THE STRATIFICATION OF CIRRHOSIS

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ABSTRACT

Cirrhosis is traditionally seen as an irreversible stage of chronic liver disease although its clinical course may last several years. Overall, the clinical management of cirrhotic patients is based on the observation of clinical events mostly related to complication of portal hypertension. Each event of cirrhosis decompensation has clear prognostic implication although it is not precisely predictable. In practice, the advancement in the knowledge of the mechanisms responsible for disease progression is not yet translated in clinical tools allowing the stratification of the cirrhotic stage according to pathophysiological mechanisms. This article provides a review of the main clinical and histopathogical features of liver cirrhosis that are relevant for its clinical stratification together with the advancements provided by the introduction of non-invasive measures of portal hypertension. Other clinical aspects with a major impact of the quality of life and the possibility of liver transplantation are also discussed.

KEY WORDS: cirrhosis, hepatocellular carcinoma (HCC), hepatic venous pressure gradient (HVPG), elastography, sarcopenia, liver transplantation

INTRODUCTION

Cirrhosis is a clinical condition characterized by a progressive hepatic angio-architectural transformation in response to chronic tissue damage. Despite different etiologies (infectious, toxic, metabolic and autoimmune) and different patterns of fibrogenesis, the chronic inflammatory response, associated with a constant effort to replace progressive parenchymal extinction, leads to the formation of typical regenerative nodules[1], with capillarization of sinusoids, neo-angiogenesis and the establishment of portal hypertension (PH). Portal hypertension represents the main cause of the life-threatening complications of cirrhosis and constitutes a key mechanism leading to the progression of the disease[2]. Indeed, established PH causes further hepatocellular damage and leads to the formation of porto-systemic shunts bypassing the cirrhotic liver. These, together with an increased intestinal permeability give access to a gut-derived antigenic load entering the systemic circulation.[23] The long-term effect of this intestinal translocation is the establishment of a systemic pro-inflammatory background and a progressive functional immune paralysis, which is pivotal for the development of bacterial infections in patients with cirrhosis.[4]

Although the complexity of the mechanisms responsible of the progressive transformation of the cirrhotic liver has been in large part elucidated, this wealth of information is not yet translated in clinical tools allowing the stratification of the cirrhotic stage of chronic liver disease according to pathophysiological mechanisms. The current clinical classification of cirrhosis[5] depends of the observation of clinical manifestations, in which the development of hepatic decompensation heralds a dramatic decline in predicted survival. However, prognostication based on these crude clinical endpoints has limitations. First, it has been defined as "an expectant algorithm that treats complications" rather than preventing them.[6] Second, the distinction between compensated and decompensated cirrhosis based on the occurrence of clinical complications and the hepatic venous pressure gradient (HVPG), but not

on other potentially relevant biological events such as altered tissue regeneration and the progressive loss of specific liver functions, does not reflect the spectrum of different stages with a range of feasible and stage related therapeutic options.[5] Progress has been made in our ability to use integrated clinical-pathological assessments to make more accurate, patient-specific risk predictions to identify appropriate interventions, such as timing of variceal screening and introduction of etiology-specific treatments in the early stages of cirrhosis, and selection for liver transplantation in advanced disease. This review will focus on the tools currently available to stratify patients at different clinical stages of cirrhosis to aid clinical decision making, but conclude with briefly discussing future directions in targeting biomarkers derived from our increasingly detailed understanding of the underpinning pathophysiology. (Figure 1)

HISTOPATHOLOGICAL STAGING OF CIRRHOSIS

Different etiologies cause different patterns of fibrotic development and regeneration and have different rates of progression. Furthermore, the magnitude of architectural distortion and the resultant clinical implications vary in severity among patients and over time within each chronic liver disease.[7] At present, there is increasing recognition of the need for a pathophysiologic staging of cirrhosis that will incorporate the etiological, clinical, histologic, and hemodynamic findings of each particular patient.[8] In order to proceed in this direction, we need first to rely on an accurate pathological stratification of the cirrhotic process from its initial development to the end-stage evolution associate with liver failure. Along these lines, when employing semi-quantitative scoring systems, a major drawback is the representation of cirrhosis as a mono-stage (e.g. Metavir F4, Ishak 5-6)[9-10] although the clinical course of the disease has often many years for further pathological development and, in addition, the possibility of fibrosis regression if a suitable treatment is introduced. An attempt to provide a

more dynamic evaluation is represented by the introduction of the Laennec staging system, a modification of the METAVIR system.[11] This system subdivides cirrhosis into three groups (4A, 4B, and 4C) based on the thickness of the fibrous septa and the size of nodules and has shown an excellent performance in predicting liver related events (LRE) therefore stratifying these patients according to prognosis.[12] This observation is in agreement with the evidence that small parenchymal nodules and thick fibrous septa are associated with higher portal hypertension expressed as HVPG.[13] Furthermore, the past decade has witnessed the introduction of quantitative morphometric evaluation of fibrosis in cirrhotic liver tissue and particularly the introduction and validation of collagen proportionate area (CPA).[14] The study from the Royal Free Hospital published in 2014 demonstrated that cirrhosis can be accurately sub-classified using quantification of fibrosis with CPA, and furthermore CPA is the only independent predictor of clinical decompensation amongst all other histological sub-classification systems described to date.[15]

HVPG

Central to the progression of cirrhosis and its complications is the development of portal hypertension. For many years, this was attributed primarily to portal venous congestion secondary to resistance from a hard, cirrhotic liver. However, it is now clear that this is only part of the story; splanchnic vasodilation with increased flow into the portal circulation, hepatic vascular vasoconstriction and endothelial dysfunction all contribute to a pathological rise in portal pressure during advanced cirrhosis.[16]

The gold standard method of evaluating the severity of portal hypertension is the HVPG, calculated through accessing the hepatic vein (HV) and subtracting the free HV pressure from the wedged HV pressure. In the healthy liver, the wedged HV pressure will be lower than the portal pressure due to dissipation of blood behind the balloon catheter through the sinusoidal

system. However, the communication between sinusoids is blocked through the extensive fibrosis and disordered intrahepatic vasculature of cirrhosis, such that the transmission of pressure across the sinusoid accurately reflects the portal pressure.

It is now well established that the development of gastroesophageal varices (GOV) and risk of bleeding is associated with significantly higher HVPG. The normal HVPG is <5mmHg, and although an HVPG 5-10mmHg reflects a rise on portal pressures, complications only tend to occur >10-12mmHg. A seminal study investigating HVPG in patients with varices found that all cases who subsequently bled had an HVPG >12mHg.[17] Subsequently, a large post-hoc analysis of subjects from a beta-blocker trial demonstrated that the risk of clinical decompensation with ascites, jaundice, variceal hemorrhage or hepatic encephalopathy begins to increase above an HVPG 10mmHg.[18]

Regarding hepatocellular carcinoma (HCC), HVPG not only has important prognostic relevance but also informs treatment options. An HVPG >10mmHg confers a 6-fold increased risk of developing HCC,[19] while in those with an established HCC the option of a curative resection is diminished with significant portal hypertension through increased morbidity and mortality. Current European guidelines recommend a cut off HVPG ≤10mmHg to consider curative resection of HCC,[20] and an Asian cohort of patients with resection confirmed worse survival in patients with established portal hypertension.[21]

The importance of HVPG in determining risk of patients with cirrhosis has been supported in the trials investigating beta blockers that target the hyperdynamic splanchnic circulation in portal hypertension. In a meta-analysis of 12 studies including 779 subjects, even if the final HVPG was >12mmHg any HVPG reduction resulted in reduced risk of bleeding (OR 0.21 95% CI 0.10-0.45), although the greatest benefit was seen if HVPG <12mmHg was achieved (OR 0.14 95% CI 0.09-0.21).[22]

A large recent trial has also investigated the impact of beta- blockers in reducing any decompensating event, not just bleeding. All subjects had an HVPG measurement at baseline, from which 'responders' to propranolol (HVPG reduction ≥10%) were randomized to propranolol or placebo, and 'non-responders' to propranolol randomized to carvedilol or placebo. Through this trial design targeting HVPG reduction through beta-blockers, they demonstrated that lowering portal pressure reduced the risk not only of future bleeding but also ascites development.[23] These studies show that just as stratification by baseline HVPG has enormous clinical significance, so too does the degree of HVPG reduction through interventions such as beta-blockers.

NON- INVASIVE EVALUATION OF DISEASE PROGRESSION (REGRESSION?)

The introduction of non-invasive approaches to assess liver fibrosis has led to a major change in the clinical practice of Hepatology. The increasing number of such techniques in the past ten years has not only resulted in earlier detection of patients with hepatic fibrosis, but also new models for the stratification, prognostication and treatment of patients with chronic liver diseases.[24] The tools available for non-invasive assessment of fibrosis range from simple scores calculated from routine laboratory parameters or biochemical tests related to the fibrotic changes in the liver, to elastography techniques to obtain a liver stiffness measurement (LSM). These methods were initially introduced to overcome the disadvantages inherent in liver biopsy/histology and HVPG measurement. However, the diagnostic efficacy of non-invasive tests has in many situations gone beyond the initial purpose of assessing the extent of fibrosis, to predicting the consequences of chronic liver disease including portal hypertensive complications and the development of HCC.[25] Overall, it is rather clear that serum markers, LSM as well as standard imaging techniques perform quite well in advanced fibrosis and cirrhosis and,

accordingly, these systems could be proposed for the stratification of cirrhosis. In particular, liver elastography performed either with FibroScan (transient elastography) or ultrasound shear-wave elastography (SWE) has greatly enhanced the likelihood of early diagnosis and the stratification of cirrhosis, facilitating the identification of patients with compensated disease who are at high risk of complications, prior to the occurrence of decompensation. Liver stiffness and more recently spleen stiffness, measured by various ultrasound elastography methods,[26] reflects the severity of liver disease and portal hypertension in patients with compensated cirrhosis.[27] In addition, elastography allows the diagnosis of clinically significant portal hypertension (CSPH; i.e. HVPG $\geq$ 10 mmHg) with an accuracy greater than 80% when using a binary cut-off approach.[28] A major drawback of these methodologies is represented by the lack of ability to monitor the effect of therapy on portal pressure. Indeed, none of the currently available non-invasive tests shows sufficient accuracy in mirroring the HVPG response. Encouraging results, although requiring further validation, emerge from a study suggesting that changes in spleen stiffness (measured by point SWE) might parallel changes in HVPG and portal pressure gradient after non selective beta blockers (NSBB) and TIPS.[29] With the continuous introduction of more and more sophisticated techniques, it is possible that methods such as subharmonic aided pressure estimation on contrast-enhanced ultrasound,[30] as well as non-invasive measurements derived by parameters from contrast-enhanced ultrasound[29] or magnetic resonance imaging[32,33] will rapidly provide further and consistent advancements.

FRAILTY AND SARCOPENIA

Frailty describes a condition of poor physiological reserve leading to increased vulnerability to stressors such as acute medical illnesses.[34] A central feature of frailty is sarcopenia, the

disproportionate depletion of skeletal muscle. Patients with cirrhosis are particularly vulnerable to developing sarcopenia due to increased gluconeogenesis from skeletal muscle protein, combined with impaired oral intake through repeated cycles of acute illness and chronic complications such as hepatic encephalopathy and severe ascites. The development of frailty in cirrhosis, however, is multifactorial and includes the systemic effects of progressive hepatic dysfunction, co-morbidities, age and reduced mobility.[35]

Quantitative assessment of the severity of frailty and sarcopenia has important prognostic implications in cirrhosis, particularly when regarding decisions on listing and prioritization for liver transplantation. Using established tools such as the Fried Frailty Instrument, one study on liver transplant candidates found that markers of frailty predicted wait-list mortality independently of MELD score.[34] The same group subsequently developed a Frailty Index incorporating gender, grip strength, chair stands and balance time. Combined with MELD-Na, the Frailty Index improved predictions of 3-month waitlist mortality compared to MELD-Na alone.[36] Similarly, imaging can be utilized to quantify muscle mass and thus the degree of sarcopenia in cirrhotic patients, such as the skeletal muscle index (SMI) derived from a measure of skeletal muscle surface area at the L3 level using CT scanning. For example, in one study of patients on the transplant wait-list, optimal cut-offs for predicting wait-list mortality were $50cm^2/m^2$ for men and $39cm^2/m^2$ for women.[37]

Applying these measures of frailty and sarcopenia has several advantages in the management of cirrhosis. First, they provide a focus for treatment, identifying the patients most in need of targeted nutrition and exercise therapy, particularly during the process of optimization for LT. Second, the decision to list a patient for LT has always involved some assessment of 'fitness' to undergo such a major operation, but these judgments can be subjective and prone to significant variability between clinicians and centers. Risk stratification using validated scores of frailty and sarcopenia can add objectivity to the 'end-of-the-bed' test and inform the consent

process if a patient may be considered high risk.[38] Conversely, techniques such as SMI could be used to assess a patient considered for LT who may be acutely ill but whose underlying physiological reserve is under represented by functional tests.[39]

LIVER TRANSPLANT: DECISIONS OVER WHO TO LIST

The only curative option for patients with advanced cirrhosis is liver transplantation (LT). All patients with features of hepatic decompensation should be considered for LT**,** [40] and the eligibility criteria for listing a patient with cirrhosis are usually based on scoring systems calculating the severity of hepatic dysfunction. The MELD score, originally designed to predict outcomes following TIPS for gastrointestinal bleeding but validated in the transplant setting, is based on renal function, bilirubin, INR and latterly sodium (from 2016) and was introduced in the USA (2002) and Eurotransplant region (2003) to stratify potential LT candidates.[41] In the UK the UKELD score is used, although the components are similar**.**[42] In both instances, cut-off scores (MELD ≥15, UKELD ≥49) are set based on the point at which one- year mortality from cirrhosis exceeds that predicted from LT (about 9%).

However, demand for LT always exceeds organ availability; therefore, some assessment of utility is also required to prioritize patients on the waiting list. Over the years, the systems for managing waiting lists and prioritizing sick patients, primarily using the MELD score, has been refined and reduced waitlist mortality. In the UK, new system of national organ allocation was introduced in 2018 in which named offers are now made in individuals based on the 'Transplant Benefit Score,' an algorithm based on 21 recipient and 7 donor characteristic designed to maximize the years of life gained with the organs available.[43]

An important and controversial concept in the stratification and prioritization of patients for LT is that of futility. Is there a point at which the patient is too sick to transplant, where death is inevitable or the anticipated gain in survival is insufficient to justify use of a scarce organ?

An active area of debate on this subject is in patients with acute-on-chronic liver failure (ACLF), defined as decompensated cirrhosis with one or more organ failures and signaling a phase of rapid clinical deterioration and poor prognosis. The CLIF-C OF Score, derived from the landmark CANONIC study, has shown superior mortality predictions compared to MELD and is based on six organ systems (liver, kidney, coagulation, brain, respiration, circulation).[44] Survival of patients with ACLF-3 (i.e. 3 organ failure) is dismal with a 90-day mortality of 75%, and emerging data from large retrospective cohorts has begun to challenge the dogma that the patient with multi-organ failure is 'too sick to transplant,' demonstrating survival rates of up to 80% at 1 year post LT.[45,46] The challenge is that these patients often have a narrow window of opportunity for LT and current allocation systems would need to be modified to prioritize these patients more effectively and make this a feasible and effective option.[41,47]

FUTURE DIRECTIONS

Overall, clinicians currently have at their disposal various diagnostic investigations and clinical algorithms to enhance their ability to stratify risk of decompensation and death in patients with cirrhosis, enhancing decisions making in the selection of appropriate patients for screening, disease-modification treatment and liver transplantation. However, there remains a large discrepancy between the accumulated knowledge on the pathophysiology of chronic liver diseases and the translation of this knowledge in clinical tools allowing a better staging of disease progression within the stage of cirrhosis. Indeed, the current methodology of stratification is based on clinical manifestations with a limited ability to predict the next stage of progression. While elastography is growing exponentially as diagnostic and prognostic tool, clinical biomarkers able to monitor the worsening of key functions such has systemic haemodynamics, innate and acquired immunity and more in general a state of systemic

inflammation would greatly improve the management of both compensated and decompensated cirrhosis.

Conclusions

Cirrhosis is not a single entity but rather represents a spectrum of disease severity. Advances in our understanding of the pathophysiological mechanisms and multi-system complications have led to the development of more detailed diagnostic tests and clinical scoring systems to provide clinicians with nuanced and accurate prognostication. At the most severe end, this supports complex decisions around listing for LT, but also provides opportunities to prevent the development of such complications through identification and treatment of cirrhosis in its earlier stages.

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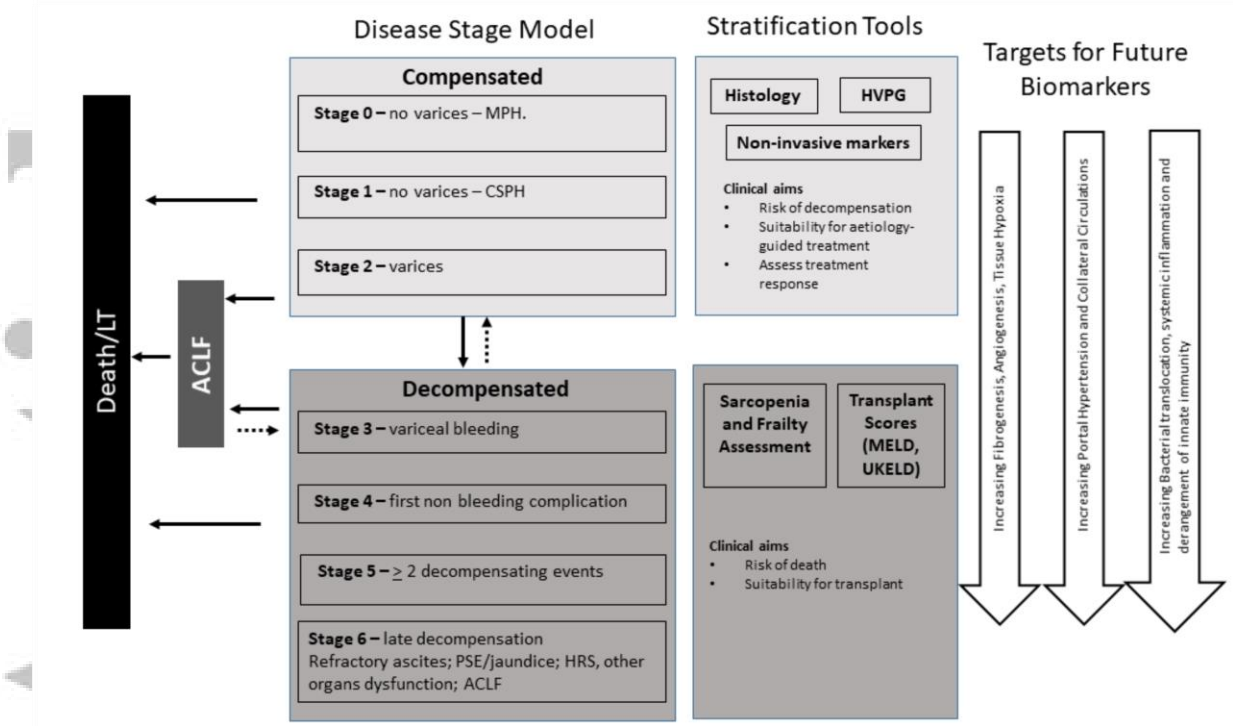

Figure 1: The Multi-stage model of the clinical course of liver cirrhosis, with current stratification tools and
targets for future biomarkers. Based on D' Amico G. et al., J Hepatol 2018; 68: 563–576. MPH: mild portal
hypertension; TE: Transient elastography; HVPG: hepatic venous pressure gradient; CSPH: clinically
significant portal hypertension; LT: liver transplantation; ACLF: acute on chronic liver failure; MELD: Model
for End Stage Liver Disease; UKELD: UK End Stage Liver Disease.