



# East meets West: what opportunities arise in comparing international guidelines for management of cirrhosis?

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The management of patients with cirrhosis is complex and subject to ever-evolving literature and recommendations. In the most recent Japanese practice guidelines for liver cirrhosis (1), Yoshiji *et al.* provide a number of key updates to guidance based on evidence reflective of practice in Japan that are worth emphasizing. The authors introduce the pathophysiology of acute on chronic liver failure (ACLF), a relatively new syndrome that has increasing relevance in clinical practice given its high short-term mortality. There are multiple definitions for ACLF that have arisen in different clinical contexts, most notably the European Association for the Study of the Liver (EASL) definition and the Asian Pacific Association for the Study of the Liver (APASL) definition, however there are also proposed ACLF diagnostic criteria in Japan (2). Evaluating the relative performance of ACLF definitions in Japan in prospective studies may help elucidate manners in which ACLF may be prevented or mitigated, in addition to identifying relevant differences in ACLF phenotypes in distinct patient cohorts. This may form the foundation for more expansive ACLF-related recommendations in future Japanese cirrhosis management guidelines. Additionally, the authors

appropriately highlight the importance of sarcopenia with regard to cirrhosis-related outcomes including poorer survival. Assessment of muscle mass and frailty have become critical elements of routine evaluation in patients with cirrhosis, and consistent with other international guidelines (3,4), Yoshiji *et al.* recommend increased physical activity, protein supplementation, and consideration of branched chain amino acid supplementation in selected patients. The guidelines also acknowledge the potential of a late evening snack, which may inhibit metabolic changes that lead to sarcopenia, thereby improving liver function and quality of life (5).

Comparing Japanese guidelines and practice to other international practice guidelines, including the American Association for the Study of Liver Diseases (AASLD) and EASL, highlights relevant differences in liver disease epidemiology, underlying patient cohorts, and practice setting that have clear impacts on guidelines, but also leads to potential research opportunities that warrant further investigation. For example, while Yoshiji *et al.* recognize the role of transjugular intrahepatic portosystemic shunt (TIPS) in managing patients with refractory ascites, it is noted that

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the TIPS procedure is not covered by insurance in Japan. This may in part explain the more limited treatment that TIPS receives in the Japanese guidelines. By contrast, per AASLD and EASL guidance (6,7), TIPS is indicated not only in the setting of refractory ascites, but also in selected patients with bleeding related to portal hypertension [e.g., recurrent esophageal variceal (EV) bleeding], Budd-Chiari syndrome, and hepatic hydrothorax. The more limited role of TIPS in Japanese practice resulting from insurance coverage constraints may lead to research opportunities regarding the natural history of portal hypertension-related complications in patients with removal or suppression of the underlying etiology of liver disease. This has relevance for the future study of recompensation of liver disease, identified as a priority area for research by the recent Baveno VII workgroup (8). However, given the relative strength of literature demonstrating the effectiveness of TIPS in the management of EV bleeding in high-risk patients (9,10), those with recurrent EV bleeding (11), or bleeding from cardiofundal gastric varices (12), it may be important for studies in Japanese cohorts to evaluate specific TIPS indications for portal hypertension-related bleeding. If favorable results are observed, these data would provide powerful support in favor of insurance approval for TIPS in this and other settings.

Another research opportunity to evaluate the natural history of chronic liver disease is noted in patients with indications for spontaneous bacterial peritonitis (SBP) prophylaxis, including those with prior SBP or low-protein ascites. Given that prophylactic antibiotics are not covered by insurance in Japan, patients with established indications may be less likely to receive antibiotics. This may allow for detailed study of emergence of multidrug resistance patterns, *Clostridium difficile* infections rates, and antibiotic-associated toxicities in patients with cirrhosis when comparing Japanese cirrhosis cohorts to those in settings where antibiotic prophylaxis is widely available. It may also allow for additional exploration of strata of patients with classic indications for SBP prophylaxis who in fact have different risk profiles and in whom the risk/benefit ratio for antibiotic prophylaxis is less favorable.

In sum, we highlight important common areas of new attention in Japanese and international guidelines, including evaluation and management of ACLF and the incorporation of sarcopenia and frailty assessments in patients with cirrhosis. However, we also note differences in management that may arise from structural differences in healthcare

delivery environments, including as applied to TIPS and prophylactic antibiotic recommendations. As international guidelines continue to be released to reflect practice considerations in unique contexts, attention should be paid to both commonalities among guidelines that may represent universalities in management of chronic liver disease, as well as to differences or omissions that may signify important areas for future inquiry.

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