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Understanding New Nomenclature in Advanced Chronic Liver Disease

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As understanding of disease processes in medicine evolves, terminology must often evolve too. Terminology related to cirrhosis has been changing to better capture the spectrum of liver disease and patients' progression along that spectrum that is not adequately captured by the terms "compensated cirrhosis" and "decompensated cirrhosis" alone. This article aims to review this newer terminology that has emerged over the past several years regarding portal hypertension and cirrhosis along the spectrum of compensated and decompensated disease. Appropriate use of terminology is important. It can help direct our conversations with patients in helping them to understand their disease and provide anticipatory guidance for what their future health may look like. It is also critically important in conveying how sick a patient may be when communicating with other providers and in conveying the complexity of medical decision making in our documentation.

BACKGROUND

In medicine, there is constant advancement in the understanding of diseases, their pathophysiology, and subsequent management. Over time, these advances necessitate changes in the nomenclature related to diseases so that the terminology used best describes the disease process a patient has. Furthermore, these changes have the potential to communicate more nuanced information about the disease to convey severity and to globally portray prognosis and course. This can be seen in the divergence from eponyms to more disease descriptive terms and attempts to identify and change stigmatizing language. The field of hepatology has gone through a significant terminology revolution recently, notably with migration away from nonalcoholic steatohepatitis and nonalcoholic fatty liver disease to metabolic dysfunction-associated steatohepatitis (MASH) and metabolic dysfunction–associated steatotic liver disease (MASLD). This has been coupled

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with the addition of the term metabolic and alcohol related/associated liver disease (MET/ALD), which captures a patient population that likely has multifactorial steatosis that was not captured with the previous nomenclature.[1] The field of hepatology has further experienced evolution in the nomenclature surrounding cirrhosis to better capture the spectrum of liver disease and patients' progression along that spectrum that is not adequately captured by the terms "compensated cirrhosis" and "decompensated cirrhosis" alone (refer to Table 1). Addition of new terms, honing of definitions and adding new classification systems will hopefully capture more patients with liver disease and be able to better convey where a patient is along the liver disease spectrum. This article aims to review this newer terminology that has emerged over the past several years regarding portal hypertension and cirrhosis along the spectrum of compensated and decompensated disease. Appropriate use of terminology is important. It can help direct our conversations with patients in helping them to understand their disease and provide anticipatory guidance for what their future health may look like. It is also critically important in conveying how sick a patient may be when communicating with other providers and in conveying the complexity of medical decision making in our documentation.

As our understanding of cirrhosis has become more nuanced, so has our understanding of prognosis, and nomenclature has had to change to match this. Previously cirrhosis was viewed in 2 major stages, "compensated" and "decompensated", with respective median survival being 10-12 years and 2-4 years.[2-4] It has previously been acknowledged that generalized life expectancy estimations are difficult to apply to individual patients, since broadly stating decompensated cirrhosis has a certain mortality rate does not account for the differences in mortality that are seen with differing decompensating events such as development of ascites versus development of varices or differences with having one decompensating factor versus having two or more.[2] Even in patients with compensated cirrhosis, generalized mortality statements do not account for possible differences related to compensated with varices versus compensated cirrhosis without varices.[2] Though we do have scoring systems, like MELD3.0, that help to convey how sick our patients are, MELD3.0 was created to predict 3-month mortality without

Table 1.

Term	Details	Effect on Life Expectancy
Chronic liver disease with LSM<10		• 3-year risk of LRD or decompensation <1%
Compensated advanced chronic liver disease (cACLD)	Includes patients with and without cirrhosis	• Median survival 12 years
Compensated cirrhosis	Not interchangeable with cACLD	
Without CSPH	HVPG < 10mmHg	
With CSPH	HVPG > 10mmHg	
Without varices		• 5-year risk of death 1.5%
With Varices		• 5-year risk of death 10%
Decompensated cirrhosis		• Median survival 2-4 years
Ascites	Clinically apparent, not small volume only seen on imaging	• 20-58% 1-year mortality • 77% 3-year mortality • 78% 5-year mortality
Hepatic encephalopathy	Overt hepatic encephalopathy (West Haven grade II-IV)	Median survival: • 3.9 years HE alone • 1.1 years HE + ascites
Variceal hemorrhage		5-year mortality: • 20% with bleeding alone • 88% bleeding + additional decompensation
Further decompensation	Additional decompensation after initial event	• Mean survival 273 days (9 months)
Acute on chronic liver		• 30-day mortality 32.8% • 90-day mortality 51.2%

Abbreviations: LSM- liver stiffness measurement; LRD- liver related death; CSPH- clinically significant portal hypertension; HVPG- hepatic venous pressure gradient

a liver transplant.[5] When discussing longer term mortality and having informed discussions with patients, it is helpful to understand their global course and how certain events in the progression of cirrhosis affect survival.

Advanced chronic liver disease, clinically significant portal hypertension and compensated cirrhosis

The term cirrhosis refers to a pathology-based diagnosis.[6-8] With increasing availability of non-invasive tests and imaging, liver biopsy and hepatic venous pressure gradients (HVPG) are being obtained less frequently.[9] Non-invasive testing (NIT) in patients that are otherwise compensated is often not able to account for the pathologic differences between advanced fibrosis and cirrhosis.[6] Regardless of the pathologic stage, patients with increased liver stiffness levels on NIT still may have liver disease worth treating and or surveying long term. To account for the increasing number of patients falling into this category, the Baveno VI consensus applied the term **compensated advanced chronic liver disease (cACLD)**, which encompassed patients with both advanced fibrosis (bridging fibrosis) and cirrhosis who did not have a liver biopsy.[6,7] Using transient elastography (TE), cACLD may be termed "possible" for patients with liver stiffness measurements (LSM) over 10kPa and "certain" for patients with LSM over 15kPa.[4,6] Patients may still have chronic liver disease with LSM under 10kPa. As with any of the more advanced stages of liver disease, the underlying etiology should be addressed but, for these patients, the 3-year risk of decompensation or liver related death is less than 1%.[1] Patients with ongoing injury and LSM between 7-10kPa may need to be monitored for progression to cACLD.[6]

Compensated cirrhosis and cACLD can be further stratified into those with clinically significant portal hypertension and those without clinically significant portal hypertension.[6,7] **Clinically significant portal hypertension (CSPH)** is defined as HVPG greater than or equal to 10mmHg and is the degree of elevation at which complications of portal hypertension can present.[6,10] As a brief review of the pathophysiology of portal hypertension in cirrhosis, current understandings suggest that early in the disease process portal hypertension is driven by changes in the hepatic parenchyma and increase in intrahepatic vascular tone in response to various vasoactive mediators.[10,11] Mild portal hypertension is defined as portal pressures between 5 and 10mmHg. As cirrhosis progresses though, changes in systemic circulation begin to contribute to portal hypertension including through increased cardiac output and increased intravascular volume.[10] Patients with mild portal hypertension (5-10mmHg), may not yet have developed the hyperdynamic state that influences portal hypertension in patients with portal pressures over 10mmHg, which is thought to be the reason patients with mild portal hypertension do not respond as well to non-selective beta blocker therapies.[10]

For patients who have undergone NIT, there are parameters to identify who likely has CSPH and therefore do not require invasive measurement. Liver stiffness measurements (LSM) over 25kPa on TE regardless of platelet count, LSM of 20-25kPa with platelet count less than 150k/mm^3 or LSM 15-20kPa with platelet count less than 110k/mm^3 are consistent with CSPH. Other cutoff values exist for non-TE elastography methods.[4] It should be kept in mind that these numbers are only validated in viral liver disease, alcohol-associated liver disease, and MASH.[6] Imaging that shows recanalization of umbilical vein, periesophageal varices, splenorenal shunt, clinically apparent ascites or hepatofugal flow in the main portal vein on doppler ultrasound are also consistent with CSPH regardless of liver disease etiology.[4]

By stating that a patient has cACLD without clinically significant portal hypertension you are implying that the patient has liver disease but is not currently experiencing complications of their liver disease and is unlikely to experience a portal hypertensive complication in their current state. Management of patients in this subset should focus on identification and treatment of the underlying etiology of liver disease. When you state that a patient has compensated advanced chronic liver disease with clinically significant portal hypertension though, not only do they require etiologic identification and management, but they may also benefit from management of the hyperdynamic element of their portal hypertension

with non-selective beta blocker therapy.[4,6,11]

Compensated cirrhosis is defined by the Baveno VII consensus statement as the absence of a present or past decompensating event (variceal bleeding, clinically apparent ascites and overt hepatic encephalopathy).[6] This definition has not changed significantly over time, though it should be noted that while multiple studies have incorporated the presence of jaundice as a decompensating event, this has not been universally agreed upon as decompensation. At this time there is not enough data to allow for the classification of jaundice, minimal ascites only seen on imaging, minimal ("covert") hepatic encephalopathy and occult bleeding from portal hypertensive gastropathy as decompensating events, so patients with these findings, at present, are still by current definitions compensated.[6] In patients with compensated cirrhosis (or cACLD) and CSPH, non-selective beta blockers should be initiated with the goal of preventing decompensation.[6] Compensated cirrhosis has historically been associated with median survival time of 12 years or more,[2-4] but the presence or absence of varices has been shown to influence risk of death, with their absence being associated with 5-year risk of death of 1.5% and presence being associated with risk of death of 10%.[18] Indeed, in patients with cACLD, progressive increase in LSM, regardless of etiology of liver disease, is associated with an increase in relative risk of decompensation and mortality.[6]

Decompensated cirrhosis, acute decompensation, further decompensation and acute on chronic liver failure

Decompensated cirrhosis refers to the development of complications of portal hypertension, specifically clinically apparent ascites, overt hepatic encephalopathy and variceal bleeding, and this has remained relatively unchanged over time.[6] Of note, some research papers will include jaundice as a defining decompensating event[12,13] and others bacterial infection[14-17] but the Baveno VII consensus statement suggests that further research is required prior to the inclusion of jaundice in the definition of decompensation, and bacterial infections are considered a possible precipitant of decompensation, not a defining characteristic.[6] After the first decompensating event occurs, median survival drops to 2-4 years.[13] **Acute decompensation** is the main cause of hospitalization in patients with cirrhosis.[14] In the coming years we may see further stratification of decompensation based on the speed at which initial decompensating events occur. This may come with recommendations as to whether treatment for the decompensating event requires inpatient admission versus outpatient treatment with proposed addition of terminology to include non-acute decompensation, but more research is needed to determine the clinical significance of the more indolent presentations of decompensation.[12]

The development of a decompensating event is a key step in the natural history of cirrhosis that portends an increase in mortality with the different decompensating events having different associated mortality. Four percent of patients may die during their initial presentation with a decompensating event.[19] Ascites is the most common initial decompensating event, reported to be seen in 36% of patients by itself and in combination with another decompensation event in 37% of patients.[19] A prospective cohort study of 494 patients showed variceal bleeding as the first decompensating event in 10% of patients and hepatic encephalopathy in 5% of patients.[18] The mortality associated with the development of ascites has been reported to be 20-58% at 1 year, 77% at 3 years, and 78% at 5 years.[10,18,20-21] The combination of ascites with hepatic encephalopathy has been associated with median survival of just 1.1 years compared to median survival of 3.9 years with hepatic encephalopathy alone.[21] Acute variceal hemorrhage is associated with significant short-term mortality of 10-15%[19] although that is often not from the bleeding itself, but from complications that arise from the bleed, including worsening liver or renal failure.[20] Estimated 5-year mortality is 20% for those presenting with bleeding alone and 88% for any combination of a bleeding event with a non-bleeding decompensation.[19] Another important clinical event that is not considered a specific decompensating event is infection, which has been associated with 1 month mortality of 30% and an additional 30% at 1 year.[20]

It has been observed that when subsequent complications of portal hypertension follow an initial event, there is an even higher associated

increase in mortality. This has been termed **further decompensation**. According to the Baveno VII consensus statement, further decompensation is defined as having a second portal hypertensive-mediated complication develop, such as the onset of ascites or hepatic encephalopathy in a patient who has had a previous variceal hemorrhage (with the caveat that it did not occur in the same time frame as the hemorrhagic event). Additional examples would be the development of recurrent variceal bleeding in a patient with previous bleeding, the requirement of more than 3 large volume paracenteses within 1 year, or recurrent hepatic encephalopathy; and although the following clinical scenarios are not defined as decompensation events, the development of jaundice, spontaneous bacterial peritonitis or hepatorenal syndrome acute kidney injury (HRS-AKI) can be defined as "further decompensation" in a patient with a prior traditional decompensation.[6] Though this definition was included in the Baveno VII consensus statement, it was based on expert opinion, without significant evidence to support it. Part of the aim of a large multicenter cohort study published in 2024 was to evaluate whether risk of death increased with further decompensation as defined by the Baveno VII consensus statement. Based on their analysis, mortality was increased by approximately 2 times that of the associated first decompensating event, with a mean survival of 273 days (9 months) after further decompensation was reported.[13]

Acute on chronic liver failure (ACLF) is another term whose definition continues to be honed. It should be noted that there is no international consensus on the definition, with noted variability between European, North American and Asian societies.[22] Despite the lack of a unifying definition of criteria, there is clear consensus that there is high short-term mortality with ACLF, and the European and North America definitions include the presence of extrahepatic organ failure.[22,23] The specific definition used by the North American Consortium for the Study of End Stage Liver Disease (NACSELD) uses the presence of at least two different extrahepatic organ failures to define ACLF. These include shock, West Haven III/IV hepatic encephalopathy, need for renal replacement therapy, and mechanical ventilation.[24] Another important concept to keep in mind with the definition used in North America is that ACLF can occur in patients with chronic liver disease even without the presence of cirrhosis.[24] A large multicenter European cohort shows that in patients with acute decompensation that were diagnosed with ACLF, the 30- and 90-day mortality rates were 32.8% and 51.2% respectively, and 1.8% and 9.8% in those that did not have ACLF.[14]

Recompensation

It is important to remember that patients who have a history of ascites or hepatic encephalopathy, and whose disease is controlled with diuretics, TIPS, and/or hepatic encephalopathy-directed therapies, do not have compensated disease[6,10] but rather decompensated disease controlled by medical and/or procedural therapies. There is, however, a subgroup of patients who have clinically meaningful response to treatment of their underlying etiology of liver disease, specifically those with hepatitis C viral infections who attain sustained viral response, hepatitis B infections with viral suppression, and sustained abstinence from alcohol. These patients, in the absence of other contributing liver disease (ex. MASH, alcohol use disorder), can experience improvement in their HVPG and consequent decrease in risk of decompensation. With sustained adequate improvement in LSM, those with cACLD can potentially stop long term liver stiffness monitoring regimens, and those with CSPH on beta blockers can potentially come off beta blockers if endoscopically proven to not have varices.[6] Furthermore, patients who have previously had a decompensating event can potentially experience recompensation. **Recompensation** is a term that was introduced in the Baveno VII consensus statement. For recompensation to be present, all of the following must have occurred: removal, suppression or cure of the primary etiology of the liver disease, resolution of ascites and/or hepatic encephalopathy for more than 12 months off of decompensation-directed therapy, absence of variceal hemorrhage for at least 12 months and, finally, stable improvement of liver function testing.[6]

CONCLUSION

The continued refinement in the terminology we use in relation to liver disease is a crucial step in the history of our understanding of liver disease that will hopefully allow us to better categorize our patients into risk strata. This is important not just at the point of care to understand our patients' individual risk, but also to ensure we can continue to advance research in the care for patients with chronic liver disease. There is currently a suggestion for application of new terminology related to the speed at which decompensation occurs (i.e., whether the first decompensating event comes on more slowly and is seen as an outpatient ("non-acute") as opposed to an acute event that leads to hospitalization). **Non-acute decompensation** potentially accounts for 45% of decompensation.[12] There is also a group of patients who have decompensated cirrhosis with symptoms that are adequately managed with medical therapy who should not be classified as recompensated as they likely do have a higher mortality than a patient who has never experienced decompensation or does not require medications anymore.

We should bear in mind that mortality prediction in cirrhosis is imperfect since the etiologies of cirrhosis are variable and the clinical outcomes of one etiology of cirrhosis do not necessarily align with those of other etiologies, but much of cirrhosis research to date has included heterogenous populations. In the future, we are likely to see further refinement of terminology in the staging of cirrhosis and chronic liver disease and continued refinement and individualization of care for patients based on that staging, their underlying etiology of liver disease and their portal pressures. As studies start to further analyze patients based on etiology of advanced chronic liver disease, we may also start to see differences in morbidity and mortality based on age and etiology of disease rather than simply type of decompensation as was shown in one population-based study evaluating mortality associated with hepatic encephalopathy.[25] Indeed in 2012, the International Liver Pathology Study Group recommended discontinuation of the term cirrhosis altogether because of the implied problems that come with trying to classify many disease processes, with different patterns of scarring, regeneration and progression, with a "morphology-based unitary term".[10] While this has not come to bear in clinical practice, it is clearly of increasing importance for all providers who see these patients to understand the terminology here described, to ensure we understand the risk stratification of each of our patients and provide care commensurate to that risk. ■

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