ABSTRACT
Cirrhosis is a dynamic process that leads to progressive liver failure with development of portal hypertension and associated complications. Our current understanding of cirrhosis has come a long way from the time Rene Laennec first coined the term. Cirrhosis can be diagnosed with conformity utilizing histology, a trend that is changing in the current era of hemodynamic studies. To understand cirrhosis and its evolutionary stages, we must first understand fibrosis, its subsequent progression and associated hemodynamic changes at each level. In this review, we discuss stages of cirrhosis from an investigational, imaging, histological and hemodynamic point of view; discuss the diagnosis of cirrhosis within the same aspects and in keeping with current changing scenarios.

KEYWORDS: Cirrhosis, portal hypertension, HVPG, fibrosis, HCV, HBV, NASH

Introduction
Cirrhosis (coined by Rene Laennec; Greek word kirrhos meaning tawny-yellow-brown color) is the end stage in the spectrum of chronic liver disease, leading to gross hepatic angio-architectural changes due to failed purposeful parenchymal regeneration with nodular transformation, intrahepatic vascular shunt formation (afferent: portal vein and hepatic artery; efferent: hepatic vein) and increase in intrahepatic resistance promoting portal hypertension (PHT). Traditionally classified as micronodular (< 3mm size regenerative nodules), macro-nodular or mixed, cirrhosis is more than just the appearance. Earlier, cirrhosis was considered progressive and irreversible, eventually leading to death related to PHT. Currently, it is described as many dynamic components acting together such that every aspect related to different etiologies have a different progression, clinical outcome, and prognosis. Currently, an etiology-driven approach to understanding and managing cirrhosis is soon becoming a reality, and the term would soon be ‘cirrhoses’ rather than cirrhosis.

Stages of cirrhosis
Initially, cirrhosis was considered a 3-stage event but was later modified to 5 stages (D’Amico and co-workers, 2010) [1]. In the modified D’Amico classification, patients in Stage 1 are compensated and without esophageal varices (EV). Approximately 6.2% patients in this stage exit to Stage 2 annually because of the development of EV and 4.2% mostly because of ascites (cumulative rate of exit to Stage 2 is 11.9% per year). In Stage 3, there is variceal bleeding in the absence of other decompensating events. Patients in Stage 4 are the ones who develop ascites, jaundice or encephalopathy and those in Stage 5 have an advanced liver disease with multiple decompensation events, predisposing to sepsis and rapid progression to multi-organ-failure (a Stage 6). This staging of cirrhosis is currently endorsed by the Baveno VI.[2] The one-year mortality rates stages 1, 2, 3, 4 and 5 are < 1%, 3% – 4%, 20%, 50% and > 60% respectively [2, 3, 4]. The benefits of this staging over the Child-Pugh system is its cumulative nature. A patient in a particular stage will always remain in that stage or progress to another stage until transplant or death. Identifying, describing and modifying risks that lead to advancement in stages makes a clinical decision and management algorithms easier, than with conventional Child staging. It has also been
shown that stages of cirrhosis correlate well with outcomes in patients who have lower MELD scores, on transplant wait list. D’Amico cirrhosis stages can help identify at-risk patients developing liver-related events despite a low MELD score.[3] A better classification of cirrhosis is one in which clinical, histological and hemodynamic parameters culminate (Figure 1A). The hemodynamic component in cirrhosis is an important driver of disease progression and clinical events. The hepatic venous pressure gradient (HVPG) is currently the gold standard for the diagnosis of cirrhosis and prediction/prognostication of PHT complications. Liver biopsy is invasive, could have erroneous sampling and a single core of liver tissue cannot fully represent the true nature of chronicity in the liver. However, the HVPG can, as it represents a larger part of the diseased liver. An HVPG > 6 mm Hg is diagnostic of sinusoidal PHT and more than 10 mm Hg is suggestive of clinically significant PHT (CSPH). The ideal classification of cirrhosis should include compensated cirrhosis without varices (Stage 1) or with varices (Stage 2) and further refined with presence or absence of subclinical or CSPH. Furthermore, in Stages 3 to 5, clinical aspects of decompensation should also include the degree PHT. Histological aspects in these stages might not be as important as in the initial stages.[3, 4]

Biochemical diagnosis of fibrosis and cirrhosis

The presence of thrombocytopenia (in the absence of another underlying condition such as paroxysmal nocturnal hemoglobinuria or idiopathic thrombocytopenia and others) is the single most useful laboratory parameter in the diagnosis of cirrhosis. A threshold of < 160 x 10³/ microliter has the highest diagnostic accuracy with a positive likelihood ratio 6.3 with a narrow confidence interval of 4.3 – 8.3. Apart from this, a serum albumin < 3.5 g/dl or INR > 1.5, globulin to albumin ratio or aspartate transaminase (AST) to alanine transaminase (ALT) ratio ≥ 1 also had a positive likelihood index of more than 3 to 4 in various studies [2, 4]. Serum markers of liver fibrosis are divided into Class I (direct markers, subcategorized into collagen and related markers, enzymatic markers, glycosaminoglycan markers, matrix-metalloproteinase markers, and glycoproteins) that reflects molecular pathogenesis and turnover of liver extracellular matrix (ECM), the primary sources being the hepatic stellate cells (HSCs) and myofibroblasts. Class II (or indirect biomarkers) reflect fibrosis activity through measurement of liver function and injury and includes, transaminases and γ-glutamyl transpeptidase (GGT), bilirubin, prothrombin time, apolipoprotein A1, albumin, haptoglobin, α2-macroglobulin, transferrin, hepcidin and ceruloplasmin and adipokines.[5] Better scores for diagnosing cirrhosis come from combination of multiple investigations that include ratios and principal scoring systems such as – the AST to ALT ratio > 1 and an AST to platelet ratio index [(APRI) > 2.9 increases the likelihood of cirrhosis]. The modified Bonacini cirrhosis discriminant score, a combination of ALT:AST ratio, platelet count, and INR are considered with total scores ranging from 0 to 11. A score more than 7 is more likely and < 3 is less likely of cirrhosis. Originally derived from the HALT-C trial, the Lok Index is an odds ratio of probabilities between 0 and 1 utilizing a logistic model with an index of < 0.2 indicating lower likelihood of cirrhosis.[6, 7] Similarly, the Forns index, (age, platelet count, and cholesterol and γ-glutamyl transferase) is useful in differentiating mild from advanced fibrosis, but is less accurate for distinguishing patients within the latter; the PGAA index correlated with both inflammation and fibrosis but is less accurate in detecting cirrhosis (66-72%). The Göteborg University Cirrhosis Index, with a cut-off value of 1.0 had a sen-
sitivity of 80% and specificity 78% for the diagnosis of cirrhosis with negative and positive predictive values of 97% and 31%, respectively in chronic hepatitis C patients [7, 8]. The King’s Score (age x AST x INR / platelets), predicts cirrhosis with scores ≥ 16.7 with sensitivity 86%, specificity 80% and a high negative predictive value of 96% and a score ≥ 12.3 predicting fibrosis (F3-6). The HALT-C model (platelet count, AST/ALT ratio, and INR), with a cut-off, predicted value of < 0.2 excluded cirrhosis, while > 0.5 identified patients with cirrhosis.[8, 9, 10] FIB-4 is a scoring system not affected by body mass index. In patients with HCV, an index < 1.45 had a negative predictive value of 95% and sensitivity of 74% in diagnosing cirrhosis whereas in HBV patients, score > 5.17 and in non-alcoholic steatohepatitis related cirrhosis a cut off > 2.67 predicted cirrhosis. Fibrotest or Fibrosure, a combination of α2-macroglobulin, apolipoprotein A1, haptoglobin, bilirubin and GGT utilizes a cut off > 0.75 for diagnosis of cirrhosis but has high false positive rates in the presence of hemolytic diseases or Gilbert’s syndrome (present in 3-7% of general population). Research tools include hyaluronic acid (HA), laminin, fibronectin, matrix-metalloproteinases and tissue inhibitors of matrix metalloproteinases (TIMPs).

Other biochemical evaluation scores include HepaScore (score 0-1, higher score, cirrhosis likely, <0.5 biopsy can be avoided in patients who are apprehensive of the same); Enhanced Liver Fibrosis (ELF) score (cut-off >9.3 sensitivity 93%, specificity 86% for cirrhosis) [7, 9, 10] and Fibrometer (represents amount of fibrosis as percentage of fibrous tissue in liver corresponding to METAVIR histologic staging).[11, 12]

Imaging diagnosis of cirrhosis

Ultrasonographic findings include (US), liver surface irregularity (88% sensitive), increased sound attenuation, diffuse heterogeneous/coarsened echotexture, nodularity along deep surfaces of liver, lobar redistribution – atrophy of right lobe and relative hypertrophy of caudate lobe (transverse diameter of caudate: right lobe > 0.6 has diagnostic accuracy of 94% for cirrhosis) [13], bluntness scoring of liver edge, scoring of surface pattern and internal echogenic bands, portal vein diameter > 13 mm with hepatofugal flow, loss of fluctuation of portal flow during respiration (<15 cm/sec), biphasic or monophasic pattern in hepatic veins, increased hepatic artery resistive index, portal vein congestion index, presence of ascites, splenomegaly and recanalized paraumbilical vein. On contrast-enhanced US reduction in hepatic vein transit time (measurement of time of onset of hepatic vein enhancement after microbubble contrast injection) and liver parenchymal enhancement in late phase is highly sensitive for diagnosis of cirrhosis, correlating negatively with severity. On CT, findings such as enlargement of hilar periportal space and increased fatty tissue in porta-hepatis, nodular hepatic margins, atrophy of right hepatic lobe, medial segments of left hepatic lobe, widening of gallbladder fossa, hypertrophy of lateral segments of left hepatic and caudate lobes, widening of interlobar fissures, presence of regenerative nodules, prominent mesen-
Table 1 Salient features in diagnosis of cirrhosis.

<table>
<thead>
<tr>
<th>Biochemical</th>
<th>Imaging</th>
<th>Histologic</th>
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| Thrombocytopenia <160 x 103/microliter | USG,  
- Liver surface irregularity  
- Diffuse heterogenous echotexture  
- Nodularity  
- Atrophy of right lobe  
- Relative hypertrophy of caudate lobe  
- Transverse diameter of caudate: right lobe ratio >0.6,  
- Portal vein diameter >13 mm  
- Biphasic or mono-phasical pattern in hepatic veins  
- Recanalization of para-umbilical vein | Extensive fibrosis |
| Serum albumin <3.5 g/dl or INR >1.5 | CT,  
- Enlargement of hilar periportal space  
- Increased fatty tissue in porta-hepatis  
- Nodular hepatic margins  
- Atrophy of right hepatic lobe  
- Atrophy of medial segments of left hepatic lobe  
- Widening of gallbladder fossa  
- Hypertrophy of lateral segments of left hepatic and caudate lobes  
- Widening of interlobar fissures  
- Presence of regenerative nodules | Parenchymal nodules  
Hepatic architecture distortion |
| Globulin to albumin ratio or AST to ALT ratio ≥ 1 | MRI,  
- Fibrotic septae low T1 and high T2 intensity | Aberrant angiogenicity |
| AST to ALT ratio >1 | Elastography imaging,  
Liver stiffness >12 to 14 kPa | Presence of intravascular shunts |
| AST to platelet ratio index >29 (APRI score) | | Capillarisation |
| Modified Bonacini cirrhosis discriminant score >7 | | Hepatocyte microvilli loss |
| Lok Index odds ratio >0.2 | | Paucity of endothelial fenestration |
| Goteborg University Cirrhosis Index ≥ 1.0 | | Deposition of Type I and Type III collagen within the sinusoids and portal tracts |
Histologic diagnosis of fibrosis and cirrhosis

Liver biopsy was considered the gold standard in diagnosing cirrhosis. An adequate diagnostic specimen should be at least 1.5 cm in length with at least 6 to 8 complete portal tracts. An ideal specimen should be 2 to 2.5 cm in length and contain 11 complete portal tracts to assess grading and staging to reduce sampling errors.[11] Histological diagnosis encompasses four most important aspects – extensive fibrosis, parenchymal nodules with hepatic architecture distortion, aberrant angiogenic and presence of intravascular shunts.[12] The sub-endothelial space of Disse consists of basement membrane matrix which is not electron dense, composed of non-fibrillar forming collagens type IV, VI and XIV along with glycoproteins and proteoglycans. The liver also contains interstitial ECM which is mostly situated in the capsule, around large vessels and portal tracts composed of fibrillar-forming collagens type I and III. In liver fibrosis and cirrhosis, there is a shift in the type of ECM in the sub-endothelial space from normal electron non-dense basement membrane like a matrix to the interstitial type matrix, a process known as capitalization leading to hepatocyte microvilli loss and the paucity of endothelial fenestration.[14] The initial step in fibrosis is an accumulation of ECM within space of Disse and in the portal tracts. Approximately 3% of ECM deposition is seen in a normal liver. This increases to above 15% in cirrhosis. Fibrosis is mainly associated with deposition of Type I and Type III collagen within the sinusoids and portal tracts leading to activation of fibro-potent cells such as HSCs (activated myofibroblasts) and portal fibroblasts. In later stages, the quantity and quality of ECM changes and liver contain around six times more ECM than normal. There is increased synthesis and decreased degradation due to increase in levels of tissue inhibitor of matrix metalloproteinases (MMP, TIMPs).[16,17,18] This leads to cirrhosis, with abnormally vascularized fibrous septa communicating between

**Table 2 Salient features in diagnosis of cirrhosis. Continued of Table 1.**

<table>
<thead>
<tr>
<th>Biochemical</th>
<th>Imaging</th>
<th>Histologic</th>
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<tr>
<td>The King’s Score $\geq$ 16.7</td>
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<td>HALT-C model &gt;0.5</td>
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<td>Fibrotest or Fibrosure &gt;0.75</td>
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<tr>
<td>Enhanced Liver Fibrosis (ELF) score &gt;9.3</td>
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*INR – international normalized ratio; AST – aspartate transaminase; ALT – alanine transaminase;
APRI score (AST/Platelet ratio index) - [(AST/ULN) x 100]/platelet count 109/L where ULN = the upper limit of normal;
Bonacini Cirrhosis Score - Platelet + ALT to AST Ratio + INR;
HALT-C Index - Log odds = - 5.56 – 0.0089 x platelet count (103/mm3) + 1.26 x (AST/ALT) + 5.27 x INR;
Lok Index - [exp (log-odds)]/[1 + exp (logodds)];
Goteborg University Cirrhosis Index - (AST / ULN-AST) x INR x 100 / Platelets;
King’s Score - age x AST x INR / platelets;
Fibrotest score - ( Age x AST ) / (Platelets x ( sQR ( ALT ) );
ELF score - ELF score = 2.494 + 0.846 ln(CHA) + 0.735 ln(CP3NP) + 0.391 ln(CTIMP1),
where ln is logarithmic, HA is hyaluronic acid, PIIINP is amino-terminal propeptide of type III procollagen and TIMP-1 is tissue inhibitor of metalloproteinase 1;
USG – ultrasonography; CT – computed tomography; MRI – magnetic resonance imaging; kPa – kilopascals.
Figure 3: Histology of fibrosis and cirrhosis – A (Masson Trichrome staining, 40X) – F1 fibrosis, B – F2 fibrosis, C – F3 fibrosis and D – F4 (cirrhosis) fibrosis; E – Cirrhosis, definite; F – Portal to central fibrosis; G1 – Stage 4A of Laennec stage of cirrhosis, G2 – Stage 4B of Laennec stage of cirrhosis, G3 – Stage 4C of Leannec stage of cirrhosis; H – Septal cirrhosis; I and K – Regression of cirrhosis with incomplete septa formation, loss of nodularity and regeneration of hepatocytes with central vein formations; J – Pericellular (chicken-wire) fibrosis.

portal tracts and central veins resulting in nodules without central veins surrounded by fibrotic bands. Angio-architectural distortion leads to shunting of blood between portal vein and artery causing disruptive gas exchange between sinusoids and liver parenchyma. Pathologically modified sinusoids (endothelial cells) become central to portal flow resistance, acquiring a vasoconstrictor phenotype secondary to heightened sensitivity to endogenous vasoconstrictors with decreased production of intrahepatic nitric oxide (NO; multifactorial reasons including, low endothelial NO synthetase activity due to caveolin-1 interaction and intrahepatic oxidative stress secondary to reduction in superoxide dismutase). Increased HSC activation, migration and actin restructuring (formation of lamellipodia and filopodia, thin filamentous cellular extensions) leads to enhanced daubing of sinusoids and remodeling. This progressive insult results in abnormal angiogenesis, intrahepatic micro-collateral circulation formation, constrictio of the sinusoidal vasculature, augmented hepatic vascular resistance and early development of intrahepatic PHT. [19, 20, 21] Histology of chronic liver disease is important in the evaluation of etiology of liver disease rather than a diagnosis of cirrhosis. In chronic biliary pathology, the fibrosis follows a portal to the portal direction leading to the portal to portal septa formation surrounding liver nodules and central vein to portal vein connections are maintained until late stages (centrilobular vein involved late, pre-sinusoidal hypertension). In chronic viral hepatitis and autoimmune hepatitis, the fibrosis follows a portal to central vein pattern and results in the portal to central septa (bridging fibrosis), with interface hepatitis leading to the portal to portal septa, a pattern that leads to rapid vascular disorganization and early PHT. In patients with hepatic outflow tract obstruction, the fibrosis is central to central veins in pattern and leads to central septa and reverse lobulation. ‘Chicken wire’ fibrosis or pericellular or sinusoidal fibrosis are seen in alcoholic, non-alcoholic steatohepatitis and metabolic liver diseases.[22, 23, 24] Fibrosis is usually assessed with trichrome and reticulin stains, and collagen deposition is utilizing Sirius stain. Recently, digital image analysis such as FibroQuant (area of fibrosis is measured by dividing the different areas such as peri-sinusoidal, portal-peri-portal, septal fibrosis, portal vessel and biliary ductal lumen areas are quantified digitally) are upcoming. Formulas are used to calculate percentage area of portal to periportal or septal fibrosis. CSPH correlates with septal thickness (cut off for thin versus thick septa is 169.0 micrometers) and small nodularity which is independent predictors. The median septal width of all fibrous septa per slide was greater in patients who developed decompensation, compared with those who remained compensated (212.56 micrometers vs. 156.59 micrometers).[25, 26] [Figure 3]. The salient features for diagnosing cirrhosis are shown in Table 1 and Table 2.

Histological assessment of fibrosis and cirrhosis: evolution of the staging and grading systems

Knodell in 1981 first described the histologic scoring system for chronic hepatitis. He utilized four histopathological aspects – perportal ± bridging necrosis, intralobular or focal necrosis, portal inflammation and fibrosis.[27] Further studies realized that fibrosis was a consequence of histological activity index (HAI)
rather than its components. Newer scoring systems were subsequently developed that used grades (to measure necroinflammatory activity) and staged (fibrosis and hepatic architectural changes). These systems used scales of 4, 5 or 7 to categorize staging of cirrhosis. Complex scoring systems include Knodell or Ishak and are primarily used in the major clinical trials. Other scoring systems such as Batts and Ludwig and METAVIR are used in day to day clinical practice. The main components of inflammatory activity include lobular necroinflammation, portal inflamation, and piecemeal lymphocytic necrosis. Similarly, fibrosis components include the length in the expansion of fibrotic areas between portal tracts. A brief overview of these systems is shown in Figure 1B and 1C. The Laennec staging is a modified METAVIR system subdividing stage 4 into 4A, 4B and 4C based on thickness of septa and nodule size, that is validated to correlate with HVPG, severity of cirrhosis, decompensation events, and hepatoma occurrence better than other systems.[28-32] Even though not fully defined, incomplete septal cirrhosis is a form of macronodular cirrhosis comprising of fine and incomplete septa, which delimit rudimentary regeneration nodules. It is found to be associated with various diseases such as idiopathic portal hypertension, regenerative nodular hyperplasia, and partial non-cirrhotic nodular transformation and is also seen with progression or regression of cirrhosis of any etiology.[33]

**Reversibility of fibrosis and cirrhosis**

Contrary to old beliefs, fibrosis and cirrhosis are reversible. Etiology of cirrhosis, stage of fibrosis and affected patient demography are important aspects in determining regression. The main components of regression include thinning of fibrous septa, hepatocyte regeneration, and restoration of lobular architecture from a nodular one. Control of ongoing inflammation and injury in the liver results in degradation of accumulated ECM proteins. The first step in this is a reduction in some activated HSCs by way of apoptosis, senescence or reversion to an inactivated state. Failure to degrade fibrillary collagen along with an imbalance between MMP and TIMPs leads to accumulation of ECM. Macrophages and HSCs are main producers of MMP-2, 9 and 13. The former inhibits type 1 collagen production, promoting apoptosis of HSCs. Macrophages are important in progression (M2 phenotype> M1) of inflammation-fibrosis and reversal of fibrosis (M1-M2, intermediate). Products of collagen degradation such as peptide E4 (or endostatin; Endostar, a human recombinant endostatin is currently utilized in antifibrotic mouse model studies) reduces fibrosis by reducing levels of lysyl oxidase (collagen cross-linking enzyme). Macrophages undergo a state known as pro-resolution and express gene products such as MMP-9 and TRAIL that promote myofibroblast apoptosis. These restorative groups of macrophages are identified as CD11b-hiF4/80intLY6C-low and are less proinflammatory and up-regulate CX3C-chemokine receptor 1 and arginase one that is anti-fibrotic. Reversal of fibrosis (improved METAVIR score, usually a -1 or -2 decrease in score) or regression of cirrhosis (≥ 1 unit decrement in Ishak score) is seen mostly with viral etiologies (with antiviral use), young patients and those without vascular thrombosis on histology. This reversal dilemma is best explained with Laennec staging of cirrhosis, in which, to simply put, Stage 4C to lower stages is unlikely.[34, 35, 36] (Figure 3)

In summary, the understanding of cirrhosis is changing. Future management will be based on traditional treatments combined with anti-fibrotic therapies targeting histological subclassification. Defining prognosis and natural history of cirrhosis will replace the current ‘singular’ natural history theory. Progress in current medical knowledge will soon make an irreversible entity reversible, with better outcomes contrary to old beliefs.

**Authors’ Statements**

**Competing Interests**

There were no financial support or relationships between the authors and any organization or professional bodies that could pose any conflict of interests.

**References**


