nature reviews gastroenterology & hepatology

https://doi.org/10.1038/s41575-024-01031-x

Supplementary information

# Preventing the progression of cirrhosis to decompensation and death

In the format provided by the authors and unedited

# Supplementary Information

**Title:**

Preventing the progression of cirrhosis to decompensation and death

**Authors:**

Càndid Villanueva[1,2,3], Dhiraj Tripathi[4,5], Jaume Bosch[3,6]

**Affiliations:**

[1] Department of Gastroenterology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau (IIB Sant Pau), Barcelona, Spain.

[2] Department of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain.

[3] Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Ministerio de Sanidad, Spain.

[4] Liver Unit, University Hospitals Birmingham NHS Foundation Trust, Birmingham Health Partners, Birmingham, United Kingdom

[5] Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom

[6] Department of Visceral Surgery and Medicine (Hepatology), Inselspital, Bern University Hospital, University of Bern, Switzerland.

**Corresponding author:** Càndid Villanueva, MD.
E-mail: cvillanueva@santpau.cat. Department of Gastroenterology, Hospital de la Santa Creu i Sant Pau. Mas Casanovas 90, 08041 Barcelona, Spain. Telephone number: 34 93 5565920, FAX number: 34 93 556 5608.

**Supplementary Table 1:** Key studies evaluating invasive and non-invasive tests predicting progression of compensated cirrhosis and decompensation

| Study | Design | Definition of decompensation | Varices at baseline | Etiology | Therapies | Prediction of clinical events | Comments |
|---|---|---|---|---|---|---|---|
| **Invasive tests** | | | | | | | |
| Groszmann et al, 2005 [1]<br>(n=213)<br><br>HVPG baseline and every 12 months | RCT.<br>Primary endpoint: development of varices or variceal hemorrhage.<br>Mean follow-up: 54.9 months<br>HVPG every 12 months | Not given | No | ArlD – 24%<br>HCV – 59% (no on antivirals) | Timolol vs placebo | Baseline HVPG ≥ 10 mmHg and HVPG > 10% increase predicted primary endpoint. | No difference in the primary endpoint when all patients were analyzed.<br>HVPG response was significantly higher with timolol than placebo. |
| Hernández-Gea et al, 2012 [2]<br>(n=83)<br><br>HVPG ≥ 12 | Prospective.<br>Median follow-up: 53 months | As, HE, PB | Large esophageal varices | ArlD – 18%<br>HCV – 62% | Primary prevention with nadolol* | Pre-therapy (with nadolol) acute HVPG response to IV propranolol. Acute HVPG reduction ≥ 10% associated with less decompensation (ascites, bleeding) and death.<br>3-month HVPG response with nadolol predicted ascites. | In hemodynamic responders, MELD threshold 10 provided additional prognostic precision.<br>Decompensation occurred in 62% regardless of aetiology. |
| Rincón et al, 2013 [3]<br>(n=145)<br><br>HVPG | Retrospective single center study. Median follow-up: 27 months. | As, HE, PB | No – 47%<br>Small – 23%<br>Large – 20% | HCV (HCC in 26%) – none had SVR (37% on antivirals) | Not given | HVPG and albumin independent predictors of decompensation.<br>Each mmHg increase in HVPG led to 11% | 1,2,5 year decompensation 8%, 25%, 44% respectively (more common if varices). |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | Unknown – 10% | | | increase in the risk of decompensation.<br>PI** model discriminative of decompensation (AUROC: 0.77 (95% CI: 0.64–0.89).<br>PI < 2.5 predictive of remaining free of decompensation. | |
| Lens et al, 2015 [4]<br>(n=100)<br>HVPG | Retrospective over four centers.<br>Median follow-up: 5.2 years. | As, HE, PB | Esophageal varices – 31% | Compensated HCV in interferon-based therapy (SVR in 35%)<br>CSPH in 74% | NSBB in 4% | Baseline HVPG (not SVR) predicted decompensation and transplant-free survival. | 1,5,7 year decompensation of 3%, 19%, and 22%, respectively (higher if CSPH). |
| Reiberger et al, 2012 [5]<br>(n=104)<br>HVPG | Prospective non-randomized study.<br>Median follow-up 19.5 months. | As, HE, PB, Ja | Small varices – 39%<br>Large varices – 61%<br>No previous bleeding | ArLD – 55%<br>Viral – 33%<br>MASLD – 10%<br>Mostly compensate | Propranolol Carvedilol (for hemodynamic non-responders). VBL in carvedilol non-responders (carvedilol stopped). | Hemodynamic response defined as >20% reduction or reduction to < 12 mmHg.<br>Less decompensation in:<br>a. propranolol non-responders on carvedilol compared to VBL<br>b. NSBB responders compared to VBL | Less decompensation in:<br>a. propranolol non-responders on carvedilol compared to VBL<br>b. NSBB responders compared to VBL |
| **Invasive and non-invasive tests** | | | | | | | |
| Ripoll et al, 2007 [6]<br>(n=213)<br>Invasive (HVPG ≥ 6 mmHg) | Nested cohort study within a RCT<br>Median follow-up: 51 months | As, HE, PB | No | ArlD – 24%<br>HCV – 59% (no | Timolol vs placebo | HVPG < 10 mmHg associated with 90% probability of absence of decompensation | Decompensation in 29% during follow-up. HVPG, MELD, and albumin predicted decompensation. HVPG had greatest discriminative ability. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Non-invasive (albumin, MELD) | . | | | on antivirals) | | (ascites 75%, variceal bleeding 105, hepatic encephalopathy 27%).<br>HVPG decrease < 10% associated with decompensation.<br>Every HVPG increase in 1mmHg associated with 19% increased risk of clinical decompensation.<br><br>Non-invasive tests (c-statistic; 95% CI)<br>Albumin (0.66; 95% CI, 0.58 – 0.74)<br>MELD (0.64; 95% CI, 0.55– 0.72)<br>HVPG (0.71; 95% CI, 0.64 – 0.78) | |
| Berzigotti et al, 2011 [7]<br>(n=172)<br>Invasive ( HVPG ≥ 10 mmHg (n=86))<br>Non-invasive (paired USS (n=86)) | Retrospective analysis<br>Median follow up: 28 months<br>73% compensated. | As, HE, PB, SBP, Ja | None – 24%<br>Small – 28%<br>Large – 48% | ArLD – 11%<br>Viral – 54% | NSBB (n=33)<br>VBL (n=5)<br>NSBB + VBL (n=3)<br>TIPS (n=2) | HVPG ≥ 16 mmHg (p=0.007) and bilirubin (p=0.06) predicted first decompensation<br><br>APC correlated with HVPG ≥ 16 mmHg, and trend in predicting decompensation. | First decompensation higher in ArLD vs other etiologies (57.1% vs 21.8%). |
| Berzigotti et al, 2011 [8]<br>(n=161) | Nested cohort study of a RCT. | As, HE, PB | No | ArlD – 24% | Timolol vs placebo | HVPG (1.14 [95% CI, 1.07-1.20]), albumin (HR 4.54 | Fewer patients with obesity had ≥ 10% reduction in HVPG at one year (24.5% vs 40.4%). |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Invasive (HVPG)<br>Non-invasive (BMI, albumin) | Median follow-up: 59 months | | | HCV – 59% (no on antivirals) | | [2.44-8.33]) and high baseline BMI (hazard ratio 1.06; 95% CI, 1.01-1.12) independent predictors decompensation. | |
| Robic, 2011 [9]<br>(n=100)<br><br>Invasive (HVPG)<br>Non-invasive (LSM) | Prospective, single center<br>Mean follow up 491 days | As, HE, PB, HRS, SBP, HCC and/or sepsis | In cirrhotic patients:<br>No varices – 27.5%<br>Small varices – 27.7%<br>Large varices – 35% | ArLD – 38%<br>Viral hepatitis – 28%<br>MASLD – 8%<br><br>All had cACLD<br>Cirrhosis – 65%<br>CSPH – 51% | Not given | AUROC (95% CI) for portal hypertension-related complications:<br>• LSM: 0.830 [0.751–0.910]. No decompensation if LSM <21.1 kPa.<br>• HVPG: 0.845 [0.767–0.920]. No patients with HVPG < 10 mmHg developed decompensation | In cirrhosis patients, 26.5% developed portal hypertension-related complications during follow-up. |
| Colecchia,2014 [10]<br>(n=92)<br><br>Prospective.<br>Invasive (HVPG)<br>Non-invasive (LSM, splenic stiffness, platelet count/spleen diameter ratio, liver stiffness-spleen diameter to platelet ratio score, APRI, liver stiffness x spleen diameter, MELD) | Prospective<br>Mean follow-up – 731 days | As, HE, PB | No varices – 53%<br>Small varices - 53% | HCV cirrhosis<br>cACLD<br>No patients on antiviral therapy at baseline | None | AUROC (95% CI) for predicting liver decompensation.<br>HVPG: 0.83 (95% CI 0.75–0.92)<br>SS: 0.85 (95% CI 0.77–0.93) (independent of the presence of varices)<br>MELD and SSM predictive model***: 0.87 (95% CI 0.80–0.94)<br>SSM < 54 kPa: NPV 0.98 (0.87-0.99) for predicting low risk of decompensation at 2 years | 33% decompensated over 2-year period. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pérez-Latorre, 2014 [11]<br>(n=60)<br><br>Invasive (HVPG)<br>Non-invasive (LSM) | Retrospective.<br>Median follow-up 42 months. | As, HE, PB, Ja | Varices in 38%. | HCV cirrhosis with and without HIV co-infection. All co-infected on therapy (86% responders)<br>CSPH in 53%. | Not given | AUROC (95% CI) for predicting liver decompensation.<br>LSM: 0.85 (.69–1.00). LSM < 25 kPa and LSM>40 kPa thresholds for absence and presence of decompensation<br>HVPG: 0.76 (0.59–0.93) | Decompensation in 13% over 42 months. |
| Sebastiani, 2015 [12]<br>(n=148)<br><br>Invasive (HVPG, histology)<br>Non-invasive (APRI, FIB-4, NAFLD fibrosis score, imaging) | Retrospective cohort study.<br>Merdian follow-up – 5 years | As, HE, PB, SBP | No given | MASLD (F3/F4 fibrosis in 34%).<br>CSPH in 18.2%. | Not given | AUROC (95% CI) for predicting liver decompensation:<br>• Histologic fibrosis stage, 0.85 ( 0.76-0.93)<br>• HVPG, 0.81 (0.70-0.91)<br>• APRI, 0.89 (0.82-0.96)<br>• FIB-4, 0.89 (0.83-0.95)<br>• NAFLD fibrosis score, 0.79 (0.69-0.91) | Clinical outcomes (decompensation, liver transplantation, HCC, or death) in 16.2% over 5 years..<br>Histological steatosis and non-invasive steatosis methods did not predict outcomes. |
| Kitson, 2015 [13]<br>(n=95)<br><br>Invasive (HVPG)<br>Non-invasive (LSM, APRI, FIB-4, PSDR) | Prospective<br>Median follow-up – 15.1 months | As, HE, PB, HRS | No varices – 28%<br>Small varices – 42%<br>Large varices – 29% | ArLD – 41%<br>HCV - 33%.<br>Compensated cirrhosis (previous decompensation in 24%). | NSBB – 22% | AUROC (95% CI):<br>• LSM: 0.73 (0.61–0.84). LSM > 34.5 kPa optimal threshold for the presence of decompensation | In those with CSPH risk of portal hypertensive complications at 1, 2, and 3 years was 20%, 35%, and 40%,<br>respectively |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | 75% had CSPH<br>Cirrhosis in 93%. | | | |
| Harrison, 2018 [14]<br>Sanyal, 2019 [15]<br>Bosch, 2021 [16]<br>Invasive (HVPG, ML-HVPG)<br>Non-invasive (ELF<br>FibroSure<br>FibroTest<br>FIB-4<br>APRI<br>Serum LOXL2)<br>NAFLD fibrosis score<br>ML (machine learning)-HVPG<br>Other lab assessments) | RCT (Simtuzumab vs placebo)<br>Median follow-up 30.9 months | As, HE, de-novo varices, PB, CPS increase ≥ 2 points | Varices – 42% in cirrhotic patients | MASLD<br>Bridging fibrosis (n=219)<br>Compensated cirrhosis (n=258, 68% had CSPH) | NSBB – 21% | Variables associated with clinical events in cirrhotic patients (HR with 95%CI):<br>• ELF score: 2.11 (1.53-2.90)<br>• FibroSure/FibroTest, per 0.1 units: 1.21 (1.06-1.38)<br>• NAFLD Fibrosis Score: 1.78 (1.43-2.21)<br>• FIB-4: 1.24 (1.14-1.35)<br>• APRI: 1.88 (1.45-2.46) sLOXL2, per 10 pg/mL 1.02 (1.01-1.04)<br>• CSPH (HVPG ≥ 10 mm Hg): 2.83 (1.33-6.02)<br>• Failure to achieve ≥ 20% decrease in HVPG: 5.38 (1.65-17.58)<br>• Failure to achieve HVPG < 10 mm Hg and/or a ≥ 20% decrease: 5.51 (1.69-17.98) | Of cirrhotics, 19% experienced clinical events over follow up 30.9 months (19% of these had HVPG < 10 mmHg) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | • ML-HPVG score per 1 unit baseline increase: 2.13 (1.26-3.59) | |
| Villanueva et al, 2019 [17]<br>Villanueva et al. 2021 [18]<br>(n=201)<br><br>Invasive (HVPG ≥10 mmHg)<br>Non-invasive (LSM ≥ 14 kPa, Child-Pugh Score)<br><br>Nicoară-Farcău et al 2022 [19]<br>(n=167)<br>Non-invasive: Metabolomics | RCT (PREDESCI). Median follow up 37 months. | As, HE, PB | No varices – 43%<br>Small esophageal varices – 57% | HCV – 56% (none on antivirals)<br>Alcohol – 16%<br>MASLD – 6.5%<br>(all compensated cirrhosis with CSPH) | NSBB (propranolol (n=67) or carvedilol in propranolol non-responders (n=33) vs placebo<br><br>VBL if high-risk varices developed | Cox proportional-hazards regression for prediction of decompensation and/or death (hazard ratio, 95% CI)):<br>• Baseline Child-Pugh score:4.13 (2.03-8.39)<br>• Baseline HVPG: 4.72 (2.24-9.95)<br>• LSM (AUROC): 0.63 (0.51 to 0.74)<br>•HVPG/Clinical/Metabolite model (AUROC): 0.808 (0.735-0.882)<br>Clinical/Metabolite model (AUROC): 0.785 (0.710-0.860) | NSBB resulted in lower decompensation and death ((HR 0.51 (0.26-0.97), p=0.0412).<br>Bacterial infection was predictive of decompensation.<br>ArLD, varices at baseline, and HVPG response (>10% decrease from baseline or to < 10 mmHg) had the most benefit from NSBB. |
| Jindal et al, 2020 [20]<br>(n=741)<br>Invasive (HVPG ≥ 6 mmHg stratified into 3 strata)<br>Non-invasive (LSM, biochemical and hematological parameters) | Retrospective<br>Median follow up 1.6 ± 0.4 years | As, HE, PB, Ja | No varices-10%<br>Small varices – 66%<br>Large varices – 24% | Alcohol - 22.9%<br>MASLD – 30.8%<br>HCV – 20.6%<br>HBV – 10.7%<br>All compensate cirrhotics | Carvedilol if HVPG ≥ 12 mmHg | Baseline HVPG ≥ 12 mmHg (HR 2.73) and HVPG ≥ 20 mmHg (HR 4.48) independent predictors of decompensation<br>Total leucocyte count (HR 1.07) and serum creatinine (HR 1.19) are associated with decompensation-free survival. | 217 (29%) developed decompensation over 1.6 year follow up (earlier if higher HPVG)<br>LSM not associated with decompensation.<br>HVPG ≥ 20 mmHg group had higher proportion of MASLD cirrhosis than lower HVPG group (35% versus 20%). |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mandorfer et al, 2020 [21]<br>(n=90)<br><br>Invasive (HVPG ≥ 6 mmHg)<br><br>Non-invasive (MELD, CPS) | Prospective.<br>Median follow-up 35.3 months (IQR 21.8 months) | As, HE, PB | Large varices – 47%<br>Small varices – 53% | HCV – all had SVR<br><br>14% had previous decompensation | NSBB (42%) | Baseline HVPG not predictive of decompensation<br>HVPG change (especially if no decrease ≥ 10%) during follow up predicted decompensation (AUROC 0.872))<br><br>Follow-up Child-Pugh Score (HR 1.484; 95% CI 1.01-2.17) and Follow-up MELD (HR 1.15; 95% CI 1.01-1.32) associated with decompensation | |
| Costa et al, 2021 [22]<br>(n=168)<br>Invasive (HVPG)<br>Non-invasive (MELD, CRP, Il-6) | Prospective<br>Single center<br>Median follow up 12.2 months | As, HE, PB. | Small varices – 32%<br>Large varices – 24% | 78 cACLD:<br>ArLD – 21.6%<br>Viral – 34.6%<br>MASLD – 20.3% | None | Variables predicting decompensation (HR with 95% CI) in Baveno stages 0-2:<br>Il-6: 1.06 (1.01-1.1) | IL-6 and CRP levels independently predicted death/liver transplantation. |
| Scheiner et al, 2022 [23]<br>(n=576)<br><br>(HVPG ≥ 6 mmHg, LSM ≥10 kPa)<br><br>Invasive (HVPG)<br>Non-invasive (FVIII/PC ratio) | Retrospective single center<br>Median follow-up 31.8 months | As, HE, PB | Varices – 68% | Viral – 38%<br>ArLD – 36%<br>MASLD – 11%<br><br>52% had history of decompensation | No data on NSBB | Predictors of decompensation or liver-related death (AUROC at 36 months):<br>FVIII/PC – 0.708<br>MELD – 0.733<br>HVPG – 0.771 | |
| Jindal et al, 2022 [24]<br>(n=261) | Retrospective single center | As, HE, PB, Ja | In compensated patients: | Compensated patients: | Carvedilol if large varices or decompensati | Baseline predictors of new decompensation (HR;95% CI): | Overall 14.4% developed new decompensation over 23.1 months (HVPG response to carvedilol |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (compensated 132)<br><br>Invasive (HPVG 6-10 mmHG)<br><br>Non-invasive (LSM > 15 kPa, portosystemic shunts, biochemical parameters) | Median follow-up 23.1 months | | No varices- 71%<br>Small varices – 24%<br>Large varices – 5.1% | Alcohol – 6.1%<br>MASLD – 37.1%<br>HCV – 21.2%<br>HBV – 12.9% | on during follow-up (n=60) | LSM > 26.6 kPa - 1.08 (1.03–1.12)<br>Portosystemic shunts - 4.42 (1.05–18.66)<br>Albumin - 0.27 (0.09–0.88) | predicted absence of decompensation)<br>New decompensation increased mortality rate by a factor of seven.<br>HVPG predictive of further but not new decompensation |
| Jachs et al 2024 [25]<br>(n=420)<br><br>Non-invasive (LSM ≥ 10 kPa, VITRO, platelet count, BMI, ANTICIPATE±NASH<br><br>Invasive (HVPG) | Retrospective single center. | As, HE, PB, | No varices- 60%<br>Small varices – 26%<br>Large varices – 14%<br><br>All patients had compensated disease | Viral – 51.9%<br>ArLD – 20.5<br>MASLD – 18.6%<br><br>119 patients had control or cure of etiological factor | No patient on NSBB at baseline.<br>Assumed nearly all patients with varices treated with NSBB | Predictors of decompensation at one year (AUROC):<br>HVPG ( 0.739)<br>VITRO (0.811),<br>ANTICIPATE±MASLD CSPH<br>probability (0.683)<br>LSM to PLT ratio (0.699)<br><br>No difference between predictors including subgroup of ArLd/MASLD<br><br>Known threshold differentiated high vs low risk of hepatic decompensation<br>(HVPG ≥ 10 mmHg vs. <10 mmHg,<br>VITRO ≥<br>2.5 vs. <2.5, and ANTICIPATE- | 16% decompensation over median follow-up 1.6 (0.5-3.8) years<br>Higher decompensation in ArLD vs MASLD (3 years 35.5% vs 14.9%) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | CSPH probability ≥<br>60% vs. <60%) | |
| **Non-invasive tests** | | | | | | | |
| Merchante et al, 2012 [26]<br>(n=239)<br><br>LSM ≥ 14 kPa,<br>APRI, FIB4 | Prospective<br>Seven centers<br>Median follow up 20.7 months | As, HE, PB, HRS, SBP | Large varices – 93%<br>Small varices – 15% | HIV/HCV co-infection<br>All on therapy – 16% had no SVR at baseline, 23% had SVR at end of study<br>cACLD with no previous decompensation | Not given | Predictors of decompensation (AUROC ; 95% CI)<br>• LSM: 0.72 (95% CI 0.61-0.82)<br>• LSM ≥ 40 kPa optimal threshold to predict decompensation<br>• Child-Pugh score: 0.76 (95% CI, 0.65-0.88)<br>• MELD: 0.71 (95% CI 0.61-0.81) | During follow up 13% developed decompensation |
| Merchante et al, 2015 [27]<br>(n=275)<br>LSM >14 kPa and < 40 kPa | Prospective<br>Seven centers<br>Median follow-up – 32 months | As, HE, PB, HRS, SBP | Not given | HIV/HCV co-infection<br>At baseline 67% had negative HIV RNA load.<br>During follow up 39% had HCV therapy (31% had SVR)<br>cACLD with no previous decompensation | Not given | Predictors of decompensation and/or HCC (AUROC ; 95% CI):<br>LSM (baseline): 0.609 (0.471–0.748)<br>LSM progression: 0.680 (0.541–0.818)<br>Only LSM progression associated with the endpoint. | LSM every 12 months with progression defined as ≥ 30% baseline.<br>6.9% decompensated and/or developed HCC over 32 month follow-up. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Guha et al, 2019 [28]<br>(n=145)<br><br>Model based on FIB-4 and ALBI which includes the following variables age, AST, Albumin, platelets, bilirubin, ALT.**** | Retrospective<br>Three centers<br>Median follow-up – 4.59 years | As, HE, PB. | Not given | ArLD – 45%<br>MASLD - 30%<br>All had cirrhosis<br>cACLD with no previous decompensation | Not given | Precision of model in predicting decompensation:<br>Harell's c statistic: 0.805 (95% CI 0.718-0.873)<br>Hazard ratio of high-risk patients was 7.1 (95% CI, 3.07 to 16.42) | Does not consider the influence of etiology. Lack of calibration of the model.<br>Decompensation in 19.3% over 4.59 years |
| Eaton et al, 2020 [29]<br>(n=204)<br><br>MRE (146 had second MRE)<br>APRI | Retrospective<br>Median follow-up – 4 years | As, HE, PB. | Not given | PSC<br>All with cACLD | Not given | Variables predicting decompensation (HR with 95% CI):<br>Single LSM > 4.32 kPa (second MRE): 60.41 (17.85-204.47)<br>Change in LSM 0.34 kPa/year: 13.29 (5.23-33.78)<br>Change in APRI/year: 0.76 (0.62-0.93) | LSM progression directly related to baseline LSM (stage 0 fibrosis – 0.03 kPa/year versus stage 4 fibrosis – 0.31 kPa/year).<br>Ascites noted in all patients that developed decompensation (n=23) |
| Han et al, 2020 [30]<br>(n=320)<br><br>MRE | Retrospective<br>Two centers | As, HE, PB. | Not given | MASLD<br>All with cirrhosis (compensated – 26, decompensated - 13) | Not given | Variables predicting decompensation or death (OR with 95% CI):<br>MRE: 3.28 per kPa increase (2.04 – 5.28) | LSM by MRE at a threshold of 3.99 kPa discriminated between cirrhosis and non-cirrhosis (AUROC 0.986).<br>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]<br>(n=299)<br><br>ABIDE<br>NAFLD fibrosis score<br>FIB-4 | Retrospective<br>Six centers<br>Median follow-up 5.6 years | As, HE, PB. | Varices – 43.1% | MASLD compensated cirrhosis | NSBB in 16.6% | 5 year prediction of decompensation (tAUC):<br>ABIDE (0.80) –<br>ABIDE vs: | ABIDE ≥ 4.1 kPa associated with an increased risk of decompensation (5-year cumulative incidence 37%). |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| MELD<br>CPS<br>ALBI<br>ALBI-FIB4 | | | | | | NAFLD fibrosis score (0.72)<br>FIB-4 (0.74)<br>MELD (0.69)<br>CPS (0.72)<br>ALBI (0.72)<br>ALBI-FIB4 (0.73) | |
| Gidener et al, 2021 [32]<br>(n=829)<br><br>MRE | Retrospective<br>Median follow up – 4 years | As, HE, PB, Ja | Not given | MASLD<br>Cirrhosis - 23.4% | Not given | Variables predicting decompensation or death (HR with 95% CI):<br>MRE: 1.32 (1.13-1.56) per 1kPA increase after adjusting for age, sex, MELD Na | In cirrhotic patients, 35% developed decompensation during follow-up. |
| Osman et al, 2021 [33]<br>(n=538)<br>LSM measured by transient elastography (n=286) and MRE (n=332) | Prospective<br>Three centers | As, HE, PB. | Not given | PBC<br>11.1% cirrhotic<br>71.5% UDCA responders | Not given | Variables predicting decompensation (HR with 95% CI):<br>Transient elastography: 1.14 (1.05-1.24); optimal threshold 10.2 kPa<br>MRE: 1.68 (1.28-2.19); optimal threshold 4.2 kPa | |
| Younes et al 2021 [34]<br>(n=1173).<br><br>NAFLD fibrosis score<br>FIB-4<br>BARD<br>APRI<br>Hepamet fibrosis score | Prospective<br>Six centers<br>Median follow up 81 months | As, HE, PB. | Not given | MASLD<br>F3/F4 fibrosis in 24.1%. | Not given | Variables predicting liver events (medial Harrell's c-indices):<br>NAFLD fibrosis score (0.796)<br>FIB-4 (0.783)<br>BARD (0.728)<br>APRI (0.6) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | Hepamet fibrosis score (0.729) | |
| Petta et al, 2021 [35]<br>(n=1039)<br><br>NAFLD F3-F4 fibrosis and/or LSM > 10 kPa<br>Minimum 6 months follow up.<br>Baseline LSM and repeat within 1 year<br>Delta LSM (improvement if > 20% reduction, stable if between -/+ 20% from baseline, impairment if 20% or more increase) | Retrospective<br>10 centers<br>Median follow-up 35 months. | As, HE, PB, Ja | Not given | MASLD with cACLD | Not given | Baseline LSM independently predicted:<br>a. Decompensation (HR 1.03; 95% CI 1.02-1.04)<br>b. Liver related death (HR 1.02;95% CI 1.02-1.03)<br><br>Delta LSM (n=533) predicted:<br>a. Decompensation (HR 1.56; 95% CI 1.05-2.51)<br>b. HCC (HR 1.72;95% CI 1.01-3.02)<br>c. Overall mortality (HR 1.73 (95% CI 1.11-2.69)<br>d. Liver related mortality (HR 1.96; 95% CI 1.10-3.38) | Threshold baseline LSM 21kPa (CSPH) independently associated with decompensation (HR 3.71; 95% CI 1.89-6.78)<br>Delta LSM associated with decompensation in patients without CSPH at baseline but not those with CSPH.<br>Age and platelet count also associated with decompensation. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Semmler et al, 2023 [36]<br>(n=2503)<br>(non-ACLD = 1647, cACLD = 757,<br>dACLD = 104)<br><br>(LSM, laboratory values, FIB-e, MELD | Retrospective single center<br>Median follow up 71.2 months | As, HE, PB | No given | Etiology (non-ACLD, cACLD):<br>AIH/cholestatic (13.3, 14.1)<br>ArLD (1.2, 7.1)<br>HBV (11.4, 6.3)<br>HCV (49.5, 50.7)<br>MASLD (18.3, 14.5) | Not given | Predictors of liver decompensation (AUROC)<br>LSM dynamics – 0.933<br>Platelet dynamics – 0.849<br>Albumin dynamics – 0.566<br>FIB-4 dynamics – 0.873<br>MELD dynamics – 0.835<br>(Dynamics in first 24 months to predict decompensation within subsequent 12 months) | Median time to second LSM 17 months<br>Higher decompensation with cACLD vs non-ACLD (0.4% vs 10.9%).<br>LSM 20% increase increased decompensation by 50% and more pronounced after etiological cure. Converse also true.<br>When looking at Baveno VII criteria for clinically significant decrease in LSM – best discrimination for decompensation if stratify by any decrease to < 20 kPa (Harrell's C-indec 0.747). |
| Schneider et al, 2022 [37]<br>(n= 25354)<br>(training – 6049; validation – 19305)<br><br>Child-Pugh Score, MELD, ALBI, PALBI, EPOD score | Retrospective population based from 2 cohorts in United States and one cohort United Kingdom.<br>Follow-up – 3.5 – 10 years | As, HE, PB, Ja, HRS | Not given | Alcohol – 9.5% to 54% in UK<br>Viral hepatitis – 12-45.22%)<br><br>All had compensated cirrhosis | No data on therapies | EPOD score prediction of 3 year decompensation (AUROC)<br>Explorys – 0.694<br>PMBB – 0.692<br>UKB – 0.770<br><br>EPOD score threshold of 10 accurately stratified into low and high risk. | EPOD score outperformed MELD and CPS in predicting decompensation.<br><br>No data on etiological control or cure. |
| Dajti et al, 2022 [38]<br>(n=195)<br><br>(114 validation cohort analysed) | Retrospective, 2 centers in Italy<br>Median follow up 42 months | As, HE, PB, | Varices – 50.9% | Viral - 57.9%<br>ARLD - 12.3% | No patient on NSBB | 1st decompensation rate (Baveno VII, Baveno VII sequential SSM, | Combined Baveno VII-SSM model had the greatest precision in CSPH diagnosis compared to Baveno VII model and Baveno VII sequential SSM Model with only 15% in grey |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| LSM ≥ 10 mmHg, SSM, platelets | | | | MASLD – 36%<br><br>All had compensated CSPH | | Baveno VII-SSM combined models)<br>Rule in group (12.5%, 15.4%, 16.1%)<br>Rule out group (0 in all models)<br>Gray zone (9.7%, 4.4%, 0%) | zone with NPV and PPV > 90% for ruling in an out CSPH:<br>Rule-out:<br>Two of: LSM ≤15 kPa PLT ≥ 150,000 SSM ≤40 kPa<br>Rule in:<br>Two of: LSM > 15 kPa, PLT < 150,000, SSM > 40 kPa |
| Asesio et al, 2022 [39]<br>(n=455)<br><br>B6C (Baveno VI criteria) – favorable LSM < 20 kPa and platelet > 150000/mm$^3$) and unfavorable Baveno VI status patients (LSM ≥20 kPa or platelet ≤150000/mm$^3$)<br>Lab assays | Retrospective single center<br>Mean follow-up – 3.6 years. | As, HE, PB, | Varices needing treatment – 17.5% (more in unfavorable Baveno VI group 25% vs 3.8% patients) | HCV – 68.4%<br>MASLD – 24.8<br>ArLD – 16.9%<br>Hep B – 10.1%<br><br>All compensated<br>Viral suppression in 82% | | Independent predictors of portal hypertensive related complication (HR (95% CI):<br>HCC (0.40 [0.19–0.83])<br>low baseline albumin (0.89 [0.84–0.93])<br>high serum total bilirubin rate (HR = 1.06 [1.03–1.08])<br>low PT (0.97, [0.96–0.99])<br>Unfavourable Baveno VI (0.46 [0.21–0.89]) | Decompensation during follow up higher in unfavourable B6C (14.3% vs 5.6%) |
| Fernández-Alvarez et al, 2023 [40]<br>(n=321)<br><br>Child-Pugh Score, FIB-4 | Retrospective single center<br>Median follow-up 48 months | As, HE, PB, | Not available | HCV with SVR and advanced fibrosis or cirrhosis<br><br>10% had previous decompensation | | Independent predictors of decompensation (HR; 95% CI):<br>CPS baseline - 4.13 (1.74-9.81)<br>FIB-4 baseline - 1.12 (1.03-1.21)<br><br>FIB-4 cut-offs for decompensation risk on follow-up (AUROC): | Decompensation in 10%<br>Only FIB-4 associated with decompensation at 1 and 2 years. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | 1 year: 2.03 )0.824)<br>2 years: 2.21 (0.819) | |
| Thorhauge et al, 2024 [41] (n=536)<br><br>LSM | Retrospective, 2 centers<br>Median follow-up - 63 months | | Not available | ArLD – 100%<br>42~% abstinent<br>All compensated - cACLD (LSM ≥ 10 kPa) and no cACLD (LSM < 10 kPa | No data on NSBB. | Independent predictors of decompensation (Harrell's c index, 95% CI):<br>Baseline LSM – 0.85 ( 0.83-0.88)<br>Follow up LSM – 0.89 ( 0.85-0.93)<br>LSM changes – 0.85 ( 0.80-0.90)<br>Delta LSM – 0.47 ( 0.34-0.60)<br>Delta LSM/year – 0.55 ( 0.42-0.68) | Decompensation higher if cACLD (31% vs 3%; HR=19.76, p<0.001))<br>Data is not sufficient to assess the impact of alcohol consumption during follow-up on LSM changes and outcomes. |
| Kobayashi et al, 2024 [42] (n=405)<br><br>LSM using MRE | Retrospective single center<br>N=405<br><br>Median follow-up 72.6 months | As, HE, PB, Ja, | No available | MASLD<br>(95% non-cirrhotic) | No data on NSBBs | Predictive value of baseline LSM (HR (95% CI) for LSM ≥ 4.69 (F4 fibrosis) vs <2.61kPa (F0 fibrosis))<br>Decompensation: 24.84 (4.51–137.0)<br>Death: 45.33 (6.17-333.0)<br><br>Predictive value of change in LSM in follow up (>19% vs <19% change; (HR, 95%CI)):<br>Decompensation:<br>12.08 (1.85 – 78.73) | Median interval between LSM 23.5 ± 0.5 months. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | Change in LSM not predictive of mortality. | |
| Shearer et al, 2023 [43]<br>(n=3028)<br><br>LSM ≥ 10 kPa, FIB-4, ALBI | Retrospective using electronic health records at 2 centers<br>Median follow up 3.1 years. | As, HE, PB, SBP | Data at baseline not available. | ArLD - 11%<br>NAFLD - 28%<br>(43% missing data)<br>All had cACLD | No data on NSBB use | Baseline LSM and 5 year decompensation risk (% (95%CI))<br><15 kPa – 3.7 (2.7-5.1)<br>15-25 kPa – 8.6 (6.4-11.1)<br>>25 – 19.0 (15.8-22.4)<br><br>Selecting only those with FIB-4 > 1.3 increased decompensation rates with maximum at 5 years with LSM > 25 of 20.3% (16.9-23.9)<br><br>Following associated with decompensation (HR (95% CI)): | 7.1% patients developed varices prior to decompensation /HCC<br>74% of patients not known to have varices at time of decompensation.<br>Patients with ArLD had highest risk of decompensation (19.2% at 5 years) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | LSM (per kPa increase) – 1.02 (1.01-1.03)<br>FIB-4 (per unit increase) – 1.05 (1.02-1.07)<br>ALBI score (per unit increase) – 2.4 (1.8-3.18) | |
| Wong et al, 2023 [44] (n=1159)<br><br>LSM<br>Laboratory values | Retrospective, four centres.<br><br>Median follow up 40 months | As, HE, PB | No varices – 60.7%<br>Low risk varices – 33.8%<br>High risk varices – 5.5% | HCV – 56.1%<br>Hepatitis B – 21.3%<br>ArLD – 9.1%<br>MASLD – 102 (8.8)<br>All patients had compensated disease (CSPH (LSM ≥ 25 kPa, 36.8%), grey zone (51.1%), CSPH excluded (LSM < 15 kPa, 12.1%)) | Patients on NSBB excluded | Predictors of decompensation (sHR (95% CI)<br><br>CSPH (2.48 (1.35-4.55)<br>Non-viral etiology (3.25 (1.83-5.76)<br>INR > 1.1 (2.08 (1.14-6.25)<br>Albumin < 37 g/L (3.38 (1.83-6.25))<br>LSM ≥ 25 kPA 8.8 (2.9–26.7)<br><br>Predictors of decompensation in grey zone (sHR (95% CI)<br>Non-viral etiology (11.34 (8.10–15.87))<br>INR (4.27 (1.33–13.70)) | During follow up 7.2% developed decompensation (lower in grey zone (2.6%) vs CSPH (13.8%))<br>Non-viral etiology had highest rate of decompensation (up to 25.5% in CSPH group) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | Albumin (0.88 (0.85–0.91))<br>Bilirubin (1.02 (1.00–1.03)) | |
| Song et al, 2023 [45]<br>(n= 1966)<br><br>LSM ≥ 10 kPa | Retrospective single center<br>Median follow-up 3.06 (IQR 1.03-6.00) years. | As, HE, PB | No available | Viral 62,6% (majority on HBV antivirals and almost all had HCV SVR)<br>NAFLD 18.1%<br>Alcohol 15.97%<br><br>All had cACLD | No data on NSBB use. | Decompensation risk in grey zone (sHR (95% CI):<br><br>ArLD (3.49 (1.65–7.37)<br>Low albumin - 0.41 (0.25–0.67)<br>Lower platelet (0.99 (0.98-1.00)<br>Higher LSM (1.14 (1.07 – 1.22) | Decompensation risk<br>CSPH– 22% at 3 y (27% in NAFLD, 37% in ArLD)<br>Grey zone high probability– 12% (17% in NAFLD, 31% in ArLD)<br>Grey zone low probability) – 3.3% (0% in NAFLD, 10% in ArLD)<br>CSPH excluded– 1.4% (2.2% in MASLD, 7.4% in ArLD)<br><br>CSPH had a higher proportion of ArLD. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Lin et al, 2023 [46]<br>(n=2763)<br><br>with cACLD (Baveno VII criteria: low risk (35.6%), grey zone (44.9%), high risk (19.4%).<br><br>LSM, ALBI, SSM (n=179) | Prospective 3 centers<br><br>Median follow up 7.2 years | As, HE, PB and/or cirrhotic-related mortality | Data at baseline not available. | ARLD – 16.2%<br>MASLD – 31.16%<br>HCV – 6.36%<br>HBV – 42.6%<br><br>35.6% on antiviral therapy | No data on NSBB use | Predictors of decompensation in grey zone (SHR (95% CI):<br>ArLD – 2.05 (1.05 – 3.99)<br>ALBI – 1.8 (1.06 – 3.04)<br>ALP (1.6 (1.09-2.32) | 5 year incidence of decompensation was 0.3%, 4.2%, 11.4% in low-risk, grey zone, and high risk, respectively<br><br>Combination of Baveno VII and spleen stiffness reduced classified in grey zone (12.8%) |
| Wong et al, 2024 [47]<br>(n=480)<br><br>with cACLD<br>LSM and delta LSM | Retrospective 5 centers<br>Median follow up 68 months | As, HE, PB | Not available | Viral hepatitis (52.7%)<br>MASLD (33.8%)<br>ArLD (4.6%)<br>Etiological control (63.5%) | NSBB use in 7.7% | Resolved cACLD (LSM<10kPa, 32%) vs persistent cACLD:<br>Liver related events (2.6% vs 7.4%, p=0.038)<br>Death (1.3% vs 4.9%, p=0.069)<br>No added predictive value of prior LSM to current LSM | Over median follow-up 34 months – 5.8% developed liver-related events. Liver-related death in 1.5%.<br>Risk of liver-related events related to baseline LSM. |

Footnotes:

As – ascites; ArLD – alcohol related liver disease; HVPG – hepatic venous pressure gradient; RCT – randomized controlled trial; H – hepatitis C virus; NSBB – non-selective beta-blocker; HCC – hepatocellular carcinoma; APC – abdominal porto-systemic collaterals; VBL – variceal band ligation; HE – hepatic encephalopathy; PB – portal hypertensive bleeding; Ja – jaundice; SBP – spontaneous bacterial peritonitis; MASLD – metabolic dysfunction-associated steatotic liver disease; MELD – model for end-stage liver disease; BMI – body mass index; SVR – sustained virological response; ACLD – advanced chronic liver disease; cCLD – compensated advanced chronic liver disease; CSPH – clinically significant portal hypertension; AUROC -area under the receiver operating characteristic; APRI - AST to Platelet Ratio Index; LSM – liver stiffness measurement; SSM - splenic stiffness measurement; FIB-4 – fibrosis 4; ELF – enhanced liver fibrosis; CPS – Child-Pugh score; LOXL2 - Lysyl Oxidase Like 2; IL-6 – interleukin 6; CRP – C-reactive protein; FVIII/PC ratio – factor VIII: protein C ratio; VITRO – von Willebrand Factor antigen to platelet ratio; ALBI -albumin bilirubin; MRE – Magnetic resonance elastography; UDCA – ursodeoxycholic acid; PBC – primary biliary cholangitis; PSDR - Platelet:spleen diameter ratio; IV – intravenous; SHR - subdistribution hazard ratios; HRS – hepatorenal syndrome; tAUC (time-dependent area under the curve); IQR – interquartile range.

* - nadolol withdrawn in 9 patients due to intolerance and offered VBL.

** - Prognostic Index (PI) = 4 + (0.11 x HVPG - 0.8 x albumin)

*** - Formula: exp(-11:5 + 0.107 * SS + 0.45 * MELD)/[1 + exp(-11:5 + 0.107 * SS + 0:45 * MELD)]

**** = * - formula available online: https://jscalc.io/calc/gdEJj89Wz5PirkSL

ABIDE ((Aspartate aminotransferase/alanine, aminotransferase ratio, bilirubin, International normalized ratio, type 2 Diabetes, and esophageal varices)

EPOD score - https://www.ukaachen.de/typo3conf/ext/wstheme/Resources/Public/Microsites/epod/

**Supplementary Table 2:** Studies comparing active therapy vs a control group, to prevent the development of decompensation in patients with cACLD

| STUDY | AGENT | DESIGN OF THE STUDY | STAGE OF CLD | ETIOLOGY | Nº OF PATIENTS | FOLLOW-UP | PRIMARY OUTCOME | MAIN RESULTS |
|---|---|---|---|---|---|---|---|---|
| Groszmann et al. [1] | NSBBs<br>Timolol | RCT<br>Double-blind<br>Placebo-controlled | cACLD with HVPG ≥6 mmHg & No varices (HVPG <10 mmHg in 37%) | ArLD 24%<br>HCV 63%<br>Cryptogenic 5% | N= 213<br>Timolol, 108<br>Placebo, 105 | 54.9 (0-99) Months | Development of varices or variceal hemorrhage | Primary outcome occurred in 39% with Timolol vs 40% with placebo. Higher incidence of adverse events with timolol.<br><br>Decompensation occurred in 14% vs 15%, with Timolol vs placebo and death in 9% vs 14% (p NS in any case) |
| Villanueva et al. [17] | NSBBs<br>- Propranolol in acute HDK responders<br>- Carvedilol in non-responders | RCT<br>Double-blind<br>Placebo-controlled | cACLD with HVPG ≥ 10 mmHg & No high-risk varices (small or no varices) | ArLD 16%<br>HCV 56%<br>ArLD & HCV 8%<br>NASH 6% | N= 201<br>NSBBs, 100<br>Placebo, 101 | 37 (26-47) Months | Decompensation or death | Decompensation in 12% vs 24%, Death in 8% vs 11%, with NSBBs vs placebo<br><br>NSBBs decreased the risk of decompensation or death (HR 0.51, 95%CI 0.26-0.97) mainly by decreasing ascites risk (HR 0.42, 95%CI 0.19-0.92) |
| Rowe et al. [48] | NSBBs<br>(Propranolol or Carvedilol) | Bayesian reanalysis of PREDESCI trial | PREDESCI cohort | PREDESCI cohort | 250 simulated trial of 2000 participants each | PREDESCI cohort | Decompensation or death | >90% probability that NSBBs reduce all-cause decompensation, with likely substantial gain in decompensation-free life years |
| Serper et al. [49] | Carvedilol | Retrospective, population based, cohort study, ACNU design (carvedilol cohort vs matched cohort with SBBs) | Cirrhosis, Child-Pugh class A | ArLD 27%<br>HCV 23%<br>ArLD & HCV 32%<br>NAFLD 15% | Carvedilol, 123<br>SBBs, 561 | 3 years | Decompensation<br><br>Decompensation or liver-related mortality | Decompensation in 9% vs 17%, Death in 22% vs 24%, with carvedilol vs SBBs<br><br>Carvedilol decreased the risk of decompensation (HR 0.59, 95%CI 0.42-0.83) and the risk of decompensation or liver-related death (HR 0.56, 95%CI 0.41-0.76) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Villanueva et al. [50] | Carvedilol | IPD-MA of RCTs comparing carvedilol vs control group (receiving EVL or placebo according to presence or not of high-risk varices) | cACLD with varices (94%) or without varices (6%) but with HVPG ≥ 10 mmHg | ArLD 25%<br>HCV 39% | N=352<br>Carvedilol, 181<br>Controls, 171 (of them 92 with placebo and 79 EVL) | 13 to 36 months (range of FU in RCTs included) | Decompensation<br><br>Death | Decompensation in 11% vs 20%, Death in 22% vs 24%, with carvedilol vs control<br><br>Carvedilol decreased the risk of decompensation (HR 0.51, 95%CI 0.29-0.89) and the risk of death (HR 0.42, 95%CI 0.19-0.89)<br>Decreased risk of ascites (HR 0.49, 95%CI 0.25-0.97) |
| Villanueva et al. [51] | NSBBs (Propranolol, Nadolol, Nadolol plus IsMn or Carvedilol) | IPD-MA of RCTs comparing NSBBs vs EVL<br>Stratified according to decompensation | cACLD with high-risk varices | ArLD 33%<br>HCV 27%<br>ArLD & HCV 9%<br>NASH 2% | N= 656<br><br>NSBBs, 291<br>EVL, 245<br>NSBBs+EVL, 120 | 13 to 34 months (range of FU in RCTs included) | Death<br><br>First bleeding | Death in 15% vs 19% vs 5%, with NSBBs vs EVL<br><br>Higher risk of death with EVL vs NSBBs (HR 1.76, 95%CI 1.11-2.77) & similar risk with NSBBs vs NSBBs+EVL<br>Similar risk of bleeding with NSBBs vs EVL (HR 1.05, 95%CI 0.75-1.49)<br>Slightly higher risk of decompensation with EVL vs NSBBs (HR 1.59, 95%CI 0.86-2.93)<br>Higher risk of ascites with EVL vs NSBBs (HR 2.66, 95%CI 1.36-5.19) |
| Yang et al. [52] | Statins | Retrospective, population based, cohort study, (statins cohort vs matched cohort) | Newly diagnosed HCV infection | HCV 100% | N= 226,856<br>Study cohort<br><br>N= 84,213<br>Matched cohort | FU of at least 1 year, up to 13 years | Development of cirrhosis | Statins use was associated with a reduced risk of cirrhosis development in a dose-dependent manner |
| Chang et al. [53]<br>. | Statins | Retrospective, population based, cohort study, (statins cohort vs PS-matched cohort) | Cirrhosis mainly compensated, HCV, HBV or alcohol related | HVB 45%<br>HCV 22%<br>ArLD 33% | N= 1350<br><br>Statin use 675<br>Nonusers 675 | 5.5±3.5 years | Decompensation<br><br>HCC<br><br>Death | Decompensation in 29% vs 14%, HCC in 10% vs 6%, death in 18% vs 9%, in nonuser vs statins user<br><br>Overall, statins use decreased the risk of decompensation, HCC and death. Decompensation risk was significantly reduced in HVB and HCV related cirrhosis with borderline significance in ArLD. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Motzus-Feagans et al. [54] | Statins | Retrospective, population based, cohort study, (statins cohort vs PS-matched cohort) | Compensated cirrhosis | HCV 50%<br>ArLD 32% | N= 19,379<br>Study cohort<br><br>N= 4,526<br>Matched cohort | 39 (12-103) months | Development of infections | Statins use decreased the risk of infections |
| Mohanty et al. [55] | Statins | Retrospective, population based, cohort study, (statins cohort vs PS-matched cohort) | Compensated cirrhosis | ArLD 54% | N= 45,350<br>Study cohort<br><br>N= 2747<br>Matched cohort | 2.5 years in users<br>1.5 years in nonusers | Decompensation<br><br>Death | Statins use was associated with a reduced risk of decompensation, with significantly lower risk of ascites and of variceal bleeding. Statins use was associated with lower risk of death. |
| Kaplan et al. [56] | Statins | Retrospective, population based, cohort study, (statins cohort vs IPTW adjusted cohort) | Newly diagnosed cirrhosis | ArLD 35%<br>HCV 14%<br>ArLD & HCV 25%<br>NAFLD/NASH 16% | N= 74,984<br>Study cohort<br><br>N= 19341<br>Matched cohort | 36-month approx.. | Death<br><br>Decompensation<br><br>Major adverse cardiovascular events | Hypercholesterolemia was associated with well-preserved hepatic function and decreased mortality. Each cumulative year of statin exposure was associated with an independent 8%-8.7% decrease of mortality in Child-Pugh classes A&B. Statin therapy was associated with a decreased risk of decompensation in Child-Pugh class A. |
| Simon et al. [57] | Aspirin | Retrospective, population based, cohort study, (low-dose aspirin cohort vs IPTW adjusted cohort) | Chronic hepatitis B or C monoinfection (around 11% with cACLD, only 3% with decompensated cirrhosis) | HCV 74%<br>HBV 26 | N= 50,275<br><br>Aspirin use 14,205<br>Nonusers 36,070 | 7.9 years | HCC<br><br>Liver-related death | Low-dose aspirin use was associated with significantly lower risk of HCC. Liver-related mortality was also significantly lower in aspirin users vs nonusers (11% vs 18%, HR 0.73 (95%CI 0.67-0.81) |
| Puente et al. [58] | Rivaroxaban | RCT<br>Double-blind<br>Placebo-controlled | Cirrhosis with PHT and Child-Pugh 7-10<br>Mainly compensated (73% Child-Pugh A) | ArLD 87% | N= 90<br><br>Rivaroxaban, 41<br>Placebo, 49 | 10.1 | Decompensation, death or OLT | Rivaroxaban decreased the risk of primary outcome, particularly in Child-Pugh class B (HR29, 95%CI 0.09-0.87), with significant reduction in ascites risk.<br>Bleeding events were more frequent with rivaroxaban. |

LEGEND: The table shows the characteristics and main results of relevant studies assessing the efficacy of different therapies to prevent decompensation in patients with cACLD. The studies included investigated the efficacy of active therapy (with NSBBs, Carvedilol, Statins or Rivaroxaban) compared to a control group without active therapy.

ACNU: active comparator new user, ArLD: alcohol related liver disease, cACLD: compensated advanced chronic liver disease, EVL: endoscopic variceal ligation, FU: follow-up, HCC: hepatocellular carcinoma, HCV: hepatitis C virus, IPD-MA: individual participant data meta-analysis, IPTW: inverse probability of treatment weighting, IsMn: isosorbide-mononitrate, NAFLD: Non-alcoholic fatty liver disease, NSBBs: non-selective β-blockers, OLT: orthotopic liver transplantation, PS: propensity score, RCTs: randomized controlled trials, SBBs: selective β-blockers.

## References


1 Groszmann, R. J. *et al.* Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* **353**, 2254-2261, doi:10.1056/NEJMoa044456 (2005).

2 Hernandez-Gea, V. et al. Development of ascites in compensated cirrhosis with severe portal hypertension treated with beta-blockers. Am J Gastroenterol 107, 418-427, doi:10.1038/ajg.2011.456 (2012).3 Rincon, D. *et al.* Prognostic value of hepatic venous pressure gradient in patients with compensated chronic hepatitis C-related cirrhosis. *Scand J Gastroenterol* **48**, 487-495, doi:10.3109/00365521.2012.711848 (2013).

3 Rincon, D. *et al.* Prognostic value of hepatic venous pressure gradient in patients with compensated chronic hepatitis C-related cirrhosis. *Scand J Gastroenterol* **48**, 487-495, doi:10.3109/00365521.2012.711848 (2013).

4 Lens, S. *et al.* Association Between Severe Portal Hypertension and Risk of Liver Decompensation in Patients With Hepatitis C, Regardless of Response to Antiviral Therapy. *Clin Gastroenterol Hepatol* **13**, 1846-1853.e1841, doi:10.1016/j.cgh.2015.04.013 (2015).

5 Reiberger, T. *et al.* Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. *Gut* **62**, 1634-1641, doi:10.1136/gutjnl-2012-304038 (2013).

6 Ripoll, C. *et al.* Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* **133**, 481-488.

7 Berzigotti, A. *et al.* Prognostic value of a single HVPG measurement and Doppler-ultrasound evaluation in patients with cirrhosis and portal hypertension. *J Gastroenterol* **46**, 687-695, doi:10.1007/s00535-010-0360-z (2011).

8 Berzigotti, A. *et al.* Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. *Hepatology* **54**, 555-561, doi:10.1002/hep.24418 (2011).

9 Robic, M. A. *et al.* Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. *J Hepatol* **55**, 1017-1024, doi:10.1016/j.jhep.2011.01.051 (2011).

10 Colecchia, A. *et al.* Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: a prospective study. *J Hepatol* **60**, 1158-1164, doi:10.1016/j.jhep.2014.02.024 (2014).

11 Perez-Latorre, L. *et al.* Prediction of liver complications in patients with hepatitis C virus-related cirrhosis with and without HIV coinfection: comparison of hepatic venous pressure gradient and transient elastography. *Clin Infect Dis* **58**, 713-718, doi:10.1093/cid/cit768 (2014).

12 Sebastiani, G. *et al.* Prognostic Value of Non-Invasive Fibrosis and Steatosis Tools, Hepatic Venous Pressure Gradient (HVPG) and Histology in Nonalcoholic Steatohepatitis. *PLoS One* **10**, e0128774, doi:10.1371/journal.pone.0128774 (2015).

13 Kitson, M. T. *et al.* Liver stiffness and the prediction of clinically significant portal hypertension and portal hypertensive complications. *Scand J Gastroenterol* **50**, 462-469, doi:10.3109/00365521.2014.964758 (2015).

14 Harrison, S. A. *et al.* Simtuzumab Is Ineffective for Patients With Bridging Fibrosis or Compensated Cirrhosis Caused by Nonalcoholic Steatohepatitis. *Gastroenterology* **155**, 1140-1153, doi:10.1053/j.gastro.2018.07.006 (2018).

15 Sanyal, A. J. *et al.* The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: Data From the Simtuzumab Trials. *Hepatology* **70**, 1913-1927, doi:10.1002/hep.30664 (2019).

16 Bosch, J. *et al.* A Machine Learning Approach to Liver Histological Evaluation Predicts Clinically Significant Portal Hypertension in NASH Cirrhosis. *Hepatology* **74**, 3146-3160, doi:10.1002/hep.32087 (2021).

17 Villanueva, C. *et al.* beta blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* **393**, 1597-1608, doi:10.1016/s0140-6736(18)31875-0 (2019).

18 Villanueva, C. *et al.* Bacterial infections adversely influence the risk of decompensation and survival in compensated cirrhosis. *J Hepatol*, doi:10.1016/j.jhep.2021.04.022 (2021).

19 Nicoară-Farcău, O. *et al.* Metabolomics as a tool to predict the risk of decompensation or liver-related death in patients with compensated cirrhosis. *Hepatology* **77**, 2052-2062, doi:10.1097/hep.0000000000000316 (2023).

20 Jindal, A., Bhardwaj, A., Kumar, G. & Sarin, S. K. Clinical Decompensation and Outcomes in Patients With Compensated Cirrhosis and a Hepatic Venous Pressure Gradient >/=20 mm Hg. *Am J Gastroenterol* **115**, 1624-1633, doi:10.14309/ajg.0000000000000653 (2020).

21 Mandorfer, M. *et al.* Changes in Hepatic Venous Pressure Gradient Predict Hepatic Decompensation in Patients Who Achieved Sustained Virologic Response to Interferon-Free Therapy. *Hepatology* **71**, 1023-1036, doi:10.1002/hep.30885 (2020).

22 Costa, D. *et al.* Systemic inflammation increases across distinct stages of advanced chronic liver disease and correlates with decompensation and mortality. *J Hepatol* **74**, 819-828, doi:10.1016/j.jhep.2020.10.004 (2021).

23 Scheiner, B. *et al.* Factor VIII/protein C ratio independently predicts liver-related events but does not indicate a hypercoagulable state in ACLD. *J Hepatol* **76**, 1090-1099, doi:10.1016/j.jhep.2021.12.038 (2022).

24 Jindal, A., Sarin, S. K., Kumar, M. & Kumar, G. Clinical Outcomes in Patients with Advanced Chronic Liver Disease and Hepatic Venous Pressure Gradient ≤ 10 mm Hg. *Dig Dis Sci* **67**, 5280-5289, doi:10.1007/s10620-021-07334-2 (2022).

25 Jachs, M. *et al.* Prognostic performance of non-invasive tests for portal hypertension is comparable to that of hepatic venous pressure gradient. *J Hepatol*, doi:10.1016/j.jhep.2023.12.028 (2024).

26 Merchante, N. *et al.* Liver stiffness predicts clinical outcome in human immunodeficiency virus/hepatitis C virus-coinfected patients with compensated liver cirrhosis. *Hepatology* **56**, 228-238, doi:10.1002/hep.25616 (2012).

27 Merchante, N. *et al.* Progression of liver stiffness predicts clinical events in HIV/HCV-coinfected patients with compensated cirrhosis. *BMC Infect Dis* **15**, 557, doi:10.1186/s12879-015-1291-3 (2015).

28 Guha, I. N. *et al.* Validation of a Model for Identification of Patients With Compensated Cirrhosis at High Risk of Decompensation. *Clin Gastroenterol Hepatol* **17**, 2330-2338.e2331, doi:10.1016/j.cgh.2019.01.042 (2019).

29 Eaton, J. E. *et al.* Changes in Liver Stiffness, Measured by Magnetic Resonance Elastography, Associated With Hepatic Decompensation in Patients With Primary Sclerosing Cholangitis. *Clin Gastroenterol Hepatol* **18**, 1576-1583 e1571, doi:10.1016/j.cgh.2019.10.041 (2020).

30 Han, M. A. T. *et al.* MR elastography-based liver fibrosis correlates with liver events in nonalcoholic fatty liver patients: A multicenter study. *Liver Int* **40**, 2242-2251, doi:10.1111/liv.14593 (2020).

31 Calzadilla-Bertot, L. *et al.* ABIDE: An Accurate Predictive Model of Liver Decompensation in Patients With Nonalcoholic Fatty Liver-Related Cirrhosis. *Hepatology*, doi:10.1002/hep.31576 (2020).

32 Gidener, T. *et al.* Liver Stiffness by Magnetic Resonance Elastography Predicts Future Cirrhosis, Decompensation, and Death in NAFLD. *Clin Gastroenterol Hepatol*, doi:10.1016/j.cgh.2020.09.044 (2020).

33 Osman, K. T. *et al.* Liver Stiffness Measured by Either Magnetic Resonance or Transient Elastography Is Associated With Liver Fibrosis and Is an Independent Predictor of Outcomes Among Patients With Primary Biliary Cholangitis. *J Clin Gastroenterol* **55**, 449-457, doi:10.1097/MCG.0000000000001433 (2021).

34 Younes, R. *et al.* Long-term outcomes and predictive ability of non-invasive scoring systems in patients with non-alcoholic fatty liver disease. *J Hepatol*, doi:10.1016/j.jhep.2021.05.008 (2021).

35 Petta, S. *et al.* Monitoring Occurrence of Liver-Related Events and Survival by Transient Elastography in Patients With Nonalcoholic Fatty Liver Disease and Compensated Advanced Chronic Liver Disease. *Clin Gastroenterol Hepatol* **19**, 806-815.e805, doi:10.1016/j.cgh.2020.06.045 (2021).

36 Semmler, G. *et al.* Dynamics in Liver Stiffness Measurements Predict Outcomes in Advanced Chronic Liver Disease. *Gastroenterology* **165**, 1041-1052, doi:10.1053/j.gastro.2023.06.030 (2023).

37 Schneider, A. R. P. *et al.* Early prediction of decompensation (EPOD) score: Non-invasive determination of cirrhosis decompensation risk. *Liver Int* **42**, 640-650, doi:10.1111/liv.15161 (2022).

38 Dajti, E. *et al.* A Combined Baveno VII and Spleen Stiffness Algorithm to Improve the Noninvasive Diagnosis of Clinically Significant Portal Hypertension in Patients With Compensated Advanced Chronic Liver Disease. *Am J Gastroenterol* **117**, 1825-1833, doi:10.14309/ajg.0000000000001887 (2022).

39 Asesio, N. *et al.* Baveno VI criteria as a prognostic factor for clinical complications in patients with compensated cirrhosis. *Dig Liver Dis* **54**, 645-653, doi:10.1016/j.dld.2021.09.004 (2022).

40 Fernández-Alvarez, P. *et al.* Dynamic Changes in Non-Invasive Markers of Liver Fibrosis Are Predictors of Liver Events after SVR in HCV Patients. *Viruses* **15**, doi:10.3390/v15061251 (2023).

41 Thorhauge, K. H. *et al.* Using liver stiffness to predict and monitor the risk of decompensation and mortality in patients with alcohol-related liver disease. *J Hepatol*, doi:10.1016/j.jhep.2024.02.019 (2024).

42 Kobayashi, T. *et al.* Prediction of outcomes in patients with metabolic dysfunction-associated steatotic liver disease based on initial measurements and subsequent changes in magnetic resonance elastography. *J Gastroenterol* **59**, 56-65, doi:10.1007/s00535-023-02049-9 (2024).

43 Shearer, J. E., Jones, R., Parker, R., Ferguson, J. & Rowe, I. A. The Natural History of Advanced Chronic Liver Disease Defined by Transient Elastography. *Clin Gastroenterol Hepatol* **21**, 694-703 e698, doi:10.1016/j.cgh.2022.03.015 (2023).

44 Wong, Y. J. *et al.* Baveno-VII criteria to predict decompensation and initiate non-selective beta-blocker in compensated advanced chronic liver disease patients. *Clin Mol Hepatol* **29**, 135-145, doi:10.3350/cmh.2022.0181 (2023).

45 Song, B. G. *et al.* Validation of non-invasive diagnosis of CSPH in patients with compensated advanced chronic liver disease according to Baveno VII. *Liver Int* **43**, 1966-1974, doi:10.1111/liv.15632 (2023).

46 Lin, H. *et al.* Risk and predictors of hepatic decompensation in grey zone patients by the Baveno VII criteria: A competing risk analysis. *Aliment Pharmacol Ther* **58**, 920-928, doi:10.1111/apt.17699 (2023).

47 Wong, Y. J. *et al.* Comparing serial and current liver stiffness measurements to predict decompensation in compensated advanced chronic liver disease patients. *Hepatology*, doi:10.1097/HEP.0000000000000891 (2024).

48 Rowe, I. A. *et al.* Quantifying the benefit of nonselective beta-blockers in the prevention of hepatic decompensation: A Bayesian reanalysis of the PREDESCI trial. *Hepatology* **78**, 530-539, doi:10.1097/HEP.0000000000000342 (2023).

49 Serper, M. *et al.* Nonselective beta blockers, hepatic decompensation, and mortality in cirrhosis: A national cohort study. *Hepatology* **77**, 489-500, doi:10.1002/hep.32737 (2023).

50 Villanueva, C. *et al.* Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis. *J Hepatol* **77**, 1014-1025, doi:10.1016/j.jhep.2022.05.021 (2022).

51 Villanueva, C. *et al.* Improving primary prophylaxis of variceal bleeding by adapting therapy to the clinical stage of cirrhosis. A competing-risk meta-analysis of individual participant data. *Aliment Pharmacol Ther* **59**, 306-321, doi:10.1111/apt.17824 (2024).

52 Yang, Y. H. *et al.* Statin use and the risk of cirrhosis development in patients with hepatitis C virus infection. *J Hepatol* **63**, 1111-1117, doi:10.1016/j.jhep.2015.07.006 (2015).

53 Chang, F. M. *et al.* Statins decrease the risk of decompensation in hepatitis B virus- and hepatitis C virus-related cirrhosis: A population-based study. *Hepatology* **66**, 896-907, doi:10.1002/hep.29172 (2017).

54 Motzkus-Feagans, C., Pakyz, A. L., Ratliff, S. M., Bajaj, J. S. & Lapane, K. L. Statin use and infections in Veterans with cirrhosis. *Aliment Pharmacol Ther* **38**, 611-618, doi:10.1111/apt.12430 (2013).

55 Mohanty, A., Tate, J. P. & Garcia-Tsao, G. Statins Are Associated With a Decreased Risk of Decompensation and Death in Veterans With Hepatitis C-Related Compensated Cirrhosis. *Gastroenterology* **150**, 430-440 e431, doi:10.1053/j.gastro.2015.10.007 (2016).

56 Kaplan, D. E. *et al.* Effects of Hypercholesterolemia and Statin Exposure on Survival in a Large National Cohort of Patients With Cirrhosis. *Gastroenterology* **156**, 1693-1706 e1612, doi:10.1053/j.gastro.2019.01.026 (2019).

57 Simon, T. G. *et al.* Association of Aspirin with Hepatocellular Carcinoma and Liver-Related Mortality. *N Engl J Med* **382**, 1018-1028, doi:10.1056/NEJMoa1912035 (2020).

58 Sanchez, A. P. *et al.* Rivaroxaban improves survival and decompensation in cirrhotic patients with moderate liver dysfunction. Double-blind, placebo-controlled trial. *Journal of Hepatology* (2023).