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Imaging in Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome

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A B S T R A C T

Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of hematopoietic cell transplantation. Early diagnosis and, subsequently, earlier intervention have been shown to be beneficial to clinical outcomes. Diagnostic criteria from the European Society for Blood and Marrow Transplantation include recommendations on the use of imaging for diagnosis. This review discusses evidence on the use of imaging in the management of VOD/SOS and how imaging biomarkers can contribute to earlier diagnosis/treatment.

INTRODUCTION

Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication primarily following myeloablative conditioning for allogeneic hematopoietic cell transplantation (HCT), but also following reduced-intensity conditioning for allogeneic HCT, as well as autologous HCT [1-7]. Sinusoidal obstruction may lead to portal hypertension, reversal of hepatic venous flow, hepatorenal syndrome, and multiorgan dysfunction [7,8]. The development of VOD/SOS is affected by numerous patient- and transplantation-related factors, some of which (eg, iron overload, changes in portal circulation) may be defined by imaging [3,9]. Historically, 2 sets of clinical criteria have been used to establish a diagnosis of VOD/SOS: the modified Seattle criteria [10] and the Baltimore criteria [11]. These criteria did not explicitly have a role for imaging. In 2016 and 2018, the European Society for Blood and Marrow Transplantation (EBMT) proposed new adult and pediatric diagnostic criteria (Table 1). [4,9]. Both sets of criteria have suggested roles for imaging from ultrasound evidence of VOD/SOS in the adult criteria to imaging-confirmed hepatomegaly and ascites in the pediatric criteria.

Early detection of VOD/SOS and prompt initiation of treatment are critical to optimal patient management, and baseline and serial ultrasound assessment may help identify early signs suggestive of VOD/SOS [7]. Defibrotide is currently the sole drug approved in the United States and the European Union for treating subsets of VOD/SOS following HCT [12-16]. Earlier treatment with defibrotide has been shown to be more beneficial than late treatment [17]. In this article, we summarize the current available evidence on the use of imaging in the management of patients with VOD/SOS and discuss how imaging biomarkers can contribute to earlier diagnosis and treatment.

USE OF IMAGING IN HEPATIC VOD/SOS

Baseline and serial ultrasound examinations may help detect early signs suggestive of VOD/SOS in both adults and children [4,9,18]. Similarly, ultrasound also may be useful for excluding diagnoses other than VOD/SOS and for confirming clinical findings (eg, hepatomegaly, ascites), especially in overweight or obese patients in whom assessment may be difficult [4,9]. Other promising strategies have been suggested; for example, data from a monocentric prospective study in adult HCT recipients showed that liver stiffness measurement evaluated by transient elastography (TE) may be a promising strategy for the early detection and follow-up of VOD/SOS [19].

A diagnosis of VOD/SOS may be supported by imaging, but imaging alone is currently not diagnostic [20]. The imaging modalities studied most extensively in VOD/SOS are gray-scale

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Table 1
EBMT Diagnostic Criteria in Adult and Pediatric Patients

EBMT diagnostic criteria in adults [9]	
Classical VOD/SOS (in the first 21 days after HCT)	Late-onset VOD/SOS (>21 days after HCT)
Bilirubin ≥2 mg/dL and 2 of the following criteria must be present: • Painful hepatomegaly • Weight gain >5% • Ascites	Classical VOD/SOS beyond day 21 OR Histologically proven VOD/SOS OR Two or more of the following criteria must be present: • Bilirubin ≥2 mg/dL (or 34 μmol/L) • Painful hepatomegaly • Weight gain >5% • Ascites • AND hemodynamic and/or ultrasound evidence of VOD/SOS
EBMT diagnostic criteria in children [4]	
No limitation on the time of onset of VOD/SOS The presence of ≥2 of the following*: • Unexplained consumptive and transfusion-refractory thrombocytopenia† • Otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics or a weight gain >5% above baseline • Hepatomegaly (best if confirmed by imaging) above baseline value‡ • Ascites (best if confirmed by imaging) above baseline value‡ • Rising bilirubin from a baseline value on 3 consecutive days or bilirubin ≥2 mg/dL within 72 hours	

EBMT, European Society for Bone and Marrow Transplantation; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; HCT, hematopoietic cell transplantation; CT, computed tomography; MRI, magnetic resonance imaging..
* With the exclusion of other potential differential diagnoses.
† ≥1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines.
‡ Suggested: imaging (ultrasound, CT, or MRI) immediately before HCT to determine baseline value for both hepatomegaly and ascites.

and color Doppler ultrasound [20]. The current role of imaging in VOD/SOS is often limited to the use of ultrasound to aid the differential diagnosis [21]. The EBMT diagnostic criteria for adults proposed in 2016 also recommend the use of hemodynamic and/or ultrasound evidence in addition to other clinical criteria for a diagnosis of late-onset VOD/SOS [9]. In addition, the American Association for the Study of Liver Diseases recommends the use of ultrasound to facilitate the diagnosis of VOD/SOS [20]. The EBMT diagnostic criteria for pediatric patients proposed in 2018 recommend imaging (ultrasound, computed tomography [CT], or magnetic resonance imaging [MRI]) immediately before HCT to determine baseline values for both hepatomegaly and ascites [4]. Joint working committees of the Pediatric Acute Lung Injury and Sepsis Investigators and the Pediatric Blood and Marrow Transplantation Consortium acknowledge that VOD/SOS is a clinical diagnosis but state that gray-scale and color Doppler ultrasound may be helpful in supporting the diagnosis and monitoring the response to treatment. The committees also noted that pretransplantation baseline ultrasound may provide a useful reference for future abnormalities in patients at risk of developing VOD/SOS [22].

Ultrasound

Ultrasound is a noninvasive method that can be repeated as needed, requires no preparation, lacks complications, and is well tolerated by patients [18]. In 1997, Lassau et al [18] published data from a prospective study describing the value of ultrasound in the prediction, diagnosis, and prognostic assessment of VOD/SOS using 7 gray-scale morphologic criteria and 7 Doppler criteria. In that study, 100 patients received total body irradiation or busulfan therapy as intensive treatment before HCT, and 25 patients developed VOD/SOS. Gray-scale and Doppler ultrasound were performed in all patients before HCT and weekly during hospitalization. The 14 criteria were used to produce a gray-scale score, a Doppler score, and a total score. A total score of 6, which was associated with a diagnosis of VOD/SOS, had a sensitivity of 83% and a specificity of 87%.

A novel ultrasound 10-parameter scoring system (HokUS-10) was recently evaluated in 10 patients diagnosed with VOD/SOS based on the Baltimore or modified Seattle criteria after HCT [23]. Gray-scale and color Doppler ultrasound were performed in all patients. Univariate analysis identified 6 scoring parameters significantly associated with a diagnosis of VOD/SOS: ascites, paraumbilical blood flow signal, paraumbilical dilatation, gall bladder wall thickening, increased vertical diameter of the hepatic right lobe, and portal vein dilatation. Four additional parameters were included in the scoring system: increased vertical diameter of the hepatic left lobe, increased resistive index of the hepatic artery, decrease in portal vein flow velocity, and contraflow of the portal vein. HokUS-10 achieved 100% sensitivity, 95.8% specificity, 71.4% positive predictive value, and 100% negative predictive value. In 4 of 10 patients, ultrasound diagnosis preceded the clinical diagnosis of VOD/SOS; this method requires further validation.

Gray-Scale Ultrasound

Gray-scale ultrasound may be useful for noting anatomic variables, such as hepatomegaly, splenomegaly, ascites, gallbladder wall thickening, and portal vein dilation (Figure 1) [21]. Its advantages include availability at most centers, feasibility of bedside use, and no need for contrast medium or radiation exposure. Disadvantages include nonuniformity of results and no specific VOD/SOS signs. Variables and measurements for gray-scale ultrasound are provided in Table 2.

Color Doppler Ultrasound

Color variables are those that involve the absence/presence of flow and flow direction (Figure 2). Doppler ultrasound shares the advantages of not requiring a contrast medium or radiation and being bedside feasible; it also has good accuracy in measurement of portal hypertension and is useful for differential diagnosis [21]. Disadvantages include being operator-dependent, requiring operator expertise, and poor uniformity of results. Variables and measurements for color Doppler ultrasound are presented in Table 2.

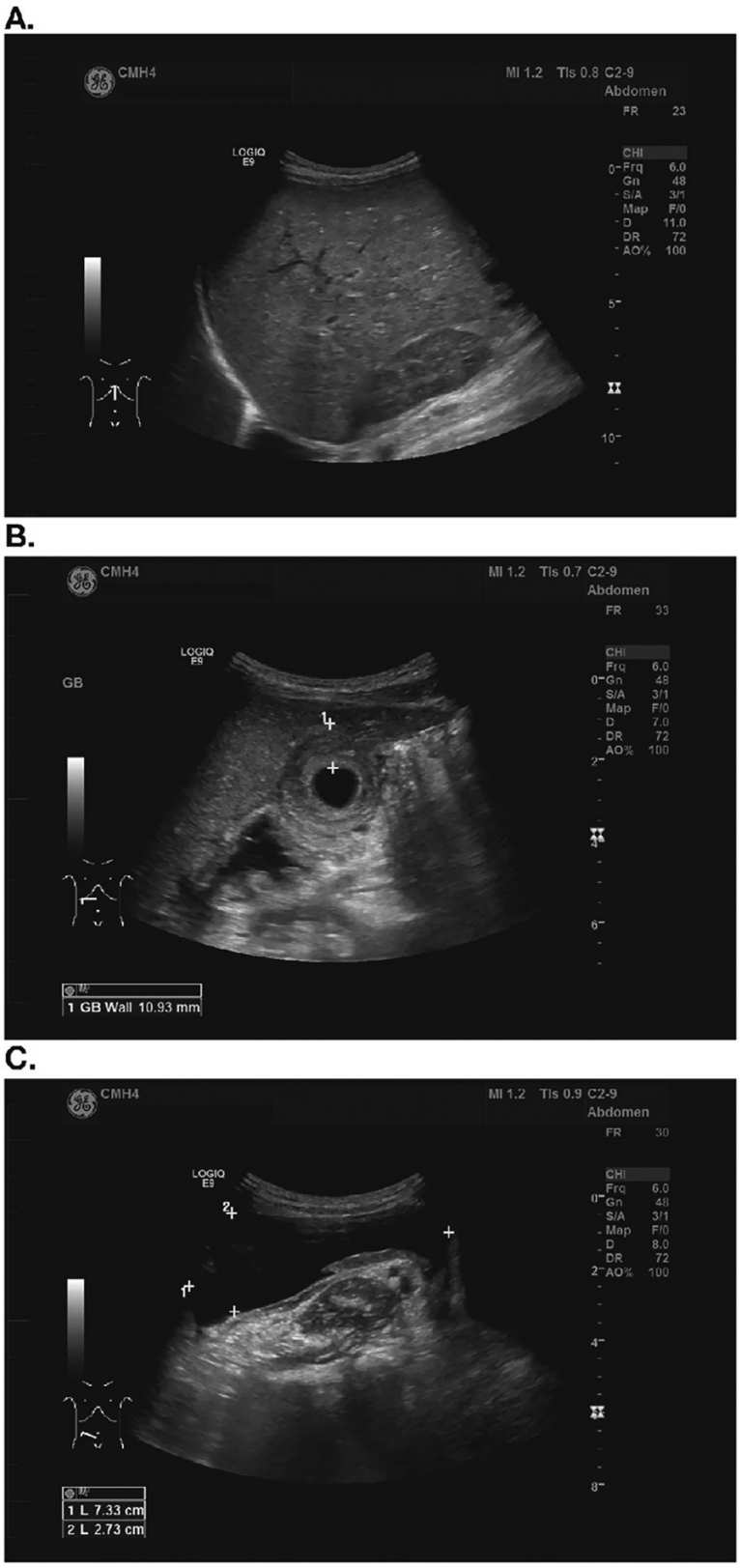

Figure 1. A 3-year-old female who developed VOD/SOS after HCT for acute myelogenous leukemia. (A) Gray-scale ultrasound image from an examination performed 19 days after HCT showing hepatomegaly with right hepatic lobe measuring 13.9 cm in the cranial-caudal dimension at the mid-clavicular line. (B) Gray-scale image in the same patient showing gallbladder wall thickening, with a wall thickness of 1.1 cm. (C) Gray-scale image in the same patient showing simple ascites in the right lower quadrant of the abdomen. VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; HCT, hematopoietic cell transplantation.

Table 2
Ultrasound Variables and Criteria Measurements

Variable	Lassau's criteria	HokUS-10 scoring
Gray-scale ultrasound		
Hepatomegaly	Liver enlargement: increase in 2 of 3 measurements of >2 cm in adults and >1 cm in children relative to baseline	Hepatic left lobe vertical diameter ≥70 mm (1 point); hepatic right lobe vertical diameter ≥110 mm (1 point)
Splenomegaly	Spleen enlargement: increase >1 cm relative to baseline measurement of the greatest axis	Long axis increase
Gall bladder wall thickening	>6 mm	≥ 6 mm (1 point)
Portal vein diameter	>8 mm in children; >12 mm in adults	≥12 mm (1 point)
Hepatic vein diameter	<3 mm	
Ascites	Presence	Mild (1 point); moderate/severe (2 points)
Paraumbilical vein	Visualization	Diameter ≥2 mm (2 points)
Color Doppler ultrasound		
Absence/presence of flow	Flow recorded in paraumbilical vein	Appearance of paraumbilical vein blood flow signal (2 points)
Flow direction	Reversed flow in the main portal vein	Congestion or hepatofugal flow in the portal vein (1 point)
Spectral Doppler ultrasound		
Portal vein velocity/density/congestion	Flow demodulation (disappearance of velocity variations with breathing); decreased spectral density in portal vein; maximal flow in the main portal vein <10 cm/s; portal vein congestion index ≥.1; monophasic flow in hepatic veins	Velocity <10 cm/s (1 point)
Hepatic artery resistive index	≥.75	≥.75 (1 point)

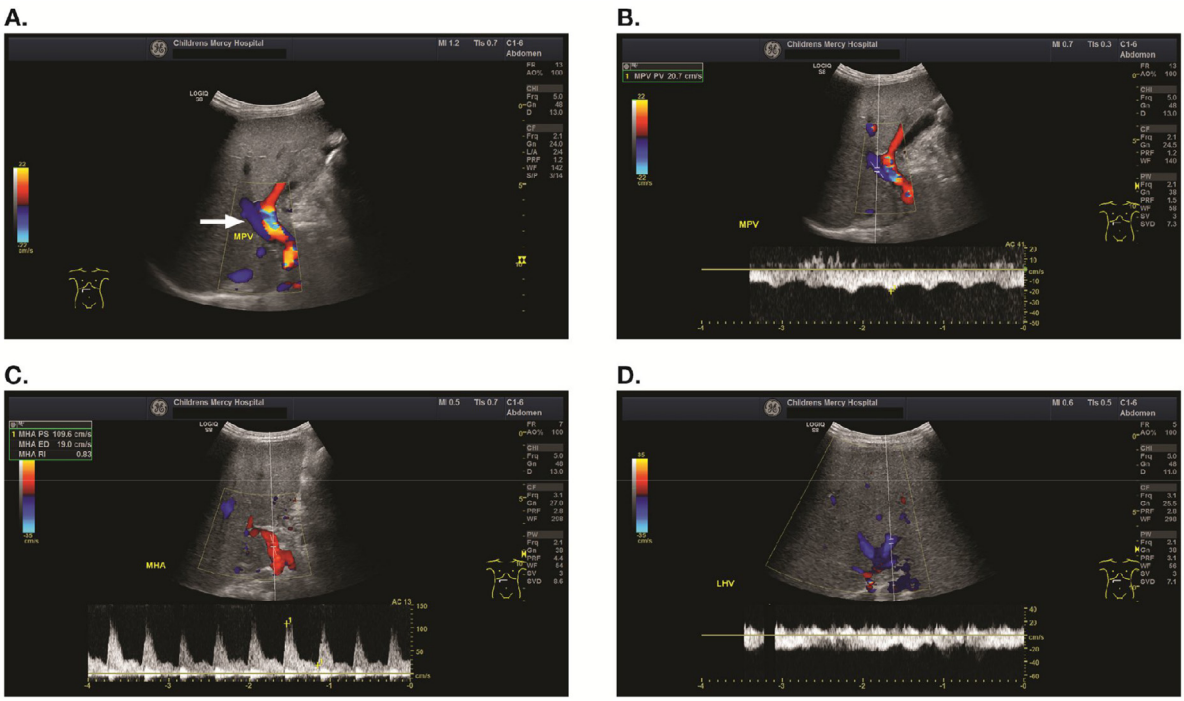

Figure 2. A 2-year-old male who developed VOD/SOS after HCT for acute myelogenous leukemia. (A) Color Doppler ultrasound images from an examination performed 16 days after HCT showing flow in the main portal vein away from the liver parenchyma (arrow). (B) Spectral Doppler image from the same patient showing flow away from the liver, with a peak velocity of 20.7 cm/s. (C) Spectral Doppler image from the same patient showing elevated peak systolic velocity in the proper hepatic artery causing an elevated resistive index of .83. (D) Spectral Doppler image from the same patient showing relatively constant flow in the left hepatic vein with lack of normal respiratory and cardiac variation. VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; HCT, hematopoietic cell transplantation.

Spectral Doppler Ultrasound

Spectral variables are those that involve flow waveforms and quantitative measures such as velocities, resistive indices, and other indices. Advantages and disadvantages are similar to those for color Doppler ultrasound. Variables and measurements for spectral Doppler ultrasound are provided in Table 2.

Ultrasound Elastography

The use of ultrasound elastography has evolved rapidly in recent years as a noninvasive method for assessing the mechanical properties of tissue [24-26]. Ultrasound elastography techniques include different methods to measure qualitative and quantitative changes in soft tissue elasticity [25]. Qualitative imaging is performed using mechanical forces or

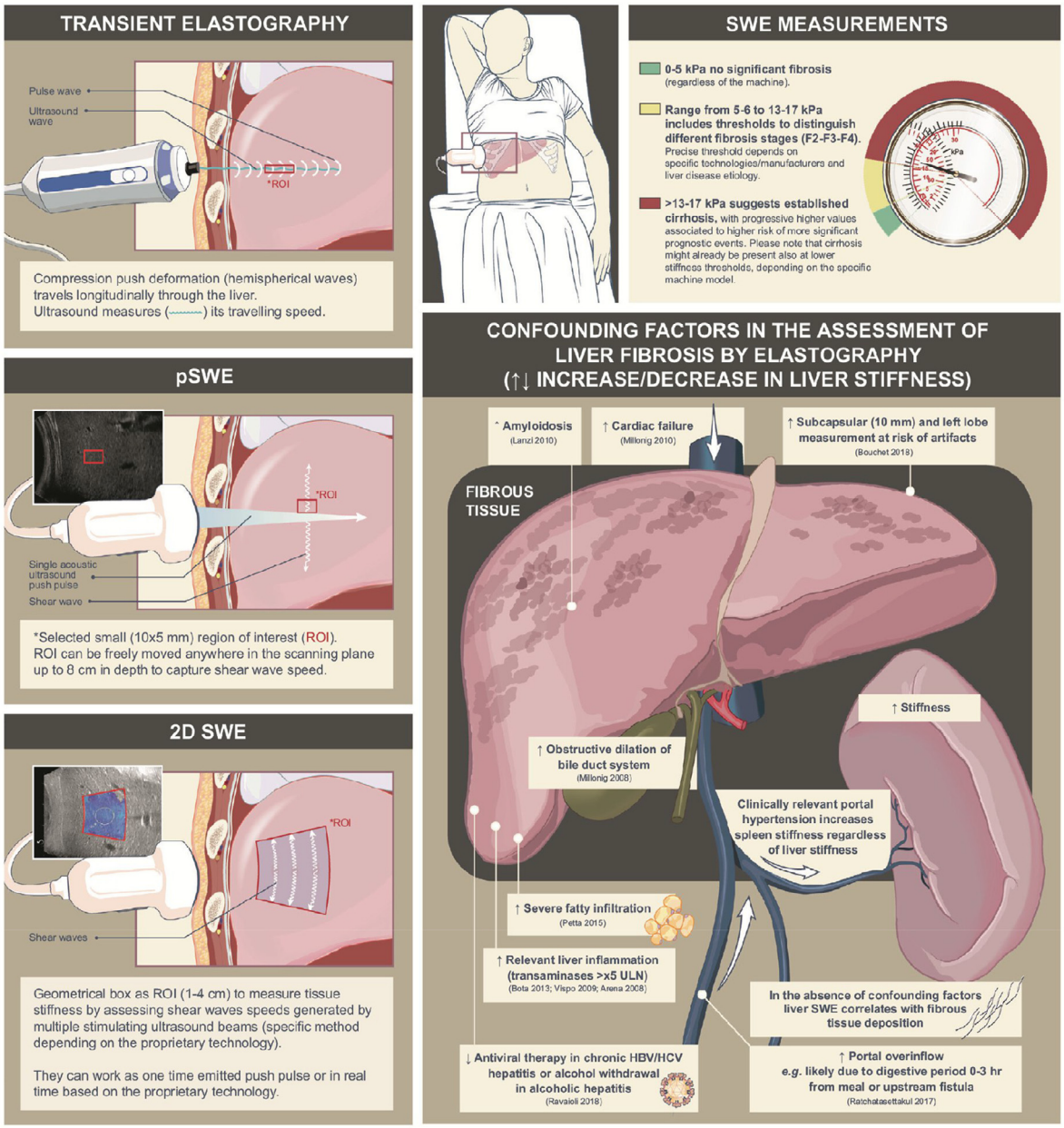

Figure 3. Different elastography techniques include TE, SWE measurements, pSWE, and 2D SWE. TE, transient elastography; SWE, shear wave elastography; pSWE, point shear wave elastography; ROI, region of interest; ULN, upper limit of normal; HBV/HCV, hepatitis B virus/hepatitis C virus. (Image reproduced from Mulazzani et al [28] with permission from Elsevier.)

intrinsic internal forces, whereas quantitative imaging is generally performed through the application of force produced by an ultrasound probe [26].

The 3 ultrasound elastography methods in use today are TE; point shear wave elastography (pSWE), also known as acoustic radiation force impulse quantification; and 2-dimensional shear wave elastography (SWE) (Figure 3) [27,28]. SWE uses qualitative and quantitative techniques (Figure 4) [26]. Among these techniques, liver stiffness measurement assessed by TE (FibroScan; Echosens, Paris, France) is the most validated approach with wide application in liver diseases [21]. Several organizations have proposed recommendations and guidelines for the use of ultrasound liver elastography, including the European Federation of Societies for Ultrasound in Medicine and Biology, World Federation for Ultrasound in Medicine and Biology, European Association for the Study of the Liver—Asociación Latinoamericana Para el Estudio del Hígado, Asian-Pacific Association for the Study of the Liver, and American Gastroenterological Association [27,29,30].

Clinical Application of Liver Ultrasound Elastography

The measurement of liver stiffness was developed to evaluate hepatic fibrosis staging in patients with chronic liver disease [31]. Since its first clinical use, changes in liver stiffness measurement have been observed for conditions other than fibrosis, which can lead to a reduction in liver elasticity (eg, congestion, portal hypertension, cholestasis) [21,25,27,32,33]. Based on these observations, the use of liver stiffness measurement has been studied for other clinical applications, in particular for the evaluation of portal hypertension and its complications [34-36].

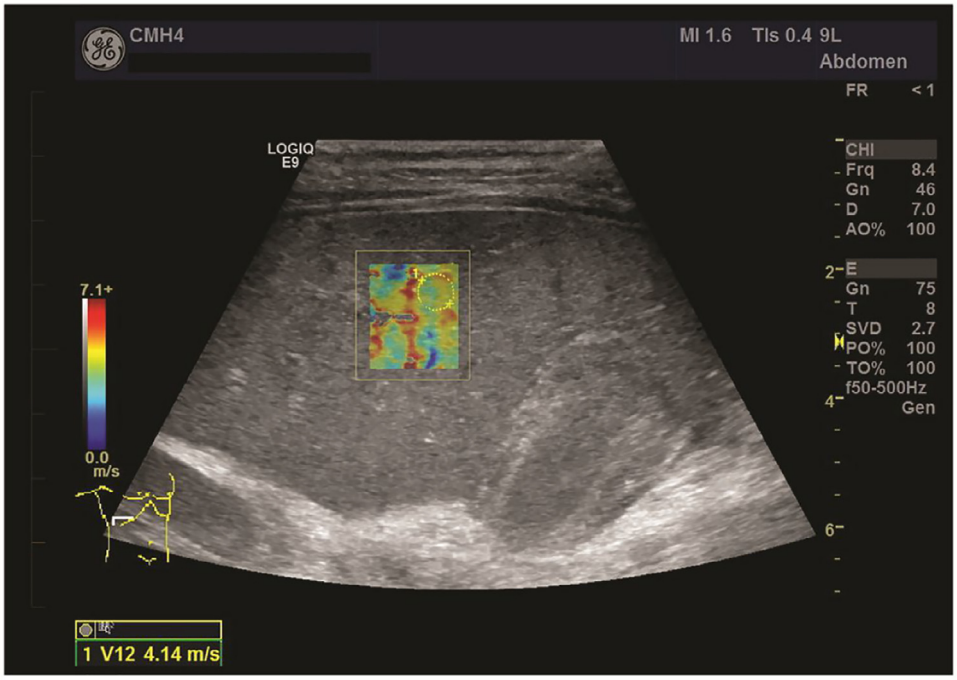

Figure 4. A 3-year-old female who developed VOD/SOS after HCT for neuroblastoma. SWE ultrasound image from an exam performed 16 days after HCT showing increased stiffness in the right hepatic lobe, with a measured shear wave velocity of 4.14 m/s. VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; HCT, hematopoietic cell transplantation; SWE, shear wave elastography.

Before describing the clinical application and performance of liver stiffness measurement, some clarification is needed to facilitate a better understanding of the reasons for the clinical utility of liver stiffness measurement in VOD/SOS diagnosis. First, VOD/SOS, as already mentioned, is a paradigmatic expression of sinusoidal (post) portal hypertension, and most of the clinical signs of VOD/SOS are an expression of the clinical complications of a portal hypertension syndrome [21]. Second, the logic of the use of liver stiffness measurement for the evaluation of portal hypertension, regardless of its causes, is based on the physical principle that it leads to an increase in portal pressure in liver disease; in fact, P (vascular pressure) = R (vascular resistance) × Q (vascular flow). According to this physical law, hepatic vascular resistance is related to hepatic fibrosis, and so an increase in hepatic fibrosis indirectly may reflect portal pressure and portal hypertension [33]. For this reason, liver stiffness measurement can be used to evaluate the degree of pressure of the portal system; furthermore, the good correlation reported in clinical studies between liver stiffness and the hepatic venous pressure gradient (HVPG), the gold standard in the evaluation of portal pressure, makes transient elastography a reasonable noninvasive strategy to evaluate the presence of portal hypertension [27,37,38]. Furthermore, according to the Baveno VI consensus criteria, a liver stiffness value >21 kPa can be used to identify clinically significant portal hypertension [33,39].

Liver stiffness correlates with HVPG and is a promising area of study. It is important to note that HVPG has not yet been fully substituted by noninvasive tests, and its measurement should be encouraged, especially in clinical trials [21]. By extension, HVPG measurement, despite its invasiveness, is also highly informative in the VOD/SOS setting and should be considered in patients with suspected/unclear diagnosis of VOD/SOS. Indeed, more studies are warranted in this context [21]. Table 3 details the evidence supporting the use of ultrasound elastography.

Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS), a specialized type of ultrasound that uses an i.v. injection of microbubble contrast agents, is an established method for detecting and characterizing focal liver lesions and allowing a better view of the microcirculation of the tissues that also has been used to diagnose liver vein thrombosis [40-42]. The value of CEUS in VOD/SOS is evolving, and findings from 2 case reports suggest that CEUS can help to facilitate early diagnosis and clinical follow-up of VOD/SOS [42,43]. In those cases, the CEUS findings were novel, representing VOD/SOS pathophysiology and hepatic microvascularization dysfunction for the first time [42]; nonetheless, although these studies are novel and promising, currently CEUS can only confirm a clinical diagnosis of VOD/SOS and may be useful in the post-treatment follow-up period.

MRI and Magnetic Resonance Elastography

MRI provides excellent cross-sectional visualization of the portal venous system and abdominal solid organs [44]. MRI can be used to assess iron overload using iron quantification sequences for risk stratification for VOD/SOS before transplantation [3,45]. It is probably only useful for risk-stratifying patients before HCT, as there is no practical reason for using it instead of ultrasound during the course of transplantation care. Ultrasound is preferred over MRI because it is quick, portable, and can be performed at the bedside in the HCT unit or intensive care unit. Although its utility for VOD/SOS is still being evaluated, magnetic resonance elastography (MRE) may have a role in risk-stratification before HCT. However, MRE shares some of the practical limitations of MRI in this setting; both techniques are expensive and can be difficult to use.

CT

Some of the limitations of MRI for use in patients with VOD/SOS (eg, transport requirements, risk of allergic reaction and nephrotoxicity) also apply to CT [44]; however, the sedation

Table 3
Evidence for the Use of Ultrasound Elastography

Authors	No. of patients	Type of elastography	Findings	Conclusion
Fontanilla et al (2011) [43]	2 with VOD/SOS	ARFI	ARFI showed median high shear wave velocities (2.75 m/s and 2.58 m/s) that normalized after specific treatment.	Quantitative information generated by ARFI helped to facilitate the diagnosis and was useful in monitoring the response to treatment.
Auberger et al (2013) [56]	67 post-HCT	TE	Maximal total serum bilirubin after HCT was found to be significantly higher in patients with pretransplant LS values >8.0 kPa than with values <8.0 kPa.	TE could potentially be useful before conditioning for risk stratification and in identifying patients at high risk of developing liver complications following HCT
Karlas et al (2014) [57]	59 before and after HCT	TE and right and left liver lobe ARFI (r-ARFI; l-ARFI)	TE and r-ARFI baseline assessments not significantly different between patients with and without severe complications during post-HCT follow-up Baseline l-ARFI was significantly elevated in patients who subsequently developed severe complications and continued to be elevated post-HCT TE showed increasing LS in patients with complications.	
Karlas et al (2019) [58]	106 before HCT conditioning (9 of 16 liver complications were VOD/ SOS)	TE and pSWE	TE and pSWE of the right liver lobe show similarly strong prognostic values, although pSWE (right) identifies a substantially larger cohort of patients at risk using established cutoffs.	TE and pSWE are promising for predicting the risk of free survival from hepatic events and all-cause mortality to 1 yr.
Colecchia et al (2017) [59]	22 patients undergoing HCT	TE	Sudden increase in LS preceded the clinical appearance of VOD/ SOS by 2-6 days.	Early specific treatment in patients with a documented sudden increase in LS values is suggested.
Reddivalla et al (2020) [60]	25 pediatric patients undergoing HCT (5 with VOD/SOS)	SWE	Velocities at day +14 were significantly higher in patients with VOD/SOS; LS increased in those with VOD/SOS.	Study shows the possibility of increasing the diagnosis lead time by 9-11 days.
Colecchia et al (2019) [19]	78 patients undergoing HCT	TE	LS measurement increases occurred at 2-12 days before clinical VOD/SOS appearance and gradually decreased following successful VOD/SOS-specific treatment; LS measurement values did not significantly increase in patients experiencing hepatobiliary complications.	LS measurement by TE can be considered a promising method to perform an early preclinical diagnosis and follow-up of VOD/SOS.

VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; ARFI, acoustic radiation force impulse; HCT, hematopoietic cell transplantation; TE, transient elastography; LS, liver stiffness; pSWE, point shear wave elastography; SWE, shear wave elastography.

Table 4
Recommendations for Imaging in the Diagnosis and Treatment of VOD/SOS

Imaging modality	At baseline	At screening	To confirm diagnosis	To monitor treatment
Gray-scale ultrasound	Yes, to document liver size	Possibly, use HokUS-10 or Lassau's criteria	Yes, use HokUS-10 or Lassau's criteria	Promising but insufficient evidence at this time
Color Doppler ultrasound	Promising but insufficient evidence at this time	Possibly, use HokUS-10 or Lassau's criteria	Yes, use HokUS-10 or Lassau's criteria	Promising but insufficient evidence at this time
Spectral Doppler ultrasound	Promising but insufficient evidence at this time	Possibly, use HokUS-10 or Lassau's criteria	Yes, use HokUS-10 or Lassau's criteria and see portal vein flow reversal	Yes, to observe improvement in reversal of flow
Ultrasound elastography	Yes	Yes	Yes	Yes
CEUS	Insufficient evidence at this time	Insufficient evidence at this time	Insufficient evidence at this time	Insufficient evidence at this time
MRI	Yes, for risk stratification in patients with iron overload conditions, including cases of elevated serum ferritin at screening	No	No	No
MRE	Yes, for risk stratification or liver fibrosis	No	No	No
CT	No	No	Possibly, but not for first line	No
HVPG	No	No	Possibly, but not for first line	No
Liver biopsy	No	No	Possibly, but not for first line	No

VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; CEUS, contrast-enhanced ultrasound; MRI, magnetic resonance imaging; MRE, magnetic resonance elastography; CT, computed tomography; HVPG, hepatic venous pressure gradient.

requirement is much less for a CT scan, which takes less than 30 seconds, than it is for an MRI examination, which takes 60 minutes. Radiation exposure is also a minor consideration with CT [44]. CT has been studied more extensively than MRI for diagnosing VOD/SOS, and has been shown to be useful in differentiating VOD/SOS from graft-versus-host disease [46]. Differentiation by CT is valuable, as patients with both conditions are usually coagulopathic, which complicates liver biopsy due to hemorrhage [46,47].

IMAGE-GUIDED INTERVENTIONAL DIAGNOSIS

HVPG is the current gold standard for assessing portal pressure, and HVPG values ≥10 mmHg are indicative of clinically significant portal hypertension [33,48]. Thus, HVPG can be useful in predicting and diagnosing VOD/SOS through assessment of the degree of portal hypertension. In addition to its diagnostic role, HVPG is also a significant prognostic factor for VOD/SOS, with HVPG ≥20 mmHg associated with poorer outcome [21]. From a clinical standpoint, the measurement of HVPG is invasive—but less so than a biopsy—and can lead to a VOD/SOS diagnosis. Factors that may limit the use of HVPG measurement include risk of bleeding at puncture site, expense, and a lack of expertise at some centers [21]. Despite these limitations, measurement via the transjugular route offers increased safety when performing liver biopsy in cytopenic patients, with an adequate sample size obtained in 98% of cases [49]. HVPG should be supported as a limited-risk procedure compared with biopsy, with a high positive predictive value [21].

LIVER BIOPSY

Invasive measures to diagnose VOD/SOS are usually not warranted [50-52]. In particular, the decision to perform a liver biopsy should be considered carefully, as the procedure carries a small risk of serious and potentially life-threatening complications. In fact, in a more recent study, the need to perform a liver biopsy to confirm VOD/SOS was very low (45 of 1472 patients; 2.8%) [53]; however, that study also showed that no patient developed complications related to the biopsy procedure, and that the biopsy results influenced patient management in 65% of the cases. If liver biopsy is required in the early stages after HCT, transjugular biopsy is recommended over percutaneous biopsy owing to the increased risk of hemorrhage associated with the latter approach [21,52]. Furthermore, if transjugular biopsy is performed, multiple attempts can be made to procure optimal tissue samples [54], and the complication rate is very low [55]. The limitations of transjugular liver biopsy include high cost, radiation requirement, longer performance time compared with percutaneous liver biopsy, and the need for a trained interventional radiologist [55]. Although liver biopsy is not routinely recommended, in doubtful cases (eg, if HVPG is also required to confirm the diagnosis), transjugular biopsy may be attempted at the same time by an experienced radiologist to confirm the diagnosis [21].

CONCLUSIONS

VOD/SOS is a serious condition associated with substantial morbidity and mortality. The strategic implementation of various imaging modalities could help predict the risk of VOD/SOS, facilitate and confirm a diagnosis, and monitor progression before and after treatment (Table 4). In particular, imaging-based findings could identify high-risk patients, enable early intervention with specific treatment, and optimize patient management throughout the VOD/SOS disease course. The current evidence supports the need to perform ultrasound. A review of the data shows that ultrasound (including gray-scale, color Doppler, spectral Doppler, and elastography) is helpful for confirming clinical diagnosis of VOD/SOS. A baseline abdominal ultrasound examination before conditioning that includes gray-scale, color Doppler, spectral Doppler, and elastography evaluations would provide a useful context for interpreting subsequent diagnostic tests. Some ultrasound variables, particularly those from ultrasound elastography, have been shown to change before clinical diagnostic criteria for VOD/SOS are met, suggesting that periodic screening ultrasounds might be performed in high-risk patients to promote earlier identification and intervention. A large, multicenter, prospective study using ultrasound (including elastography) at

multiple time points during the post-transplantation course is needed to validate the utility of these approaches.

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