi.org/10.7326/0003-4819-126-2-199701150-00008>
- SHRESTHA, S. M., OKUDA, K., UCHIDA, T., MAHARJAN, K. G., SHRESTHA, S., JOSHI, B. L., ... & VAIDYA, Y. (1996). Endemicity and clinical picture of liver disease due to obstruction of the hepatic portion of the inferior vena cava in Nepal. *Journal of gastroenterology and hepatology*, 11(2), 170-179. <https://doi.org/10.1111/j.1440-1746.1996.tb00056.x>
- Smith, B. D., Morgan, R. L., Beckett, G. A., Falck-Ytter, Y., Holtzman, D., Teo, C. G., ... & Ward, J. W. (2012). Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965. *Morbidity and Mortality Weekly Report: Recommendations and Reports*, 61(4), 1-32.
- Valla, D. C. (2008). Budd–Chiari syndrome and veno-occlusive disease/sinusoidal obstruction syndrome. *Gut*, 57(10), 1469-1478. <https://doi.org/10.1136/gut.2007.133637>
- Verma, S., Torbenson, M., & Thuluvath, P. J. (2007). The impact of ethnicity on the natural history of autoimmune hepatitis. *Hepatology*, 46(6), 1828-1835. <https://doi.org/10.1002/hep.21884>
- Villeneuve, J. P., Desrochers, M., Infante-Rivard, C., Willems, B., Raymond, G., Bourcier, M., ... & Richer, G. (1994). A long-term follow-up study of asymptomatic hepatitis B surface antigen—Positive carriers in montreal. *Gastroenterology*, 106(4), 1000-1005. [https://doi.org/10.1016/0016-5085\(94\)90760-9](https://doi.org/10.1016/0016-5085(94)90760-9)
- Williams, C. D., Stengel, J., Asike, M. I., Torres, D. M., Shaw, J., Contreras, M., ... & Harrison, S. A. (2011). Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology*, 140(1), 124-131. <https://doi.org/10.1053/j.gastro.2010.09.038>

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