INTRODUCTION

Liver Cirrhosis

Definition

Cirrhosis is a chronic liver disease in which diffuse destruction and regeneration of hepatic parenchymal cells have occurred, resulting in diffuse increase in connective tissue deposition and disorganization of the lobular architecture. The triad of parenchymal necrosis, regeneration and scarring is always present regardless of individual clinical manifestations, these "regenerative" nodules lack normal lobular organization and are surrounded by fibrous tissue. [(1)]

Epidemiology

The prevalence of chronic liver disease or cirrhosis worldwide is estimated to be 100 (range, 25 to 400) per 100,000 subjects, but it varies widely by country and by region.[(1)]

Cirrhosis is an important cause of morbidity and mortality worldwide, and is considered the 14th leading cause of death overall.[(1)]

Pathophysiology

Liver cirrhosis is a process involving the whole liver and is essentially irreversible; histologically it is "all or nothing" diagnosis.

The underlying immunological response has usually been acting for months or years where inflammation and tissue repairing are in progress simultaneously which leads in the end to fibrosis and cirrhosis [(2)]

Certain reversible components of cirrhosis have been identified where significant histological improvement have occurred with regression of cirrhosis, but complete resolution with a return to normal architecture seems unlikely.[(3-6)]

The key pathogenic feature underlying liver fibrosis and cirrhosis is activation of hepatic stellate cells. Hepatic stellate cells, which are known as *Ito cells* or *perisinusoidal cells*, are located in the space of Disse between hepatocytes and sinusoidal endothelial cells. Normally, hepatic stellate cells are quiescent and serve as the main storage site for retinoids (vitamin A). In response to injury, hepatic stellate cells become activated, as a result of which they lose their vitamin A deposits, proliferate, develop a prominent rough endoplasmic reticulum, and secrete extracellular matrix (collagen types I and III, sulfated proteoglycans, and glycoproteins). Additionally, they become contractile hepatic myofibroblasts.

Unlike other capillaries, normal hepatic sinusoids lack a basement membrane. The sinusoidal endothelial cells themselves contain large fenestrae (100 to 200 nm in diameter) that allow the passage of large molecules weighing up to 250,000.

Collagen deposition in the space of Disse, as occurs in cirrhosis, leads to defenestration of the sinusoidal endothelial" cells ("capillarization" of the sinusoids),

thereby altering exchange between plasma and hepatocytes and resulting in a decreased sinusoidal diameter that is further exacerbated by the contraction of stellate cells.[1]

Pathological features of cirrhosis

The diagnosis of cirrhosis depends on demonstrating widespread nodules in the liver combined with fibrosis. Cirrhosis may be classified as micronodular, macronodular or mixed.

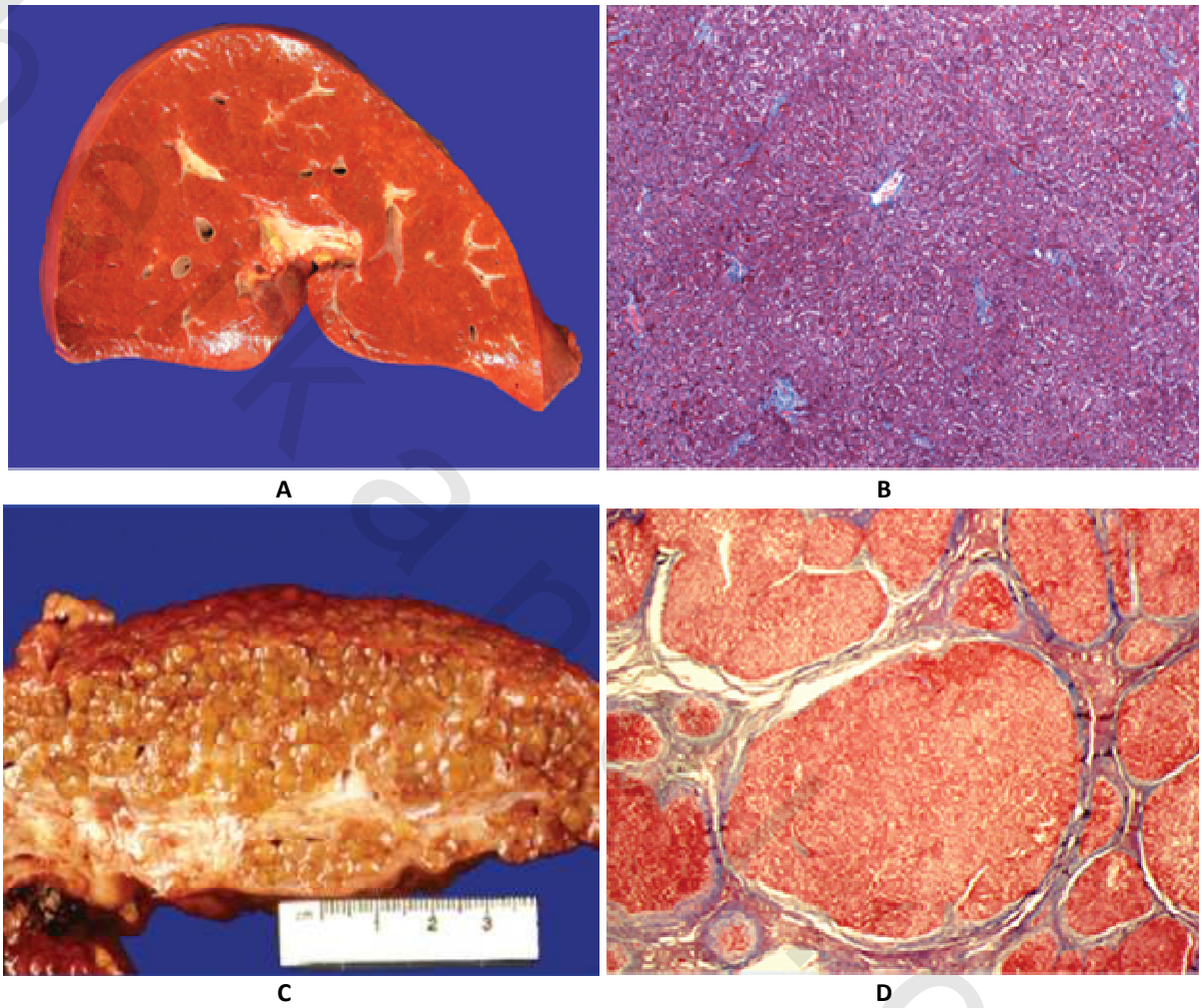

Figure (1): Gross and microscopic images of a normal and cirrhotic liver. A, Gross image of a normal liver with a smooth surface and homogeneous texture. B, Microscopically, liver sinusoids are organized, and vascular structures are normally distributed. C, Gross image of a cirrhotic liver. The liver has an orange-tawny color with an irregular surface and a nodular texture. D, Microscopically, the architecture is disorganized, and there are regenerative nodules surrounded by fibrous tissue.[1]

Causes of cirrhosis: [1,7]

More than 95% of cirrhotic cases are caused by

- Chronic hepatitis B,C
- Nonalcoholic fatty liver disease.
- Alcoholic liver disease

Other Causes of Cirrhosis (<2% OF CASES)

Cholestatic and autoimmune liver diseases
Primary biliary cirrhosis
Primary sclerosing cholangitis
Autoimmune hepatitis
Intrahepatic or extrahepatic biliary obstruction
Mechanical obstruction
Biliary atresia
Cystic fibrosis
– **Drugs and toxins**

Metabolic disorders
Hemochromatosis
Wilson's disease
α1-Antitrypsin deficiency
Glycogen storage diseases
Abetalipoproteinemia
Porphyria
Hepatic venous outflow obstruction
Budd-Chiari syndrome
Veno-occlusive disease
Right-sided heart failure

When all the causes have been investigated and excluded, cirrhosis is considered "cryptogenic." Many cases of cryptogenic cirrhosis are now thought to be due to nonalcoholic fatty liver disease. [1]

Diagnosis of cirrhosis

I- Clinical Manifestation[8, 9]

Cirrhosis is characterized by a two phases: an initial phase, termed compensated cirrhosis, and a rapidly progressive phase marked by the development of complications of portal hypertension or liver dysfunction (or both), termed decompensated cirrhosis.

Compensated Cirrhosis:[9]

In this stage, cirrhosis is mostly asymptomatic and is diagnosed either during the evaluation of chronic liver disease or during routine physicalexamination, biochemical testing, imaging for other reasons, endoscopy showing gastroesophageal varices, or abdominal surgery in which a nodular liver is detected. Some clinical signs help in diagnosis e.g; spiders angiomas, palmar erythema, unexplained epistaxis or lower limb edema, also firm enlargementof the liver, particularly in the epigastrium, and splenomegaly are helpful diagnostic signs. Confirmation should be sought by biochemical tests, abdominal ultrasonography and, if necessary, liver biopsy. [8]

Biochemical tests may be quite normal in this group. The most frequent changes are a slight increase in the serum transaminases or γ - glutamyltranspeptidase concentration.

These patients may remain compensated until they die from another cause. Decompensation may be precipitated by bacterial infection, surgery, trauma or medication.[9]

Decompensated Cirrhosis

The patient usually seeks medical advice because of ascites, jaundice or gastrointestinal bleeding. General health fails with weakness, muscle wasting and weight loss. Continuous mild fever (37.5 – 38 ° C) is often due to Gram - negative bacteremia, continuing hepatic cell necrosis, ongoing alcoholic hepatitis or complicating hepatocellular carcinoma. Cirrhosis is the commonest cause of hepatic encephalopathy.[8]

Jaundice implies that liver cell destruction exceeds the capacity for regeneration and is always serious. The deeper the jaundice the greater the inadequacy of liver cell function.[10]

Patients with decompensated cirrhosis often exhibit malnutrition, severe muscle wasting, vascular spiders, hypotension and tachycardia as a result of hyperdynamic circulatory state.

The skin may be pigmented. Clubbing of the fingers is occasionally seen. Purpura over the arms, shoulders and shins may be associated with a low platelet count, Sparse body hair, palmar erythema, white nails and gonadal atrophy are common.[8]

Hepatocellular carcinoma occurs at a rate of 1 – 3% per year and appropriate screening is recommended.

II- Laboratory Tests:

Laboratory test results suggestive of cirrhosis include even subtle abnormalities in serum levels of albumin or bilirubin or elevation of the international normalized ratio.

III- Imaging Studies:

Confirmatory imaging tests include ultrasound, computed tomography, and magnetic resonance imaging.

1- Ultrasound

Has helpful Findings consistent with cirrhosis, including a nodular contour of the liver, a small liver with or without hypertrophy of the left or caudate lobe,splenomegaly, ascites,and in particular, identification of intraabdominal collateral vessels indicative of portal hypertension .[11]

2- CT scan

It can assess liver size and shape and identify liver nodules. It provides an objective, record for evaluating changes over time. Fatty change and space occupying lesions can be recognized.

After intravenous contrast, the portal vein and hepatic veins can be identified, and a collateral circulation with splenomegaly may confirm the diagnosis of portal hypertension. Multiphase CT is useful in the evaluation of focal liver lesions and directed biopsy of a selected area can be performed safely.

However, the radiation dose with repeated multislice CT scans is substantial and may be an issue, particularly in younger patients. [8,12]

3-MRI:

It may identify cirrhosis of the liver. It is most useful for evaluating possible malignancy in liver nodules (contrast enhanced MRI). [13]

4-Transient elastography (fibroscan):

It is a noninvasive technique based on ultrasound wave propagation. It measures liver stiffness and appears to be useful in the diagnosis of cirrhosis. It is painless, rapid, and easy to perform. Studies suggest that TE is highly reproducible and reliable but that patient related and liver disease related factors may have a negative effect on the reproducibility of this technique. [14]

Typical findings on any of these imaging studies, together with a compatible clinical picture, are indicative of the presence of cirrhosis.

VI-liver biopsy:

Liver biopsy is the gold standard for diagnosis.[15] It contributes to the diagnosis of the etiology of cirrhosis. The biopsy may help in the reclassification of cryptogenic cirrhosis by identifying histological markers of etiology, such as steatosis indicating NASH, or inflammation suggesting autoimmune hepatitis.

Complications of Cirrhosis

The two main consequences of cirrhosis are portal hypertension, with the accompanying hyperdynamic circulatory state, and liver insufficiency.

The development of varices and ascites is a direct consequence of portal hypertension and the hyperdynamic circulatory state, whereas jaundice occurs as a result of an inability of the liver to excrete bilirubin (i.e; liver insufficiency).[1]

Encephalopathy is the result of both portal hypertension and liver insufficiency. Ascites, in turn, can become complicated by infection, which is called spontaneous bacterial peritonitis, and by functional renal failure, which is called hepatorenal syndrome.[1]

1-Variceal Hemorrhage

Gastroesophageal varices are present in approximately 30% of patients with newly diagnosed cirrhosis. The prevalence of varices correlates with the severity of liver disease. 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. [1]

2-Ascites

It is free fluid within the peritoneal cavity. Cirrhosis is the commonest cause of ascites in more than 75 % of cases. [16]

In patients with cirrhosis, the development of ascites marks the transition from compensated to decompensated cirrhosis [9, 17] It is the most frequent first decompensating event, occurring in 48% [18].

Ascites in cirrhosis is secondary to sinusoidal hypertension and retention of sodium. Cirrhosis leads to sinusoidal hypertension by blocking hepatic venous outflow both anatomically by fibrosis and regenerative nodules and functionally by increased post sinusoidal vascular tone. Similar to the formation of esophageal varices, A threshold hepatic venous pressure gradient of 10 mm Hg is needed for the formation of ascites. In addition, retention of sodium replenishes the intravascular volume and allows the continuous formation of ascites. Retention of sodium results from vasodilation that is mostly due to an increase in nitric oxide (NO) production.

With progression of cirrhosis and portal hypertension, vasodilation becomes more pronounced, thereby leading to further activation of the renin-angiotensin-aldosterone and sympathetic nervous systems and resulting in further sodium retention (refractory ascites), water retention (hyponatremia), and renal vasoconstriction (hepatorenal syndrome) While one - year -survival in patients who develop ascites is 85%, it decreases to 25% once it has progressed to hyponatraemia, refractory ascites or HRS. [1, 18]

3-Hepatorenal Syndrome[19]

Hepatorenal syndrome (HRS) is the development of renal failure in patients with severe liver disease in the absence of any identifiable renal pathology. It is a functional rather than structural disturbance in renal function.

The histology of the kidney is virtually normal. It may be classified into two types:

Type 1: Patients have a rapidly progressive (less than 2 weeks) reduction of renal function with doubling of the initial serum creatinine to greater than 2.5 mg/dL.

Type 2: Patients satisfy the criteria for the diagnosis of HRS but the renal failure does not progress rapidly and is characterized by maximal peripheral vasodilation as well as maximal activation of hormones that cause the retention of sodium and water and intense vasoconstriction of renal arteries. [20]Ascites unresponsive to diuretics is universal, and dilutional hyponatremia is almost always present.

Hepatorenal syndrome, which is a diagnosis of exclusion, should be made only after discontinuing diuretics, expanding intravascular volume with albumin, and excluding or treating any condition that leads to worsening of the hemodynamic status of the cirrhotic patient.

Without liver transplantation and prior to the recent studies of treatment using vasoconstrictors, recovery of renal function was unusual (< 5% of patients) and prognosis was poor with a median survival of 2 weeks [21].

4-Spontaneous Bacterial Peritonitis

It is an infection of ascitic fluid, which occurs in the absence of perforation of a hollow viscus or an intra-abdominal inflammatory focus such as an abscess, acute pancreatitis, or cholecystitis. The main mechanisms implicated in spontaneous bacterial peritonitis are:

A- Bacterial translocation, or the migration of bacteria from the intestinal lumen to mesenteric lymph nodes and other extra intestinal sites.

B- Impaired local and systemic immune defenses are a major element in promoting bacterial translocation together with shunting of blood away from the hepatic Kupffer cells through portosystemic collaterals, allowing a transient bacteremia to become more prolonged, thereby colonizing ascitic fluid. It occurs in patients with reduced ascites defense mechanisms, such as a low complement level in ascitic fluid.

C- Bacterial overgrowth attributed to a decrease in small bowel motility and intestinal transit time.

Infections, particularly from gram-negative bacteria, can precipitate renal dysfunction through worsening of the hyperdynamic circulatory state.

Diagnosis of spontaneous bacterial peritonitis is established by an ascitic fluid PMN count greater than 250/mm3. Bacteria can be isolated from ascitic fluid in only 40 to 50% of cases, even with sensitive methods such as inoculation directly into a blood culture bottle. Spontaneous bacterial peritonitis is mostly a monobacterial infection, usually with gram-negative enteric organisms.[22,23]

5-Hepatic Encephalopathy (HE)

HE is a syndrome of neurocognitive impairment that is clinically manifested as a range of signs from subtle behavioral deficits to stupor and coma.[24,25] The pathogenesis is multifactorial, and associated with toxins derived from the gastrointestinal tract that bypass hepatic metabolism.[26]

Ammonia derived primarily from the action of colonic bacteria on the breakdown products of ingested protein is one of the most important toxins.

Ammonia, which normally is transported to the liver via the portal circulation where it is metabolized in the urea cycle, directly enters the systemic circulation through porto-systemic shunt (PSS). The excess blood ammonia penetrates the blood brain barrier and causes neuronal dysfunction by incompletely understood mechanisms. Current evidence supports a central role of ammonia-induced astrocyte dysfunction.[24-26]

The diagnosis of hepatic encephalopathy is clinical and based on the history and physical examination, and is classified into 4 stages as shown in table (1):

Table (1): Stages of hepatic encephalopathy.[24]

Grade	Criteria
1	Trivial lack of awareness
	Shortened attention span
	Impaired performance of addition
	Euphoria or anxiety
2	Lethargy or apathy
	Minimal disorientation for time or place
	Subtle personality change
	Inappropriate behavior
	Impaired performance of subtraction
3	Somnolence to semistupor, responsive to verbal stimuli
	Confusion
	Gross disorientation bizarre behavior
4	Coma (unresponsive to verbal or noxious stimuli)

6- Pulmonary complications:

Hepatopulmonary syndrome (HPS) is defined as a clinical disorder associated with advanced liver disease, pulmonary vascular dilatation and a defect in oxygenation in the absence of detectable primary cardiopulmonary disease.[27] Hepatopulmonary syndrome occurs due to microvascular pulmonary arterial dilatation (most likely because of NO overproduction in the lung) leading to ventilation perfusion mismatch.[28-30]

Portopulmonary hypertension is another complication of liver cirrhosis, it is likely mediated by humoral substances that enter the systemic circulation through portosystemic circulation (PSS). Initially these substances cause vasoconstriction, but subsequent thrombosis leads to vessel obliteration.[29, 31]

Hepatic hydrothorax is the presence of pleural effusion in patients with hepatobiliary disease. It likely arises because of direct passage of ascites from the abdomen to the thorax through undetectable diaphragmatic rents. [30]

Prognosis of cirrhosis:

Poor prognosis is associated with a prolonged prothrombin time, marked ascites, gastrointestinal bleeding, advanced age, high daily alcohol consumption, high serum bilirubin and alkaline phosphatase, low albumin values and poor nutrition. The availability of liver transplantation has emphasized the need for an accurate prognosis so that surgery may be performed at the right time.

I- Child's classification (grades A – C):[33]

Child–Turcotte–Pugh (CTP) score which depends on jaundice, ascites, encephalopathy, serum albumin concentration and prothrombin time gives a good short - term prognostic guide. The total score classifies patients into grade A, B or C as shown in table (2).

II- Model for End - stage Liver Disease (MELD) score: [34,35]

It was developed to determine prognosis in patients undergoing trans jugular intrahepatic portosystemic shunt (TIPS) insertion. It is calculated from serum creatinine, prothrombin time or international normalization ratio (INR) and serum bilirubin as shown in (table 3). MELD was applied to liver transplantation and found to accurately predict waiting list mortality in cirrhotic patients. It is now widely used as a criterion for liver transplant listing and to determine priority for organ allocation. [34] The addition of serum sodium to the calculation may further improve its predictive ability — MELD – Na [35]

The two most commonly used scoring systems in cirrhosis

Table (2): Child-Turcotte-Pugh (CTP) score [33]

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	**Points***		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points (least severe liver disease)			
Class B = 7 to 9 points (moderately severe liver disease)			
Class C = 10 to 15 points (most severe liver disease)			

Table (3): Model of End-Stage Liver Disease (MELD) score [36]

Model for End Stage Liver Disease (MELD) Score
MELD = 3.78 x $\log_e$ serum bilirubin (mg/dL) + 11.20 x $\log_e$ INR + 9.57 x $\log_e$ serum creatinine (mg/dL) + 6.43 (constant for liver disease etiology)
NOTES: • If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0 • Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)

III- Clinical staging of cirrhosis:[37, 38]

Dividing the patients into compensated and decompensated cirrhosis groups is very useful in terms of prognosis as these are two distinct stages of cirrhosis with different predictors of survival, as shown in table 4.

Table (4): Stages of cirrhosis[39]

	Compensated Cirrhosis		Decompensated Cirrhosis	
Stage	Stage 1	Stage 2	Stage 3	Stage 4
Clinical	No Varices No Ascites	Varices No Ascites	Ascites +/- Varices	Bleeding +/- Ascites
Death (at 1 Year)	1%	3%	20%	57%

Compensated cirrhotic patients have a 50% ten-year-survival as compared to 50% survival at 18 months for decompensated patients. [9]

Cirrhotic patients become decompensated at the rate of approximately 10% per year. Decompensated patients can improve and become compensated with an associated improvement in prognosis.[9]

Portal Hypertension

Anatomy of portal venous system

Portal venous system includes all veins, which carry blood from the abdominal part of the alimentary tract, the spleen, pancreas and gall bladder. [40]

The portal vein is approximately 6-8cm long, 1.2cm in diameter and valveless. It is formed by the union of superior mesenteric vein and the splenic vein just posterior to the head of pancreas at about the level of the second lumbar vertebra. [41]

Physiology of portal venous system

Portal blood flow is about 1000-1200 ml/min. The liver receives dual blood supply 25% from hepatic artery, 75% from portal vein. [42,43] These two inflows have distinct characteristics in terms of pressure, flow and composition. Arterial flow is nutritive while the mesenteric portal drainage represents the consequences of gastrointestinal function activity.

Portal pressure is determined by the product of portal venous inflow and the vascular resistance to this flow.[44] The main site of portal vascular resistance appears to reside at the level of the hepatic sinusoids.[45] Portal blood flow accounts for about 3/4 of the total oxygen entering the liver. About 4/5 of this flow originates from the intestine and the stomach and the remaining 1/5 originates from the spleen and pancreas. [46] Flow is stream like rather than turbulent.[47]

Definition of portal hypertension (PH)

It is a pathologic increase in the portal venous pressure, in which the hepatic venous pressure gradient (HVPG) is increased above normal values (1-5 mmHg). [48] An increase (>12 mmHg) in HVPG directly correlate with the clinical consequences of PH in cirrhotic patients. In addition, the success of treatment for PH is defined either by a >20% decrease in HVPG orreduction to <12 mmHg.[49-52]

Complications of portal hypertension include upper gastrointestinal bleeding from ruptured gastroesophageal varices and portal hypertensive gastropathy (PHG), ascites, renal dysfunction, hepatic encephalopathy, disorder in the metabolism of drugs or endogenous substances that are normally eliminated by the liver, Portopulmonary hypertension, Portal vein thrombosis bacteremia, and hypersplenism.[53]

These complications are major causes of death and the main indications for liver transplantation in patients with liver cirrhosis.

Etiology of portal hypertension: [54]

PH is classified based on anatomical location as prehepatic, intrahepatic, or posthepatic:

Prehepatic

- Splenic vein thrombosis
- Portal vein thrombosis
- Congenital stenosis of the portal vein
- Extrinsic compression of the portal vein
- Arteriovenous fistulae (splenic, aortomesenteric, aortoportal, and hepatic artery–portal vein)

Posthepatic

- Budd–Chiari syndrome
- Congenital malformations and thrombosis of the inferior vena cava
- Constrictive pericarditis
- Tricuspid valve diseases

Intrahepatic

- Nodular regenerative hyperplasia
- Congenital hepatic fibrosis
- Polycystic disease
- Idiopathic portal hypertension
- Hypervitaminosis A
- Arsenic, copper sulfate, and vinyl chloride monomer poisoning
- Infiltrative diseases: Sarcoidosis, Amyloidosis,Liver infiltration in hematologic diseases
- Granulomatous diseases: Tuberculosis,

Schistosomiasis

- Primary biliary cirrhosis
- Acute fatty liver of pregnancy
- Hepatocellular carcinoma
- Metabolic: Hemochromatosis, Wilson disease
- Hepatic porphyrias
- Antitrypsin deficiency
- Chronic biliary obstruction
- Cirrhosis: alcoholic,hepatitis B and C virus infection
- Peliosishepatis
- Venoocclusive disease

Pathophysiology of PH in liver cirrhosis

The hallmark of portal hypertension is a pathologic increase in the pressure gradient between the portal vein and the inferior vena cava, which is measured by the hepatic venous pressure gradient (HVPG).

The wedged hepatic vein pressure (WHVP), a marker of sinusoidal pressure, and the free hepatic vein pressure (FHVP) are measured with radiologic assistance. HVPG is calculated by the following formula: [55,56]

$$HVPG=WHVP - FHVP$$

In cirrhosis, portal hypertension results from the combination of

1- Increased intrahepatic vascular resistance

2- Increased blood flow through the portal venous system

(A)Increased Hepatic Vascular Resistance

In cirrhosis, the principal site of increased resistance to outflow of portal venous blood is within the liver itself. This results from 2 components:

(1) The mechanical component stems from intrahepatic fibrosis development; various pathologic processes are thought to contribute to increased intrahepatic resistance at the level of the hepatic microcirculation (sinusoidal portal hypertension): architectural distortion of the liver due to fibrous tissue,regenerative nodules, and collagen deposition in the space of Disse.[57,58]

(2) The dynamic component results from a vasoconstriction in portal venules secondary to active contraction of portal and septalmyofibroblasts, to activated hepatic stellates cells and to vascular smooth muscle cells. [59] Intrahepatic vascular tone is modulated by endogenous vasoconstrictors (e.g., norepinephrine, endothelin-1, angiotensin II, leukotrienes and thromboxane A2) and enhanced by vasodilators (e.g., nitric oxide).[60]

In cirrhosis, increased intrahepatic vascular resistance results also from an imbalance between vasodilators and vasoconstrictors.[61]

The role of several other vasoactive mediators such as carbon monoxide, adrenergic tone, endotoxemia, and inflammatory cytokines are currently under investigation.[61]

(B) Increased Portal Venous Inflow

Mesenteric arterial vasodilation is a hallmark of cirrhosis and contributes to both increased portal venous inflow and a systemic hyperdynamic circulatory state (low systemic vascular resistance and mean arterial pressure with high cardiac output). [49,62] Increased NO production because of increased eNOS activity in the systemic circulation is a major driver of arterial vasodilation.

Shear stress, increased vascular endothelial growth factor (VEGF), and tumor necrosis factor alpha are causes of increased splanchnic NO production in cirrhosis.[63] Increased hemeoxygenase activity and carbon monoxide (CO) production may also contribute to the hemodynamic disturbances. Bacteremia can increase vasodilation by stimulating tumor necrosis factor production and activation of endocannabinoids, which are potent vasodilators.

The net result is impaired sinusoidal relaxation. The combined action of all these vasodilatory compounds mediates progressive and sustained vasodilatation of the splanchnic circulation leading to higher portal blood flow, which maintains and aggravates the development of PH.

An increase in the portocaval pressure gradient leads to the formation of portosystemic venous collaterals in an attempt to decompress the portal venous system.

Esophageal varices, drained predominantly by the azygos vein, are clinically the most important collaterals because of their propensity to bleed.

Esophageal varices can develop when the hepatic venous pressure gradient rises above 10 mm Hg.[64-66]

All factors that increase portal hypertension can increase the risk of variceal bleeding, including also deterioration of liver disease, [67] food intake [68] ethanol intake,[69]circadian rhythms,[70] physical exercice[71] and increased intra-abdominal pressure. [72]Factors that alter the variceal wall, such as non steroidal anti inflammatory drugs (NSAIDs), could also increase the risk of bleeding. [73] Bacterial infection can promote initial and recurrent bleeding.[74]

(C)Increase angiogenesis

Recent studies suggest that angiogenesis also contributes to the establishment and maintenance of PH.[75]

The development of fibrotic septa and capillarization of the hepatic sinusoids results in relative hepatic hypoxia stimulating the release of angiogenic factors from hepatic stellate cells . These factors, particularly vascular endothelial growth factor and platelet-derived growth factor, stimulate angiogenesis fueling higher PBF and worsening PH.[75]

Porto-systemic collateral circulation

Increased portal pressure is the main factor leading to the formation of porto-systemic collaterals which develop by opening, dilatation and hypertrophy of pre-existing vascular channels. Possibly a component of active angiogenesis is also involved. Normally, 100% of Portal blood flow (PBF) can be recovered from the hepatic veins, whereas in advanced cirrhosis only 13% is obtained. The remainder enters collateral channels.[8]

Portal hypertension caused by cirrhosis persists and progresses due to

(1) Prominent obstructive resistance within the liver,

(2) Continued increase in portal vein inflow.

This hypertension leads to the formation of collaterals that decompress the portal circulation by returning blood to the heart via the systemic venous circulation, as shown in figure(2)

The major sites of collaterals are (fig.3)

- Rectum, where the systemic inferior mesenteric vein connects with the portal pudendal vein and results in rectal varices.
- Umbilicus, where the vestigial umbilical vein communicates with the left portal vein and gives rise to prominent collaterals around the umbilicus (caput medusa).
- Retroperitoneum, where collaterals, especially in women, communicate between ovarian vessels and iliac veins.
- Distal esophagus and proximal stomach, where gastroesophagealvarices form major collaterals between the portal venous system and the systemic venous system.

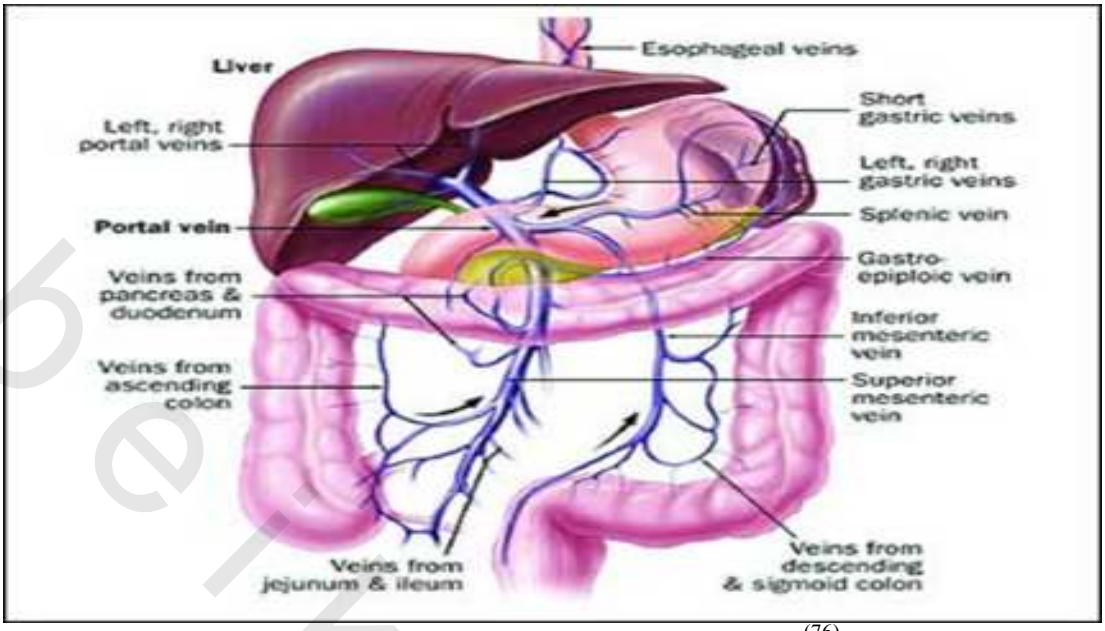

Figure (2): Hepatic portal vein tributaries[76]

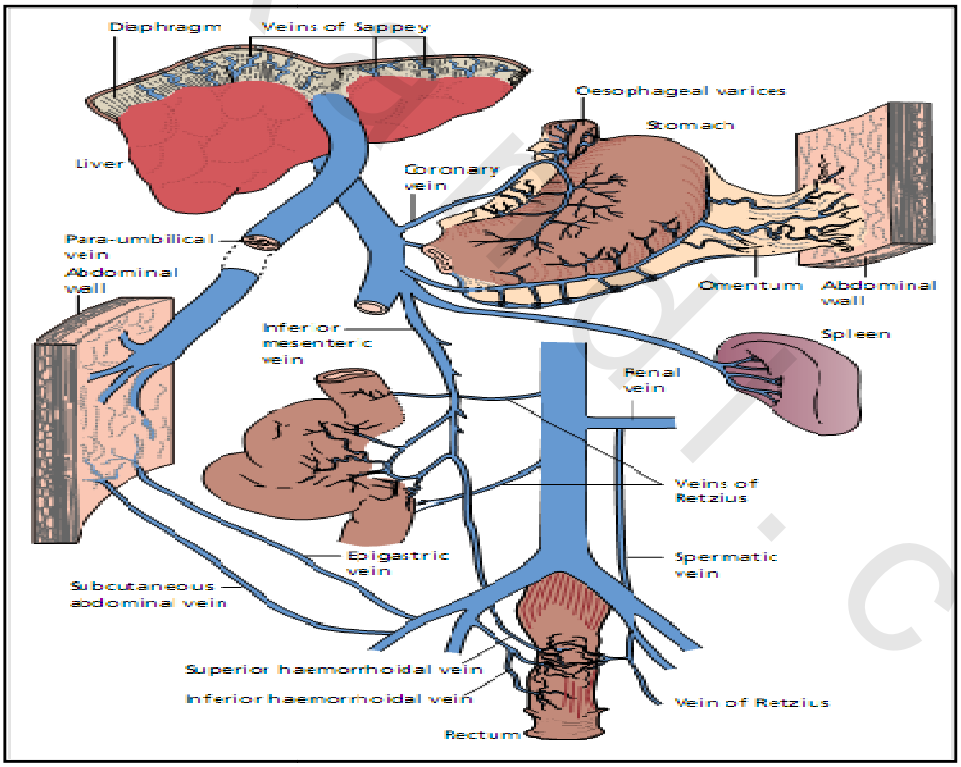

Figure (3): Major sites of Porto-systemic collateral circulation [8]

Gastro-esophageal varices

Most patients who have intrahepatic causes of portal hypertension have gastroesophageal varices because this provides the largest collateral flow via the short and left gastric veins.

❖ Anatomy of the venous structure of the esophagus

The venous structure of the esophagus is classified into three groups: [77-80]

a) Extrinsic veins.

b) Intrinsic veins.

c) Venae comitantes of the vagal nerves

The following four zones of venous drainage are involved in the formation of gastroesophageal varices[81]:

(1) The gastric zone is 2 to 3 cm below the gastroesophageal junction, where the veins meet at the upper end of the cardia of the stomach, drain into short gastric and left gastric veins, and then drain into the splenic and portal veins, respectively.

(2) The palisade zone is 2 to 3 cm proximal to the gastric zone into the lower esophagus, where the veins communicate with extrinsic (periesophageal) veins in the distal esophagus. This zone forms the dominant watershed area between the portal and the systemic circulations, where venous flow is bidirectional with turbulent flow which may explain frequent rupture. Thus esophageal bands should be applied as close to the GOJ as possible.

(3) More proximal to the palisade zone in the esophagus is the perforating zone, where a network of submucosal veins in the esophagus connects to the periesophageal veins, which drain into the azygous system and subsequently into the systemic circulation.

(4) The truncal zone is approximately 10 cm in length and is located proximally to the perforating zone in the esophagus. It typically has four longitudinal veins in the lamina propria.

❖ Pathogenesis of esophageal varices

Once portal hypertension ensues, there is development of porto-systemic collateral formation in an attempt to decompress the rising portal pressure.

Physical laws that govern the flow of fluids into tubes can be used to understand the circulatory derangements that cause the development of varices according to La Place's law. [82]

$$T=TP \times r/w$$

Where T is wall tension, TP is transmural pressure, i.e. the difference between the intraluminal vessel pressure and esophageal luminal pressure, r is radius of the vessel and w is the wall thickness. The tension of a vessel wall is an inwardly directed force however

intravariceal pressure appears as an outwardly directed expanding force, which is a property of the vessel wall.[83] Accordingly, initial dilatation of the esophageal collaterals probably depends upon the elevation of portal pressure above a threshold that has been found to be 12mmHg over the caval pressure.[84,85] Further distension of the varices may result as a consequence of loss of tissue resilience and compliance of the vein wall as a result of diffuse thinning and fibrotic replacement of both smooth muscle and elastic tissue caused by venous congestion and stasis.[86]

❖ Mechanism of variceal rupture

Several etiopathogenic factors have been proposed for the development of variceal bleeding, but the precise cause is controversial. However, the most popular theories are; erosion of the esophageal mucosa by external agents (Erosive theory) and primary rupture due to raised portal pressure (Eruptive theory). [86,87]

I- Erosive theory

The esophageal mucosa is subjected to various kinds of local trauma that could lead to erosion of the varix wall.[88] The most likely agent of erosion is acid/bile reflux esophagitis.[89] However, while several investigators believed in the important role of esophagitis in the rupture of esophageal varices,[90,91] evidence from histological,[92,,93] endoscopic,[94] manometric[95] and pH monitoring[96] studies failed to incriminate reflux esophagitis as a cause of variceal bleeding.

Nevertheless, Tsao et al [97] could not rule out the possibility that an esophagus with inefficient blood flow would be damaged by a normal amount of acid pepsin reflux in the presence of normal lower esophageal sphincter pressure and delayed acid clearance.

II- Eruptive theory

Generally, eruption of varices from within may be related to primary abnormalities in the variceal system itself and/or alterations in the portal venous system.

(1) Primary abnormalities in the variceal system

The suggestion that the gastro-esophageal collateral system might be functionally separated from the portal trunk has directed the attention toward the assessment of hemodynamics in the target organ, the varix, as risk factors for variceal bleeding.[98,99]

a- Variceal pressure

The relationship between variceal pressure and risk of bleeding is undefined. While Poaluzi et al [100] failed to find a correlation between the intravariceal pressure and bleeding, Bosch et al [65] found a higher variceal pressure in bleeders than in patients who have not yet bleed.

Moreover, marked rise in intravariceal pressure occurring during acts of physical violence as coughing, vomiting, straining and valsalva maneuver can precipitate variceal rupture.

b- Transmural pressure:

It has been suggested that the transmucosal pressure or portal venous esophageal luminal pressure gradient (PEPG) rather than the absolute variceal pressure might be related to the likelihood of variceal bleeding. Therefore, the more positive the pressure in the esophageal lumen, the less will be the PEPG, hence the likelihood of variceal rupture.[101,102]

c- Variceal size

This is best assessed endoscopically. Numerous studies have shown that the risk of variceal hemorrhage increases with the size of varices. haemorrhage from larger varices (>5mm) is 30% at 2 years, compared to 10% from small varices at 2 years [103,104]

d- Structural abnormalities in variceal wall:

Variceal wall thickness and the thickness of the overlying esophageal mucosa may contribute to varix rupture. Endoscopic observations of blue variceal discoloration may indicate thin variceal wall and overlying mucosa as a consequence of distension and hypoxia of chronic venous congestion which produce atrophic changes causing the wall to lose its elastic and muscle support and become non-compliant.[105]

When tissue support is not available, as happens with varices protruding into the lumen of the esophagus, the "yield point" of the vessel can occur even at relatively low pressure.[106] Moreover, the presence of different arrangements of dilated small vessels on the variceal surface, described endoscopically as "varices overlying varices" by Clason et al[107] "erosions and microtelangectasia" by Paquet, [108]"red color sign" by Beppu et al[109] have been proposed to be related to the risk of variceal bleeding .

These vessels were intra and subepithelial blood filled channels surrounded by fibrinogen polymers that act as "diffuse block" to oxygen aid nutrient transversing from the papillary capillary lumen to the overlying epithelial cells. Therefore, it seems possible that these fragile, poorly supported and congested channels which are separated from the lumen by only few cells may rupture during increased intravariceal pressure and produce significant haemorrhage from a pin hole opening as they are connected with underlying vessels by way of the papillae.

e- Variceal wall tension

Polio and Groszmann[110] using an in vitro model showed that rupture of varices was related to the tension on the variceal wall.

The tension depends on the radius of the varix. In this model, increasing the size of the varix and decreasing the thickness of the variceal wall caused variceal rupture.

Endoscopic features such as “red spots” and “wale” markings were first described by Dagradi.[111] They have been described as being important in the prediction of variceal hemorrhage.

These features represent changes in variceal wall structure and tension associated with the development of microtelangiectasias.

In a retrospective study by the Japanese Research Society for Portal Hypertension, Beppu and colleagues[109] showed that 80% of patients who had blue varices or cherry red spots bled from varices, suggesting that this was an important predictor of variceal hemorrhage in cirrhosis.

(2) Alterations in the portal venous system. [112]

a- Degree of portal pressure elevation:

In most cases, portal pressure reflects intravariceal pressure [113] and a hepatic venous pressure gradient greater than 12 mm Hg is necessary for the development of and bleeding from esophageal varices but there is no linear relationship between the severity of portal hypertension and the risk of variceal hemorrhage.[96] However, the hepatic venous pressure gradient (HVPG) tends to be higher in bleeders as well as in patients with larger varices. In a prospective study comparing propranolol with placebo for the prevention of first variceal haemorrhage, Groszmann and colleagues [114] showed that bleeding from varices did not occur if the portal pressure gradient could be reduced to less than 12 mm Hg.

This pressure has since been accepted as the aim of pharmacological therapy of portal hypertension. Patients with a hepatic venous pressure gradient > 20 mmHg within 24 h of variceal hemorrhage, in comparison with those with lower pressure, are at higher risk for recurrent bleeding within the first week of admission, or of failure to control bleeding (83% vs. 29%) and have a higher 1-year mortality rate (64% vs. 20%).

b- Compliance of the splanchnic bed:

Some clues suggest that the splanchnic blood flow and the compliance of the splanchnic bed (pressure-volume relationship) may be important than absolute pressure. The less compliant the system, the more the increase in pressure even with small increments of splanchnic flow as occurs post prandially or with volume expansion, and the greater the chance of bleeding and vice versa .[115-117]

Moreover, there was evidence that large caudal single collaterals might result in relief of portal hypertension. [118,119]

❖ **Epidemiology of esophageal varices and correlation with liver disease:** [120]

1. At the time of diagnosis, approximately 30% of cirrhotic patients have esophageal varices, reaching 90% after approximately 10 years
2. Bleeding from esophageal varices is associated with a mortality rate of at least 20% at 6 weeks, although bleeding ceases spontaneously in up to 40% of patients
3. Variceal hemorrhage is the most common fatal complication of cirrhosis

A strong correlation exist between presence of varices the and the severity of liver disease. [121]Child–Pugh A patients: 40% have varices with< 10% mortality rate in any bleeding episode Child–Pugh C patients: 85% have varices with< 70% mortality rate in any bleeding episode and risk of re-bleeding is high, reaching 80% within 1 year.

❖ Classification and grading of EV

Endoscopically, esophageal varices can be diagnosed as straight linear or rather tortuous venous columns, which distend slowly with valsava's manoeuvre giving a "knotted' "wrinkled" appearance.

1-The American Association for the Study of Liver Diseases (AASLD) recommends the classification of esophageal varices according to size into small and large esophageal varices based on a cut-off of 5mm.[122,123]

2-Japanese Research Society for Portal Hypertension has classified varices according to the general rules for recording endoscopic findings on esophageal varices as follow:

I - Fundamental color

- **White varices (Cw):**Varices that are of white color and those that look like large folds of the esophageal mucosa.
- **Blue varices (Cb):**Varices that are of blue color and those that are distended by blood and look bluish-white or cyanotic. The overlying mucosa is markedly thin.[96]

II - Red-color sign on the variceal surface(R-C) sign:[124]

- Red wale markings (RWM)
- Cherry-red spots (CRS)
- Haematocystic spot (HCS)
- Diffuse redness (DR)

3- Another popular (Japanese) grading system according toBeppu as follows: [109]

F0 no varices

F1 (small) Small straight varices

F2 (medium) Enlarged tortuous varices occupying less than one third of the lumen

F3 (large) Large coil-shaped varices occupying more than one third of the lumen

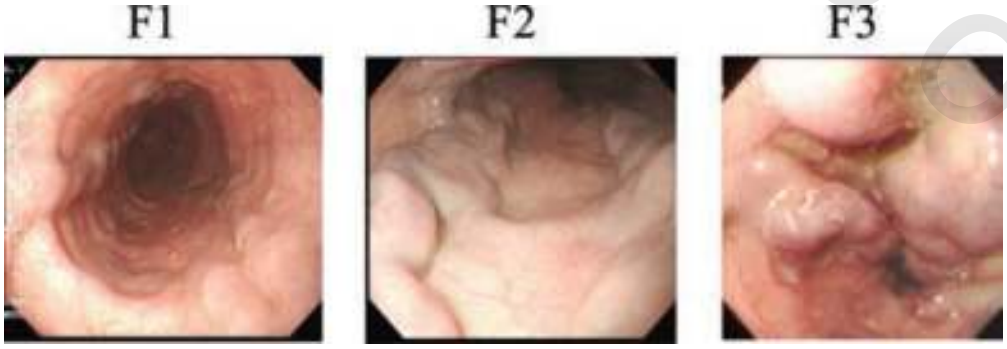

Figure (4): Endoscopic grades of esophageal varices[13]

4- According to paquet another grading system as shown in table (5): [108]

Table (5): Endoscopic classification of esophageal varices according to Paquet

Grade 0	Absence of esophageal varices
Grade I	Microcapillars located on esophagogastric transition or distal esophagus
Grade II	1 or 2 small varices located on distal esophagus
Grade III	Medium varices
Grade IV	Large varices in any part of the esophagus

Gastric varices

Gastric varices are supplied by the short gastric veins, draining into the deep intrinsic veins of the lower esophagus, Gastric varices account for 10-30% of variceal haemorrhage and can occur in up to 20% of patients with portal hypertension [125,126] and can be classified according to site by the Sarin classification of gastric varices. [127] as shown in figure (5):

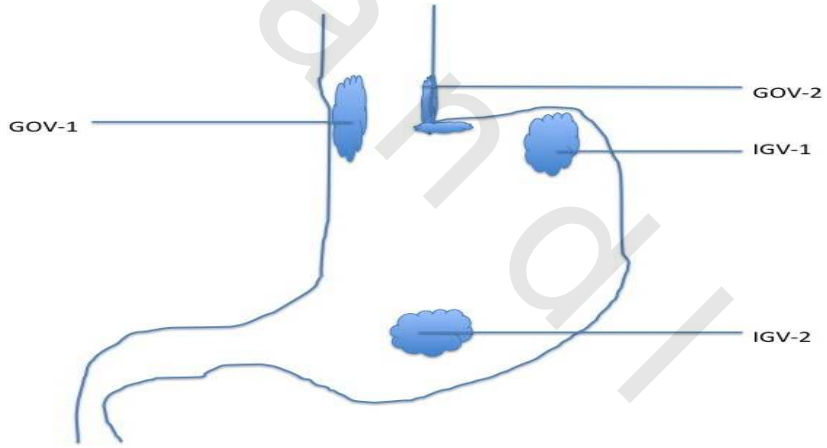

Figure (5): Sarin classification of gastric varices[127]

- **Gastric varix description/location**

Gastric varices are classified primarily by location. As agreed upon at the Baveno Consensus Conference, they are described as follows:

- **Gastroesophageal varices (GOVs)**: gastric varices in continuity with esophageal varices:

Type 1 (GOV1): along the lesser curve (usually 2–5 cm in length);

Type 2 (GOV2): along the greater curve extending towards the fundus of the stomach.

- **Isolated gastric varices (IGVs)**:

Type 1 (IGV1): isolated cluster of varices in the fundus of the stomach.

Type 2 (IGV2): isolated gastric varices in other parts of the stomach.

Risk factors for gastric variceal hemorrhage include the size of fundal varices (large-medium-small, defined as (10 mm, 5-10 mm, and _5 mm) respectively, Child class (C-B-A), and endoscopic presence of variceal red sign.[128]

❖ **Portal hypertensive gastropathy:**

Gastric mucosal lesions associated with portal hypertensive gastropathy are present in 51–98% of patients with PH.[129] Histologically, this gastropathy is defined by mucosal and submucosal vascular ectasia in the absence of inflammation.

Many factors including alterations in splanchnic blood flow, humoral factors, and local dysregulation of vascular tone have been implicated in the pathophysiology. [130]

Portal hypertensive gastropathy (PHG) is a macroscopic finding classified according to North Italian Endoscopic Club (NIEC) into:

''Mild'' PHG: mosaic-like pattern of the gastric mucosa as shown in figure (6).

''Severe'' PHG: cherry red spots, and/or black-brown spots. These lesions, however, are not entirely specific, that is, they can occur in the absence of portal hypertension.

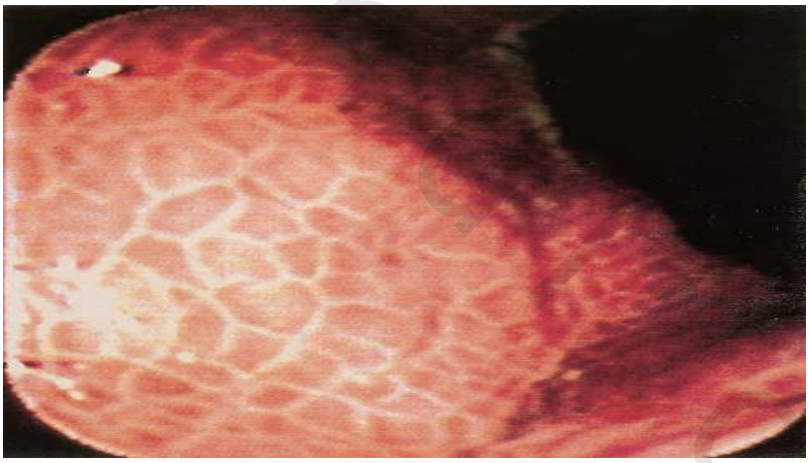

Figure (6): mosaic pattern of portal hypertensive gastropathy[131]

❖ **Prediction of variceal hemorrhage**

The identification of those at high risk of bleeding and the prevention of the first bleeding episode are critical objectives

A-Role of endoscopy

Upper GI endoscopy remains the gold standard for the diagnosis of esophageal varices [132] in cirrhotic patients. At least two thirds of cirrhotic patients develop esophageal varices during their lifetime so; cirrhotic patients should be endoscopically screened for varices at the time of diagnosis.

Current guidelines recommend that all cirrhotic patients should be screened for varices at diagnosis, with follow up every 2-3 years for patients without varices (depending upon liver disease severity) and 1-2 years for patients with small varices and particularly if hepatic synthetic function worsens. [132]

Several endoscopic parameters appear to be related to variceal bleeding. Those are: variceal size, cherry red spots described as "varices on top of varices" and the presence of gastric varices. The first attempt to establish a quantitative relation between variceal features and risk of bleeding was made by Beppu et al.[109] This classification is extremely detailed and includes the assessment of a number of endoscopic features of esophageal varices extent and color of varices, presence and grade of several red signs on the variceal wall (cherry red spots, red wale marking, hematocystic spots, diffuse erythema) and presence of esophagitis.[133]

The larger the varix the more likely is to bleed.[134,135] Color is an important sign to detect varices usually appear white and opaque. Red color correlates with blood flow through dilated subepithelial and communicating veins. Dilated subepithelial veins may appear as raised cherry red spots and red wale markings (longitudinally dilated veins resembling whip marks). They lie on top of large subepithelial vessels. [136]

The haematocystic spot is approximately 4 mm in diameter and it represents blood coming from the deeper extrinsic veins of the esophagus straight out towards the lumen through a communicating vein into the more superficial submucosal veins.[102,137] Red color is usually associated with large varices. All these color changes and particularly red color signs predict variceal bleeding. [138]

Combination of clinical and endoscopic parameters and risk of first bleeding was analyzed by NIEC for the study and treatment of esophageal varices. An index known as NIEC index was easily applied to research and clinical practice for prediction of variceal rupture. [139] (Table.6)

With the use of NIEC index, the estimated 1-year percentage probability of bleeding was calculated (Table 7) [140]

Table (6): Rocket chart for easy calculation of the NIEC index. [139]

Variable	Points to add
Child class	
A	6.5
B	13.0
C	19.5
Size of varices	
Small	8.7
Medium	13.0
Large	17.4
Red wale markings	
Absent	3.2
Mild	6.4
Moderate	9.6
Severe	12.8

North Italian Endoscopic Club (NIEC) index and risk of bleeding.

Table (7): Risk of bleeding according to NIEC index.[140]

Risk class	NIEC index	Rate of bleeding %		
		6Months	1Years	2Years
1	<20	0	1.6	6.8
2	20-25	5.4	11.0	16.0
3	25.1-30	8.0	14.8	25.5
4	30.1-35	13.1	23.3	27.8
5	35.1-40	21.8	37.8	58.8
6	>40	58.5	58.5	68.9

B-Noninvasive parameter for prediction of esophageal varice and variceal hemorrhage:

The ideal marker needs to be simple, quick, reproducible, cost effective, easy access, and high-clinical sensitivity and specificity.

Several authors studied a number of clinical signs, laboratory and radiological markers and use them either alone or in combination as factors predicting the presence of esophageal varices.

Some examples of current Perspectives Possible Approaches to noninvasive diagnosis of esophageal varices

I clinical and laboratory:

These include the presence of spider naevi, splenomegaly or ascites, Child-Pugh classification, thrombocytopenia, serum albumin, ALT, and prothrombin time.[141,142]On the other hand, the Baveno IV International Consensus Workshop on methodology of diagnosis and treatment concluded that no study reached a high enough level of significance to warrant the widespread use of such noninvasive markers of esophageal varices.[132]

II Radiological:

a-Ultrasound.

Doppler ultrasonography (US) imaging provides a real-time, inexpensive, and repeatable examination of the portal system and allows estimation of both arterial and venous flow. It is considered the first-line imaging technique in patients with cirrhosis. Portal vein diameter, portal blood velocity and congestion index, spleen size, flow pattern in the hepatic veins, and the presence of abdominal portosystemic collaterals are all US parameters previously thought to have with prognostic significance but all with poor sensitivity and specificity.[143]

b- Computed tomography

It was found to have approximately 90% sensitivity in the identification of esophageal varices determined to be large on endoscopy, but only about 50% specificity. Use of CT as the initial screening modality for the detection of varices was significantly cost effective compared to endoscopy irrespective of the prevalence of large varices. [144]

c- Capsule Endoscopy

New capsule endoscopy devices have been developed, specifically for use in the esophagus, acquiring images from both ends of the device. Several studies have been performed, assessing the ability of these capsule endoscopy devices to detect any varices and identify large varices requiring primary prophylaxis.[145,146]

Capsule endoscopy is reported to be feasible in 94–99% of patients with the main reasons for failure being because patients were unable to swallow the capsule or due to technical problems with the recording or function of the capsule. Adverse events have been reported in 0–1.4% of cases, including episodes of capsule retention necessitating removal. Tolerability of the capsule is found to be better than conventional OGD, with better preprocedure perception and post procedure satisfaction.[147]

d- Transient Elastography(liver stiffness, fibroscan)

It is a noninvasive technique based on ultrasound wave propagation. It is painless, rapid, and easy to perform. Significant correlation between liver stiffness measurements and the presence of esophageal varices. In different studies the presence of large EV was predicted with a sensitivity 77%, specificity 85%, PPV 56%, and NPV 94%, and correctly classified 79% of patients so it may be useful as a screening test to identify patients in whom variceal screening is not required.(148)

III Predictive Scores

The most popular noninvasive ratios are platelet Count/spleen diameter ratio, right Lobe Liver albumin ratio and AST/ platelet index (APRI) neither of them could be used as a reliable screening test due to either different cut off points making them not reliable tests.

IV New markerse.g:

a- Nitric oxide

Some studies of cirrhotic patients examined the predictive capability of serum nitrate levels to detect esophageal varices. (149) Significant differences in serum nitrate levels were found between patients with large esophageal varices compared to patients without esophageal varices.

b- Vascular endothelial growth factor (VEGF)

As a noninvasive biomarker has only been investigated in a single study, and no correlation between VEGF levels and grade of esophageal varices was detected.(150)

c- Ammonia

One study has examined the role of blood ammonia concentrations in the noninvasive detection of esophageal varices. (151)In this study of 153 cirrhotic patients, a significant correlation was demonstrated between esophageal variceal grade and venous ammonia levels and this gave a sensitivity of 92% and a specificity of 60%.

Therefore, these variables associated are not accurate enough to be used as noninvasive markers of esophageal varices.

Based on all the available evidence to date, upper GI endoscopy remains the gold standard for the diagnosis of esophageal varices in cirrhotic patients despite its own limitations. Clinical, biochemical, and radiological parameters currently are not accurate enough to avoid screening endoscopy, due to the risks associated with missing patients with large esophageal varices. A screening test must be simple and inexpensive, cost effective and suitable for repeated measurement.

Glycated proteins

Glycation, i.e., the non-enzymatic addition of carbohydrate moieties to protein reactive residues, has been the subject of many studies over the last decade.

It is a general spontaneous process in proteins which has significant impact on their physical and functional properties.From several studies, it has become evident that protein glycation has important implications for protein activity, unfolding, and degradation, as well as for cell functioning. [152,153]

The changes in protein properties could be related to several pathological consequences such as diabetes millets, cataract, arteriosclerosis and Alzheimer's disease.

In vivo glycation has been described in proteins such as the lens crystallins, collagen, ferritin, apolipoprotein, and serum albumin. In addition to glucose, sugars such as galactose, fructose, ribose sialic acid, mannose, glucose 6-phosphate, glyceraldehydes , and fucose have been used in vitro as glycating agents, sometimes to fasten the process.

Among the proteins; glycation of heamoglobin and Human serum albumin (HSA) are of special interest.[154]

➢ Glycated Hemoglobin

It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Glycated hemoglobin, intermediary compound is reversible but after some internal rearrangement of the compound, a stable HbA1c is formed. [155]

Several glycation sites of the HbA molecule exist; N-terminal valine residue of the beta chain is the predominant glycation site, accounting for 60% of bound glucose. There are three types of HbA1 namely; HbA1a, HbA1b, and HbA1c. HbA1c represents the most prevalent glycated species.

It is measured primarily to identify the average plasma glucose concentration over prolonged periods of time.[156,157] HbA1c has been accepted as the gold standard measurement for the assessment of chronic hyperglycaemia for nearly three decades.

Normal levels of glucose produce a normal amount of glycated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycated hemoglobin increases in a predictable way.[158]

In the normal about 120-day lifespan of the red blood cell, glucose molecules react with hemoglobin, forming glycated hemoglobin. Once a hemoglobin molecule is glycated, it remains that way.

Glycated hemoglobin acquires importance as a test for glycaemia because it has less intraindividual variation and is a better predictor of cardiovascular complications compared to fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT). In addition, it is used for glucose monitoring of diabetic patients. [159,160]

However, several studies have reported that in some case, HbA1C values should be considered cautiously. As a matter of fact, glycated hemoglobin levels have invalid correlation to blood glucose levels in patients with hemolytic anemia, or those having hemodialysis or iron deficiency aneamia. HbA1c gives incorrect values and is not suitable marker as a control.[161,162]

Glycated Albumin

Human serum albumin is the most abundant protein in the plasma. It represents about 50% of the normal individual's plasma protein. [163]. It is produced in the liver with a widevariety of physiological functions. The reference range for albumin concentrations in blood is 3.4 to 5.4 g/dL.

Its serum half-life of approximately 21 days and a structurally; It is soluble, monomeric and it is one of longest known proteins of plasma [164] its molecular mass is of 67 kDa. The protein is organized into three domains, I, II and III, each subdivided into two subdomains, A and B,[165] with 17 intramolecular disulfide bonds which makes it suitable for a wide variety of modifications including response to pH and other biophysical compounds. [166]

Normally about 10% of the albumin in normal human serum is modified by nonenzymatic glycosylation. [167]

Because of its high sensitivity for glycation, it undergoes structural and functional changes due to binding of reducing sugars in vitro.[168]

The glycation process occurs by plasma glucose in vivo which has great impacts on the three dimensional structure of protein. These changes are efficient and stable enough which makes the protein to be considered as a new special disease marker instead of HbA1C for diabetes in which it is markedly elevated, [169,170] It reflects the plasma glucose level during the past few weeks, because the turnover of albumin is about 3 weeks.[171,172]

➢ Glycatedalbmuin versus glycated hemoglobin

Advantage of glycated albumin is based on two facts. First, the amount of in vivo non enzymatic glycation of albumin is approximately 9 times more than HbA1C. [173] Secondly, albumin glycation reaction occurs ten times more quickly than hemoglobin glycation[174]so, the glycation phenomenon in plasmatic protein occurs more easily than hemoglobin, which all make the glycated albumin a good additional marker for evaluating glycemic control in type 1 and 2 diabetes. [175]Also it has advantage over HbA1c that it could not to be easily altered by abnormal hemoglobin metabolism. [176]

On the other hand in cases of thyroid dysfunction, nephrotic syndrome or liver cirrhosis in which the amounts of albumin is affected, and so, glycated albumin level is not a suitable indicator [177] Similarly, glycated albumin could be influenced by other conditions, such as body mass index (BMI) [178] or the age of diabetic patients[179]Therefore a combined detection of HbA1C and glycated albumin may improve the efficacy of diagnosis and improvement of a novel therapeutic potential [180].

Glycated albumin to glycated hemoglobin ratio (GA/HbA1c)

Different studies has focused on the usefulness of the GA/HbA1c ratio in diabetes treatment as a marker to reflect glycemic excursions.[180,181]

Although the ratio of GA/HbA1c is usually close to 3, the value changes based on the patient's condition.[182] In patients with chronic liver disease (CLD), hypersplenism causes a shortened lifespan of erythrocytes, leading to lower HbA1c levels relative to the plasma glucose level. In contrast, the turnover periods of serum albumin in CLD patients is prolonged in order to compensate for the reduced production of albumin. Therefore, the GA levels in CLD patients are higher relative to the degree of glycemia.[182]

Since the HbA1c level is lower and the GA shows higher values, the GA/HbA1c ratio is assumed to be increased in CLD patients, especially in cirrhotic patients. In fact, the GA/HbA1c ratio in patients with CLD has been reported to show a reciprocal correlation with some indicators of hepatic function, irrespective of the mean plasma glucose levels,[183] thus suggesting that the GA/HbA1c ratio increases as the liver cirrhosis progresses.[183]However, few studies were done in this issue.