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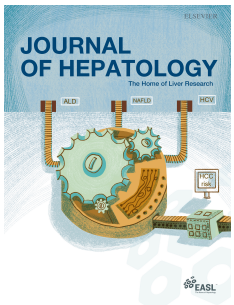

Non-invasive tests for clinically significant portal hypertension after HCV cure

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Pooled analysis

418 patients with paired HVPG-measurements +/- NIT before and after HCV-cure

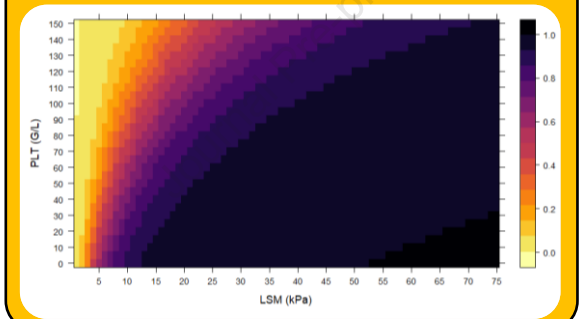
! Etiological cure modifies relationship between NIT and HVPG !

- **Increased correlation LSM/HVPG**
- **Numerically higher accuracy for diagnosing CSPH**

Clinical decision rules

LSM <12kPa & PLT >150G/L → CSPH excluded

Estimated probability of CSPH



LSM ≥25kPa → CSPH ruled-in

Validation vs. direct endpoints

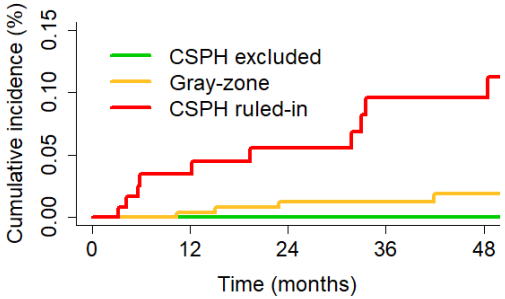
755 cACLD patients followed for a median of 38 months

Prevalence

42.5%	40.7%	16.8%

Cumulative incidence of hepatic decompensation at 3 years

0%	1.3%	9.6%



Non-invasive tests for clinically significant portal hypertension after HCV cure

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FOOTNOTE PAGE

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Supplementary tables:	9
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A.P. has nothing to disclose.

J.I.F. has nothing to disclose.

M.A. has nothing to disclose.

A.Z. has nothing to disclose.

A.C. has nothing to disclose.

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ABSTRACT

Background & Aims: Non-invasive tests (NIT)s for clinically significant portal hypertension (CSPH; hepatic venous pressure gradient [HVPG] ≥10mmHg) have predominantly been studied in patients with active HCV-infection. Investigations after HCV-cure are limited and yielded conflicting results. We conducted a pooled analysis to determine the diagnostic/prognostic utility of liver stiffness-measurement (LSM)/platelet count (PLT) in this setting.

Methods: 418 patients with pre-treatment HVPG≥6mmHg who achieved sustained virological response (SVR) and underwent post-treatment-HVPG-measurement were assessed, of which 324 (**HVPG/NIT-cohort**) also had paired data on pre-/post-treatment-LSM/-PLT.

The derived LSM/PLT-criteria were then validated against the direct endpoint decompensation in 755 compensated advanced chronic liver disease (cACLD) patients with SVR (**cACLD-validation-cohort**).

Results: HVPG/NIT-cohort: Among cACLD patients, the pre-/post-treatment prevalence of CSPH was 80%/54%. The correlation between LSM/HVPG increased from pre- to post-treatment (r=0.45 vs. 0.60), while that of PLT/HVPG remained unchanged. For given LSM/PLT-values, HVPG tended to be lower post- vs. pre-treatment, indicating the need for dedicated algorithms. Combining post-treatment-LSM/-PLT yielded a high diagnostic accuracy for post-treatment-CSPH in cACLD (AUC: 0.884 [95%CI: 0.843-0.926]). Post-treatment-LSM<12kPa & PLT>150G/L excluded CSPH (sensitivity: 99.2%), while LSM≥25kPa was highly specific for CSPH (93.6%).

cACLD-validation-cohort: The LSM<12kPa & PLT>150G/L-criterion was achieved in 42.5% of patients and their 3-year decompensation risk was 0%. In patients with post-

treatment-LSM≥25kPa (prevalence: 16.8%), 3-year decompensation risk was 9.6%, while it was 1.3% in those meeting none of the above criteria (prevalence: 40.7%).

Conclusions: NITs can estimate the probability of CSPH after HCV-cure and predict clinical outcomes. cACLD patients with LSM<12kPa & PLT>150G/L (CSPH-excluded; no decompensation risk) may be discharged from portal hypertension surveillance (NITs and/or endoscopy), if no co-factors are present, while patients with LSM≥25kPa require surveillance/treatment (CSPH-ruled-in; increased decompensation risk).

LAY SUMMARY

Measurement of liver stiffness by a specific ultrasound device and platelet count (a simple blood test) are broadly used for the non-invasive diagnosis of increased blood pressure in the veins leading to the liver, which drives the development of complications in patients with advanced liver disease. The results of our pooled analysis refute previous concerns that these tests are less accurate after the cure of hepatitis C virus (HCV) infection. We have developed diagnostic criteria that facilitate the personalized management after HCV-cure and allow for a de-escalation of care in a high proportion of patients, thereby decreasing disease burden.

INTRODUCTION

Portal hypertension (PH) is the key driver of hepatic decompensation in patients with advanced chronic liver disease (ACLD) [1]. Accordingly, interventions that ameliorate portal hypertension have been shown to prevent hepatic decompensation in patients who are at risk, i.e., those with clinically significant portal hypertension (CSPH), which is defined by an HVPG ≥10mmHg. In addition to non-selective beta-blockers (NSBB) [1, 2], removal/suppression of the primary aetiological factor may lead to substantial reductions in HVPG, thereby decreasing the risk of hepatic decompensation. With the availability of interferon (IFN)-free regimens, sustained virological response (SVR; i.e., HCV-cure) is achieved in nearly all patients, despite the presence of pre-treatment ACLD and CSPH [3]. Previous studies in patients achieving SVR have reported an amelioration of PH across all pre-treatment HVPG strata [4-9]. In those with pre-treatment CSPH, HVPG-decreases ≥10% were achieved in 60-63% [5-7]. However, only the absence/resolution of CSPH eliminates the risk of post-treatment hepatic decompensation, and thus, identifies patients who should be considered for de-escalation of care to avoid unnecessary investigations and costs. The latter has profound economic implications, as the number of individuals who will achieve HCV-cure world-wide is expected to exceed 1 million per year for the next decade, with a relevant proportion having compensated ACLD (cACLD) [10]. On the other end of the disease severity spectrum, those with post-treatment CSPH may remain at considerable risk. Since HVPG-measurement is invasive, resource-intensive, and requires considerable expertise [11, 12], CSPH risk stratification by non-invasive tests (NIT)s is key to individualize post-treatment management in patients with cACLD [13]. Platelet count (PLT) and liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) are the most extensively studied NITs for CSPH in cACLD patients [14, 15] and have been implemented in clinical practice

recommendations for the management of PH with Baveno VI [16]. However, their diagnostic ability for CSPH has predominantly been studied in patients with active HCV-infection, while investigations after HCV-cure are limited and yielded conflicting results [5-7, 17], which has led to considerable scepticism regarding their clinical use in this steadily increasing patient population [18].

Thus, we conducted a pooled analysis to investigate **(i)** the diagnostic performance of NITs for CSPH (primary objective) as well as **(ii)** the relationship between NITs and pre- and post-treatment HVPG and **(iii)** to validate the derived LSM/PLT criteria against the direct endpoint of hepatic decompensation (secondary objectives).

In addition, we **(iv)** described the evolution of PH after HCV-cure and **(v)** evaluate the diagnostic utility of NITs for varices and **(vi)** the relationship between PH and *de-novo* hepatocellular carcinoma (HCC) development.

METHODS

Patients

HVPG-cohort

After removing duplicates, 675 individual patients from 8 cohorts investigating HVPG in patients undergoing HCV-treatment (both IFN-containing and IFN-free) were evaluated for inclusion in this pooled analysis (Fig. 1) [4-9, 17, 19-22]. Information on exclusion criteria and patient selection is provided in Fig. 1. Authors of the 3 additional studies that have been published until 2020 were contacted, however, did not provide individual patient data [23-25]. Specifically, patients without paired HVPG-measurements before (baseline [BL]) and after (follow-up [FU]) HCV-treatment (n=166), without SVR (n=59), or without pre-treatment PH (i.e., HVPG <6mmHg) (n=32) were excluded. Finally, 418 patients were included to study the dynamics of HVPG after HCV-cure (**HVPG-cohort**). In patients undergoing repeated HVPG-assessments after HCV-cure, only the first post-treatment measurement was considered. All contributing centres had previously established protocols for measuring HVPG, which are in line with the technical description provided in the Baveno VII consensus [26].

HVPG/NIT-cohort

For the evaluation of the diagnostic performance of NITs for PH, 94 patients were additionally excluded due to missing information on either PLT or LSM (performed by vibration-controlled transient elastography [FibroScan, Echosens, Paris, France]) before and/or after HCV-treatment, resulting in 324 patients with paired data on HVPG/NITs pre- and post-treatment (**HVPG/NIT-cohort**). While we focused on the subgroup of patients with cACLD (i.e., absence/no history of hepatic decompensation defined by clinically evident ascites, portal-hypertensive bleeding, or overt hepatic

encephalopathy; n=241) and the overall cohort (i.e., including decompensated patients; n=324) in the main manuscript, subgroup analyses in patients with BL-CSPH (i.e., HVPG ≥10mmHg; n=274), and clinical evidence of CSPH at BL (i.e., varices or presence/history of ascites/bleeding; n=184) can be found in the Supplementary materials.

The **HVPG/NIT-cohort** was further analysed in regard to the diagnostic utility of NITs for varices (n=201) and the relationship between PH and *de-novo* hepatocellular carcinoma (HCC; n=190) development.

Confirmation of the proposed criteria for excluding CSPH during long-term FU

To confirm the sensitivity/robustness of the proposed criteria for excluding CSPH based on NITs, they were additionally evaluated in a highly selected and particularly challenging series of 83 patients with pre-treatment CSPH in whom CSPH persisted 24 weeks after the end-of-treatment (EoT) and who underwent a third HVPG-measurement 96 weeks after EoT from Lens and Baiges et al (2020) [17].

Unselected cACLD-validation-cohort

Finally, two cohorts of cACLD patients (BL-LSM ≥10kPa, BL-HVPG ≥6mmHg, or advanced fibrosis/cirrhosis on liver histology [F3/4]) who have been followed for hepatic decompensation after achieving HCV-cure were included <u>to validate NITs against the direct endpoint</u>. The first cohort (n=368 from the Medical University of Vienna [MUV]) was partly overlapping (n=77) with the **HVPG-cohort**; the second multicentre cohort (n=387; centres Ordensklinikum Linz Barmherzige Schwestern, Padua University Hospital, and Klinikum Ottakring) was an entirely unrelated cohort recruited at centres which did not contribute to the **HVPG-cohort**. Of note, these

patients have previously been reported in the context of hepatic decompensation [27] and/or HCC [28] risk stratification.

Statistics

Statistical analyses were performed using R 4.1.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were reported as mean ±standard deviation or median (interquartile range), while categorical variables were reported as absolute and relative frequencies of patients with/without a certain characteristic. Repeated measures Pearson's correlation coefficients (to determine correlation coefficients within centres) and a summary coefficient were calculated using the 'rmcorr'-package [29]. Local regression (locally estimated scatterplot smoothing; LOESS) was applied as a non-parametric approach to visualize the relationship between two continuous variables (HVPG and LSM/PLT). The default span was α=0.75. Linear mixed effects regression models were fitted to study the relationship between NITs and HVPG, logistic mixed effects regression models to analyse the relationship between NITs and CSPH (HVPG ≥10mmHg) before and after HCV-cure using the 'lm4'-package [30]. For both approaches, NITs were treated as linear variables and modelled using natural B splines (i.e., restricted cubic splines) using the 'splines'-package to account for non-linear effects. Specifically, splines with 4 degrees of freedom were used. For linear regressions, marginal R^2 according to Nakagawa et al [31] were provided as a goodness-of-fit measure. For logistic regressions, the 'Akaike information criterion' (AIC) was reported. Relationships between CSPH and NITs were visualized using the 'effects'-package [32].

The area under the curve (AUC) and respective 95% confidence intervals (95%CI) of receiver operating characteristic (ROC) analyses were calculated based on predictions from fixed effects of respective mixed effects models adjusting for clustering across

centres as random term using the ‘pROC’-package [33]. For prediction of CSPH after HCV-cure (FU-CSPH), PLT-values were capped if >150G/L to account for non-linearity above this cut-off, while LSM-values were log-transformed to account for non-normal-distribution [14]. These results from ordinary logistic regression analyses were compared to other methods popular in machine learning such as penalized regressions, naive Bayes and neural nets. Finally, nomograms and 3-D plots were developed using the ‘rms’-package to provide clinically applicable prediction tools for FU-CSPH.

Fine & Gray competing risk regression analysis was performed for the outcomes HCC (**HVPG/NIT-cohort**) and hepatic decompensation (**cACLD-validation-cohort**) using the ‘cmprsk’-package and cumulative incidence curves were plotted.

A two-sided p-value <0.05 was considered statistically significant for all analyses.

RESULTS

Evolution of PH after HCV-cure in the HVPG-cohort

Among 418 patients with paired HVPG-measurements, mean BL-HVPG was 14.2±4.8mmHg corresponding to 353 (84 %) patients with BL-CSPH and 153 (37%) with BL-HVPG ≥16mmHg.

Median time between end-of-treatment (EoT) and post-treatment HVPG (FU-HVPG) was 28.4 (24-44) weeks (Supplementary Fig. 2).

HVPG decreased in 333 patients (80%), remained stable in 23 (5.5%) patients, and increased in 62 (14.8%), resulting in a mean FU-HVPG of 11.8±5.4mmHg. The median absolute difference between BL-HVPG and FU-HVPG was -2.5 (-4.3-[-0.50])mmHg, while the relative difference was -18.8 (-32.8-[-4.8])%.

Of 65 patients (16%) with BL-HVPG 6-9mmHg, 44 (68%) resolved PH (i.e., FU-HVPG <6mmHg) while 21 (32%) still had PH at FU (Fig. 2). Importantly, no patient progressed to FU-CSPH. Of 353 with BL-CSPH, 12 (3.4%) resolved PH, and 75 (21%) decreased to 6-9mmHg while 266 (75%) still had FU-CSPH. An HVPG-decrease ≥10% was observed in 226/353 (64%) of patients with BL-CSPH. In the subgroup of patients with a BL-HVPG of 10-15mmHg (n=200, 48%), 80 (40%) resolved CSPH, and 9 (0.5%) progressed to HVPG ≥16mmHg. Among patients with a BL-HVPG ≥16mmHg (n=153, 37%), 7 (4.6%) resolved CSPH and 71 (46%) regressed to 10-15mmHg.

For analyses on the time-dependency of the relative decrease in HVPG after EoT, see the Supplementary materials/Supplementary Fig.s 1 and 2.

Relationship between HVPG and NITs before and after HCV-cure in the HVPG/NIT-cohort

The median time between EoT and assessment of FU-HVPG was 28.8 (IQR: 25-45) weeks. While the median time between laboratory assessment and FU-HVPG was 0

(IQR: 0-6) weeks, the median time period between FU-LSM and FU-HVPG was 0.6 (IQR: 0-14) weeks.

Importantly, comparisons of patient characteristics of the **HVPG/NIT-cohort** and the **HVPG-cohort** revealed no relevant differences (Supplementary Table 1). Characteristics of the individual subgroups of the **HVPG/NIT-cohort** are shown in Supplementary Table 2. Supplementary Fig. 3 shows scatterplots of HVPG and NITs before and after HCV-cure with regression lines for individual centres as well as the pooled regression lines/coefficients.

Of note, we observed an association of moderate strength between BL-PLT and BL-HVPG (summary r=-0.39) as well as BL-LSM and BL-HVPG (r=0.45) in the cACLD subgroup. Interestingly, the correlation of LSM/HVPG was stronger post-treatment (r=0.60), while it remained unchanged for PLT/HVPG. These observations were confirmed in the overall cohort.

Interestingly, the relationship between PLT/HVPG was nearly linear both at BL and FU, with lower predicted HVPG at FU than at BL given the same PLT count (Fig. 3). Thus, applying a PLT-based model/PLT cut-off derived in patients with active HCV-infection to patients who have achieved HCV-cure may result in an overestimation of the severity of PH. For LSM/HVPG, no linear relationship was observed at both time points, with an inflection point at 15-20kPa. Interestingly, after having achieved HCV-cure, lower levels of HVPG were observed for the same LSM until ~15kPa, i.e., in the range that is relevant for ruling-out/excluding CSPH. Even for values up to ~30kPa, LSM tended to overestimate the severity of PH after HCV-cure, although the 95%CIs were clearly overlapping.

Moreover, we investigated the explanatory ability, i.e., what proportion of the variance can be explained by PLT and LSM before and after treatment (Supplementary Table 3). LSM explained more variance in HVPG than PLT both before and after HCV-

treatment, and the application of non-linear modelling increased the goodness-of-fit in the cACLD subgroup and the overall cohort. Of note, combined models of PLT+LSM yielded the best explanatory ability, which was even numerically higher at FU, as compared to BL.

Estimating the probability of CSPH using NITs in the HVPG/NIT-cohort

After HCV-treatment, the prevalence of CSPH was 64% in the overall cohort and 54% in the cACLD subgroup. Again, the predictive ability was higher for LSM than for PLT (Supplementary Table 4; indicated by a lower AIC relative to each other). Of note, non-linear modelling improved FU- but not BL-models (predicted probability of FU-CSPH based on FU-PLT and FU-LSM using natural B splines are illustrated in Supplementary Fig. 4).

ROC curves with respective AUCs are shown in Fig. 4. Of note, the AUC was similar/numerically higher at FU compared to BL. Although FU-LSM already yielded a high accuracy in the cACLD subgroup (AUC: 0.837 [95%CI: 0.786-0.887]), the AUCs showed numerical increases when combining FU-PLT and FU-LSM (AUC: 0.876 [95%CI: 0.831-0.920]). Comparable results were obtained in the overall cohort with an AUC of 0.895 (95%CI: 0.860-0.932) for FU-PLT+FU-LSM. Capping PLT-values at 150G/L and log-transforming LSM-values slightly increased diagnostic accuracy (cACLD subgroup AUC: 0.884 [95%CI: 0.843-0.926]). Of note, more complex models or methods popular in machine-learning did not increase the predictive ability (data not shown). To increase the clinical applicability of our model, nomograms and 3-D plots for estimating the probability of post-treatment CSPH based on post-treatment LSM/PLT in individual cACLD patients are provided (Fig. 5).

Moreover, similar graphs for the overall cohort are provided in the Supplementary Fig. 5. Further subgroup analyses can be found in Supplementary Table 5. Of note, the

diagnostic accuracies for CSPH (i.e., AUCs) were comparable, indicating the generalizability of our findings to these specific subgroups.

Notably, the timing of FU-HVPG/NIT-assessment had no major impact on the diagnostic accuracy of NITs. Detailed information is provided in the Supplementary materials.

Criteria to exclude and rule-in post-treatment CSPH in the HVPG/NIT-cohort

Potential criteria to rule-out FU-CSPH (different cut-offs for LSM and PLT as well as combinations such as the Baveno VI criteria and RECIST-HCV [34]) were compared in Table 2. Based on these data, post-treatment LSM <12kPa & PLT >150G/L was chosen for excluding post-treatment CSPH in cACLD patients (FU-CSPH prevalence in those meeting this criterion: 3.3%), as the sensitivity of not meeting this criterion was 99.2%. In contrast, post-treatment LSM ≥25kPa was highly specific (93.6%) for CSPH after HCV-cure, with a FU-CSPH prevalence of 87.7% in those meeting this criterion.

Confirmation of the proposed criteria for excluding CSPH during long-term FU

In brief, post-treatment LSM <12kPa & PLT >150G/L was capable of excluding FU-CSPH in a highly selected cohort of patients who were evaluated 96 weeks after EoT. See Supplementary materials for detailed information.

Validation against direct endpoints in the unselected cACLD-validation-cohort

The median durations from EoT to post-treatment evaluation were 11.6 (0.4-19.3) and 13.4 (12.0-26.6) weeks in the MUV and external cACLD-validation-cohorts, respectively, and patients were followed for clinical events for 55.4 (51.5-59.4) and 24.4 (21.0-27.5) months after EoT.

The LSM <12kPa & PLT >150G/L criterion was achieved in 43.2% and 41.9% in the MUV and external cACLD-validation-cohorts (Supplementary Table 7), respectively; the 3-year hepatic decompensation risk in patients meeting this criterium was 0% in both cohorts (Fig. 6). In patients with post-treatment LSM ≥25kPa (prevalence: 16.8% and 16.8%), 3-year hepatic decompensation risk was 9.0%/11.0%, while it was 1.6%/0.8% in those meeting none of the above criteria (prevalence: 39.9% and 41.3%). When merging these two cohorts to a single **cACLD-validation-cohort** (n=755), 3-year hepatic decompensation risk was 0% in the 42.5% of patients who met the LSM <12kPa & PLT >150G/L criterion, 9.6% in the 16.8% with post-treatment LSM ≥25kPa, and 1.3% in the 40.7% who met none of the above criteria (i.e., the diagnostic gray-zone in which CSPH can neither be excluded nor ruled-in).

Role of PH for *de-novo* HCC risk stratification in the HVPG-cohort

See Supplementary materials.

Use of NITs for ruling-out (large) varices in the HVPG-cohort

See Supplementary materials.

DISCUSSION

In this pooled analysis, we have synthesized the data of individual studies to provide robust information on the relationship between NITs and HVPG after HCV-cure. We have developed clinically useful tools for estimating the probability of CSPH and established that NITs are capable of excluding and ruling-in CSPH in the majority (i.e., 59.3%) of unselected patients with cACLD who have achieved SVR. The same criteria may be applied for non-invasive risk stratification. Finally, our pooled analysis may close a chapter ('evolution of PH after HCV-cure'), as it provides a comprehensive synthesis of the available data.

At a median of 28 weeks, we observed that HCV-cure was associated with a decrease in HVPG in ~80% of patients (on average: -18.8%) and none of the patients with pre-treatment subclinical PH progressed to CSPH. We cannot discard that the changes observed at this time point may primarily reflect the amelioration of hepatic inflammation [20], as liver fibrosis regression may require long-term follow-up [35].

When evaluating the association between NITs and HVPG, we found a stronger correlation between LSM/HVPG after HCV-cure, as compared to patients with active HCV-infection, while no changes in the correlation between PLT/HVPG were observed. The observation of an increasing strength of the association between LSM/HVPG but not PLT/HVPG is also reflected by an increase in the goodness-of-fit (as measured by R^2) after HCV-cure for LSM but not PLT. The findings regarding LSM/HVPG may be explained by the treatment-induced decrease in PH severity, as the correlation between HVPG and LSM has previously been shown to be stronger in patients with values <10-12mmHg and weaker above this threshold [36-38]. This hypothesis is also supported by the lower R^2 for LSM observed in the subgroups of patients with pre-treatment CSPH (as assessed by HVPG/clinical findings) as these subgroups have a higher severity of PH.

Recent EASL guidelines on NITs urged for further studies/evidence regarding the use of NITs after SVR [18]. Importantly, our data refute the concern/paradigm, that LSM/PLT are less accurate for diagnosing CSPH in patients who have attained SVR. However, modelling the relationship of pre-/post-treatment LSM and PLT with pre-/post-treatment HVPG revealed that generalizing models that have been derived in patients with active HCV-infection would result in an overestimation of post-treatment HVPG by LSM/PLT. Accordingly, the estimated HVPG for a given LSM/PLT within the range that is relevant for clinical decision making was lower at FU, as compared to BL. These data clearly indicate that LSM/PLT-based models and algorithms specifically designed for patients who have achieved HCV-cure are required, highlighting the significance of our LSM/PLT-based criteria.

Excluding and ruling-in of CSPH has wide-ranging consequences, as patients without CSPH may be discharged from PH surveillance, while those with CSPH remain at considerable risk. Thus, we have analyzed this potential clinical application of NITs in more detail. Our study indicates that in cACLD patients, the diagnostic performance of LSM/PLT for CSPH was comparable or tended to be even better after HCV-cure, as compared to pre-treatment (AUC 0.753 vs. 0.800 for PLT, 0.831 vs. 0.837 for LSM and 0.871 vs 0.884 for the combination of both). This underscores their utility after HCV-cure and possibly also after the suppression/removal of other primary aetiological factors – a clinical scenario that is becoming increasingly common due to considerable progress in the field of aetiological therapies. Focusing on potential clinical utility, the nomograms and 3-D plots derived from our study allow to estimate the probability of CSPH in a given patient. To simplify clinical decision making, we developed criteria for excluding and ruling-in CSPH. Based on our data, Post-treatment LSM <12kPa and PLT >150G/L showed a sensitivity of 99.2% for CSPH, and thus, would be the best criterion to exclude CSPH. The sensitivity/robustness of this criterium was further

confirmed in a highly selected cohort of patients who were evaluated 96 weeks after EoT and in whom previous research indicated that LSM <13.6kPa is incapable of ruling-out CSPH, thereby fuelling the debate on the utility of NITs for CSPH after HCV-cure [17]. However, lowering the LSM cut-off, but also considering PLT substantially increased the sensitivity. The significance of PLT in this context may be explained by persistence of histological lesions after HCV-cure [39, 40], which may lead to low LSM despite CSPH. However, persistent thrombocytopenia may still reveal CSPH in these patients. Of note, Baveno VI criteria also yielded a high sensitivity for post-treatment CSPH (94.7%), with a CSPH prevalence of only 14% in patients meeting these criteria and no large varices being missed. While RECIST-HCV criteria [34] (which do not require LSM) identified a substantially higher proportion of patients being at low risk and did not miss any patient with large varices, the CSPH prevalence in the low-risk group was comparatively high (28%) and we also observed hepatic decompensation events in the cACLD-validation-cohort. Accordingly, these criteria were suboptimal for identifying patients who may be safely discharged from PH surveillance. LSM ≥25kPa was highly specific for CSPH (93.1%), with a post-treatment CSPH prevalence of 87.7% - i.e., CSPH can be ruled-in in these patients, arguing for maintaining carvedilol/NSBB therapy. Although the probability of post-treatment CSPH can be estimated based on the provided nomogram, HVPG-measurement [11, 12] is the only method to ascertain the absence/presence of CSPH in patients within the gray-zone. Nevertheless, the risk of decompensation in the gray-zone was very low (1.3% at 3 years) indicating that future studies comprising even higher numbers of patient years may help to broaden the low-risk group by identifying additional patients in whom the risk of hepatic decompensation is negligible.

Since the LSM <12kPa and PLT >150G/L criterion will be applied to identify patients without post-treatment CSPH (i.e., a surrogate endpoint) who are candidates for being

discharged from PH surveillance, this decision rule needed to be thoroughly validated against direct outcomes (i.e., hepatic decompensation). Therefore, we included two large cohorts of cACLD patients (**cACLD-validation-cohort**); one of them was an entirely unrelated cohort recruited at academic but also non-academic centres which did not contribute to the other cohorts. This approach confirmed that no hepatic decompensation occurred in patients meeting these criteria when considering HCC development and death as competing events. Accordingly, there is no room for preventive strategies (no risk – no risk reduction achievable) in terms of hepatic decompensation in cACLD patients meeting these criteria, which strongly argues for their discharge from PH surveillance (NITs and/or endoscopy), if improvements in NITs are consistent and no co-factors are present. This finding has important practical implications for descalating care – an aspect that has largely been neglected by previous research, but seems to be crucial for regaining quality of life and decreasing resource utilization**.** Importantly, risk stratification approaches for post-treatment HCC differ [28], and thus, discontinuation of NITs and/or endoscopy does not include discontinuation of HCC screening. While we observed that *de-novo* HCC development was more common in patients with CSPH after HCV-cure, HVPG did not improve risk stratification on top of previously established non-invasive algorithms [28].

We must acknowledge several limitations of our study. First, the **HVPG/NIT-cohort** is not fully representative for the spectrum of (c)ACLD patients achieving HCV-cure, since due to the intrinsic characteristics of the included studies, the pre-treatment severity of PH was high. Accordingly, the proportions of patients meeting non-invasive criteria and information regarding the sensitivity/specificity as well as the proportion of patients having CSPH within different strata have to be interpreted with caution, as they directly depend on the prevalence of CSPH. However, the CSPH prevalence after HCV-cure was comparable to the ANTICIPATE study [14]. Moreover, unbiased

estimates regarding the proportion of patients meeting the non-invasive criteria are provided in the two separate cACLD cohorts and the event rates in the LSM <12kPa & PLT >150G/L and LSM ≥25kPa were in line with expectations – no risk in those in whom CSPH can be excluded [7, 17] and increased risk of hepatic decompensation in those in whom CSPH was ruled-in [7, 17]. However, event rates in those with ≥25kPa seemed to be lower than those of CSPH patients included in previous studies [2, 41]. Due to the removal of the primary aetiological factor, LSM (and HVPG) are likely to have decreased over time in our patients, thereby further mitigating the risk of hepatic decompensation. Accordingly, reassessments of LSM at later time points may have re-classified patients and provided more accurate prognostic information, which is a second limitation of our study. Third, we cannot rule-out entirely that the association between NITs and HVPG differs, if re-evaluated at late time points. However, stratifying by time from EoT to HVPG/NITs, there was no clear evidence for a decreasing diagnostic ability of NITs for CSPH throughout the time from EoT to NIT-strata.

In conclusion, the results of this pooled analysis refute the previous concern that NITs are less capable of staging PH after HCV-cure. Indeed, NITs can estimate the probability/exclude/rule-in CSPH after HCV-cure and predict clinical outcomes. Based on these findings, Baveno VII [26] recommends that patients with LSM <12kPa & PLT >150G/L (CSPH-excluded; no decompensation risk) may be discharged from portal hypertension surveillance (NITs and/or endoscopy), if no co-factors are present, while continuation of carvedilol may be considered in those with LSM ≥25kPa (CSPH-ruled-in; increased decompensation risk).

ABBREVIATIONS:

95%CI 95% confidence interval

ACLD advanced chronic liver disease

aSHR adjusted subdistribution hazard ratio

AUC area under the curve

BL baseline

cACLD compensated ACLD

CSPH clinically significant portal hypertension

EOT end-of-treatment

FU follow-up

HCC hepatocellular carcinoma

HVPG hepatic venous pressure gradient

IQR interquartile range

LSM liver stiffness measurement

MUV Medical University of Vienna

NIT non-invasive test

NSBB non-selective beta-blocker

PLT platelet count

ROC receiver operating characteristic

SHR subdistribution hazard ratio

SVR sustained virologic response

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Author names in bold designate shared co-first authorship

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FIGURE LEGENDS

Fig. 1. Patient flow-chart. Abbreviations: BL baseline; cACLD compensated advanced chronic liver disease; CSPH clinically significant portal hypertension; HVPG hepatic venous pressure gradient; NIT non-invasive test

Fig. 2. The dynamics of HVPG from pre- (BL) to post-treatment (FU). Abbreviations: BL baseline; FU follow-up; HVPG hepatic venous pressure gradient

Fig. 3. Relationship between NITs (i.e., PLT and LSM) and HVPG before and after HCV-treatment in the HVPG/NIT-cohort modelled with local regression (LOESS). (A) cACLD subgroup (n=241), and (B) overall cohort (n=324). Red and blue lines indicate the relationship before and after HCV-cure, respectively. For this analysis, no adjustment for clustering was performed/possible. Abbreviations: BL baseline; cACLD compensated advanced chronic liver disease; FU follow-up; HVPG hepatic venous pressure gradient; LSM liver stiffness measurement; NIT non-invasive test; PLT platelet count

Fig. 4. ROC-curves of NITs to detect CSPH before and after HCV-cure. (A-C) cACLD subgroup (n=241), and (D-F) the overall HVPG/NIT-cohort (n=324). Abbreviations: AUC area under the curve; BL baseline; cACLD compensated advanced chronic liver disease; CSPH clinically significant portal hypertension; FU follow-up; HVPG hepatic venous pressure gradient; NIT non-invasive test; ROC receiver operator characteristics; 95%CI 95% confidence interval

Fig. 5. Nomogram and 3-D plot for the prediction of FU-CSPH based on FU-PLT and FU-LSM in the cACLD subgroup (n=241). FU-PLT were truncated at 150 G/L and FU-LSM log-transformed. Amplified graphs can be found in the supplementary materials. Abbreviations: cACLD compensated advanced chronic liver disease; CSPH clinically significant portal hypertension; FU follow-up; LSM liver stiffness measurement; PLT platelet count

Fig. 6. Cumulative incidence of hepatic decompensation in cACLD patients stratified according to non-invasive criteria for excluding (FU-LSM <12kPa & FU-PLT >150G/L) or ruling-in CSPH (FU-LSM ≥25kPa) after HCV-cure. (A) Medical University of Vienna (MUV-cohort, n=368), (B) independent tertiary centers (external cohort, n=387), and (C) a combined cACLD-validation-cohort (n=755). HCC and death were considered competing risks (dashed lines). Abbreviations: cACLD compensated advanced chronic liver disease; CSPH clinically significant portal hypertension; FU follow-up; HCC hepatocellular carcinoma; HVPG hepatic venous pressure gradient; LSM liver stiffness measurement; MUV Medical university of Vienna; NA not applicable; PLT platelet count; SHR subdistribution hazard ratio

TABLES

Table 1. AUC and respective performance metrics of NITs for CSPH before and after HCV-cure in the HVPG/NIT-cohort: cACLD subgroup (n=241; A), and the overall cohort (n=324; B). Predictions were obtained from fixed effects of the respective linear mixed effects models adjusting for the centre as random effect.

Variables	Outcome	AUC	95%CI
A – cACLD subgroup			
BL-PLT	BL-CSPH	0.753	0.677-0.828
BL-LSM	BL-CSPH	0.831	0.769-0.894
BL-PLT + BL-LSM	BL-CSPH	0.859	0.807-0.912
BL-PLT + BL-LSM – transformed[1]	BL-CSPH	0.871	0.819-0.923
FU-PLT	FU-CSPH	0.800	0.745-0.855
FU-LSM	FU-CSPH	0.837	0.786-0.887
FU-PLT + FU-LSM	FU-CSPH	0.876	0.831-0.920
FU-PLT + FU-LSM - transformed[1]	FU-CSPH	0.884	0.843-0.926
B – overall cohort			
BL-PLT	BL-CSPH	0.778	0.709-0.847
BL-LSM	BL-CSPH	0.854	0.800-0.908
BL-PLT + BL-LSM	BL-CSPH	0.883	0.840-0.926
BL-PLT + BL-LSM - transformed[1]	BL-CSPH	0.894	0.852-0.937
FU-PLT	FU-CSPH	0.823	0.777-0.869
FU-LSM	FU-CSPH	0.857	0.815-0.900
FU-PLT + FU-LSM	FU-CSPH	0.895	0.860-0.932
FU-PLT + FU-LSM - transformed[1]	FU-CSPH	0.902	0.868-0.936

[1]PLT were capped at 150G/L if >150G/L and LSM were log-transformed;

Abbreviations:

AUC area under the curve

BL baseline

cACLD compensated advanced chronic liver disease

CSPH clinically significant portal hypertension

FU follow-up

HVPG hepatic venous pressure gradient

LSM liver stiffness measurement

NIT non-invasive test

PLT platelet count

Table 2. Prevalence and sensitivity/specificity of selected NIT-criteria for diagnosis of CSPH after HCV-cure in the HVPG/NIT-cohort: cACLD subgroup (n=241; A) and the overall cohort (n=324; B). Although the primary intention behind these criteria is to rule-out/exclude FU-CSPH, diagnostic indices are reported for FU-CSPH.

Variables	Patients meeting the criterion	Prevalence of FU-CSPH when meeting the criterion[1]	Prevalence of FU-CSPH when not meeting the criterion[2]	Sensitivity for FU-CSPH[3]	Specificity for FU-CSPH[3]
A – cACLD subgroup (n=241)					
FU-LSM <10kPa	51 (21%)	7/51 (14%)	124/190 (65%)	124/131 (95%)	44/110 (40%)
FU-LSM <12kPa	73 (30%)	13/73 (18%)	118/168 (70%)	118/131 (90%)	60/110 (55%)
FU-LSM <15kPa	109 (45%)	26/109 (24%)	105/132 (80%)	105/131 (80%)	83/110 (76%)
FU-LSM <20kPa	159 (66%)	62/159 (39%)	69/82 (84%)	69/131 (53%)	97/110 (88%)
FU-LSM <25kPa	**184 (76%)**	**81/184 (44%)**	**50/57 (88%)**	**50/131 (38%)**	**103/110 (94%)**
FU-PLT >150G/L	58 (24%)	12/58 (21%)	119/183 (65%)	119/131 (91%)	46/110 (42%)
FU-LSM <12kPa and FU-PLT >150G/L	**30 (12%)**	**1/30 (3.3%)**	**130/211 (62%)**	**130/131 (99%)**	**29/110 (26%)**
FU-LSM <15kPa and FU-PLT >150G/L	42 (17%)	4/42 (9.5%)	127/199 (64%)	127/131 (97%)	38/110 (35%)
FU-LSM <20kPa and FU-PLT >150G/L (Baveno VI criteria)	50 (21%)	7/50 (14%)	124/191 (65%)	124/131 (95%)	43/110 (39%)
FU-albumin >36g/L and FU-PLT >120G/L (RECIST-HCV criteria)[4]	91 (39%)	25/91 (28%)	102/143 (71%)	102/127 (80%)	66/107 (62%)
B – overall cohort (n=324)					
FU-LSM <10kPa	54 (17%)	9/54 (17%)	199/270 (74%)	199/208 (96%)	45/116 (39%)
FU-LSM <12kPa	79 (24%)	16/79 (20%)	192/245 (78%)	192/208 (92%)	63/116 (54%)
FU-LSM <15kPa	121 (37%)	34/121 (28%)	174/203 (86%)	174/208 (84)%	87/116 (75%)
FU-LSM <20kPa	190 (59%)	88/190 (46%)	120/134 (90%)	120/208 (58%)	102/116 (88%)
FU-LSM <25kPa	222 (69%)	114/222 (51%)	94/102 (92%)	94/208 (45%)	108/116 (93%)
FU-PLT >150G/L	62 (19%)	15/62 (24%)	193/262 (74%)	193/208 (93%)	47/116 (41%)
FU-LSM <12kPa and FU-PLT >150G/L	31 (9.6%)	2/31 (6.5%)	206/293 (70%)	206/208 (99%)	29/116 (25%)
FU-LSM <15kPa and FU-PLT >150G/L	43 (13%)	5/43 (12%)	203/281 (72%)	203/208 (98%)	38/116 (33%)
FU-LSM <20kPa and FU-PLT >150G/L (Baveno VI criteria)	53 (16%)	9/53 (17%)	199/271 (73%)	199/208 (96%)	44/116 (38%)

FU-albumin>36g/L and FU-PLT>120G/L (RECIST-HCV criteria)[4]	102 (32%)	34/102 (33%)	169/214 (79%)	169/203 (83%)	68/113 (60%)

[1] Corresponding to the false-negative rate or the reciprocal of the negative predictive value when not meeting the criterion; [2] Corresponding to the positive predictive value for FU-CSPH when not meeting the respective criterion; [3] Calculated for patients not meeting the respective criterion; [4] Available in 234 cACLD patients and 316 in the overall cohort

Abbreviations:

BL baseline

cACLD compensated advanced chronic liver disease

FU follow-up

LSM liver stiffness measurement

PLT platelet count

TABLES

Table 1. AUC and respective performance metrics of NITs for CSPH before and after HCV-cure in the HVPG/NIT-cohort: cACLD subgroup (n=241; A), and the overall cohort (n=324; B). Predictions were obtained from fixed effects of the respective linear mixed effects models adjusting for the centre as random effect.

Variables	Outcome	AUC	95%CI
A – cACLD subgroup			
BL-PLT	BL-CSPH	0.753	0.677-0.828
BL-LSM	BL-CSPH	0.831	0.769-0.894
BL-PLT + BL-LSM	BL-CSPH	0.859	0.807-0.912
BL-PLT + BL-LSM – transformed[1]	BL-CSPH	0.871	0.819-0.923
FU-PLT	FU-CSPH	0.800	0.745-0.855
FU-LSM	FU-CSPH	0.837	0.786-0.887
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LSM liver stiffness measurement

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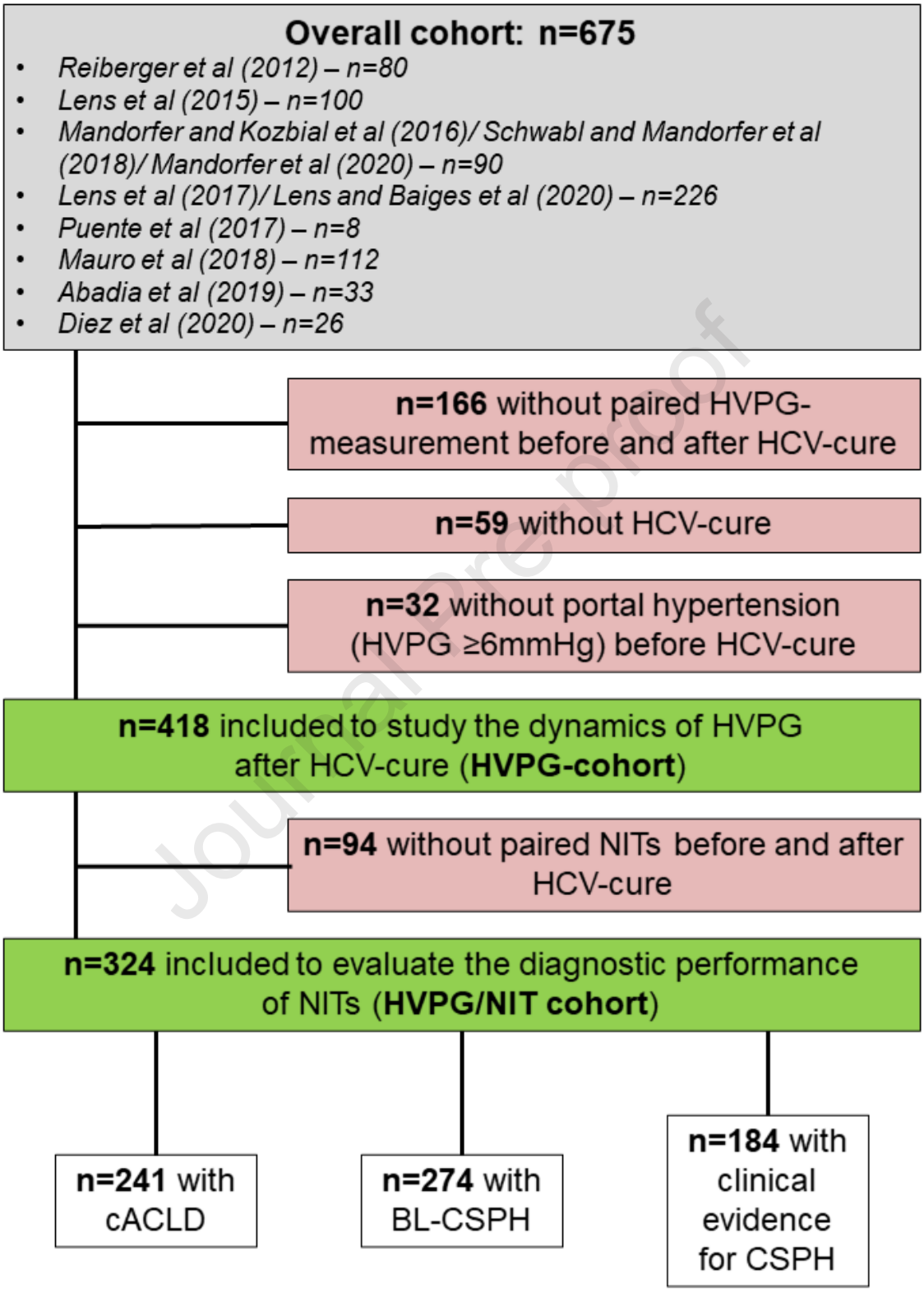

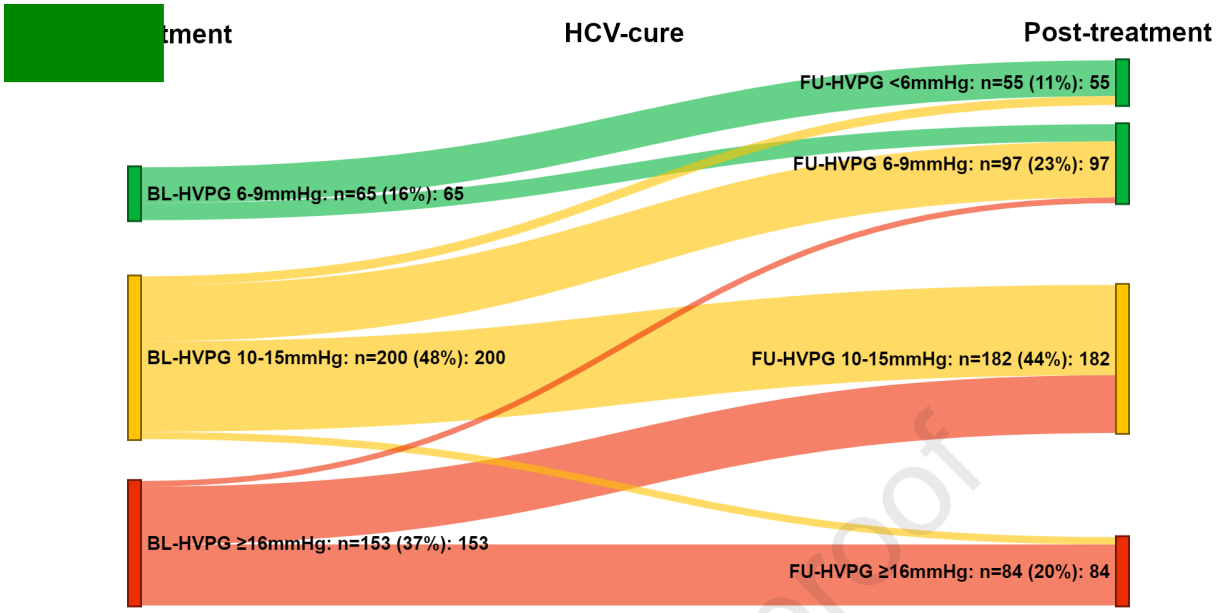

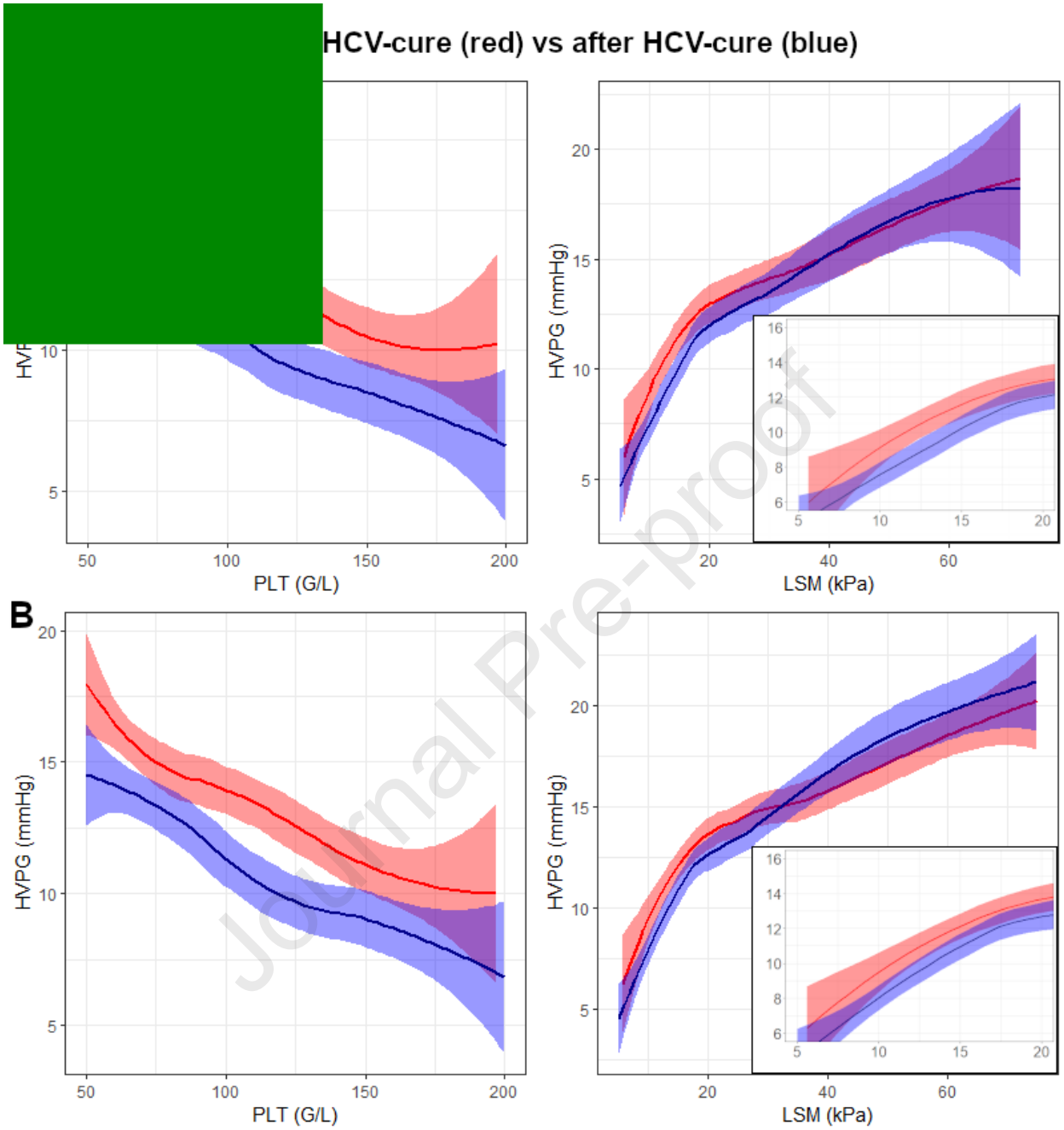

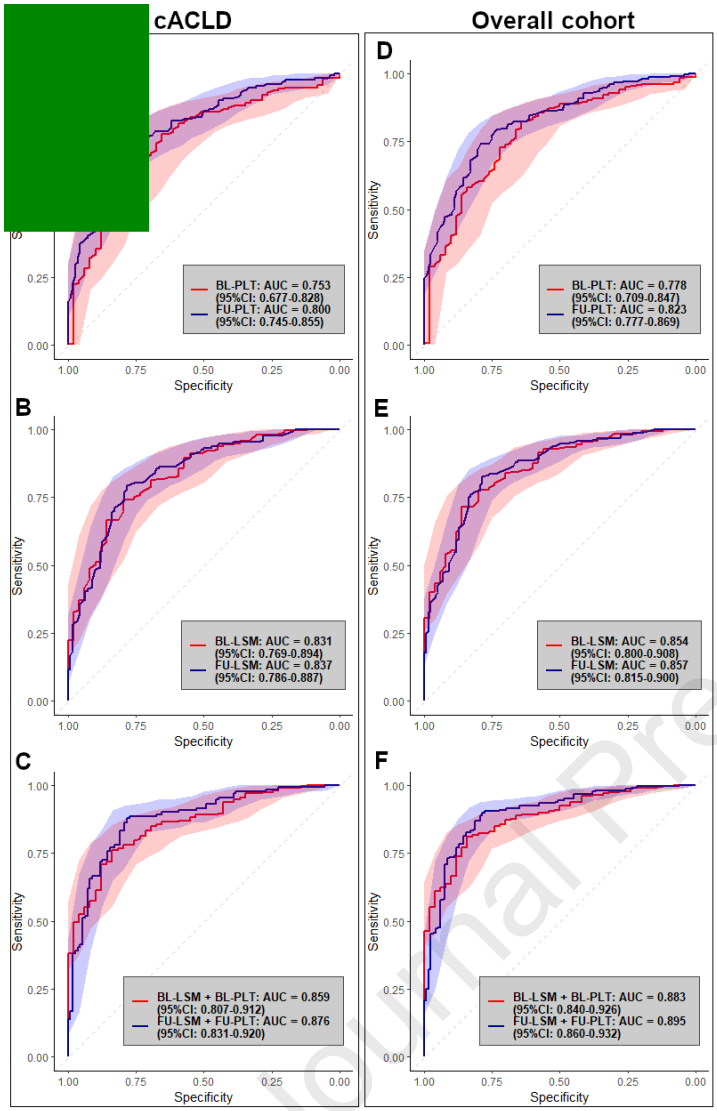

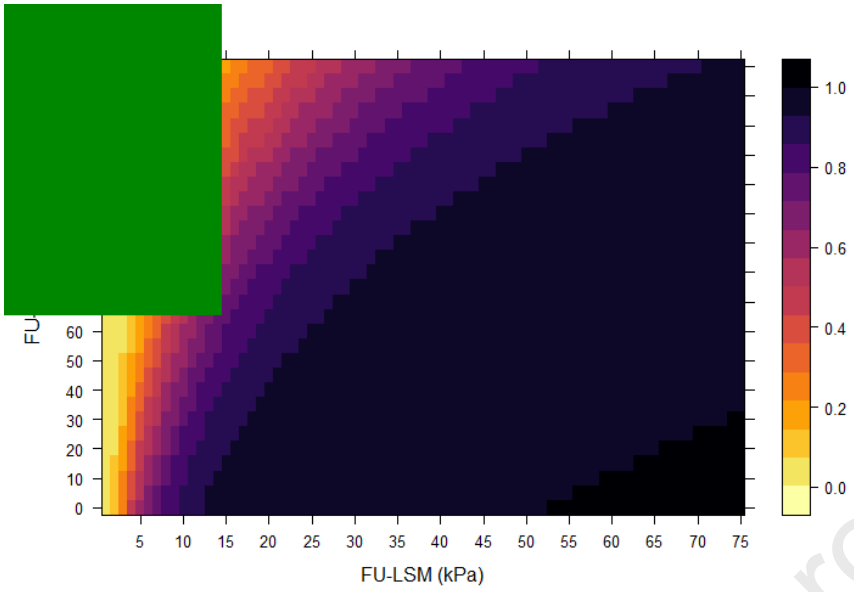

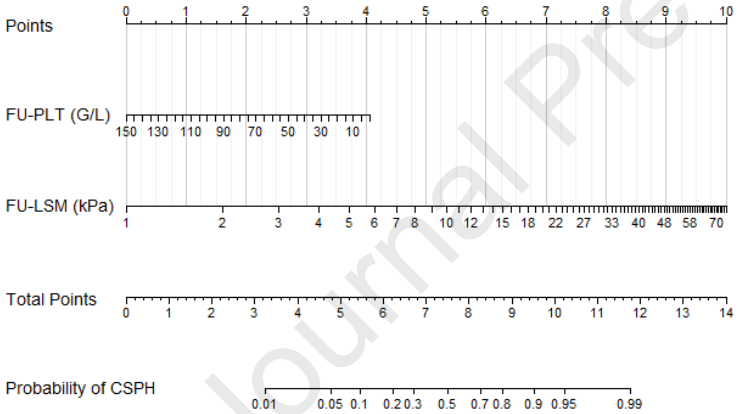

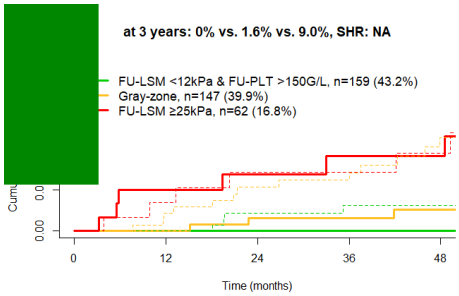

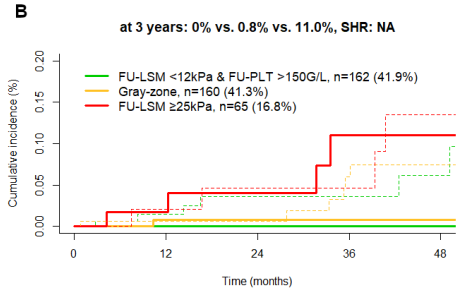

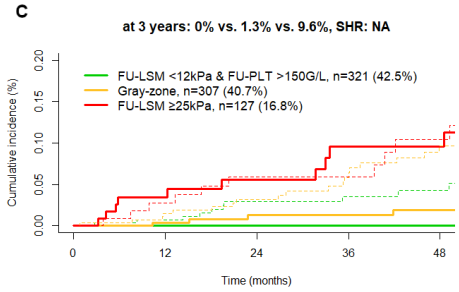

HIGHLIGHTS

- Pooled analysis on hepatic venous pressure gradient and liver stiffness-measurement (LSM)/platelet count (PLT) in advanced chronic liver disease (ACLD) patients achieving HCV-cure
- Post-treatment LSM/PLT can estimate the probability of clinically significant portal hypertension (CSPH) and predict clinical outcomes in compensated ACLD (cACLD)
- cACLD patients with LSM<12kPa & PLT>150G/L (CSPH-excluded; no decompensation risk) may be discharged from portal hypertension surveillance
- cACLD patients with LSM≥25kPa require surveillance/treatment (CSPH-ruled-in; increased decompensation risk)