13 Emerging Non-invasive Markers: Imaging, Blood, and Liver Clearance Tests

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Emerging Non-invasive Methods as a Surrogate for HVPG Measurement

Imaging Markers

Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS) involves the intravenous administration of minute, gas-filled microbubbles that enhance the intravascular signal. The hepatic vein arrival time (HVAT) of the microbubble agent has been studied as a diagnostic tool for detecting advanced fibrosis and cirrhosis [1]. The peak enhancement time of the microbubble, which is defined as the interval time from the contrast onset in the splenic artery to the time to reach maximum intensity in the splenic vein, was shown to correlate with HVPG [2].

Several characteristics of the contrast agents have been studied in relation to PH. The subharmonic signal from the US contrast agents reflected pressure changes in the ambient fluid. This was the basis of the subharmonic-aided pressure estimation technique (SHAPE) [3]. The SHAPE gradient between the portal vein and the hepatic vein was initially shown to correlate with HVPG in a pilot study of 45 patients [4] and validated in a prospective cohort of 125 patients [5]. Assessment of the hepatic vascular network using computer-based analysis of the videos generated from CEUS yielded the 'hepatic vascular connectome' [6]. Patients with cirrhosis

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had a lower clustering coefficient of the hepatic vascular connectome compared to healthy controls, and the clustering coefficient correlated with HVPG in 15 patients [6]. This method has been evaluated further in a multicentre study, but the results have not yet been published in detail. Although an excellent correlation with HVPG was reported in the initial results, the automated software was only able to provide portal pressure estimation in 56% of the patients studied [7]. The poor technical success rate may limit the generalisability of this technique.

Computed Tomography

The ratio of liver to spleen volume measured on contrast-enhanced computed tomography (CT) images was shown to correlate with HVPG [8]. These CT scans were obtained preoperatively in patients being evaluated for hepatocellular carcinoma (HCC) resection, and the CT-based model was developed to stratify patients for resection surgery and liver transplantation. However, the correlation was poor in patients at extremes of the HVPG spectrum (i.e., normal, or very high) [9, 10].

Advances in the imaging-based 3D modelling with computational fluid analysis allow non-invasive assessment of intravascular blood flow and pressure, and these techniques are used in cardiology for the assessment of coronary arteries [11]. Qi et al. recently used triple-phase CT angiography of the liver to develop a 'virtual HVPG' (vHVPG) [12]. The vHVPG was calculated using a mathematical model that included the portal vein velocity measured using Doppler US. There was a moderate positive correlation between vHVPG and invasive HVPG ($R = 0.61$), with an AUROC of 0.88 for diagnosing CSPH. Notably, interpretation of the vHVPG was time-consuming (~2.5 h/case) and the study included small numbers of patients without CSPH.

The development of a radiomics signature involves machine learning to extract high-dimensional quantitative features from radiological images. This was explored as a method to evaluate PH [13]. Regions of interest were drawn on portal venous phase CT images of the liver and spleen, and 20,648 radiomics features were retrieved. This was reduced to seven features from the liver and four features from the spleen, which were included in a regression model to develop radiomics-based HVPG (rHVPG). The rHVPG had an AUROC of 0.85 for diagnosing CSPH and was validated in four external cohorts. The direct correlation between rHVPG and HVPG was not reported.

These CT-based methods involve ionising radiation, which limits utility especially for repeated measurements. The intravenous contrast for CT is also recognised to be nephrotoxic and can cause contrast-induced acute kidney injury [14].

Magnetic Resonance Imaging

Haemodynamic Measures

Phase contrast (PC)-MRI is a non-invasive technique to measure flow in a blood vessel without the use of intravenous contrast. PC-MRI measures blood flow with high accuracy, confirmed by phantom models [15, 16] and by in vivo studies with direct measurement in deep canine arteries and veins [17].

Table 13.1 Summary of MRI parameters evaluated for the assessment of portal hypertension

MRI parameters	Study	Correlation with HVPG	Notes
Vessel flow (PC-MRI)			
• Azygous vein flow	Gouya et al. 2016 [18]	$r^2 = 0.77$	$n = 69$; HVPG range 3 to 25 mmHg
	Palaniyappan et al. 2016 [19]	$r = 0.66$	$n = 30$; mean HVPG 9.8 ± 6.1 mmHg
• Superior mesenteric artery velocity	Palaniyappan et al. 2016 [19]	$r = 0.53$	
• Splenic artery velocity	Palaniyappan et al. 2016 [19]	$r = 0.58$	
• Caval subtraction hepatic artery fraction	Chouhan et al. 2017 [20]	$r = 0.78$	$n = 12$; mean HVPG 12.3 ± 1.6 mmHg
Tissue perfusion (arterial spin labelling (ASL)			
• Liver tissue perfusion	Palaniyappan et al. 2016 [19]	$r = 0.38$	Correlation was absent in HVPG >10 mmHg
• Arrival time		$r = -0.47$	
Structural measures			
• Liver T1	Palaniyappan et al. 2016 [19]	$r = 0.84$	
• Spleen T1	Palaniyappan et al. 2016 [19]	$r = 0.40$	Correlation was absent in HVPG >10 mmHg
	Levick et al. 2019 [25]	$r = 0.69$	$n = 19$, median HVPG 9.0 (IQR 4.0–14.0)
Dynamic contrast-enhanced MRI (DCE-MRI)			
• Liver distribution volume (DV)	Wagner et al. 2018 [31]	$r = 0.49$	$n = 34$; 12 patients <5 mmHg, 13 patients 5–10 mmHg, 9 patients ≥10 mmHg
• Liver time to peak (TTP)		$r = 0.52$	
• Liver upslope		$r = -0.57$	

PC-MRI measured azygous vein flow that has been shown to correlate with grade of oesophageal varices [16] and HVPG [18, 19] (Table 13.1). However, the correlation was absent in patients with CSPH [19]. The relationship between hepatic inflow and portal pressure is less well established. Portal venous flow does not correlate with HVPG [18–20], but hepatic arterial fraction of the hepatic inflow was shown to correlate with HVPG in 12 patients [20]. The hepatic artery flow in this study was obtained indirectly by subtracting the portal vein flow from the total hepatic blood flow (the difference between infra- and suprahepatic vena cava). PC-MRI measured flow in the splanchnic circulation (splenic artery and superior mesenteric artery) correlated significantly with HVPG [19].

Arterial spin labelling (ASL)-MRI is a non-invasive technique that quantifies tissue perfusion by using magnetically labelled arterial blood water protons as an

endogenous tracer [21]. The liver perfusion and tissue arrival time measured using ASL-MRI have been shown to correlate with HVPG [19].

Structural and Architectural Changes

Native (non-contrast) longitudinal relaxation time (T1) can detect pathologically important processes in tissues [22] and is an established composite marker of liver inflammation and fibrosis [23, 24]. Furthermore, liver T1 correlated with HVPG, and this relationship was maintained in patients with CSPH [19]. The T1 measurement was respiratory-triggered and multi-slice, and therefore a large volume of the liver could be sampled in a reasonable timeframe. Interestingly, the distribution of liver T1 values was shown to increase with worsening of PH, reflecting the increasing heterogeneity of T1 values across the liver volume. This underscores the sampling variability associated with liver biopsy (and potentially transient elastography).

A subsequent study reported an association between splenic T1 and HVPG but failed to show a correlation with liver T1 [25]. The methodology used to measure T1 could potentially explain this difference. In this study, a modified look-locker inversion recovery (MOLLI) T1 mapping method was used which requires breath-holding for every image slice acquired. The T1 measurements were obtained from regions of interest drawn on the liver and spleen and therefore could be susceptible to sampling variability due to the heterogeneity of T1 values across the organ. In addition, it has been shown that the hepatic fat content can be large enough to cause substantial MOLLI T1 alterations [26].

An MRI-based scoring system of the features of PH was studied as a surrogate measure of HVPG [27]. The PH score included the number of variceal sites, volume of ascites and maximum splenic diameter, with scores between 0 and 3 in each domain yielding a total score of 0 to 9 for each patient. The PH score correlated with HVPG and the AUROC for detection of PH and CSPH was 0.78 and 0.83, respectively.

Dynamic Contrast-Enhanced MRI (DCE-MRI)

Perfusion-weighted MRI can be performed by measuring the signal intensity in the tissue of interest after injection of contrast against time. Initial assumption of a linear relationship between the signal intensity and the concentration of gadolinium in the liver using a single-input single-compartment model is simplistic and inaccurate, as it does not take into account the separate portal venous and hepatic arterial contributions [28]. However, subsequent analysis of signal intensity over the portal vein, aorta and liver parenchyma against time can be fitted to a dual-input single-compartment model [29].

Decreased portal fraction, total liver perfusion, increased arterial fraction as well as increased mean transit time (MTT) were related to severity of PH [30]. Significant correlation of DCE-MRI parameters including contrast time-to-peak, liver distribution volume and liver upslope correlated with HVPG [31].

4D flow MRI mapping with gadolinium-based contrast allows 3D vascular coverage and is a promising technique for comprehensive haemodynamic analyses.

Increased 4D flow parameters in the splanchnic circulation (splenic artery peak velocity, superior mesenteric vein, and splenic vein flow) were related to severity of PH. However, HVPG was not measured in this study and the composite PH score [27] was used as a surrogate measure of portal pressure.

The potential adverse events associated with the use of contrast agents limit the use of DCE-MRI in patients with chronic liver disease. Gadolinium-based contrast agents are reported to cause nephrogenic systemic fibrosis in patients with renal failure [32].

Combination MRI Markers

The combination of liver T1 and splenic artery velocity correlated with HVPG [19]. These MR markers reflect the underlying pathophysiological changes (structural and haemodynamic) in the development and progression of PH. Moreover, the linear model provided good prediction of HVPG across the spectrum of HVPG values from normal to CSPH and performed better than liver T1 or splenic artery velocity alone.

Magnetic Resonance Elastography (MRE)

Magnetic resonance elastography (MRE) is an alternative to the ultrasonography-based method to evaluate liver and spleen stiffness. Recent studies have validated the use of MRE for evaluating liver fibrosis [33]. MRE has the theoretical advantage over ultrasonography-based elastography methods of evaluating stiffness over a larger area of liver, hence reducing sampling variability. Using MRE, the shear modulus can be assessed using either a 2D or 3D technique. MRE requires special hardware and software which could limit its widespread use.

In a recent meta-analysis, the diagnostic accuracy of spleen stiffness was higher than liver stiffness using MRE. The AUROC for detection of CSPH was 0.88 and 0.92 for liver and spleen stiffness, respectively [34]. The correlation of MRE-measured liver and spleen stiffness with HVPG is summarised in Table 13.2.

Table 13.2 Summary of the relationship between MRE measured liver and spleen stiffness with portal hypertension

Parameter	Sample size, *n*	Study	Correlation with HVPG (Correlation coefficient, *r*)
Liver stiffness	34	Wagner et al. 2018 [31]	0.486
	36	Ronot et al. 2014 [35]	0.44
	15	Gharib et al. 2017 [36]	0.64
	52	Danielsen et al. 2021 [37]	0.96
Spleen stiffness	34	Wagner et al. 2018 [31]	0.099 (NS)
	36	Ronot et al. 2014 [35]	0.57
	52	Danielsen et al. 2021 [37]	0.97

NS not significant

Serum Markers

Simple liver fibrosis scores were developed using combinations of routine blood tests as indirect markers of liver scarring. Although these markers only correlate moderately with HVPG, some (e.g., Lok score) can diagnose CSPH and the presence of varices (Table 13.3). Thrombocytopenia is an important indication of PH and many of the simple marker panels contain platelet count. The Enhanced Liver Fibrosis (ELF) test is derived from direct markers related to hepatic extracellular matrix turnover and has been extensively validated for the non-invasive assessment of liver fibrosis [38]. The direct and indirect markers of fibrosis perform well in identifying advanced liver fibrosis and early stages of PH when it is largely driven by increased intrahepatic vascular resistance due to structural changes. However, these markers are unlikely to reflect the haemodynamic changes that occur with severe PH. The ALBI score was originally devised as a measure of liver function in patients with hepatocellular carcinoma (HCC) [39]. There was a weak positive correlation between ALBI score and HVPG ($r = 0.307$, $P < 0.001$) [40]. The ALBI score has also been shown to predict patients at risk of decompensation [41].

sCD163, a scavenger receptor expressed on macrophages, is a specific marker of macrophage activation and is related to the severity of cirrhosis and PH [42]. Combination of ELF and sCD163 had a superior diagnostic accuracy in identifying CSPH compared to each component individually (AUROC of 0.82, 0.88 and 0.90 for sCD163, ELF and combination, respectively) [43]. Von Willebrand factor (vWF) is related to endothelial dysfunction and circulating levels of vWF correlated with HVPG [44]. vWF was also reported to be related to bacterial translocation and inflammation and associated with clinical outcomes independent of HVPG [45]. The VITRO score is calculated as the ratio of vWF to thrombocytes, and the diagnostic accuracy of the VITRO score for detecting cirrhosis [46] and CSPH [47] was superior to vWF alone.

Indocyanine green (ICG) is administered intravenously and nearly exclusively extracted by the hepatic parenchyma and rapidly excreted in bile. Therefore, ICG clearance, which is quantitatively assessed by spectrophotometry, reflects both hepatic function and hepatic blood flow. The ICG 15-minute retention test (ICG-R15) is performed on peripheral blood samples following a bolus injection of ICG and has been shown to be linearly correlated with HVPG ($r = 0.57 – 0.78$) [50, 74, 75]. The ICG-R15 can also be assessed in vivo using pulse dye densitometry finger probes, but this has not yet been correlated with HVPG.

The HepQuant SHUNT test quantifies hepatic function by simultaneously measuring flow-dependent clearance of cholate from both portal and systemic circulations. In a small study of 20 patients, the SHUNT test was shown to correlate with HVPG [76]. The derived disease severity index (DSI) has been shown to predict decompensation independent of MELD [77]. The 13C-methacetin breath test is another potential method to assess hepatic function and, in a study of 155 patients with NASH-related cirrhosis, detected CSPH with an AUROC of 0.83 [78].

These promising results with different liver ‘clearance’ tests need further validation in large multicentre studies.

Table 13.3 Summary of Serum Marker Tests in Evaluating Portal Hypertension; Correlation with Hepatic Venous Pressure Gradient (HVPG), Diagnostic Accuracy in Estimating Clinically Significant Portal Hypertension (CSPH), and High-Risk Varices (HRV)/Varices Needing Treatment (VNT) Liver Clearance Tests

Blood-based biomarkers		Sample size, *n*	Correlation with HVPG (Correlation coefficient, r)	Diagnosis of CSPH (AUROC)	Diagnosis of HRV/VNT (AUROC)	Notes
Indirect fibrosis markers						
ALBI *(albumin, bilirubin)*	Hsieh et al. [40]	242	0.31			Retrospective, predominantly viral hepatitis (81%)
Lok index *(platelet, AST, ALT, INR)*	Zhou et al. [48]	132			0.81	Retrospective, CHB cirrhosis patients who did not meet Baveno VI criteria
	Hsieh et al. [40]	242	0.30			Retrospective, predominantly viral hepatitis (81%)
	Cho et al. [49]	219		0.76 (cut-off 0.8)	0.65 (cut-off 1.5)	Retrospective, alcohol-related cirrhosis
	Lisotti et al. [50]	96		0.83		Prospective, mixed etiology
	Sebastiani et al. [51]	510			0.70 (cut-off 1.5)	Retrospective, patients with cirrhosis and gastroscopy
	Wang et al. [52]	238		0.74 (cut-off 1.3)		Retrospective, mixed etiology
	Hassan et al. [53]	65			0.72 (cut-off 0.7)	Prospective, CHC cirrhosis
	Stefanescu et al. [54]	231			0.73 (cut-off 0.796)	Prospective, biopsy proven cirrhosis secondary to alcohol and CHC
	Farid et al. [55]	277			0.72	Prospective, CHC (Egypt)
	Alam et al. [56]	153			0.6 (cut-off 0.62)	Prospective, CHC cirrhosis (Pakistan)
Forns' index *(platelets, GGT, age, cholesterol)*	Cho et al. [49]	219		0.64 (cut-off 8.9)	0.52 (cut-off 9.1)	Retrospective, alcohol-related cirrhosis
	Sebastiani et al. [51]	510			0.66 (cut-off 8.8)	Retrospective, patients with cirrhosis and gastroscopy
	Wang et al. [52]	238		0.66 (cut-off 11.05)		Retrospective, mixed etiology
	Siregar et al. [57]	51			0.72 (cut-off 7.92)	Retrospective, predominantly CHB and CHC cirrhosis
	Hassan et al. [53]	65			0.73 (cut-off 6.9)	Prospective, CHC cirrhosis
	Stefanescu et al. [54]	231			0.65 (cut-off 8.54)	Prospective, biopsy proven cirrhosis secondary to alcohol and CHC

Table 13.3 (continued)

Blood-based biomarkers		Sample size, *n*	Correlation with HVPG (Correlation coefficient, r)	Diagnosis of CSPH (AUROC)	Diagnosis of HRV/ VNT (AUROC)	Notes
AST-to-ALT ratio (AAR)	Lisotti et al. [50]	96		0.71		Prospective, mixed etiology
	Sebastiani et al. [51]	510			0.64 (cut-off 1.1)	Retrospective, patients with cirrhosis and gastroscopy
	Wang et al. [52]	238		0.57 (cut-off 1.59)		Retrospective, mixed etiology
	Farid et al. [55]	277			0.58	CHC (Egypt), prospective
Fibrosis-4 (FIB-4) score *(platelet count, AST, ALT, age)*	Hsieh et al. [40]	242	0.27			Retrospective, predominantly viral hepatitis (81%)
	Zhou et al. [48]	132			0.59 (NS)	Retrospective, CHB cirrhosis patients who did not meet Baveno VI criteria
	Cho et al. [49]	219		0.65 (cut-off 4.1)	0.56 (cut-off 2.6)	Retrospective, alcohol-related cirrhosis
	Lisotti et al. [50]	96		0.766		Prospective, mixed etiology
	Sebastiani et al. [51]	510			0.63 (cut-off 4.3)	Retrospective, patients with cirrhosis and gastroscopy
	Wang et al. [52]	238		0.69 (cut-off 2.72)		Retrospective, mixed etiology
	Hassan et al. [53]	65			0.76 (cut-off 3.3)	Prospective, CHC cirrhosis
	Stefanescu et al. [54]	231			0.63 (cut-off 6.75)	Prospective, biopsy proven cirrhosis secondary to alcohol and CHC
	Farid et al. [55]	277			0.7	CHC (Egypt), prospective
	Alam et al. [56]	153			0.6 (cut-off 3.07)	Prospective, CHC cirrhosis (Pakistan)

Table 13.3 (continued)

Blood-based biomarkers		Sample size, *n*	Correlation with HVPG (Correlation coefficient, r)	Diagnosis of CSPH (AUROC)	Diagnosis of HRV/ VNT (AUROC)	Notes
AST to platelet ratio index (APRI)	Hsieh et al. [40]	242	0.24			Retrospective, predominantly viral hepatitis (81%)
	Zhou et al. [48]	132			0.59 (NS)	Retrospective, CHB cirrhosis patients who did not meet Baveno VI criteria
	Cho et al. [49]	219		0.64 (cut-off 1.0)	0.42 (cut-off 1.2)	Retrospective, alcohol-related cirrhosis
	Lisotti et al. [50]	96		0.74		Prospective, mixed etiology
	Sebastiani et al. [51]	510			0.57 (cut-off 1.5)	Retrospective, patients with cirrhosis and gastroscopy
	Hametner et al. [58]	236		0.62 (cut-off 1.74)		Retrospective, mixed etiology
	Wang et al. [52]	238		0.74 (cut-off 0.73)		Retrospective, mixed etiology
	Stefanescu et al. [42]	231			0.54 (cut-off 2.2)	Prospective, biopsy proven cirrhosis secondary to alcohol and CHC
	Farid et al. [55]	277			0.63	CHC (Egypt), prospective
	Alam et al. [56]	153			0.6 (cut-off 1.03)	Prospective, CHC cirrhosis (Pakistan)
Cirrhosis discriminant score (CDS) *(platelet count, ALT/AST ratio, INR)*	Hsieh et al. [40]	242	0.26			Retrospective, predominantly viral hepatitis (81%)
	Alam et al. [56]	153			0.6 (cut-off 6.5)	Prospective, CHC cirrhosis (Pakistan)
Goteborg university cirrhosis index (GUCI) *(AST, INR)*	Hsieh et al. [40]	242	0.21			Retrospective, predominantly viral hepatitis (81%)
	Farid et al. [55]	277			0.66	CHC (Egypt), prospective
	Alam et al. [56]	153			0.6 (cut-off 1.02)	Prospective, CHC cirrhosis (Pakistan)

(continued)

Table 13.3 (continued)

Blood-based biomarkers		Sample size, *n*	Correlation with HVPG (Correlation coefficient, r)	Diagnosis of CSPH (AUROC)	Diagnosis of HRV/ VNT (AUROC)	Notes
FibroIndex *(platelet count, AST, gamma globulin)*	Sebastiani et al. [51]	510			0.65 (cut-off 2.5)	Retrospective, patients with cirrhosis and gastroscopy
Kings score *(age, AST, INR, platelet count)*	Wang et al. [52]	238		0.76 (cut-off 23.47)		Retrospective, mixed etiology
	Alam et al. [40]	153			0.6 (cut-off 20)	Prospective, CHC cirrhosis (Pakistan)
P2/MS (platelet count $[10^9/L])^2$/ (monocyte fraction [%] × segmented neutrophil fraction [%]) *(platelet count, monocyte fraction, segmented neutrophil fraction)*	Cho et al. [49]	219		0.67 (cut-off 60.2)	0.47 (cut-off 69.4)	Retrospective, alcohol-related cirrhosis
Direct fibrosis markers						
ELF	Hametner et al. [58]	236		0.68 (cut-off 11.4)		Retrospective, mixed etiology
	Palaniyappan et al. [19]	30	0.758			Prospective, mixed etiology
	Sandahl et al. [43]	80		0.88		Prospective, mixed etiology
	Mauro et al. [59]	112	0.671		0.884 (cut-off 10.83)	HCV infected OLT recipients achieving SVR
	Frankova et al. [60]	109	0.349			Liver transplant candidates, mixed etiology
	Ishida et al. [61]	127			0.48 (cut-off 11.75)	Retrospective (Japan), mixed etiology
	Simbrunner et al. [62]	201	0.443	0.833 (cut-off 10.5)	0.552	Prospective, mixed etiology

Table 13.3 (continued)

Blood-based biomarkers		Sample size, *n*	Correlation with HVPG (Correlation coefficient, r)	Diagnosis of CSPH (AUROC)	Diagnosis of HRV/ VNT (AUROC)	Notes
HA	Palaniyappan et al. [19]	30	0.752			Prospective, mixed etiology
	Sandahl et al. [43]	80		0.86		Prospective, mixed etiology
	Frankova et al. [60]	109	0.288			Liver transplant candidates, mixed etiology
	Ishida et al. [61]	127			0.50 (cut-off 110.63)	Retrospective (Japan), mixed etiology
	Simbrunner et al. [62]	201	0.419	0.828 (cut-off 71.4)		Prospective, mixed etiology
TIMP1	Busk et al. [63]	84	0.40			Retrospective, alcohol
	Palaniyappan et al. [19]	30	0.512			Prospective, mixed etiology
	Sandahl et al. [43]	80		0.85		Prospective, mixed etiology
	Frankova et al. [60]	109	0.434			Liver transplant candidates, mixed etiology
	Ishida et al. [61]	127			0.48 (cut-off 379.9)	Retrospective (Japan), mixed etiology
	Simbrunner et al. [62]	201	0.368	0.722 (cut-off 281.4)		Prospective, mixed etiology
PIIINP	Palaniyappan et al. [19]	30	0.607			Prospective, mixed etiology
	Sandahl et al. [43]	80		0.74		Prospective, mixed etiology
	Frankova et al. [60]	109	0.271			Liver transplant candidates, mixed etiology
	Ishida et al. [61]	127			0.48 (cut-off 0.60)	Retrospective (Japan), mixed etiology
	Simbrunner et al. [62]	201	0.332	0.748 (cut-off 16.9)		Prospective, mixed etiology
FibroTest *(α2-macro-globulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, age, gender)*	Thabut et al. [64]	130	0.58			Prospective, mixed etiology
	Thabut et al. [65]	99			0.77	Retrospective
Procollagen type V (pro-C5)	Leeming et al. [66]	94	0.33	0.73 (cut-off 330)		Retrospective, alcohol cirrhosis (90%)

(continued)

Table 13.3 (continued)

Blood-based biomarkers		Sample size, *n*	Correlation with HVPG (Correlation coefficient, r)	Diagnosis of CSPH (AUROC)	Diagnosis of HRV/ VNT (AUROC)	Notes
Pro-peptide of type lll collagen (pro-C3)	Jansen et al. [67]	58	0.354			Retrospective, HIV/HCV co-infection
Osteopontin	Bruha et al. [68]	154	0.25	0.763 (cut-off 80 ng/ mL)		Retrospective
	Frankova et al. [60]	109	0.514			Liver transplant candidates, mixed etiology
Markers of inflammation						
Soluble CD163 (sCD163)	Holland-Fisher et al. [69]	36	0.49 [portal venous pressure gradient (PVPG) measured during TIPS]			Prospective, mixed etiology
	Grønbæk et al. [42]	81	$R^2 = 0.90$ (hyperbolic model, Michaelis-Menten function)	0.83 (cut-off 3.95)		Prospective, mixed etiology
	Sandahl et al. [43]	80		0.82		Prospective, mixed etiology
Combination of sCD163 and ELF	Sandahl et al. [43]	80		0.91		Prospective, mixed etiology
Markers of endothelial dysfunction						
Von Willebrand factor (vWF)	La Mura et al. [70]	42	0.47			Prospective, mixed etiology
	Ferlitsch et al. [71]	286	0.687	0.884 (cut-off 241)		Prospective, mixed etiology
	Horvatits et al. [72]	61	0.43			Prospective, mixed etiology
	Wu et al. [73]	60	0.696	0.885 (cut-off 1510.5)	0.83 (cut-off 1990)	Retrospective, cirrhosis due to chronic hepatitis B
	Hametner et al. [58]	236		0.79 (cut-off 226)		Retrospective, mixed etiology
	Mandorfer et al. [45]	225	0.333			Retrospective, mixed etiology
VITRO test (vWF/ thrombocyte ratio)	Hametner et al. [58]	236		0.86 (cut-off 1.58)		Retrospective, mixed etiology

Non-invasive Methods for Assessment of HVPG Response

The non-invasive assessment of haemodynamic response following treatment for PH has been considered an unmet need in hepatology. Historically, a reduction in heart rate (HR) was assessed as a proxy for therapeutic response to non-selective beta-blockers (NSBB). However, changes in heart rate do not correlate with the changes in HVPG [79, 80]. Nevertheless, the absolute benefit of identifying HVPG 'responders' is not fully established. Indeed, in the PREDESCI study, NSBB treatment without using portal pressure response in the follow-up to guide therapy improved decompensation-free survival. There are two important attributes for a non-invasive test to reliably monitor HVPG response. Firstly, the test should correlate with HVPG across a broad spectrum of HVPG values. As discussed previously, most non-invasive methodologies have been developed and validated as a binary predictor of CSPH and/or presence of varices, but the data on correlation with HVPG as a continuous variable are limited. Secondly, the inherent variability of the measurement should be small enough to detect the relatively modest changes in HVPG that may occur with pharmacological treatments. The haemodynamic response is defined by 10%–20% changes in HVPG from baseline which could correspond to absolute pressure changes as small as 2–4 mmHg. It follows that any non-invasive test with significant variability will lack sufficient sensitivity to detect the minor differences in HVPG. Notwithstanding, in the context of clinical trials, the within-individual variance of HVPG itself is a potential confounder in evaluating the haemodynamic response to interventions, especially in decompensated patients [81].

Doppler US-based assessment of blood flow showed some promise in detecting HVPG response following treatment with terlipressin [82] and propranolol [83]. However, the initial results have not been reproduced [84]. This is likely due to the technical variation associated with Doppler US which limits the ability to reliably detect changes in HVPG. PC-MRI is another potential method to non-invasively evaluate blood flow alterations. In a small feasibility study, a reduction in cardiac output as measured by PC-MRI flow in the abdominal aorta was reported following NSBB, but there were no statistically significant changes in flow in the other vessels analysed [85]. In this study, there were also no contemporaneous HVPG measurements.

Spleen stiffness measured using MRE significantly decreased following the administration of intravenous NSBB, but no change was observed in liver stiffness [37]. However, the changes in spleen stiffness were not related to HVPG response.

In addition, non-imaging-based markers of HVPG response have been evaluated. The expression of specific vasoactive proteins of Ras homolog family member A (RhoA) and Rho-kinase (ROCK) pathway in the gastric mucosa correlated with acute haemodynamic response following intravenous propranolol [86]. The haemodynamic responders showed lower expression of beta-arrestin2 (βArr2) in antral biopsies. This is not strictly a non-invasive test as the tissue samples are obtained by upper gastrointestinal endoscopy. Alternatively, using a serum metabolomic profiling approach, the combination of two metabolites (phosphatidylcholine and eicosadienoic acid) also identified acute HVPG responders to intravenous propranolol with an AUROC of 0.801 [87].

Conclusion

Although HVPG is an invasive and highly specialised method for the diagnosis of PH and assessment of treatment response, it has an important role in specific clinical circumstances and in interventional trials. A number of non-invasive tests (other than ultrasound elastography) have been shown to correlate with HVPG and perform well for the diagnosis of CSPH [59], but further validation in larger cohorts of patients with diverse etiologies is generally required. Variability and reproducibility will remain a challenge for development of suitable PH monitoring biomarkers.

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