Update on the Evaluation and Management of Portal Hypertension

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Abstract: The development of clinically significant portal hypertension (CSPH) in patients with chronic liver disease is an important predictor of varices, variceal hemorrhage, ascites, hepatic encephalopathy, and death. The nomenclature of compensated advanced chronic liver disease, revised from compensated cirrhosis, recognizes the importance of portal hypertension (PH), rather than the histologic finding of cirrhosis, in clinical outcomes. Recent advances in the field have focused on the development of noninvasive methods, including transient elastography (TE), magnetic resonance elastography, and multiparametric magnetic resonance imaging, for predicting PH. TE is evolving to be the most widespread clinical tool to estimate PH, with a liver stiffness (LS) measurement cutoff of greater than or equal to 25 kilopascals (kPa) ruling in CSPH, and that of less than 15 kPa combined with a platelet count of greater than 150 × 10^9/L ruling out CSPH. Extending utilization of TE to not only LS measurement but also splenic stiffness measurement using the same probes may augment the sensitivity of detecting CSPH and thus selecting candidates warranting endoscopic evaluation for high-risk varices. With respect to management of PH, the role of nonselective β blockers continues to evolve and may extend beyond variceal bleed in preventing decompensation and development of ascites. Statins have a burgeoning well of data supporting their use, but large, prospective, controlled trials with clinical endpoints are awaited. Further data are still warranted regarding the use of long-term albumin therapy to prevent complications of PH.

Keywords
Portal hypertension, liver stiffness, splenic stiffness, transient elastography, magnetic resonance elastography, multiparametric magnetic resonance imaging, cirrhosis

Portal hypertension (PH) is defined as increased pressure in the portal venous system, which most often results from elevated intrahepatic vascular resistance caused by cirrhosis. Advances in the field of PH have impacted 3 main areas. First, there have been changes in nomenclature, with compensated cirrhosis now referred to as compensated advanced chronic liver disease (cACLD). This change recognizes that PH can occur in the absence of cirrhosis and that portal pressure,

rather than histology, drives outcomes. Second, research has focused on better noninvasive methods to predict PH and related complications. These methods involve estimates of liver stiffness (LS) as well as splenic stiffness (SS) using transient elastography (TE), magnetic resonance elastography (MRE), and multiparametric magnetic resonance imaging (MRI). Third, in the field of therapeutics, there have been advances in the use of nonselective β blockers (NSBBs) for the treatment of nonvariceal complications of cirrhosis. There are now evolving data on the role of statins and albumin in the management of PH. With the recent publication of the PREDESCI study showing potential benefits of NSBBs in reducing decompensation or death, the importance of noninvasive measurement of PH has increased. This article describes recent advances in the evaluation and treatment of PH that are relevant for current medical practice.

Definitions

cACLD is defined as advanced progressive hepatic fibrosis with a hepatic venous pressure gradient (HVPG) greater than 5 mm Hg. The compensated disease state can be further classified into patients with mild PH and patients with clinically significant portal hypertension (CSPH).[1,2] Mild PH is essentially defined as an HVPG greater than 5 mm Hg but less than 10 mm Hg, and CSPH is designated as an HVPG greater than or equal to 10 mm Hg.[2] CSPH is associated with PH complications such as esophageal varices (EVs) and hemorrhage, ascites, hepatic encephalopathy (HE), reduced tolerance to liver resection for hepatocellular carcinoma, and death.[3-5] The presence of PH has also been associated with response to treatment for many chronic liver diseases and has been shown to be a marker of prognosis and a predictor of drug-induced liver injury.[6-9]

Over the years, research geared toward noninvasive techniques to monitor PH has rapidly expanded. The 2015 Baveno VI Consensus Workshop highlighted that patients with LS less than 20 kilopascals (kPa) and a platelet count greater than 150 × 10^9/L are at significantly low risk for high-risk varices (HRVs).[1] American Association for the Study of Liver Diseases guidelines stated that although HVPG measurement is the current standard for assessing CSPH, noninvasive methods such as assessing LS alone or in combination with platelet count and spleen size can also be used to diagnose CSPH.[2]

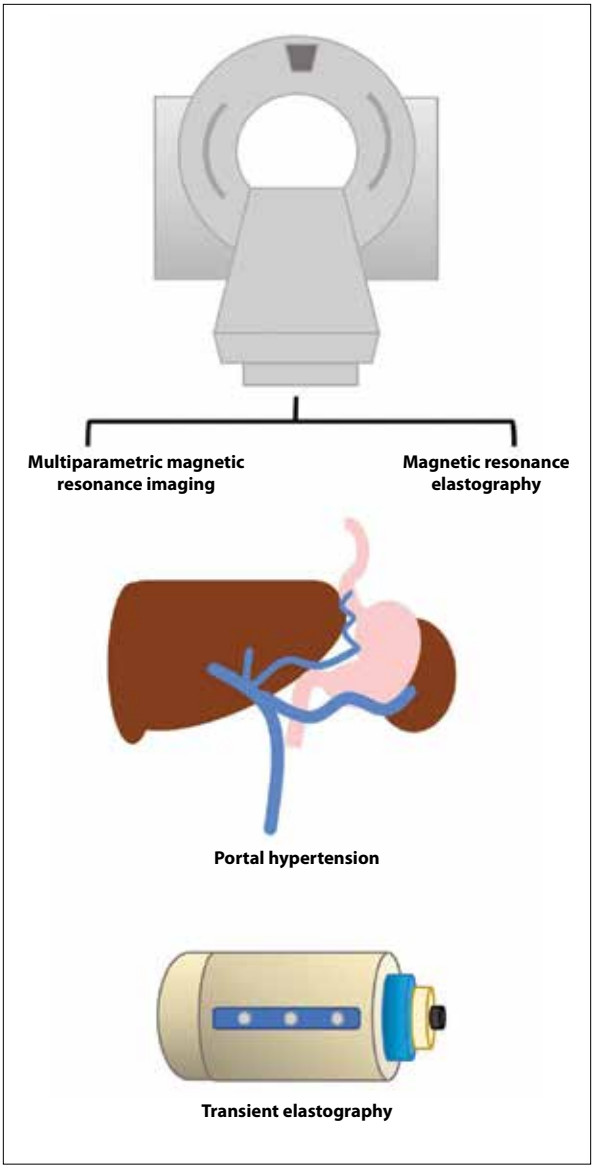

Figure. Portal hypertension (PH) results from increased pressure in the portal venous system (shown in the center of the figure). PH can be measured using liver and splenic stiffness as proxies via transient elastography (represented by the probe shown on the bottom of the figure) as well as magnetic resonance elastography and multiparametric magnetic resonance imaging (shown on the top of the figure).

Noninvasive Methods to Evaluate Portal Hypertension

Although HVPG is the gold standard for diagnosing PH, this method is invasive because it uses central venous pressure, is expensive, is prone to interobserver variability, and requires a trained team, which is why it is not available at every facility. Over the years, new noninvasive imaging modalities have been shown to accurately predict PH and may obviate the need for endoscopy in many patients with compensated liver disease. These modalities include TE, MRE, and multiparametric MRI (Figure).

Transient Elastography

TE has been successfully used as a means of risk stratification.[2] TE uses a probe that combines a low-frequency vibrator and ultrasound probe. The transducer generates a vibration that induces a shear wave that propagates through the liver and measures its velocity.[10] This shear wave velocity is then quantified as LS in the form of fibrosis. Given the greater use of TE in clinical practice and several studies demonstrating that LS positively correlates with HVPG and PH severity when assessing both the liver and the spleen, this article will focus on the utilization of TE.

Liver Stiffness In the years preceding the Baveno VI recommendation that patients with LS less than 20 kPa and a platelet count greater than 150 × 10^9/L could avoid endoscopic evaluation for varices, multiple studies demonstrated the utility of TE to assess CSPH in the setting of cACLD. In France, Kazemi and colleagues conducted one of the earliest of these studies, which evaluated 165 patients with cirrhosis who required variceal screening.[11] TE to assess LS was typically completed on the same day as or within the days preceding or following the screening esophagogastroduodenoscopy. Ultimately, an LS cutoff of 13.9 kPa detected any varices with a minimal sensitivity of 95% and a specificity of 43%, and a cutoff of 19 kPa detected grade 2 EVs with 90% sensitivity (95% CI, 0.80-0.98) and 60% specificity (95% CI, 0.51-0.69). With these criteria, approximately 43% of the study population could have avoided evaluation with endoscopy.

A meta-analysis of subsequent studies showed cutoff values for LS in CSPH ranging from 13.6 kPa to 21.0 kPa overall (19.0-34.9 kPa in alcohol-related cirrhosis) with a positive predictive value (PPV) of 0.84 (0.56-0.97) and area under the receiver operating characteristic (ROC) of 88% (0.76-0.99).[12] The diagnostic accuracy of LS compared with HVPG showed a significant correlation of 0.7480 (95% CI, 0.6464-0.8236; $P<.001$). Another meta-analysis evaluating publications as of 2015 found that in patients with cACLD, the Baveno VI criteria missed only 0.3% of HRVs (95% CI, 0.001-0.006; $P=.037$) and the evitable endoscopy rate was 32.8%.[13] Further analysis revealed that this very low likelihood of missing HRVs applied across all common etiologies.

The Expanded-Baveno VI criteria attempted to further increase spared endoscopies while maintaining a maximum threshold of 5% for missed HRVs. The criteria were developed using the international, multicenter Anticipate cohort, which consisted of 499 patients from France, Romania, Spain, and Canada with Child-Pugh class A cACLD of any etiology without prior decompensation.[14] The analysis found that 14% of patients met the Baveno VI criteria to avoid endoscopy, and only 3% of these patients had HRVs. Various combinations of platelet count and LS were used to spare endoscopies while also minimizing missed HRVs. Ultimately, a platelet count greater than 110 × 10^9/L and LS less than 25 kPa was the optimal combination to maximize spared endoscopies at 32% while keeping missed HRVs to 1.9% (95% CI, 0.006-0.054). Decreasing the platelet threshold to 100 × 10^9/L increased both the amount of spared endoscopies (36.5%) as well as missed varices requiring treatment (5%; 95% CI, 0.026-0.09).

More recently, Pons and colleagues performed a study to validate data from the Anticipate cohort.[15] The study considered a PPV of 90% appropriate to validate an LS cutoff to rule in CSPH and a negative predictive value (NPV) of 90% to rule out CSPH. LS greater than or equal to 25 kPa was found to be the best cutoff to rule in CSPH, with a high PPV for all etiologies except for obese patients with nonalcoholic fatty liver disease. The authors generated a model incorporating body mass index, LS, and platelet count to estimate the probability of CSPH. LS less than or equal to 15 kPa plus a platelet count greater than 150 × 10^9/L was able to rule out CSPH in a high proportion of cases. These data suggest that the need for HVPG measurement can be obviated in the majority of patients by using these criteria.

Stafylidou and colleagues assessed the performance of both the original and Expanded-Baveno VI criteria using systematic review and meta-analysis.[16] They estimated that in 1000 patients with cACLD, the use of Baveno VI criteria would prevent endoscopy in 262 patients but miss 6 patients with HRVs. On the other hand, use of the Expanded-Baveno VI criteria would result in avoiding endoscopies in 428 patients but miss 20 patients with HRVs. With both criteria, the missed HRV rate was below the acceptable rate of 5%.

More recently, Berger and authors of the Expanded-Baveno VI criteria attempted to augment the landscape of noninvasive testing by determining an optimal platelets/liver elastometry ratio (PLER) as well as developing the VariScreen^{PLI} algorithm.[17] The PLER intends to provide a single discrete cutoff value in lieu of the varying combinations of platelet-LS cutoffs and is calculated by dividing the platelet count by the LS (in kPa). With a PLER of greater than or equal to 17, the rate of HRVs was close to 0%, whereas a PLER of less than or equal to 6.2 yielded a HRV prevalence of 25.3%. The significant influence of etiology of liver disease as well as age, sex, and international normalized ratio when predicting HRVs fostered the PLEASE score, which adjusts the PLER according to these factors. The VariScreen^{PLI} algorithm, which aims to minimize unnecessary calculation, implements the PLEASE score for patients with a PLER between 6.2 and less than 17.

Splenic Stiffness Splenomegaly is commonly seen in liver cirrhosis in the setting of untreated PH.[18] The progression of splenic hyperplasia, angiogenesis, and fibrogenesis ultimately leads to SS, which can be used to assess PH and the presence of varices.[19] TE is the most common technique used to assess SS and uses the same probes as for LS. The duration of fasting and instructions to patients for assessing SS are similar to those for measuring LS. However, owing to the smaller size of the spleen, the likelihood of failure of TE to assess SS is higher, at approximately 10%, than to assess LS. The procedure can be performed with the patient lying supine or prone.[20]

Colecchia and colleagues conducted one of the first studies to delve into the utility of SS, which showed a 0.885 correlation between SS and HVPG in patients with hepatitis C cirrhosis, and a 0.836 correlation for LS.[21] A meta-analysis showed that SS had a pooled sensitivity of 85% (95% CI, 0.69-0.93) and specificity of 86% (95% CI, 0.74-0.93) for CSPH.[22] A later paper by Colecchia and colleagues determined that an SS cutoff of less than or equal to 46 kPa was highly sensitive for ruling out HRVs.[23] Combining Baveno VI criteria and the SS cutoff maintained the high sensitivity while improving specificity. The proportions of spared endoscopies using the Baveno VI criteria, an SS cutoff less than or equal to 46 kPa, and the combination of those criteria were 21.7%, 35.8%, and 43.8%, with 2.2%, 2.2%, and 4.3% of HRVs missed, respectively.

Magnetic Resonance Elastography

MRE is an additional modality to glean information on LS or SS in patients with cirrhosis. Unlike in TE, in MRE the shear waves generated by low-frequency vibrations are collated during a modified phase contrast sequence. This creates a visual map in the liver and spleen of stiffness of body tissues caused by inflammation and fibrosis and provides mechanical parameters to detect different pathologies of the liver.[24] Advances in MRE technology such as spin-echo MRE (SE-MRE) enhance image quality by reducing the effects that motion artifact, obesity, and liver iron overload have on the final image, and 3-dimensional MRE allows for greater volume covered and processes more complex shear wave motion, increasing accuracy of tissue stiffness measurement, which has proven to be useful in diagnosing fibrosis in nonalcoholic fatty liver disease.[24,25]

A retrospective study by Shin and colleagues sought to assess the diagnostic performance of LS and SS obtained from SE-MRE compared with dynamic contrast material–enhanced (DCE) MRI and spleen length in predicting the presence of EVs, particularly HRVs.[26] The study examined 139 patients with liver cirrhosis, mainly viral in etiology, and used endoscopy as the reference standard. Of note, the study excluded patients who had undergone endoscopic EV ligation, which may affect lesion characteristics. With endoscopic findings known at the time of analysis, patients were divided according to risk of EV bleed, with grade 0 or 1 EVs in the low-risk group and grade 2 or 3 EVs in the high-risk group.

Overall, LS and SS from SE-MRE and DCE MRI performed better than splenic length measurement in predicting varices. LS and SS cutoff values determined by ROC analysis were 4.58 kPa and 7.23 kPa, respectively.[27] LS and SS from SE-MRE and DCE MRI were also superior to splenic length measurement at predicting HRVs. According to ROC analysis, optimal LS and SS cutoff values for predicting HRVs were 4.81 kPa and 7.60 kPa, respectively. LS was noted to be the only significant independent predictor for variceal bleeding (P=.0038). However, the use of both LS and SS by SE-MRE had several false positives for the detection of both EVs and HRVs.

A recent systematic review and meta-analysis sought to evaluate the accuracy of MRE in measuring LS and SS as predictive measures of PH defined as EVs, refractory ascites, encephalopathy, or death.[28] Pooled summary sensitivity for LS to detect PH was 83% (95% CI, 72%-90%) and 79% (95% CI, 61%-90%) for SS. Pooled summary specificities were 80% (95% CI, 70%-88%) for LS and 90% (95% CI, 80%-95%) for SS. Overall, the meta-analysis determined diagnostic accuracy of MRE to detect CSPH as 88% for LS and 92% for SS.

A recent prospective study from Denmark explored the correlation of LS and SS based on MRE with HVPG.[29] LS was found to have a correlation of 0.92 to HVPG and SS a correlation of 0.94. ROC analysis to predict HVPG greater than or equal to 12 mm Hg determined an LS cutoff at 7.7 kPa with a specificity of 64% and sensitivity of 78% and an SS cutoff at 10.5 kPa with a sensitivity of 79% and specificity of 80%. These data are consistent with previously noted positive correlations of LS and SS with HVPG. The study from Denmark additionally attempted to explore the effect of nonselective β blockade on LS and SS, but no notable effects were seen. Overall, MRE proves to be an effective tool for measuring both LS and SS, as well as confirming some predictive value for PH, CSPH, and EV bleed risk. However, cost and difficulty obtaining serial images appear to be limiting factors.

Multiparametric Magnetic Resonance Imaging

Although TE can be inexpensive, it is of limited use in patients with obesity (despite use of an XL probe) and ascites. MRE is also less reliable in patients with iron disposition, massive ascites, and obesity. An alternative imaging modality, multiparametric MRI is not limited by

these factors and captures liver fibrosis while assessing PH. Multiparametric MRI uses a series of images to delineate liver tissue by quantifying hepatic fat, iron, and inflammatory fibrotic changes. These images are combined into a parametric map that differentiates these changes by color, using a proprietary software. Multiparametric MRI creates a comprehensive picture of liver tissue and its pathology.

Multiparametric MRI can also be used to predict clinical outcomes in patients with liver disease. A study by Pavlides and colleagues assessed the liver inflammation and fibrosis (LIF) score.[30] This score, derived from Ishak fibrosis stages, identified categories as no (LIF <1), mild (LIF 1-1.99), moderate (LIF 2-2.99), or severe (LIF 3-4) risk for liver disease. This study found that patients with LIF greater than 3 had initial baseline decompensation and later developed further liver-related clinical events. No patient with LIF less than 2 developed liver-related clinical events. This suggests that multiparametric MRI to assess LIF could identify patients at high risk for liver complications from cirrhosis.

A study by Levick and colleagues hypothesized that iron-corrected T1 (cT1) measured from the spleen could be used as a biomarker for CSPH.[31] In this study, 19 patients with liver disease, 10 of whom had cirrhosis, were evaluated, and measurements for HVPG and spleen cT1 were obtained by multiparametric MRI. The study also measured secondary variables such as liver cT1, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, AST to platelet ratio index, and Fibrosis-4. Results showed that spleen cT1 was the only noninvasive biomarker to demonstrate significant correlation with HVPG (P=.001). For the diagnosis of CSPH, spleen cT1 had a sensitivity of 89%, specificity of 100%, PPV of 100%, and NPV of 91%. Although this study shows some encouraging results with the use of splenic cT1 as an additional biomarker for PH, the study was limited by a small sample size and inclusion of patients with limited liver disease etiologies.

Advances in Management

Evolution in Beta Blocker Use for the Treatment of Cirrhosis-Related Complications

NSBB use and benefit in the management of cirrhosis-related complications is debated. Although numerous retrospective, prospective, and randomized studies since 1980 have noted increased survival with the use of NSBBs in cirrhosis, other studies assert a lack of benefit or even harm.[32,33] Strong evidence supports that NSBBs reduce the risk of initial variceal bleeding in compensated patients, but this has not been replicated in decompensated patients, especially in patients who have ascites.[34-38]

A meta-analysis of 15 studies from 1990 to 2013 investigating primary or secondary variceal hemorrhage prophylaxis found that NSBB-induced portal pressure reduction in both patients with and without ascites led to lower rates of decompensation and progressive decompensation as well as death and liver transplantation.[34] Portal pressure reduction was defined as an HVPG less than 12 mm Hg or a 20% or greater reduction from baseline.[35] Of patients without ascites, 50% were HVPG reduction responders to NSBBs, vs 42% of patients with ascites.[34] In patients without ascites, NSBBs were associated with reductions in clinical events such as variceal hemorrhage, ascites, and encephalopathy (odds ratio [OR], 0.35; 95% CI, 0.22-0.56). In patients with ascites, NSBBs were associated with reductions in variceal hemorrhage, refractory ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, and encephalopathy at a slightly lower rate (OR, 0.27; 95% CI, 0.16-0.43). NSBBs were associated with a nearly 50% reduction in death and liver transplant rates in patients with and without ascites.

The PREDESCI study, a phase 4, multicenter, randomized controlled trial (RCT) based in Spain, explored the efficacy of β blockers in preventing decompensation or mortality in patients with CSPH and compensated cirrhosis.[36] Patients underwent HVPG measurements with evaluation of acute HVPG response to the administration of intravenous propranolol. Patients who experienced an HVPG decrease of 10% or greater were deemed to be responders and were randomly allocated into groups receiving propranolol as treatment or placebo. Patients deemed to be nonresponders were given carvedilol or placebo. Of 631 patients evaluated over a 3-year period, 201 were randomly assigned, with 101 receiving placebo and 100 receiving active treatment. The treatment group consisted of 67 individuals receiving propranolol and the remaining 33 receiving carvedilol. Cirrhosis decompensation occurred in 16% of the treatment group and 27% of the placebo group (hazard ratio [HR], 0.51; P=.041). The authors attribute this difference to the reduced incidence of ascites in the treatment group vs the placebo group (HR, 0.44; P=.0297).

The 38-patient, dual-center ALB-BET study in Spain demonstrated differences in outcomes with NSBB use in patients with ascites responsive to diuretics compared with patients with refractory ascites.[37] Although propranolol similarly reduced heart rate and HVPG in both groups, patients with refractory ascites experienced a more profound reduction in renal perfusion pressure (RPP) evidenced by impaired renal function. At baseline, the refractory ascites group had a notably lower RPP at 69 mm Hg compared with 81 mm Hg in patients with diuretic-responsive ascites. For the kidneys to maintain an appropriate level of blood flow, RPP should be greater

than 65 mm Hg to 75 mm Hg.[38] The reduction of RPP to 62 mm Hg as well as cardiac index reduction as a consequence of significantly reduced stroke volume and heart rate likely impeded renal function, leading to renal injury.[37] Patients with refractory ascites also experienced more profound reduction in their left ventricular contractility capacity compared with patients with diuretic-responsive ascites. Similarly, a retrospective analysis by Giannelli and colleagues of liver transplant candidates with refractory ascites found cardiac reserve compromise defined by a left ventricular stroke work index (LVSWI) of less than 64.1 g-m/m^2.[39] In the study, patients below this LVSWI level who received NSBBs experienced greater mortality while on the liver transplant waiting list. Ultimately, in the ALB-BET study, the degree of portal pressure, and RPP reduction in diuretic-responsive patients, maintained the mortality benefit demonstrated in prior studies.[40-42]

Statins

A similar evolution has occurred with statin use. Once deemed to provide more harm than good owing to their potential for hepatotoxicity, statins have become an ally in improving mortality in cirrhosis. Multiple retrospective and small prospective clinical trials have demonstrated the potential benefit of statins in patients with PH.[43-46]

Statins contribute to improving angiogenesis, reducing endothelial dysfunction, and regressing fibrosis. Statins increase nitric oxide (NO) bioavailability in the liver by increasing NO production in the liver vasculature. This upregulation of NO decreases intrahepatic vascular resistance and consequently decreases portal pressure. Additionally, statins have been found to have anti-inflammatory effects that in turn reduce the occurrence of fibrosis.[47]

One of the first human studies to investigate the effect of statins on hepatic portal pressure in patients with cirrhosis was by Zafra and colleagues.[47] This study observed the acute effects of simvastatin on systemic and splanchnic hemodynamics in 13 patients. Oral simvastatin 40 mg increased hepatic blood flow by approximately 17% (*P*=.01), decreased hepatic vascular resistance by approximately 10% (*P*=.04), and increased hepatic NO products by 14% (*P*=.04) in the 60-minute observation period but did not significantly affect HVPG. In the second part of the study, the investigators performed a double-blinded RCT that assessed the effects of simvastatin on the postprandial increase in splanchnic flow in 17 patients. Compared with placebo, treatment with simvastatin was associated with an attenuation in the postprandial increase in HVPG. These results provided a proof of concept for a potential role of statins in decreasing hepatic portal pressure.

In a subsequent RCT, 59 patients with cirrhosis and PH with an HVPG greater than or equal to 12 mm Hg were randomized to simvastatin or placebo.[45] Investigators studied splanchnic and systemic hemodynamics at the onset and completion of 1 month of treatment. The study showed that simvastatin was associated with a significantly reduced HVPG (-8.3%), with decreases observed both in patients who were receiving β blockers (-11.0%; *P*=.033) and in patients who were not (-5.9%; *P*=.013).

The BLEPS trial, the largest multicenter RCT investigating statin use in the prevention of variceal bleeding to date, attempted to expand these findings and demonstrate that the addition of simvastatin to standard prophylaxis with NSBBs and endoscopic band ligation would reduce rebleeding and death after variceal bleeding in cirrhotic patients.[48] Although the study failed to show a reduction in rebleeding and did not prevent further complications of PH, it did reveal that simvastatin confers increased survival in decompensated patients after an acute variceal bleeding episode. A post hoc analysis of patients who were randomized into the study and initiated the study medication revealed that although there was no significant effect on a composite endpoint of death or hemorrhage (HR, 0.822; 95% CI, 0.473-1.427; *P*=.423), a significant mortality benefit was noted in patients designated Child-Pugh class A and B. The study also found that 2 patients with decompensated cirrhosis developed rhabdomyolysis; therefore, simvastatin should be used with caution in patients with decompensated cirrhosis.

Although further prospective data are forthcoming, several retrospective analyses of large national registries have helped to validate the results of these RCTs. One meta-analysis evaluated 13 studies, 10 cohort studies, and 3 RCTs that met the criteria of studying patients with chronic liver disease, clearly defined exposure to statins, and relationships between statin exposure and cirrhosis-related outcomes that were reported with acceptable measures of association (ie, HRs, relative risk [RR], or ORs).[49] Six studies included patients with chronic liver disease, including chronic hepatitis B and C infection, but without cirrhosis,[50-55] and other studies included patients with compensated and decompensated cirrhosis.[56-60] Although there were no significant differences in patients with chronic liver disease, the meta-analysis found that patients with cirrhosis had a 46% lower risk of hepatic decompensation (RR, 0.54; 95% CI, 0.46-0.62) and 46% lower mortality (RR, 0.54; 95% CI, 0.47-0.61) with statin use.[49] In the 3 RCTs investigated, statin use was associated with 27% lower risk of variceal bleeding or progression of PH (HR, 0.73; 95% CI, 0.59-0.91). A more recent meta-analysis with 5 RCTs and 12 cohort studies also demonstrated a decreased mortality rate (HR, 0.782; 95% CI, 0.718-0.846).[61] There was no

decreased risk of esophageal variceal bleeding and SBP, but there was an associated decrease in HE and ascites. Additionally, the data analyzing components of hepatic portal hemodynamics showed a decreased standard mean difference (SMD) of HVPG for patients on statins compared with those on placebo (SMD_{HVPG} = -1.146; 95% CI, -1.3120-0.981).

A recent retrospective case-control study found that patients on statin therapy had a lower mean LS at 10.7 kPa compared with 15.5 kPa for patients who did not receive statins.[62] A higher proportion of statin users were found to have LS values less than 6 kPa, and a higher proportion of patients not using statins had LS values greater than 14 kPa. These findings can be attributed to postulated roles of statins in decreasing inflammation, oxidative stress, and consequently fibrosis. Risk of liver decompensation as cause of death and a secondary composite endpoint including ascites warranting paracentesis, varices with bleeding, and HE were also less frequent in the statin group. Although these results are notable, they warrant further investigation under more rigorous study design and standardization of intervention to parse the influence of statins on fibrosis progression. An important confounder in the interpretation of statin studies in cirrhosis is the impact of cirrhosis on cholesterol levels, as cholesterol is synthesized in the liver, and patients with decompensated cirrhosis have lower serum cholesterol levels than patients with compensated cirrhosis. Therefore, it is important to match statin-exposed and -unexposed patients when associations of liver function with statin exposure are studied.[44]

Despite the repeated demonstrations of improved mortality from statin use in cirrhosis, the mechanism of this benefit continues to require elucidation. A recently published RCT explored the potential added benefits of simvastatin to carvedilol as primary prophylaxis for variceal bleeding.[63] HVPG significantly decreased in both the simvastatin-carvedilol combination therapy group (17.73 ± 3.78 mm Hg to 14.58 ± 3.86 mm Hg; *P*<.001) and the carvedilol monotherapy group (17.18 ± 3.19 mm Hg to 14.23 ± 4.59 mm Hg; *P*<.001), but the difference was not significant (*P*=.98). At the end of a 3-month follow-up period, there was no difference between intervention groups in esophageal or gastric variceal status (*P*=.18; *P*=1.0), portal hypertensive gastropathy (*P*=.58), or gastric antral vascular ectasia (*P*=1.0). Regarding adverse events, lethargy and weakness occurred more frequently in the dual-therapy group (17.3% vs 3.7%; *P*=.03). In the combination group, 3 patients with severe muscle pain were found to have aminotransaminase elevations greater than 20 times the upper limit of normal (ULN). Of note, all 3 patients were designated Child-Pugh class C and were taking simvastatin 40 mg at the time of the events.

The LIVERHOPE-SAFETY trial, a phase 2, double-blind RCT, found that simvastatin 40 mg in patients with decompensated cirrhosis led to more frequent adverse events, especially rhabdomyolysis.[64] The trial studied the safety and tolerability of rifaximin (Xifaxan, Salix) 1200 mg daily combined with simvastatin daily doses of 20 mg or 40 mg in patients with Child-Pugh class B and C decompensated cirrhosis. Patients in the simvastatin 40-mg combination group experienced more frequent and significant increases in AST and ALT levels when compared with placebo (130 IU/L; 95% CI, 54-205; *P*<.001 and 61 IU/L; 95% CI, 22-100; *P*=.003) and the simvastatin 20-mg group (143 IU/L; 95% CI, 66-220; *P*<.001 and 69 IU/L; 95% CI, 29-109; *P*<.001). One of the 3 patients with increases in AST or ALT at least 3 times the ULN qualified for drug-induced liver-related injury in relation to simvastatin. Given its lower adverse events, daily simvastatin 20 mg was determined to be more optimal than daily simvastatin 40 mg and will be utilized in the subsequent LIVERHOPE-EFFICACY trial to investigate the effect of rifaximin combined with simvastatin 20 mg on the occurrence of acute-on-chronic liver failure in patients with decompensated cirrhosis (NCT03780673).

Research is currently underway to investigate the effects of atorvastatin or simvastatin on hepatic decompensation, survival, and statin-related hepatotoxicity.[65] Another recruiting RCT will explore the effect of propranolol vs carvedilol followed by rosuvastatin vs placebo on PH, represented by HVPG, in patients with hepatic cirrhosis and prior variceal bleeding (NCT03720067). More rigorous evidence from these trials will likely aid in designating a role for statins in medical management of cirrhosis.

Albumin

Utilization of albumin in patients with decompensated cirrhosis and ascites is another topic of debate. Ascites occurs in 5% to 10% of compensated patients annually and heralds both decompensation and worsening prognosis, as ascites onset increases 1-, 2-, and 5-year mortality rates to approximately 30%, 50%, and 70%, respectively.[66,67] Albumin is regularly employed in the context of volume expansion following paracenteses, but further clarity on the pathophysiology of decompensated cirrhosis has shown other conferred benefits. Human albumin has the potential to bind to damaged molecules; decrease systemic inflammation and oxidative stress, which in turn reduces endothelial damage; and prevent decreases in cardiac output and consequent increase in plasma renin.[68] Approximately 20 years after the pioneering RCT by Gentilini and colleagues[69] investigating albumin patients with decompensated cirrhosis and ascites, the Italian

Association for the Study of the Liver and the Italian Association of Transfusion Medicine and Immunohaematology issued new clinical recommendations for the role of long-term albumin use in decompensated cirrhosis. This 2020 update recommended long-term albumin therapy as a medical treatment option for patients with ascites, particularly patients with at least grade 2 noncomplicated ascites refractory to moderate diuretic dosing (at least 200 mg of a mineralocorticoid receptor antagonist paired with furosemide 25 mg daily) and patients with generally refractory ascites.[70]

A recent systematic review of 45 RCTs and 10 meta-analyses published between 1985 and February 2020 found albumin to be efficacious in preventing paracentesis-induced circulatory dysfunction, treating SBP and hepatorenal syndrome (HRS), and providing survival benefits for patients with decompensated cirrhosis.[71] Of these studies, the ANSWER trial was one of the most pivotal in assessing long-term albumin administration in the context of decompensated cirrhosis.[72] This trial found that patients with at least grade 2 noncomplicated ascites refractory to moderate diuretic dosing saw greater benefit from standard medical treatment (SMT) with albumin 40 g twice weekly for 2 weeks followed by 40 g weekly compared with SMT alone. Patients on albumin had an 18-month overall survival of 77% with the Kaplan-Meier method vs 66% (P=.028) for patients on SMT, which corresponded to a 38% decrease in the mortality HR (0.62; 95% CI, 0.40-0.95). The albumin group also had better ascites control and consequently underwent significantly fewer paracenteses. Cumulative incidence of refractory ascites was also markedly reduced, with an HR of 0.43 (95% CI, 0.29-0.62; P<.0001). Although occurrence of variceal bleed did not differ, incidence rate ratios of SBP, non-SBP bacterial infections, renal dysfunction, HRS type 1, grade 3 or 4 HE, and diuretic-induced side effects (eg, hyponatremia, hyperkalemia) decreased 30% to 67.5% in the albumin group.

A post hoc analysis showed that serum albumin levels after 1 month of treatment were more effective in guiding albumin use compared with baseline serum albumin levels.[73] The goal albumin level was determined to be 4.0 g/dL, although it was noted that patients with albumin levels below normal received benefits from long-term albumin treatment. The Pilot-PRECIOSA study aimed to identify an albumin dosage that normalized serum albumin concentration.[74] Albumin normalization and greater clinical benefits in circulatory and inflammatory regulation were seen with high-dose albumin at 1.5 g/kg per week compared with 1 g/kg every 2 weeks. These 2 studies not only challenge but also further qualify the findings of the MACHT trial, which showed no significant change with 40 g of albumin every 2 weeks.[75]

Recently, the ATTIRE trial, a randomized, multicenter, open-label, parallel-group trial in the United Kingdom, explored the benefit of repleting serum albumin to a goal of 3.0 g/dL or greater in patients with decompensated cirrhosis.[76] Most patients in the study had alcohol-induced cirrhosis and presented with new-onset or worsening ascites. Patients were randomized into 2 groups: one group received SMT and the other group received daily 20% albumin infusions to maintain a goal albumin level of at least 3.5 g/dL over a maximum 14-day period. Ultimately, the albumin group received a median of 200 g of albumin per patient with a range from 140 g to 280 g, and the SMT group received a median of 20 g of albumin per patient with a range of 0 g to 120 g (with 49.4% of the SMT group not receiving any albumin). Comparing endpoints in the albumin group and the SMT group, infection rates were 20.8% vs 17.9%, renal dysfunction was 10.5% vs 14.4%, and death occurred in 7.9% vs 8.3%, respectively. These rates as well as the composite of these 3 endpoints were all statistically insignificant. Time to death between the albumin group and the SMT group was also noted to be statistically insignificant, with 14.0% vs 15.6% at 28 days, 24.2% vs 23.4% at 3 months, and 34.7% vs 30.0% at 6 months, respectively. There was also no difference in hospital stay, and the occurrence of pulmonary edema was higher in the albumin group. Overall, the study failed to show significant benefits from albumin administration and noted a greater number of adverse events in the albumin group. Therefore, although long-term administration of albumin is attractive from a pathophysiologic standpoint, current guidelines do not recommend long-term administration of albumin in patients with cirrhosis.[66,77]

Conclusion

Progression to PH is a defining point in the clinical management of patients with chronic liver disease. The preferred term of cACLD recognizes that the development of PH, rather than the histologic finding of cirrhosis, is associated with adverse outcomes. With diagnostic focus shifting to developing noninvasive methods to predict PH, modalities such as TE, MRE, and multiparametric MRI have emerged as viable options. Among these, TE may be the most effective tool, given its current widespread adoption in outpatient clinical practice. This is further supported by studies on the Expanded-Baveno VI criteria showing that an LS cutoff of greater than or equal to 25 kPa can rule in CSPH and an LS cutoff less than 15 kPa combined with a platelet count greater than 150 × 10^9/L can rule out CSPH.[16] The use of TE can be expanded beyond LS measurement to SS measurement, augmenting the sensitivity of detecting CSPH and thus

detecting candidates warranting endoscopic evaluation for HRVs. Regarding the management of PH, NSBBs may have a role beyond variceal bleed in preventing decompensation and development of ascites. The case has been made for the utility of statins, but further data are still warranted regarding expanded use of albumin to prevent complications of PH.

Disclaimer

The authors prepared this work in their personal capacity. The opinions expressed in this article are the authors' own and do not reflect the views of the Department of Veterans Affairs or the US government.

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