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One - or more - blind spot(s) unveiled in the new definition of decompensated cirrhosis

Florent Artru ^{1,2}, Thomas Reiberger ^{3,4,5}

¹ Liver department, Rennes University Hospital

² Inserm U1241, NuMeCan Institute - University of Rennes

³ Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria

⁴ Vienna Hepatic Hemodynamic Lab, Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria

⁵ Christian Doppler Lab for Portal Hypertension and Liver Fibrosis, Medical University of Vienna, Vienna, Austria

Correspondance

Florent Artru, MD

Liver department, Rennes University Hospital and University of Rennes

2 rue Henri Le Guilloux, 35000 Rennes, France

Tel : +33299284298 ; Fax : +33299284112

Mail: florent.artru@univ-rennes.fr

AND

Prof. Thomas Reiberger

Division of Gastroenterology and Hepatology, Department of Internal Medicine III,

Waehringuer Guertel 18-20, A-1090Vienna, Austria.

Tel.: +4314040065890; Fax: +4314040047350

Mail: thomas.reiberger@meduniwien.ac.at

By traditional textbook knowledge, the development of variceal bleeding, hepatic encephalopathy (HE), jaundice, and ascites denotes the transition from compensated to decompensated cirrhosis [1,2]. Decompensation usually occurs in patients with clinically significant portal hypertension (CSPH) as defined by a hepatic venous pressure gradient ≥ 10 mmHg. The critical importance of decompensation in the natural history of cirrhosis has been recently emphasized by analyses considering death as a competing event of decompensation itself acknowledging that decompensation usually precedes death in patients with compensated cirrhosis. Hence, the long-term mortality risk of a patients who remain compensated is dramatically lower than another one experiencing decompensation (respectively $< 15\%$ and $> 90\%$ at 20 years) [2]. Multiples states of cirrhosis based on prognostic considerations of increased risks of decompensation (compensated state 0 to 2, depending on the presence of varices), and of death (decompensated state 3 to 5, according to the presence variceal bleeding, other decompensating event or any second decompensating events) were proposed. The most advanced state of cirrhosis was recently named “end state” and illustrated by the occurrence of severe complication of liver disease such as recurrent/refractory ascites, infections, renal or other extra-hepatic organ dysfunction paving the way for the development of acute-on-chronic liver failure (ACLF). Such approach has been taken up by recent AASLD guidance for portal hypertension [3] as well as in the recent Baveno VII consensus [4] where a of further decompensation state was defined as a development of a second or recurrent portal hypertension-driven decompensating event and/or the occurrence of jaundice, spontaneous bacterial peritonitis and/or hepatorenal syndrome-acute kidney injury. An illustration of the traditional multistate model of the natural history of cirrhosis is provided in Figure 1.

In parallel to the recent characterization of ACLF, the concept of acute decompensation (AD) has been introduced. It refers to a sudden, within a short time period, and severe occurrence of complications of cirrhosis which require an emergent hospitalisation. Such complications include ascites, variceal bleeding, HE but also bacterial infection. Considering the role of infections, there is ongoing clinical/scientific controversy if bacterial infections per se should define decompensation (AD) or rather are triggers (precipitants) of AD. Importantly, both the CANONIC and PREDICT studies included only hospitalized individuals with cirrhosis and the definition of AD also included infections [5,6]. Notably, up to 80% of patients included in both studies experienced a previous decompensated event. When trying to integrate the clinical condition of AD into the traditional multistate model of cirrhosis, AD seem to best fit the state of late decompensation. Lastly, in the CANONIC and PREDICT studies, AD was mostly characterized by ≥ 2 decompensating events while first decompensation commonly manifests by only a single event with ascites representing the most frequent first

decompensating event [7]. These observations has led to the hypothesis that the concept of AD has left a blindspot, not investigated so far, that may be defined as non-acute decompensation (NAD) of cirrhosis. This concept of NAD has been the subject of the present study investigating the incidence, progression, and long-term impact of NAD on the outcomes of patients with cirrhosis [8].

NAD corresponds to a more gradual occurrence of complications as compared to AD, and in the present study specifically refers to the development of grade 2 ascites or grade 1 or 2 HE, which did not require a hospitalisation [9]. Notably, in the present study infections (with the exception of spontaneous bacterial peritonitis) were not considered as decompensating events. The authors included 617 patients with compensated cirrhosis managed in specialized care programs in Padova and Milano from 2003 to 2021. During a median follow-up duration of 60 months, 154 patients (25%) developed complications of cirrhosis of which almost half (44.8%) were defined as NAD events while 55.2% experienced AD events. Notably, about 42% of patients with NAD later developed AD after a median of 11 months, a timeframe that may well allow the initiation of potential disease modifying treatments. Multivariable analysis identified AD, NAD, etiological cure of the underlying liver disease, and MELD as independent predictors of mortality in this cohort. AD was associated with a greater risk of mortality compared to NAD. Besides, high MELD and interestingly a prophylaxis with non-selective beta-blockers (NSBBs) were associated with a higher risk of both NAD and AD. Conversely, effective etiological treatment was linked to a lower risk of both NAD and AD emphasizing the importance of addressing the underlying cause of liver disease even though less than 10% of patients in both groups experienced cirrhosis recompensation as per rather stringent Baveno VII criteria [4].

This proof-of-concept study provides a pivotal step in understanding the intricate pathways of cirrhosis decompensation and places the emphasis on the non-acute vs. the acute nature of the decompensation rather than the sole type of decompensating event (Figure 2). While it highlights the potential value of using the NAD concept for description and definition of the clinical trajectory of cirrhosis patients, further research is required to solidify and expand upon these findings as some intrinsic limitations of the NAD concept may temper drawing strong conclusion for clinical management/practice:

In the present study, the fact that NSBBs use was associated with a higher risk of both NAD and AD. Such relationship is rather associative than causal as patients with varices did more often receive NSBBs than patients without which potentially resulted from the lack of available surrogates for portal hypertension severity (e.g. hepatic venous pressure gradient or platelet count). Concerning NSBBs use, we would be specifically interested in verifying PREDESCI 's findings in this cohort [10]. This

would involve comparing outcomes between patients with varices who did not receiving NSBBs (n=64, 10.4%) vs. patients with varices treated with NSBBs (n=176, 28.5%).

Besides these considerations, one of the main criticisms of the concept of NAD is the inconsistency in the indication for hospitalisation which remains the decisive discriminant feature between NAD and AD. Indeed, the policies and abilities to hospitalize a patient change over time especially in a time course of >18 years. Furthermore, hospital admission will also be depending on patient-related factors (e.g. willingness or compliance), physician-related factors (e.g. experience with management of complications and subjective attitude), and finally center-specific factors (e.g. available of a dedicated hepatology ward and capacity for inpatient care). The definition of NAD would then deserve a refinement helping in the identification of a homogeneous population. In our view, it would be important to reconsider jaundice, taken alone or accompanied with moderate ascites or HE in the definition of NAD as it could be perceived as a second blind spot in the modern approach of NAD and AD patterns of decompensation. Indeed, in our clinical practice it is not rare, especially in the setting of moderate alcohol related hepatitis, that patients experienced a first episode of moderate jaundice, that could be managed on an outpatient basis (and would then represent NAD). Accumulating evidence, however, suggest a higher risk of short-term mortality in this population compared to compensated patients [11,12]. Hence, prospective studies should be dedicated to this population potentially highlighting again a window of opportunity before occurrence of severe liver dysfunction and the risk of AD and ACLF development. Another example of the fragility of the AD vs. NAD definition lies in the spectrum of severity of different types decompensating events: For example patients with mild ascites, that may be easily mobilized with diuretics and subsequently controlled may still be hospitalized for diagnostic workup. In turn, patients with severe (grade 3) ascites may be managed by repeated paracenteses and albumin infusion in an outpatient setting. In this scenario the estimated risk of mortality seems not reflected by results of this study assigning a higher risk of death to AD vs. NAD [13].

Taken all aspects together, the type, severity and number of decompensating events all impact on the prognosis of patients with cirrhosis, and a compromise must be made considering clinical applicability and accuracy of prognostication when novel definitions for the natural history of cirrhosis are made.

While this study throws a wrench into the works of traditional textbook knowledge, the concepts of NAD vs. AD remain to be formally debated and investigated prospectively in a contemporary cohort of patients with advanced chronic liver disease taking into account the recent advances in nomenclature (e.g. metabolic dysfunction-associated steatotic liver disease classification [14]) and the management

of liver diseases (cured/suppressed viral hepatitis, dynamic assessment of liver and spleen stiffness by elastography [15], etc.). Loads of work ahead but for patients' goods that will eventually end up to a more complete picture of the natural history of cirrhosis and help tailoring the daily clinical management of our patients to prevent decompensation, ACLF and liver-related mortality.

Conflict of interests and acknowledgments

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Figure 1. Multistate model of cirrhosis stages based on prognostic considerations, adapted from [10]

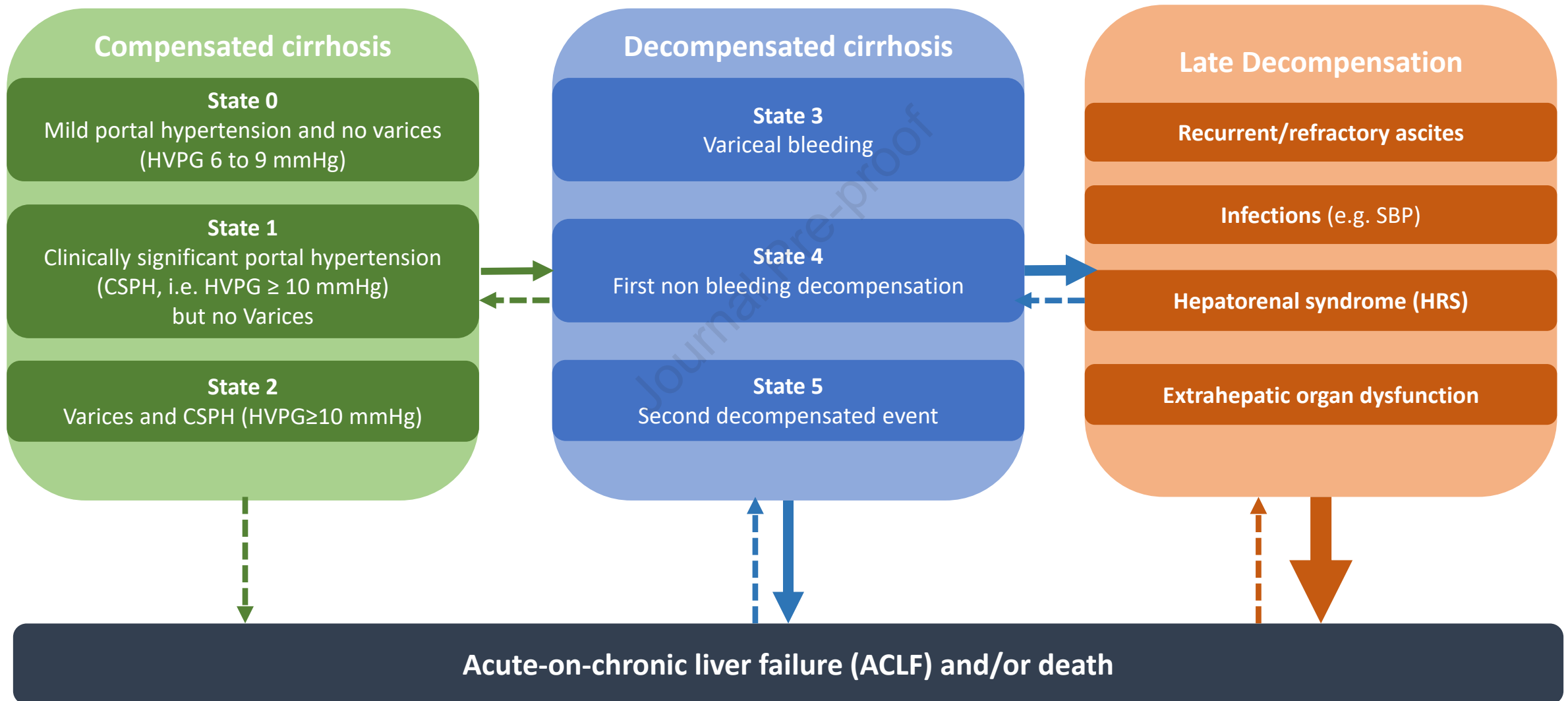


Figure 2. Novel proposition of decompensation model, adapted from [12]