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Evaluation of the Effect of CSPH, Reduction of HVPG, and Other Factors Predicting the First Decompensation in Cirrhosis

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Abbreviations

ACLD	Advanced chronic liver disease
HVPG	Hepatic venous pressure gradient
CSPH	Clinically significant portal hypertension
ACLF	Acute on chronic liver failure
NAFLD	Non-alcoholic fatty liver disease
RCT	Randomised controlled trial
RNA	Ribonucleic acid
HCV	Hepatitis C virus

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BMI	Body mass index
APC	Abdominal porto-systemic collaterals
MELD	Model for end stage liver disease
HCC	Hepatocellular carcinoma
NASH	Non-alcoholic steatohepatitis
NSBB	Non-selective beta blocker
SVR	Sustained virological response
VBL	Variceal band ligation
As	Ascites
HE	Hepatic encephalopathy
PB	Portal hypertensive bleeding
Ja	Jaundice
SBP	Spontaneous bacterial peritonitis
LSM	Liver stiffness measurement
IQR	Interquartile range
SS	Splenic stiffness
LSPS	LSM x spleen diameter/platelet count
TE	Transient elastography
SWE	Shear wave elastography
ARFI	Acoustic radiation force impulse
BI	Bacterial infections
SHR	Subdistribution hazard ratios
tAUC	Time-dependent area under the curve
ABIDE	Aspartate aminotransferase/alanine, aminotransferase ratio, bilirubin, International normalized ratio, type 2 Diabetes, and oesophageal varices

Stages of Cirrhosis and Clinically Significant Portal Hypertension

In ACLD, stages 0–2 (compensated phase) have a median duration of over 10 years, and further progression leads to decompensation (Fig. 35.1) with variceal bleeding, ascites, and hepatic encephalopathy (alone or in combination). Some patients may recompensate to stages 0–2, but a second decompensation invariably leads to the downward spiral to end-stage liver disease, ACLF, or death. Mortality from decompensated cirrhosis is much higher at 40%, 65%, and 80% at 1, 2, and 5 years respectively, compared to 1% in the compensated state [1].

Portal hypertension in cirrhosis results from increased intra–hepatic resistance due to fibrosis and contraction of sinusoidal and peri-sinusoidal cells due to interplay between vascular mediators favoring vasoconstriction with reduced intrahepatic eNOS activity. There is also increased portal inflow due to splanchnic vasodilatation driven by nitric oxide (NO) and sGC-PKG signaling, which perpetuates the initial rise in portal pressure [2, 3]. These hemodynamic changes result in the development of the hyperdynamic circulation. HVPG is an estimation of the true

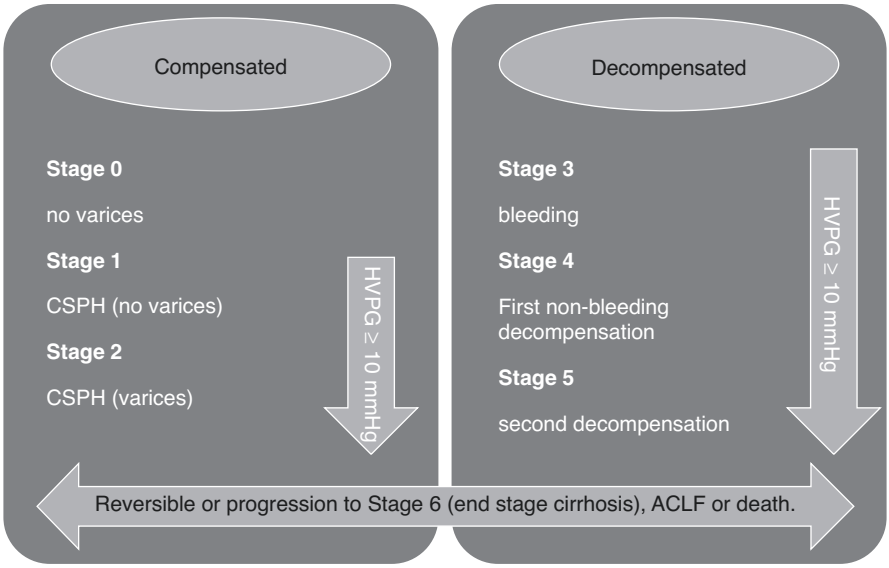

Fig. 35.1 Clinical stages of cirrhosis [1]

portal pressure in sinusoidal portal hypertension and is the Wedge Hepatic Venous Pressure (WHVP) minus Free Hepatic Venous Pressure (FHVP). The method of accurately measuring HVPG is described elsewhere [4].

Normal HVPG is between 1–5 mmHg and is described as CSPH at ≥10 mmHg. The hyperdynamic circulation has not yet fully developed at HVPG <10 mmHg where portal inflow has less of a contribution. Thus, the therapeutic effect of NSBB on portal hypertension is more pronounced at HVPG ≥10 mmHg [5]. Above this threshold varices may develop with progression to ascites or hepatic encephalopathy [6, 7]. Studies consistently show that the more common first decompensating event is ascites [7–9].

Thus, the discovery of surrogate markers predicting decompensation is an important clinical goal. These tools can aid in patient selection for therapies such as beta-blockers (or future therapies), or closely monitor those at low risk.

Hepatic Venous Pressure Gradient in Predicting Decompensation

HVPG as a marker of prognosis in cirrhosis and decompensation has been widely studied. Table 35.1 provides summaries of the important studies investigating the role of HVPG in predicting decompensation [6–16]. Significant heterogeneity exists in baseline characteristics with regards to the presence of CSPH, cirrhosis, varices, use of NSBB as prophylaxis against bleeding, etiology, the definition of decompensation and presence of hepatocellular carcinoma. Decompensation can vary

Table 35.1 Key studies evaluating HVPG for predicting progression of compensated cirrhosis and decompensation

Study	Design	Definition of decompensation	Patient selection and characteristic	Therapies	HVPG threshold predicting clinical events	Comments
Groszmann et al., 2005 [6]	RCT Primary endpoint: Development of varices or variceal hemorrhage Mean follow up: 54.9 months HVPG every 3/12	Not given	Patients without varices and HVPG ≥6 mmHg ($n = 213$) Etiology: Alcohol (24%), HCV (59%, non on treatment). Cholestatic diseases excluded	Timolol vs. placebo	HVPG ≥10 mmHg at baseline and HVPG >10% increase associated with the primary endpoint HVPG >10% decrease predicted being free of the primary endpoint	No difference in the primary endpoint when all patients were analyzed HVPG response was significantly higher with timolol than with placebo
Ripoll et al., 2007 [7]	Nested cohort study within an RCT Median follow-up: 51.1 months Endpoint: Development of clinical decompensation	As, HE, PB	Patients without varices and HVPG ≥6 mmHg ($n = 213$, 154 patients had repeat HVPG)	Timolol vs. placebo	HVPG <10 mmHg is associated with a 90% probability of absence of decompensation (ascites 75%, variceal bleeding 105, hepatic encephalopathy 27%) HVPG decrease <10% associated with decompensation Every HVPG increase in 1 mmHg is associated with a 19% increased risk of clinical decompensation	Decompensation in 29% during follow-up. HVPG, MELD, and albumin predicted decompensation. HVPG has the greatest discriminative ability

Villanueva et al., 2009 [16]	Prospective analysis	Not given	Patients with large varices that had not bled (n = 105) Mean follow 25 ± 21 months Etiology: Alcohol (39%), HCV (42%) A mixture of compensated and decompensated patients	Primary prevention: Nadolol (n = 96), VBL (n = 9)	HVPG response (defined as reduction ≥10% or <12 mmHg) to acute intravenous propranolol. Nadolol commenced. Second HVPG at 1–3 months Lower risk of variceal bleeding in both acute (c statistic, 0.83; 95% CI, 0.75–0.9) and chronic ((c statistic, 0.83; 95% CI, 0.72–0.91) responders The risk of ascites was also lower in acute and chronic responders (p = 0.001)	15% bled from varices during follow-up HVPG HVPG reduction ≥10% had the greatest discriminative ability to predict bleeding
Berzigotti et al., 2011 [11]	Retrospective analysis Median follow up: 28 months	As, HE, PB, SBP, Ja	Patients with HVPG ≥10 mmHg (n = 86) 73% compensated Etiology: Viral (54%), alcohol (11%)	Primary prevention: NSBB (n = 33) VBL (n = 5) Secondary prevention (n = 3): NSBB + VBL	HVPG ≥16 mmHg and bilirubin predicted the first decompensation with HVPG having the greatest discriminative ability	APC correlated with HVPG ≥16 mmHg, with a trend towards predicting decompensation
Berzigotti et al., 2011 [10]	Post hoc analysis of an RCT Median follow up: 59 months	As, HE, PB	Patients without varices and HVPG ≥6 mmHg and where BMI available (n = 161)	Timolol vs. placebo	HVPG (1.14 [95% CI, 1.07–1.20]), albumin (HR 4.54 [2.44–8.33]) and high baseline BMI (hazard Ratio 1.06; 95% CI, 1.01–1.12) independently predicted decompensation	Decompensation in 30% of patients (ascites, 69%; encephalopathy, 31%, variceal bleeding 10%)

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Table 35.1 (continued)

Study	Design	Definition of decompensation	Patient selection and characteristic	Therapies	HVPG threshold predicting clinical events	Comments
Hernández-Gea et al., 2012 [9]	Prospective analysis Median follow up: 53 months	As, HE, PB	Large varices, no previous bleeding or other decompensation (n = 83, 78 with HVPG data) Etiology: Alcohol (18%), HCV (62%)	Primary prevention with nadolol[a]	Pre-therapy (with nadolol) acute HVPG response to IV propranolol. HVPG reduction ≥10% defined response. Non-response predicted decompensation (ascites, bleeding) and death Ascites independently predicted nonresponse while refractory ascites, hepatorenal syndrome, and bacterial peritonitis did not Chronic HVPG response at 3 months predicted ascites	In hemodynamic responders, MELD provided additional prognostic information No control group 62% of patients decompensated during follow-up
Ripoll et al., 2012 [15]	Retrospective single center Median follow up: 11 months (compensated); 10 months (decompensated)	As, HE, PB	Compensated (n = 51). Decompensated (n = 66). HCC in 29% of compensated patients (within Milan criteria) Varices in 48% Aetiology: Viral (62%), alcohol (30%)	NSBB use: Compensated (50%), decompensated (73%)	HVPG × 2 measurements were done at median 13 months (compensated) and 8 months (decompensated) intervals HVPG ≥10 mmHg and MELD ≥10 independent predictors of decompensation in compensated patients. MELD ≥12 independent predictors of death in decompensated patients. MELD had a much narrower variation range than HVPG in compensated cirrhosis	Changes in HVPG and MELD did not influence outcomes after multivariate analysis (only on univariate analysis). This may reflect the short time and loss of patients between HVPG measurements. Baseline single measurement had the greatest discriminate function (c-statistic (95% CI) 0.792 (0.655–0.893)) No association between NSBB and endpoints During follow up 29% developed decompensation

Rincón et al., 2013 [14]	Retrospective single-center study. Median follow-up: 27 months	As, HE, PB	Compensated stage 1 HCV cirrhosis ($n = 145$, 76 with varices, HCC 26%)	37% on antiviral therapy without SVR (those without SVR excluded)	Baseline HVPG was done. HVPG ≥10 mmHg in 72%) HVPG and albumin independently predicted decompensation Each mmHg increase in HVPG led to an 11% increase in the risk of decompensation PI[b] model discriminative for decompensation with good calibration (AUROC: 0.77 (95% CI: 0.64–0.89). PI <2.5 is highly predictive of compensated state even after excluding HCC patients	29% suffered decompensation (ascites most common, and especially varices at baseline). No data on NSBB use
Lens et al., 2015 [12]	Retrospective over four centers. Median follow-up: 5 years	As, HE, PB	Compensated HCV on interferon-based antiviral therapy ($n = 100$). CSPH in 74% (35% achieved SVR)		HVPG at baseline before antiviral therapy and at 12 weeks ($n = 30$) and 23 weeks ($n = 62$) Baseline HVPG but not SVR predicted decompensation and transplant-free survival	31% had varices (4% on NSBB). 19% developed decompensation. Higher if CSPH at baseline

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Table 35.1 (continued)

Study	Design	Definition of decompensation	Patient selection and characteristic	Therapies	HVPG threshold predicting clinical events	Comments
Reiberger et al., 2012 [13]	Prospective non-randomized study Median follow-up was 19.5 months	As, HE (grade 3, 4), PB, Ja	Oesophageal varices and HVPG ≥12 mmHg. (n = 104) Aetiology: Alcohol (55%), viral (33%) A mixture of compensated and decompensated patients	Primary prevention: Propranolol and carvedilol (for hemodynamic non-responders). VBL in carvedilol non-responders (carvedilol stopped)	Baseline HVPG, and at 4 weeks (hemodynamic response defined as >20% reduction or reduction to <12 mmHg) 56% not respond to propranolol responded to carvedilol. Overall 72% of NSBB had a hemodynamic response	Less bleeding and mortality in hemodynamic responders Less decompensation in: (a) Propranolol non-responders on carvedilol compared to VBL (b) NSBB responders compared to VBL
Villanueva et al., 2019 [8]	RCT (PREDESCI). Median follow-up 37 months	As, HE, PB	Small oesophageal varices (57%) or no varices (43%). HVPG ≥10 mmHg. N = 201 Aetiology: HCV (56%, none treated), alcohol (16%)	Pre-primary prevention: NSBB vs. placebo	NSBB allocation according to acute response (HVPG >10% reduction from baseline). Responders—Propranolol (n = 67). Non-responders—Carvedilol (n = 33) HVPG annually Reduced decompensation and death in NSBB group (HR 0.51 (0.26–0.97), p = 0.0412). HVPG reduction from baseline ≥10% was seen in 51% on NSBB and 29% on placebo. Carvedilol decreased HVPG more than propranolol	Annual endoscopies. Development of high-risk varices treated with variceal band ligation Decompensation mostly ascites The benefit of NSBB is greater in ArLD and if HVPG response (>10% decrease from baseline or to <10 mmHg) Bleeding only in 3%

Jindal et al., 2020 [20]	Retrospective study of prospectively collected data. Median follow up 1.6 ± 0.4 years	As, HE, PB, Ja	*N* = 741 Large varices (24%), small oesophageal varices (66%), or no varices (10%) HVPG ≥6 mmHg: • HVPG 6 to <12 mmHg (group A; *n* = 163) • HVPG 12 to <20 mmHg (group B; *n* = 437) • HVPG ‡ 20 mmHg (group C; *n* = 141)	Pre-primary and primary prevention: Carvedilol in all patients with baseline HVPG ≥12 mmHg	Baseline HVPG ≥12 mmHg and HVPG ≥20 mmHg independent predictors of decompensation (HR 2.73 & 4.48 respectively) Hemodynamic response to carvedilol not associated with decompensation	217 (29%) developed decompensation during follow-up Total leucocyte count (HR 1.07), serum creatinine (HR 1.19) are associated with decompensation-free survival MELD is not associated with decompensation Group C had a higher proportion of NASH cirrhosis than group A (35% vs. 20%) Baseline LSM did not correlate with decompensation

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Table 35.1 (continued)

Study	Design	Definition of decompensation	Patient selection and characteristic	Therapies	HVPG threshold predicting clinical events	Comments
Mandorfer et al., 2020 [22]	Prospective. Median follow up 35.3 months (IQR 21.8 months)	As, HE, PB	*N* = 90. Varices in 40% (small, 53%; large, 47%). LSM 23.4 kPa. HVPG ≥6 mmHg: • HVPG 6–9 mmHg (*n* = 23) • HVPG 10–15 mmHg (*n* = 29) • HVPG ≥16 mmHg (*n* = 38) *N* = 67 underwent third HVPG Etiology: HCV (100%)—All achieved SVR with antiviral therapy	NSBB (42%)	<u>Baseline HVPG</u> No progression with HVPG <10 mmHg (no decompensation) In those with CSPH at baseline, this persisted in 76%, but a decrease in HVPG ≥10% occurred in 60% Baseline HVPG did not predict decompensation <u>Change in HVPG</u> HVPG change during follow up predicted decompensation • Absolute change (AUROC 0.872) • Relative change (AUROC 0.877) • Where CSPH at baseline, HVPG decrease ≥10% had ess decompensation (2.5% vs. 40.5%) HVPG change after third HVPG (*n* = 67): • HVPG reduction was 24.4% • 46% had CSPH HVPG decrease ≥10% in the second measurement maintained and had no decompensation	Previous decompensation in 14% Three patients underwent a liver transplant Decompensation associated with child-Pugh score, MELD

Turco et al. 2020 [23]	Meta-analysis of primary ($n = 7$) and secondary prophylaxis ($n = 7$) studies or both ($n = 1$). Ten case series and five RCTs. Total number = 1113 unique patients	As, HE, PB	Cirrhotic patients had at least two measurements of HVPG pre-therapy and during NSBB therapy. Most had ArLD Ascites is 40.6%	Propranolol or nadolol was used (carvedilol or propranolol in one study) 332 patients were compensated	HVPG response defined as >20% reduction from baseline or < 12 mmHg in 14 studies In patients without ascites and no previous variceal bleeding, significantly lower decompensation (OR 0.28; 95% CI 0.13–0.58) and death (OR 0.44; 95% CI 0.20–0.98) in responders	A mixture of data from RCTs and observational studies Most studies were performed before effective antiviral therapy

As ascites, *HE* hepatic encephalopathy, *PB* portal hypertensive bleeding, *Ja* jaundice, *SBP* spontaneous bacterial peritonitis, *RCT* randomized controlled trial, *VBL* variceal band ligation, *APC* abdominal portosystemic collaterals, *LSM* liver stiffness measurement, *IQR* interquartile range

[a]Nadolol withdrawn in nine patients due to intolerance and offered VBL

[b]Prognostic Index (PI) = 4 + (0.11 × HVPG − 0.8 × albumin)

considerably from 12.8% to 33.6% for cholestatic diseases and alcohol-related liver diseases respectively [17]. HVPG may underestimate the true portal pressure in cholestatic diseases due to the pre-sinusoidal component. Recent data also suggests patients with NAFLD can decompensate on follow-up even with baseline HVPG slightly <10 mmHg [18] and at a higher frequency for a given HVPG than RNA positive HCV [19], although this requires further validation. There is also variability with regards to antiviral therapy, and one can argue that studies using interferon-based regimens are outdated in the current era of directly acting antiviral therapy. However, a study showed that baseline HVPG influenced decompensation rates rather than interferon-based regimens [12]. One can infer that the results would apply to current antiviral therapies.

Baseline HVPG as a Marker of Risk of Decompensation

A seminal placebo-controlled trial investigating the role of timolol in preventing the development of varices and variceal bleeding in patients without varices and HVPG ≥6 mmHg showed that varices only developed at HVPG ≥10 mmHg [6]. The primary endpoint occurred in 84 out of 213 patients, without any difference between timolol and placebo. A nested cohort study within this RCT showed that HVPG mmHg <10 mmHg was associated with reduced decompensation, in particular ascites [7]. A further post hoc analysis of the timolol study showed that baseline BMI was a predictor of decompensation, although the association was stronger with baseline HVPG and albumin [10].

A retrospective analysis of patients with ACLD (73% compensated) showed that baseline HVPG ≥16 mmHg and bilirubin predicted the first decompensation, with HVPG having the greatest discriminative ability. In this study, the presence of abdominal portosystemic collaterals (APC) was only seen with HVPG ≥10 mmHg, and strongly correlated with HVPG >16 mmHg and suggests that APC on ultrasound scan could be a non-invasive tool to categorize patients with high HVPG [11]. This requires validation in prospective studies.

A single-center retrospective study with a mixture of compensated and decompensated patients showed that baseline HVPG >10 mmHg and MELD >12 predicted decompensation [15]. Furthermore baseline single HVPG had the greatest discriminative ability and patients with HVPG <10 mmHg were unlikely to decompensate, The high decompensation rate of 29% most likely reflects patients with HCC and varices being included.

Another retrospective study identified baseline HVPG and albumin to predict decompensation in compensated patients with HCV infection [14]. Patients with prognostic index <2.5 were very unlikely to decompensate. As in the study by Ripoll et al. [15], the high decompensation rate appears to reflect the inclusion of patients with HCC and varices. Lens and colleagues found that baseline HVPG before HCV treatment but not sustained viral response predicted decompensation and transplant-free survival [12]. These patients had interferon-based antiviral therapies.

A large recent study of 741 consecutive compensated patients with cirrhosis (predominantly NASH, 30.8%) and HVPG ≥6 mmHg, showed that decompensation developed in 29.2% over a mean follow-up of 1.6 ± 0.4 years [20]. Decompensation occurred earlier and more frequently in patients with high HVPG (≥20 mmHg, 35.5% NASH) with higher mortality. Baseline HVPG independently predicted decompensation. Limitations of this study include retrospective uncontrolled design, small numbers of patients in the high HVPG group (n = 18), and short follow-up.

HVPG Response as a Marker of Risk of Decompensation

Studies show the role of HVPG response to drug therapies as a prognostic marker predicting decompensation. In these studies, the protocols involve acute HVPG response and repeat HVPG measurements performed at variable intervals. The latter can make a comparison of studies challenging. There could also be a degree of selection bias since not all patients would have repeat HVPG measurements due to dropout or censoring events such as decompensation, death, or transplantation.

Acute HVPG response to NSBB is consistently reliable in predicting decompensation. A retrospective study found that a 12% reduction in HVPG in response to intravenous propranolol had the greatest discriminative ability for rebleeding and mortality [21]. Acute and chronic (1–3 months) HVPG response to NSBB, defined as reduction ≥10% or to <12 mmHg, was associated with a lower risk of variceal bleeding and ascites in a prospective study of 105 patients [16]. Another prospective series with a similar study design investigated the role of HVPG response to NSBB in a purely compensated cirrhotic population and mirrored these findings [9]. Baseline MELD >9 and chronic hemodynamic nonresponse were associated with ascites development. MELD added additional prognostic data in hemodynamic responders.

In the nested study of the timolol RCT, HVPG reduction of <10% from baseline predicted decompensation [7]. An increase of 1 mmHg in HVPG led to an 11% increased risk of decompensation. Multivariate analysis revealed that a lack of hemodynamic response at 12 months predicted decompensation (HR, 2.6; 95% CI, 1.1–5.6). A retrospective study found that, unlike baseline HVPG, delta HVPG at 1 year did not influence outcomes after multivariate analysis [15]. Furthermore, NSBB therapy did not appear to influence clinical outcomes. Heterogeneity with the inclusion of both compensated and decompensated patients, and those with HCC, along with low sample size and retrospective design are limitations.

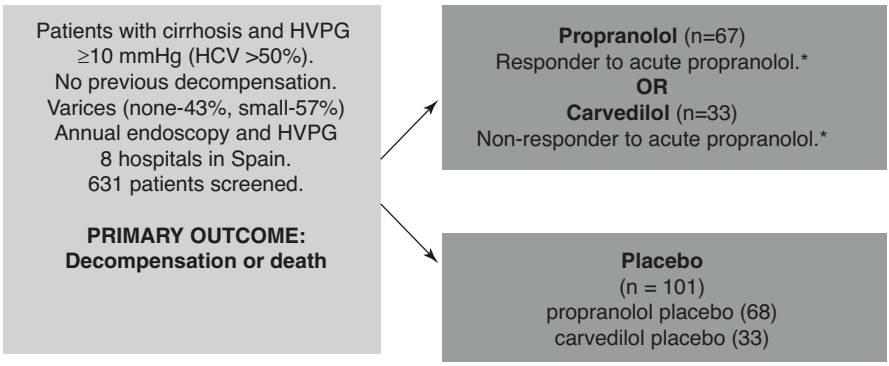
A retrospective study of 100 compensated HCV patients on antiviral therapy over 24 weeks found that repeat HVPG decreased significantly and was related to high baseline viral load. After 24 weeks only those with SVR had HVPG reduction [12]. There was a trend toward higher decompensation in patients failing to achieve HVPG <10 mmHg. The small sample size in this study is a limitation. In a prospective study, 90 HCV patients treated with interferon-free therapies underwent hemodynamic studies. All patients had portal hypertension (HVPG ≥6 mmHg) and

underwent follow-up HVPG assessment at 8.79 months [22]. Patients with HVPG <10 mmHg at baseline did not progress to CSPH. Follow-up HVPG was associated with decompensation (per mmHg rise, HR 1.18 (95% CI 1.08–1.28; AUROC 0.819)). By contrast, baseline HVPG was not associated with decompensation during follow-up.

A prospective study of patients treated with either propranolol or carvedilol (in propranolol nonresponders) as primary prevention, found less decompensation in the carvedilol group when compared with VBL (p = 0.035) [13]. Haemodynamic responders on propranolol or carvedilol also suffered less decompensation (ascites (p = 0.031) and variceal bleeding (p = 0.012) than those on VBL. There was a history of previous ascites in 10% of patients. In the large hemodynamic study from India mentioned earlier, 20 patients with HVPG ≥12 mmHg were started on carvedilol, and the hemodynamic response was less in the high HVPG group [20]. Moreover, reductions in portal pressure did not influence the risk of decompensation.

The PREDESCI RCT, compared NSBB with placebo in patients with compensated liver disease (Fig. 35.2) [8]. The rigorous protocol comprised a hemodynamic study at baseline to assess for the presence of CSPH and determine acute hemodynamic response to intravenous propranolol. Responders received propranolol and non-responders were given carvedilol. A placebo arm was required for each NSBB. The HVPG measurements were repeated annually. Decompensation was inversely associated with HVPG reduction >10% from baseline or to <10 mmHg at 1 year. Indeed, the primary outcome was significantly reduced in these hemodynamic responders compared to non-responders (HR = 0.32, 95% CI = 0.13 to 0.75; p = 0.008).

A recent meta-analysis of over 1100 patients showed that HVPG response (<12 mmHg or >20% from baseline) to NSBB as part of primary or secondary prevention was associated with significantly fewer clinical events and lower deaths [23].



*HVPG > 10% from baseline 20mins after IV propranolol (0.15 mg/kg)
NSBB dose titration as per tolerated and HR 55bpm, SBP 90 mmHg.
Randomisation 1:1 after stable dose

Fig. 35.2 Schema of PREDESCI trial [8]

The Role of Other Factors in Predicting Decompensation

Although HVPG remains the gold standard for predicting decompensation it is invasive, with limited availability in many countries. Therefore, non-invasive markers predicting decompensation have an important role (Table 35.2).

Ripoll found that MELD, albumin, and HVPG predicted decompensation [7], and a nomogram based on this study incorporating platelet count, MELD, albumin, and AST has been proposed [24]. Markers of systemic inflammation predicting decompensation have also been studied. Obesity has also been associated with decompensation [10]. The role of nutrition and etiology is covered elsewhere.

Simple serum markers of fibrosis have been assessed in several studies [25–29]. Prospective studies in patients with compensated cirrhosis have failed to show APRI

Table 35.2 Candidates for noninvasive markers predicting decompensation

Study	Markers	Predictive ability of decompensation	Comments
Ripoll, 2007 [7] *N* = 213	Albumin MELD HVPG	c statistic: Albumin (0.66; 95% CI, 0.58–0.74) MELD (0.64; 95% CI, 0.55–0.72) HVPG (0.71; 95% CI, 0.64–0.78)	Nested study of RCT of timolol vs. placebo (see Table 35.1)
Guha, 2019 [25] Retrospective study *N* = 145	FIB-4 and ALBI which includes the following variables age, AST, albumin, platelets, bilirubin, ALT[a]	Harell's c statistic: 0.805 (95% CI 0.718–0.873) Hazard ratio of high-risk patients was 7.1 (95% CI, 3.07–16.42)	Etiology mainly ArLD (45%) and NASH (30%) Does not take into account the influence of etiology. Lack of calibration of the model. Decompensation in 19.3% over 4.59 years
Colecchia, 2014 Prospective [26] *N* = 92	HVPG, LSM, splenic stiffness, platelet count/ spleen diameter ratio, liver stiffness-spleen diameter to platelet ratio score, APRI, liver stiffness x spleen diameter, MELD	AUROC HVPG: 0.83 (95% CI 0.75–0.92) SS: 0.85 (95% CI 0.77–0.93) (independent of the presence of varices) SS < 54 kPa: Sensitivity 97% Specificity 63%, LR-0.05, NPV 97%) for predicting low risk of decompensation MELD and SS predictive model[b]: 0.87 (95% CI 0.80–0.94)	Compensated HCV cirrhosis. No patients on NSBB or antiviral therapy at baseline Varices in 53% (F1) 33% decompensated over 2 year period Calibration done

(continued)

Table 35.2 (continued)

Study	Markers	Predictive ability of decompensation	Comments
Pérez-Latorre, 2014 [37] Retrospective *N* = 60	LSM, HVPG	AUROC (95% CI) for predicting liver decompensation: LSM: 0.85 (.69–1.00). LS < 25 kPa and LS > 40 kPa thresholds for absence and presence of decompensation HVPG: 0.76 (0.59–0.93)	HCV cirrhosis with and without HIV co-infection CSPH in 53% Varices in 38% Decompensation in 13% over 42 months
Sebastiani, 2015 [27] Retrospective cohort study *N* = 146	HVPG, APRI, FIB-4, NAFLD fibrosis score, histology, imaging	Area under curve: • Histologic fibrosis stage, 0.85 (95% CI 0.76–0.93) • HVPG, 0.81 (95% CI 0.70–0.91) • APRI, 0.89 (95% CI 0.82–0.96) • FIB-4, 0.89 (95% CI 0.83–0.95) • NAFLD fibrosis score, 0.79 (95% CI 0.69–0.91)	Only NASH patients (F3/F4 fibrosis in 34%) CSPH in only 18.2% cases Clinical outcomes (decompensation, liver transplantation, HCC, or death) in 16.2% over 5 years Histological steatosis and non-invasive steatosis methods did not predict outcomes
Kitson, 2015 [28] *N* = 95 Prospective	HVPG, LSM, APRI, FIB-4, PSDR	AUROC: • LSM: 0.73 (95% CI 0.61–0.84). LS > 34.5 kPa optimal threshold for the presence of decompensation	Compensated cirrhosis (previous decompensation in 24%) 75% had CSPH Aetiology: Alcohol (41%), HCV (33%) Varices (72%) Cirrhosis in 93% NSBB in 22%
Merchante, 2012 [29] *N* = 239 Prospective	LSM, APRI, FIB4.	AUROC • LSM: 0.72 (95% CI 0.61–0.82) • LS ≥ 40 kPa optimal threshold to predict decompensation • Child-Pugh score: 0.76 (95% CI, 0.65–0.88) • MELD: 0.71 (95% CI 0.61–0.81)	All compensated with no previous decompensation HCV/HIV co-infection. Previous HCV therapy, 39% Varices in 100% (93% small) 13% decompensated over 20 months (most commonly ascites)

Table 35.2 (continued)

Study	Markers	Predictive ability of decompensation	Comments
Merchante, 2015 [36] *N* = 275 Prospective	LSM	AUROC (decompensation and/or HCC): LSM (baseline): 0.609 (0.471–0.748) LSM progression: 0.680 (0.541–0.818) Only LSM progression is associated with the endpoint.	All compensated cirrhosis with no previous decompensation Baseline LS < 40 kPa HCV/HIV co-infection. SVR in 31% No data on varices 6.9% decompensated and/or developed HCC over 32 months follow up
Robic, 2011 [35] Prospective *N* = 100	LSM HVPG	AUROC (95% CI) for portal hypertension related complications: • LSM: 0.830 [0.751–0.910]. No decompensation if LS < 21.1 kPa • HVPG: 0.845 [0.767–0.920]. No patients with HVPG <10 mmHg developed decompensation	65% had cirrhosis (72% had varices) 51% had CSPH 66% had ArLD or viral hepatitis (none on antivirals)
Villaneuva, 2019 [8] RCT *N* = 201 (see Table 35.1) Villanueva et al. 2021 [46]	LSM HVPG Child Pugh score	Cox proportional-hazards regression for decompensation and/or death (hazard ratio, 95% CI)): • Baseline child-Pugh score:4.13 (2.03–8.39) • Baseline HVPG: 4.72 (2.24–9.95) • LSM (AUROC): 0.63 (0.51–0.74). The optimal threshold was 22 KPa, with an NPV of 0.92 but a PPV of only 0.31	All compensated cirrhotic patients with CSPH Decompensation developed in 18% over 37 months No effect of etiology, portosystemic collaterals, presence of varices or not Bacterial infections were associated with decompensation (SHR 2.98 (95% CI, 1.02–8.42) and mortality (SHR 6.93 (95% CI, 2.64–18.18)

(continued)

Table 35.2 (continued)

Study	Markers	Predictive ability of decompensation	Comments
Harrison, 2019 [30] Sanyal, 2019 [18] RCT (Simtuzumab vs. placebo) Bridging fibrosis (n = 219) Compensated cirrhosis (n = 258)	HVPG (in compensated cirrhosis, 68% had CSPH) ELF FibroSure FibroTest FIB-4 APRI Serum LOXL2 NAFLD fibrosis score Other lab assessments	Variables associated with clinical events in cirrhotic patients (HR with 95%CI): • ELF score: 2.11 (1.53–2.90) • FibroSure/FibroTest, per 0.1 units: 1.21 (1.06–1.38) • NAFLD fibrosis score: 1.78 (1.43–2.21) • FIB-4: 1.24 (1.14–1.35) • APRI: 1.88 (1.45–2.46) sLOXL2, per 10 pg/mL 1.02 (1.01–1.04) • CSPH (HVPG ≥10 mmHg): 2.83 (1.33–6.02) • Failure to achieve ≥20% decrease in HVPG: 5.38 (1.65–17.58) • Failure to achieve HVPG <10 mmHg and/or $a \geq 20\%$ decrease: 5.51 (1.69–17.98)	Of cirrhotics 42% had varices, 19% experienced clinical events over a median follow-up of 30.9 months
Eaton et al., 2020 [39] Retrospective (n = 204, PSC)	LSM measured by MRE (146 had second MRE) APRI	Variables predicting decompensation (HR with 95% CI): Single LSM > 4.32 kPa (second MRE): 60.41 (17.85–204.47) Change in LSM 0.34 kPa/year: 13.29 (5.23–33.78) Change in APRI/year: 0.76 (0.62–0.93)	LSM progression directly related to baseline LSM (stage 0 fibrosis—0.03 kPa/year vs. stage 4 fibrosis—0.31 kPa/year) Ascites was noted in all patients that developed decompensation (n = 23)
Osman et al., 2021 [40] Prospective (n = 538, PBC)	LSM measured by transient elastrography (n = 286) and MRE (n = 332)	Variables predicting decompensation (HR with 95% CI): Transient elastrography: 1.14 (1.05–1.24); optimal threshold 10.2 kPa MRE: 1.68 (1.28–2.19); optimal threshold 4.2 kPa	

Table 35.2 (continued)

Study	Markers	Predictive ability of decompensation	Comments
Gidener et al., 2020 [41] Retrospective (n = 194/829 with cirrhosis, NAFLD)	MRE	Variables predicting decompensation or death (HR with 95% CI): MRE: 1.32 (1.13–1.56) per 1 kPA increase after adjusting for age, sex, MELD Na	In non-cirrhotic group: Baseline LSM by MRE predicted risk of cirrhosis (HR 2.93, (95% CI, 1.86–4.62) per 1 kPa increase, AUROC 0.86)
Han et al., 2020 [42] Retrospective (n = 39/320 with NAFLD cirrhosis (compensated, 26))	MRE	Variables predicting decompensation or death (OR with 95% CI): MRE: 3.28 (2.04–5.28)	LSM by MRE at a threshold of 3.99 kPa discriminated between cirrhosis and non-cirrhosis (AUROC 0.986) LSM by MRE at a threshold of 6.48 kPa discriminated between compensated and decompensated cirrhosis (AUROC 0.707)
Calzadilla-Bertot et al., 2020 [31] Retrospective (n = 299) Biopsy proved NAFLD cirrhosis	ABIDE NAFLD fibrosis score FIB-4 MELD CPS ALBI ALBI-FIB4	5-year prediction of decompensation (tAUC): ABIDE (0.80) ABIDE vs.: NAFLD fibrosis score (0.72) FIB-4 (0.74) MELD (0.69) CPS (0.72) ALBI (0.72) ALBI-FIB4 (0.73)	
Younes et al. 2021 [32] Prospective (n = 1173) Biopsy proven NAFLD	NAFLD fibrosis score FIB-4 BARD APRI Hepamet fibrosis score	Variables predicting liver events over a median follow up of 81 months (medial Harrell's c-indices): NAFLD fibrosis score (0.796) FIB-4 (0.783) BARD (0.728) APRI (0.6) Hepamet fibrosis score (0.729)	F3/F4 fibrosis in 24.1%

(continued)

Table 35.2 (continued)

Study	Markers	Predictive ability of decompensation	Comments
Costa et al., 2021 [45] Prospective (n = 168, 78 cACLD)	HVPG MELD CRP Il-6	Variables predicting decompensation (HR with 95% CI) in Baveno stages 0–2: Il-6: 1.06 (1.01–1.1)	In decompensated patients, Il-6 also independently predicted death/ transplantation CRP and IL-6 increased only in decompensated patients
Petta et al., 2021 [38] NAFLD F3–F4 fibrosis and/or LSM > 10 kPa Minimum 6 months follow-up Repeat LSM within 1 year Median FU 35 months	Baseline LSM Delta LSM (improvement if >20% reduction, stable if between −/+ 20% from baseline, impairment if 20% or more increase)	Baseline LSM independently predicted: (a) Decompensation (HR 1.03; 95% CI 1.02–1.04) (b) Liver related death (HR 1.02; 95% CI 1.02–1.03) Delta LSM (n = 533) predicted: (a) Decompensation (HR 1.56; 95% CI 1.05–2.51) (b) HCC (HR 1.72; 95% CI 1.01–3.02) (c) Overall mortality (HR 1.73 (95% CI 1.11–2.69) (d) Liver related mortality (HR 1.96; 95% CI 1.10–3.38)	Threshold baseline LSM 21 kPa (CSPH) independently associated with decompensation (HR 3.71; 95% CI 1.89–6.78) Delta LSM was associated with decompensation in patients without CSPH at baseline but not those with CSPH Age and platelet count also associated with decompensation Retrospective design

LSM liver stiffness measurement, *SHR* subdistribution hazard ratios, *tAUC* time-dependent area under the curve, *ABIDE* aspartate aminotransferase/alanine, aminotransferase ratio, bilirubin, International normalized ratio, type 2 Diabetes, and oesophageal varices

[a]Formula available online: https://jscalc.io/calc/gdEJj89Wz5PirkSL

[b]Formula: exp.(−11:5 + 0.107 * SS + 0.45 * MELD)/[1 + exp.(−11:5 + 0.107 * SS + 0:4 5 * MELD)]

nor FIB-4 to predict decompensation [28, 29]. A recently published retrospective study found FIB-4 and ALBI to predict decompensation [25]. A study on the predictive value of non-invasive markers and HVPG in NASH cirrhosis was published recently [18, 30]. ELF was the serum marker with greater prognostic capacity. Other large retrospective [31] and prospective studies [32] in NAFLD cirrhosis have found noninvasive markers to be highly predictive of decompensation.

Liver stiffness (LS) has been shown to accurately reflect HVPG ≤12 mmHg, but at higher pressures correlation with HVPG is less strict and likely to reflect other factors in the pathogenesis of portal hypertension, in particular increased portal inflow [33]. A large multicentre study found that LSM ≥ 25 kPa correlates with

CSPH in cACLD apart from obese NASH patients. In obese NASH, the ANTICIPATE-NASH model was proposed based on a nomogram [34]. A prospective study showed that LSM < 21.1 kPa predicted freedom from decompensation with similar precision to HVPG [35]. Other studies have confirmed these findings in patients with HCV cirrhosis with or without HIV co-infection and alcohol-related liver disease [28, 29, 36, 37]. The LS thresholds for predicting the presence of decompensation varied between 34.5 and 40 kPa. However, in the PREDESCI trial [8], LS at baseline had low precision in predicting decompensation and/or death. Another study confirmed this finding [20]. However, sequential LSM was found to be accurate for diagnosing CSPH [22]. Baseline (threshold LSM 21 kPa) and changes in repeated LSM were found to predict decompensation, HCC, and mortality in a large retrospective cohort of NAFLD patients with F3–F4 fibrosis [38]. Studies have shown that LSM obtained using MRE was strongly associated with the development of decompensation in different aetiologies [39–42].

Spleen Stiffness (SS) has been suggested to correlate better with portal hypertension at higher portal pressures. In a prospective study [43] of 100 patients with compensated HCV cirrhosis, LS, and SS were more precise than other noninvasive makers (platelet/spleen ratio, LSPS) in predicting CSPH. The "Anticipate" study, revealed that LSM x spleen diameter/platelet count (LSPS) score values >2.65 were associated with an 80% risk of CSPH with AUC of 0.88 [44]. In a study of HCV patients with compensated cirrhosis, SS value of 54 kPa had sensitivity and specificity of 97% and 63% respectively in predicting low risk of decompensation [26]. Using TE and 2D-SWE, there can be greater non-valid or failed reading of SS compared with LS due to small-sized spleens. pSWE such as ARFI can be more reliable since it can compensate for high BMI, ascites, or small spleens. However, the data on variability is somewhat limited.

A prospective study found that IL-6 levels correlated with risk of decompensation (hazard ratio 1.06 (96% CI 1.01–1.10), with CRP and HVPG showing a strong trend, highlighting the importance of markers of systemic inflammation [45].

In a nested study of the PREDESCI trial, Bacterial Infections (BI) were developed in 36 patients that presented with decompensation [46]. BI occurred invariably before decompensation, with the principal sources being community-acquired respiratory and urinary tract and predominantly gram-negative organisms. Decompensation and particularly mortality were associated with BI, with subdistribution hazard ratios of 2.98 (95% CI, 1.02–8.42) and 6.93 (95% CI, 2.64–18.18) respectively. Age, lower albumin, lower BMI, and HCC were noted to be risk factors for BI in compensated cirrhotic patients. NSBB use showed a trend towards reduced risk of developing BI.

Conclusions

The development of CSPH has profound effects on the natural history of ACLD, and much research has been undertaken to understand factors predicting decompensation. Although HVPG, both at baseline and change over time or in response to

pharmacotherapy, remains the gold standard, there is an unmet need to identify noninvasive surrogate makers of CSPH and decompensation. Liver and spleen stiffness are promising in this regard, although a lack of large, controlled studies including different etiologies with extended follow-up prevents universal adoption of these tools.

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