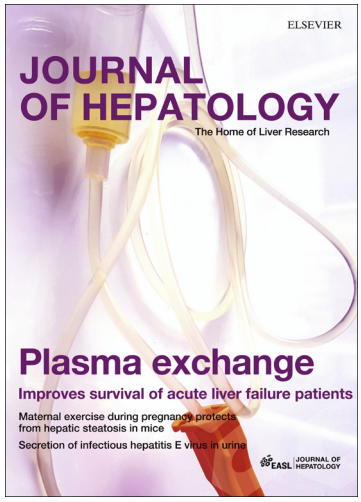

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Mattias Mandorfer, Karin Kozbial, Philipp Schwabl, Clarissa Freissmuth, Rémy Schwarzer, Rafael Stern, David Chromy, Albert Friedrich Stättermayer, Thomas Reiberger, Sandra Beinhardt, Wolfgang Sieghart, Michael Trauner, Harald Hofer, Arnulf Ferlitsch, Peter Ferenci, Markus Peck-Radosavljevic

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Title page

Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension

Mattias MANDORFER[1, 2], M.D.

Karin KOZBIAL[1], M.D.

Philipp SCHWABL[1, 2], M.D.

Clarissa FREISSMUTH[1], M.D.

Rémy SCHWARZER[1, 2], M.D.

Rafael STERN[1], M.D.

David CHROMY[1, 2]

Albert Friedrich STÄTTERMAYER[1], M.D.

Thomas REIBERGER[1, 2], M.D.

Sandra BEINHARDT[1], M.D.

Wolfgang SIEGHART[1], M.D.

Michael TRAUNER[1], M.D.

Harald HOFER[1], M.D.

Arnulf FERLITSCH[1, 2], M.D.

Peter FERENCI[1], M.D.

Markus PECK-RADOSAVLJEVIC[1, 2], M.D.

Mattias Mandorfer and Karin Kozbial contributed equally to this manuscript.

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

[2]Vienna Hepatic Hemodynamic Lab

Corresponding author: Markus Peck-Radosavljevic, M.D.

Division of Gastroenterology and Hepatology,

Department of Internal Medicine III,

Medical University of Vienna,

Waehringer Guertel 18-20,

1090, Vienna, Austria

Phone: +43 1 40400 47440

Fax: +43 1 40400 47350

E-Mail: markus.peck@meduniwien.ac.at

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Abbreviations: HVPG hepatic venous pressure gradient

ACLD advanced chronic liver disease

HCV hepatitis C virus

PEGIFN/RBV pegylated interferon and ribavirin

SVR sustained virologic response

IFN interferon

SOF sofosbuvir

TE transient elastography

BL baseline

MELD model for end-stage liver disease

CP Child-Pugh

SMV simeprevir

DCV daclatasvir

LDV ledipasvir

NSBB non-selective beta blocker

CSPH clinically significant portal hypertension

NPV negative predictive value

PPV positive predictive value

AUROC area under the receiver operating characteristic curve

HCC hepatocellular carcinoma

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Supplementary tables:	4

Supplementary figures: 3

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Abstract

Background&aims

We aimed to investigate the impact of sustained virologic response (SVR) to interferon (IFN)-free therapies on portal hypertension in patients with paired hepatic venous pressure gradient (HVPG) measurements.

Methods

One hundred and four patients with portal hypertension (HVPG≥6mmHg) who underwent HVPG and liver stiffness measurement before IFN-free therapy (baseline [BL]) were retrospectively studied. Among 100 patients who achieved SVR, 60 patients underwent HVPG and transient elastography (TE) after antiviral therapy (follow-up [FU]).

Results

SVR to IFN-free therapies significantly decreased HVPG across all BL-HVPG strata: 6-9mmHg (BL:7.37±0.28vs.FU:5.11±0.38mmHg;-2.26±0.42mmHg;*P*<0.001), 10-15mmHg (BL:12.2±0.4vs.FU:8.91±0.62mmHg;-3.29±0.59mmHg;*P*<0.001) and ≥16mmHg (BL:19.4±0.73vs.FU:17.1±1.21mmHg;-2.3±0.89mmHg;*P*=0.018).

In the subgroup of patients with BL-HVPG of 6-9mmHg, HVPG normalized (<6mmHg) in 63%(12/19) of patients, while no patient progressed to ≥10mmHg. Among patients with BL-HVPG≥10mmHg, a clinically relevant HVPG-decrease ≥10% was observed in 63%(26/41); 24%(10/41) had a FU-HVPG<10mmHg.

Patients with Child-Pugh stage B were less likely to have a HVPG-decrease (HR:0.103;95%CI:0.02-0.514;*P*=0.006), when compared to Child-Pugh A patients. In the subgroup of patients with BL CSPH, the relative change in liver stiffness (per %;HR:0.972;95%CI:0.945-0.999;*P*=0.044) was a predictor of a HVPG-decrease ≥10%. The area under the receiver operating characteristic curve for the diagnosis of FU CSPH by FU liver stiffness was 0.931(95%CI:0.865-0.997).

Conclusions

SVR to IFN-free therapies might ameliorate portal hypertension across all BL HVPG strata. However, changes in HVPG seemed to be more heterogeneous among patients with BL-HVPG of ≥16mmHg and a HVPG-decrease was less likely in patients with more advanced liver dysfunction. TE might be useful for the non-invasive evaluation of portal hypertension after SVR.

Lay summary

We investigated the impact of curing hepatitis C using novel interferon-free treatments on portal hypertension, which drives the development of liver-related complications and mortality. Cure of hepatitis C decreased portal pressure, but a decrease was less likely among patients with more pronounced hepatic dysfunction. Transient elastography, which is commonly used for the non-invasive staging of liver disease, might identify patients without clinically significant portal hypertension after successful treatment.

Text

Introduction

Portal pressure, assessed by hepatic venous pressure gradient (HVPG) measurement, drives the development of liver-related complications and mortality in patients advanced chronic liver disease (ACLD) [1-3]. Since a decrease in HVPG translates into a clinically meaningful benefit, it is an acceptable surrogate endpoint [1-3].

Hepatitis C virus (HCV) eradication with pegylated interferon and ribavirin (PEGIFN/RBV) has been shown to ameliorate portal hypertension in patients with HCV-monoinfection [4, 5] and HIV/HCV-coinfection [6]. In patients with a HVPG ≥12mmHg and sustained virologic response (SVR) to PEGIFN/RBV, a HVPG decrease ≥20% or to <12mmHg was observed in 82% [4] and 71% [5] of patients, indicating an important change in the natural history of the disease [1-3]. Together with modest efficacy, substantial rates of serious adverse events greatly limited the use of interferon (IFN)-based therapies in patients with portal hypertension [7, 8]. In contrast, IFN-free regimens are highly effective and generally well tolerated, even in patients with cirrhosis [9]. In addition to improvement in liver function [10-14], HCV eradication was associated with an increase in platelet count, which was paralleled by a decrease in liver stiffness, suggesting an anti-portal hypertensive effect [11]. However, in a recent study by Afdhal and co-workers [15], only 24% of HCV-monoinfected patients with a HVPG ≥12mmHg treated with 48 weeks of sofosbuvir (SOF)/RBV achieved a HVPG decrease ≥20% and none of the patients had a follow-up (FU) HVPG <12mmHg.

We aimed to **(I)** investigate the impact of SVR to IFN-free therapies on HCV-induced portal hypertension and **(II)** elucidate predictors of HVPG decrease, as well as to **(III)** evaluate the usefulness of transient elastography (TE) for the non-invasive evaluation of portal hypertension after SVR.

Patients and methods

Study design and population

One hundred and four patients with portal hypertension (HVPG ≥6mmHg [8]) who underwent HVPG and TE before IFN-free therapy (baseline [BL]) were retrospectively studied (Figure 1).

The effect of SVR on portal pressure was investigated in patients with SVR who also underwent FU HVPG and TE after IFN-free therapy (group A; n=60). To demonstrate the generalizability of our results, we included a second group (group B; n=40), comprising all patients who achieved SVR, but did not undergo FU HVPG measurement. In these patients, only information on FU TE was available. Moreover, we also included 4 patients who did not achieve SVR.

Assessed parameters

Epidemiological characteristics were assessed from patients' medical history. Model for end-stage liver disease (MELD) and Child-Pugh (CP) score were calculated at BL based on laboratory parameters and patients' medical history. HCV-genotype was determined using the VERSANT® HCV Genotype 2.0 Assay Line Probe Assay (LiPA) (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). HCV-RNA was assessed using the Abbott RealTime HCV assay (Abbott Molecular, Des Plaines, IL, USA) with a lower limit of quantification and detection of 12IUxmL^{-1}. SVR was defined as undetectable HCV-RNA 12 weeks after the end of therapy.

HCV therapy

Patients were treated with SOF in combination with RBV, simeprevir (SMV), daclatasvir (DCV), or ledipasvir (LDV), SMV/DCV, or the 3D regimen ±RBV. SOF (Sovaldi® [Gilead, Cambridge, UK] 400mg once daily), RBV (weight based Copegus® [Roche, Vienna, Austria] doses ranged from 1000-1200mg daily), SMV (Olysio® [Janssen, Beerse, Belgium] 150mg once daily), SOF/LDV (Harvoni® [Gilead, Cambridge, UK] 400mg/90mg once daily), and the 3D regimen (Viekirax® [AbbVie, Maidenhead, UK] 12.5mg ombitasvir, 75mg paritaprevir, and 50mg ritonavir once daily plus Exviera® [AbbVie, Maidenhead, UK] 250mg dasabuvir twice daily with or without RBV) were covered by the Austrian health insurance and provided by the local pharmacy. Bristol-Myers Squibb provided DCV (60mg once daily) within a named patient program. After the approval by the European Medicines Agency, DCV was provided by the local pharmacy (Daklinza® [Bristol-Myers Squibb, Uxbridge, UK] 60mg once daily). Treatment durations ranged from 12 to 24 weeks.

HVPG and liver stiffness measurement

The Vienna Hepatic Hemodynamic Lab at the Medical University of Vienna performed the HVPG measurements in accordance with a standardized operating procedure [16]. HVPG measurements were performed in the absence of non-selective beta blockers (NSBB) and nitrates. In patients on NSBBs, NSBBs were paused 5 days prior to HVPG measurements.

Measurement of liver stiffness was performed by TE (Fibroscan®, Echosens, Paris, France), as previously described [17, 18].

Among patients with clinically significant portal hypertension (CSPH; ≥10mmHg [1-3]), a clinically relevant HVPG response was defined as a decrease ≥10%, as recommended by the Baveno VI consensus for etiologic therapies [3]. Moreover, the proportion of patients with a HVPG decrease ≥20% or to <12mmHg was assessed in the subgroup of patients with a BL HVPG ≥12mmHg [1-3]. Subclinical and pronounced portal hypertension were defined by a HVPG of 6-9mmHg and ≥16mmHg, respectively [1-3, 19].

Statistics

Statistical analyses were performed using IBM SPSS Statistics 23 (IBM, Armonk, NY, USA) and GraphPad Prism 6 (GraphPad Software, La Jolla, CA, USA). Continuous variables were reported as mean ±standard error of the mean or median (25^{th} percentile/75^{th} percentile), while categorical variables were reported as number of patients with (proportion of patients with) the certain characteristic.

Student's t test was used for group comparisons of continuous variables when applicable. Otherwise, Mann-Whitney U test was applied. Group comparisons of categorical variables were performed using Chi squared or Fisher's Exact test. Intraindividual comparisons were performed using Student's t-test for paired samples, Wilcoxon matched-pairs signed rank test, or repeated measures one-way ANOVA and Tukey's test for post-hoc comparisons. Multivariate analyses were performed using binary logistic regression analysis with backward elimination. A *P* value ≤0.05 was considered as statistically significant.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Medical University of Vienna (No. 1975/2014). No written informed consent was required for this retrospective study.

Results

A comparison of characteristics of patients with suspected/confirmed ACLD due to hepatitis C who underwent interferon-free therapy and were included or excluded from the study is shown in Supplementary table 1.

Patient and treatment characteristics (group A)

At BL, the majority of patients had compensated (93%[52/56]) CP stage A (84%[47/56]) cirrhosis (Table 1). CP stage B cirrhosis was observed in (16%[9/56]) of patients, while no patient with CP stage C cirrhosis was included. The median BL MELD was 8(7/9) points. Varices were observed in 20(36%) patients (small: 65%[13/20]; large: 35%[7/20]) and 3(5%) patients had a history of variceal bleeding.

Additional patient and treatment characteristics of group A and characteristics of group B are shown in Table 1.

BL HVPG and its change after antiviral therapy (group A)

The median time between BL HVPG measurement and treatment initiation, as well as the median time between end of antiviral therapy and FU HVPG measurement was 103(8/482) and 114(84/179) days, respectively.

At BL, the proportions of patients with subclinical portal hypertension (6-9mmHg), HVPG of 10-15mmHg, and patients with pronounced portal hypertension (≥16mmHg) were 32%(19/60), 35%(21/60), and 33%(20/60), respectively. Thus, 68%(41/60) of patients had CSPH at BL.

SVR to IFN-free therapy resulted in a statistically significant decrease in HVPG (BL: 13.1±0.7 vs. FU: 10.4±0.79 mmHg; mean of differences: -2.63±0.38mmHg; *P*<0.001; Figure 2). The mean relative change was -23±2.9%. HVPG decreased in 80%(48/60), remained unchanged in 10%(6/60), and increased in 10%(6/60) of patients.

Importantly, HVPG decreased statistically significantly across all BL HVPG strata: subclinical portal hypertension (BL HVPG of 6-9mmHg; BL: 7.37±0.28 vs. FU: 5.11±0.38mmHg; mean of differences: -2.26±0.42mmHg; *P*<0.001), BL HVPG of 10-15mmHg (BL: 12.2±0.4 vs. FU: 8.91±0.62mmHg; mean of differences: -3.29±0.59mmHg; *P*<0.001), and pronounced portal hypertension (BL: 19.4±0.73 vs. FU: 17.1±1.21mmHg; mean of differences: -2.3±0.89mmHg; *P*=0.018). The relative changes in HVPG were -29.8±5.4%, -26.6±4.8%, and -12.6±4.5% in patients with subclinical portal hypertension (6-9mmHg), HVPG of 10-15mmHg, and patients with pronounced portal hypertension (≥16mmHg) at BL, respectively.

In the subgroup of patients with subclinical portal hypertension at BL (6-9mmHg), portal hypertension resolved in 63%(12/19), while no patient had an increase in HVPG at FU. Among patients with a BL HVPG of 10-15mmHg, portal hypertension was resolved in 14%(3/21), 29%(6/21) had subclinical portal hypertension, while no patient showed a progression of portal hypertension at FU. Finally, in the subgroup of patients with pronounced portal hypertension at BL (≥16mmHg), 5%(1/20) and 35%(7/20) of patients had a regression to subclinical portal hypertension or a HVPG of 10-15mmHg, respectively. However, portal hypertension did not resolve in any patient and 20%(4/20) of patients showed an increase in HVPG at FU.

Among patients with BL CSPH, HVPG decreased from 15.7±0.7mmHg at BL to 12.9±0.9mmHg at FU (mean of differences: -2.8±0.53mmHg; *P*<0.001). The mean relative change was -19.8±3.4%. In this subgroup, a HVPG decrease ≥10% was observed in 63%(26/41). A decrease >20% or to <12mmHg was observed in 52%(15/29) of patients with a BL HVPG ≥12mmHg.

BL liver stiffness and its change after antiviral therapy (group A)

In the subgroup of 57 patients with paired liver stiffness measurements, there was a statistically significant absolute decrease in liver stiffness (BL: 21.13[16.4/34] vs. FU: 15.4[9.6/27.4]kPa; median of differences: -4.6[-9.45/-1.15]kPa; *P*<0.001). The median relative change in liver stiffness was -18.9(-41.2/-7.4)%.

Predictors of HVPG decrease (group A)

When comparing patients with or without HVPG decrease (Table 2), the proportion of patients with decompensated cirrhosis (36%[4/11] vs. 7%[3/45]; *P*=0.022) and CP stage B (45%[5/11] vs. 9%[4/45]; *P*=0.01) was higher among patients without a HVPG decrease. Moreover, there was a trend toward higher MELD scores (8[6.5/9] vs. 9[8/10] points; *P*=0.123) and less pronounced relative decreases in liver stiffness (-8.38±6.59 vs. FU: -24.7±3.7%; *P*=0.054) among patients without HVPG decrease. Thus, CP stage (as a measure of liver dysfunction) and the relative decrease in liver stiffness were included in a binary logistic regression model (Table 3). After backward elimination, only CP stage remained in the final model. Patients with CP stage B were less likely to have a HVPG decrease (HR: 0.103; 95%CI: 0.02-0.514; *P*=0.006), when compared to CP stage A patients.

Predictors of HVPG response among patients with BL CSPH (group A)

Furthermore, we investigated predictors of a clinically relevant HVPG decrease among patients with BL CSPH (Supplementary table 2). We observed a trend toward a higher proportion of patients with CP stage B (40%[6/15] vs. 12%[3/26]; *P*=0.053) and higher MELD score (9[8/10] vs. 8[7/9] points; *P*=0.052) among patients without a HVPG decrease ≥10%. Furthermore, the relative decrease in liver stiffness (-8.94±5.92 vs. -27.1±5.4%; *P*=0.035) was less pronounced among patients without HVPG decrease ≥10%. Again, a measure of liver dysfunction (MELD score) and the relative decrease in liver stiffness were included in a binary logistic regression model (Supplementary table 3). Only the relative decrease in liver stiffness remained in the final model. Thus, the relative change in liver stiffness (per %; HR: 0.972; 95%CI: 0.945-0.999; *P*=0.044) was a predictor of a HVPG decrease ≥10% among patients with CSPH.

Non-invasive diagnosis of FU CSPH (group A)

The areas under the receiver operating characteristic curves (AUROCs) for the diagnosis of FU CSPH were 0.9 (95%CI: 0.822-0.977), 0.49 (95%CI: 0.335-0.645), 0.659 (95%CI: 0.516-0.802) and 0.931 (95%CI: 0.898-0.997), for BL liver stiffness, the absolute and relative change after antiviral therapy, as well as FU liver stiffness, respectively (Figure 3; Supplementary table 4). The BL and FU liver stiffness cut-offs were 18.8 (sensitivity: 100%; specificity: 71%; negative predictive value [NPV]: 100%) and 12.4kPa (sensitivity: 100%; specificity: 69%; NPV: 100%) to rule-out FU CSPH. The cut-offs for ruling-in FU CSPH were 27.2 (sensitivity: 59%; specificity: 96%; positive

predictive value [PPV]: 94%) and 25.3kPa (sensitivity: 57%; specificity: 97%; PPV: 94%) for BL and FU liver stiffness, respectively.

The following AUROCs were observed when considering only patients with BL CSPH (Figure 3): 0.766 (95%CI: 0.602-0.929), 0.579 (95%CI: 0.392-0.767), 0.769 (95%CI: 0.594-0.944) and 0.847 (95%CI: 0.691-1) for BL liver stiffness, absolute and relative change after antiviral therapy, as well as FU liver stiffness, respectively. While the FU liver stiffness cut-offs were similar, the diagnostic performance differed in this setting: 18.8kPa (sensitivity 100%; specificity 40%; NPV: 100%) at BL and 12.4kPa at FU (sensitivity 100%; specificity 60%; NPV: 100%) to rule-out FU CSPH. The BL and FU liver stiffness cut-offs for ruling-in FU CSPH were 27.2kPa (sensitivity: 59%; specificity: 90%; PPV: 94%) and 25.3kPa (sensitivity: 57%; specificity: 90%; PPV: 94%), respectively.

Evolution of platelet count (group A)

The mean time between end of treatment and last visit was 292±15 days. The mean platelet count increased statistically significantly (BL: 116±7 vs. FU: 121±7 vs. last visit: 129±8GxL^{-1}; *P*=0.022; Supplementary figure 1). The changes from BL to FU (*P*=0.02) and BL to last visit (*P*=0.043) attained statistical significance, while the change from FU to last visit did not (*P*=0.19).

Comparison of patient and treatment characteristics, as well as their change after antiviral therapy between groups A and B

Except for treatment regimens and durations, BL patient characteristics were comparable between groups A and B (Table 1).

In analogy to group A, we observed a statistically significant absolute decrease in liver stiffness after antiviral therapy (BL: 23.6[16.3/35.4] vs. FU: 17.5[11.8/27.3]kPa; median of differences: -4.35[-8.23/-0.63]kPa; *P*<0.001) in group B. The median relative change in liver stiffness was -18.3(-37.5/-1.9)%.

The absolute (*P*=0.728) and relative (*P*=0.541) changes in liver stiffness after antiviral therapy were comparable between groups A and B (Supplementary figure 2). Moreover, there were no group differences regarding the median changes in platelet count (group A: 4[-7.5/17.5] vs. B: 3.5[-7.5/19.5]GxL^{-1}; *P*=0.954), prothrombin time (group A:-0.5[-6.75/7.5] vs. B:-1.5[-9.5/7.75]%; *P*=0.395), and bilirubin level (group A: -0.14[-0.36/0.02] vs. B: -0.155[-0.373/0.06]mgxdL^{-1}; *P*=0.696) after antiviral therapy (Supplementary figure 3). There was only a trend toward a more pronounced median increase in albumin level in group B (group A: 1.8[-0.25/4] vs. B: 2.8[0.35/5.9]gxL^{-1}; *P*=0.054).

Patients without SVR

Among the 4 patients without SVR, one patient underwent FU HVPG and TE (HVPG increased from 18 to 20mmHg; liver stiffness increased from 45 to 75kPa), while 3 patients only underwent FU TE measurement (16.5 to 14.8kPa, 72 to 72kPa and 10.2 to 10.5kPa).

Discussion

With the availability of highly effective and well-tolerated IFN-free regimens, focus of attention has shifted to the regression of liver fibrosis and portal hypertension after HCV eradication in patients with HCV-induced cirrhosis [20, 21].

Even after achieving SVR, patients with CSPH remain at considerable risk for complications related to portal hypertension [22]. Recent observations [23] suggest that portal hypertension may persist despite normalization of liver function tests. On the other hand, in parallel to the hemodynamic response to NSBBs, HVPG response to antiviral therapy may translate into a clinically meaningful benefit in patients with CSPH, in that it results in reduction of the risks for development of varices and variceal bleeding as well as ascites and its complications [1-3].

In our study, SVR to IFN-free therapies ameliorated portal hypertension across all BL HVPG strata.

In patients with subclinical portal hypertension, HVPG decreased significantly after SVR to IFN-free therapy. In this subgroup, the relative change in HVPG was almost -30%. HVPG normalized (<6mmHg) in 63% of patients, while no patient progressed to CSPH. The efficacy of NSBBs in decreasing HVPG in patients with subclinical portal hypertension is modest (relative change in HVPG of only -8%), since these patients have less pronounced hyperdynamic circulation when compared to patients with CSPH [24]. In contrast, etiologic therapies are thought to be highly effective in the setting of subclinical portal hypertension, as they assumedly reduce intrahepatic resistance. Interestingly, although this concept is widely accepted, it is supported by very limited

clinical data. Thus, out study provides important information on the impact of etiologic treatment on subclinical portal hypertension. In these patients, a decrease in HVPG or even the resolution of portal hypertension will not provide an immediate clinical benefit, since they are at negligible risk for hepatic decompensation. Nevertheless, the Baveno VI consensus defines the prevention of progression to CSPH as the main goal of etiologic treatments (e.g. antiviral therapy) in patients who have not yet developed CSPH. In our study, the vast majority of these patients showed a decrease in HVPG and no patient had a progression of portal hypertension at FU.

Among patients with a BL HVPG of 10-15mmHg (intermediate risk [2]), CSPH resolved in 43%, while no patient had a progression of portal hypertension at FU. Since the risk of hepatic decompensation in patients without CSPH is negligible, this would indicate a significant impact on the natural history of the disease in this stratum. Moreover, HVPG is an independent risk factor for development of hepatocellular carcinoma (HCC) and the presence of CSPH increases HCC risk 6-fold [25]. Thus, further studies should investigate the potential reduction in HCC risk to allow for personalized surveillance strategies [26, 27].

In contrast, in the stratum with pronounced portal hypertension (BL HVPG ≥16mmHg [2] – high risk of hepatic decompensation and death), portal hypertension did not resolve in any patients and only one patient (5%) regressed to subclinical portal hypertension at FU. Thus, although the severity of portal hypertension decreased in a relevant proportion of patients (35% had a FU HVPG of 10-15mmHg), the vast majority of patients remained at considerable risk for complications of portal hypertension. In 20% of patients, there was even an increase in HVPG from BL to FU.

Whether patients with pronounced portal hypertension have reached a point of no return in the natural history of HCV-induced portal hypertension, or only require a longer time period for resolving CSPH, is unclear. Afdhal an co-workers [28] reported HVPG 48 weeks after the end of treatment in 9 patients who achieved SVR in their initial study [15]. Interestingly, there was a further decrease in HVPG within 48 weeks after the end of treatment. Although the small number of patients limits the significance of this observation, it suggests long-term decreases in HVPG. In our study, there was a numerical increase in platelet count from FU to last visit. However, due to the complex pathophysiology of thrombocytopenia in ACLD (reduced trombopoietin production as a consequence of hepatic dysfunction vs. splenomegaly as a result of portal hypertension [29]), we cannot rule out, that the increase in platelet count is just lagging behind the evolution of portal hypertension, since platelet count has been shown to continuously increase for years after SVR to IFN-based regimens [29].

In our study, a clinically relevant HVPG response [3] was observed in 63% of patients with CSPH. The change in HVPG observed in our study is consistent with previous studies using PEGIFN/RBV [4, 5, 22], and more pronounced than in a study by Afdhal and co-workers using SOF/RBV [15]. However, only 35% of patients included in the latter study had a MELD score <10, which has been found to be associated with HVPG response. Similarly, we observed an association between HVPG decrease and less advanced liver dysfunction. Thus, the high proportion of patients with HVPG response in our study may be explained by the patient characteristics of group A: Eighty-two percent had a MELD score <10 points and 84% were CP stage A, while some patients did not have cirrhosis. Importantly, the severity of portal hypertension per se had no effect on

the decrease in HVPG after SVR to IFN-free therapy. Nevertheless, changes in HVPG seemed to be more heterogeneous among patients with pronounced portal hypertension, which might be explained by the declining pathophysiologic relevance of intrahepatic resistance in these patients who show more pronounced hepatic dysfunction and a higher prevalence of decompensated cirrhosis. Thus, our results support the timely initiation of antiviral therapy.

The clinical use of HVPG measurement is limited by its invasiveness. Moreover, its availability is mostly restricted to academic centers. Thus, the non-invasive monitoring of the regression of liver fibrosis and portal hypertension after HCV eradication will be a major challenge in the post-HCV era. Although non-invasive methods cannot substitute HVPG measurement [3, 30], TE showed an excellent correlation with HVPG in patients without CSPH, while there was only a weak correlation in patients with a HVPG >12mmHg [31]. From a clinical perspective, the absence or presence of CSPH after antiviral therapy is the most intriguing question due to broad implications on patient management. FU liver stiffness had the highest AUROC, followed by BL liver stiffness. Since the sample size of our study is limited, we chose rather conservative cut-offs to rule-in and rule-out CSPH at FU. These were FU liver stiffness values of 12.4 and 25.3kPa to rule-in or rule-out portal hypertension. However, the diagnostic performance decreased when only patients with BL CSPH were considered, which might be explained by weak correlation in patients with a HVPG >12mmHg [31]. This is the first study to assess the value of TE for the evaluation of portal hypertension after HCV eradication. Recent studies suggest that the XL probe measures slightly lower liver stiffness values, when compared to the M probe [32-34]. This might also apply to

patients with liver fibrosis stage F3/F4 [32-34]. In our study, the XL probe was only used if no valid liver stiffness measurement was obtained with the M probe. Although this approach decreased the proportion of patients without paired liver stiffness measurements, it could have inflated the diagnostic performance of TE. Especially the AUROCs of the absolute and relative change in liver stiffness could have been affected. Thus, diagnostic accuracy of TE and the proposed cut-offs therefore must be confirmed by further studies. Nevertheless, the use of TE for ruling-in and ruling-out FU CSPH seems promising. In contrast, although we observed an association between the relative change in liver stiffness and HVPG response, the value of TE for monitoring changes in HVPG in patients with BL CSPH is questionable [30].

Importantly, although the small number of patients limits the significance of this observation, patients who did not achieve SVR showed either no significant improvement or even worsening of liver disease.

The main limitations of our study arise from its retrospective design. Firstly, patients included in this study had more severe liver disease than the cohort comprising all other patients with suspected/confirmed ACLD treated at our center. More than one third of patients in this cohort did not have cirrhosis, while nearly all patients included in our study population had cirrhosis. Thus, the results of our study should not be extrapolated to patients with ACLD in general, since the definition of ACLD includes a significant proportion of patients without portal hypertension in whom the prognostic relevance of HVPG has not been established. Moreover, these results suggest that patients with subclinical portal hypertension, who had a particularly strong relative decreases in HVPG, might have been underrepresented in our study. Secondly, not all patients with

SVR to IFN-free therapy underwent FU HVPG measurement. However, all patients were invited to FU HVPG measurements and the changes in liver stiffness, platelet count, and liver function tests were comparable between patients with (group A) and without FU HVPG measurement (group B), providing an argument for the generalizability of our results. Thirdly, the time interval between BL HVPG measurement and treatment initiation, treatment duration, and the time interval between the end of treatment and FU HVPG measurement were not standardized, although within a reasonable range in all patients. Lastly, the Baveno VI consensus considers HVPG an acceptable surrogate endpoint for etiologic therapies [3]. However, its impact on direct endpoints (e.g. liver-related events and mortality) has not been fully explored in this setting, as available data are primarily based on the effect of hemodynamic response to NSBBs. Thus, our results have to be confirmed by long-term follow-up studies assessing well-defined direct endpoints. Moreover, as mentioned above, a decrease in HVPG or even the resolution of portal hypertension will not provide an immediate clinical benefit in patients with subclinical portal hypertension, since they are at negligible risk for hepatic decompensation [1-3].

The mechanism by which HCV eradication leads to a decrease in portal pressure and liver stiffness in this short time period remains unclear. We hypothesize that short-term effects on HVPG are induced by decreases in hepatic necroinflammation and sinusoidal endothelial dysfunction, rather than by a reduction in liver fibrosis [20]. Similarly, potential mechanisms for the decrease in liver stiffness in this short time period include changes in tissue contraction/relaxation and hepatic necroinflammation, rather than a reduction in liver fibrosis or cholestasis [18, 20]. Based on the histological correlates of

liver stiffness regression after initiation of antiviral therapy in patients with hepatitis B, there might be a biphasic decline in liver stiffness, reflecting the amelioration of hepatic necroinflammation followed by the regression of hepatic fibrosis [35]. Thus, antifibrotic effects may have been relevant if assessed after a longer interval, as they lead to durable and maybe even more pronounced long-term decreases in HVPG and liver stiffness [20, 22, 28].

SVR to IFN-free therapies might ameliorate portal hypertension across all BL HVPG strata. However, amelioration of portal hypertension was less likely in patients with more advanced liver dysfunction. TE might be useful for the non-invasive evaluation of portal hypertension after SVR.

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Author names in bold designate shared co-first authorship.

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Tables

Table 1

	Group A, n=60	Group B, n=40	*P* value
Age, years	52.6 ±1.2	54.6 ±1.5	0.294
Sex			
Male	44 (73%)	25 (63%)	0.251
Female	16 (27%)	15 (38%)	
PNPLA3			
C/C	26 (43%)	19 (48%)	
C/G	27 (45%)	17 (43%)	0.918
G/G	7 (12%)	4 (10%)	
HCV-genotype			
1	39 (65%)	33 (83%)	
2	1 (2%)	0 (0%)	0.038
3	15 (25%)	2 (5%)	
4	5 (8%)	5 (13%)	
BL cirrhosis	56 (93%)	38 (95%)	1
Compensated	52 (93%)	36 (95%)	0.535
Decompensated	4 (7%)	2 (5%)	
BL CP			
Stage A	47 (84%)	30 (79%)	0.538

Stage B	9 (16%)	8 (21%)	
BL MELD			
Points	8 (7/9)	7.5 (7/9.25)	0.968
<10 points	46 (82%)	29 (76%)	0.49
Previous variceal bleeding	3 (5%)	0 (0%)	0.27
Varices	20 (36%)	18 (47%)	0.259
Small	13 (65%)	10 (56%)	0.552
Large	7 (35%)	8 (44%)	
Statin treatment	2 (3%)	2 (5%)	1
BL HVPG, mmHg	12 (9/16)	13.5 (9.25/17.75)	0.336
BL HVPG strata			
5-9mmHg	19 (32%)	10 (25%)	
10-15mmHg	21 (35%)	15 (38%)	0.763
≥16mmHg	20 (33%)	15 (38%)	
BL CSPH	41 (68%)	30 (75%)	0.472
BL HVPG ≥12mmHg	29 (48%)	21 (53%)	0.683
BL liver stiffness, kPa	21.3 (16.4/34)*	23.6 (16.3/35.4)	0.725
BL platelet count, GxL^{-1}	116 ±7	110 ±7	0.595
BL albumin, gxL^{-1}	39.6 ±0.6	39.1 ±0.9	0.615
BL bilirubin, $mgxdL^{-1}$	0.78 (0.57/1.12)	0.925 (0.63/1.16)	0.593
BL prothrombin time, %	75.6 ±2	76.1 ±3.3	0.886
Treatment-experienced	33 (55%)	29 (73%)	0.077
Treatment regimen			

SOF/RBV	8 (13%)	0 (0%)	
SOF/SMV	13 (16%)	8 (20%)	
SOF/DCV	35 (58%)	17 (43%)	0.012
SOF/LDV	8 (13%)	11 (28%)	
SMV/DCV	0 (0%)	1 (3%)	
3D	1 (2%)	3 (8%)	
Treatment duration			
12 weeks	17 (28%)	18 (45%)	
16 weeks	8 (13%)	7 (18%)	0.016
20 weeks	1 (2%)	4 (10%)	
24 weeks	34 (57%)	11 (28%)	

* Available in 57 patients.

Table 1. Patient and treatment characteristics of groups A and B.

Statistics: Continuous variables were reported as mean ±standard error of the mean or median (25^{th} percentile/75^{th} percentile), while categorical variables were reported as number of patients with (proportion of patients with) the certain characteristic. Student's t-test was used for group comparisons of continuous variables when applicable. Otherwise, Mann-Whitney U test was applied. Group comparisons of categorical

variables were performed using Chi squared or Fisher's Exact test.

Abbreviations:

HVPG hepatic venous pressure gradient

MELD model for end-stage liver disease

PNPLA3 patatin-like phospholipase domain-containing protein 3

HCV hepatitis C virus

BL baseline

CP Child-Pugh score

CSPH clinically significant portal hypertension

SOF sofosbuvir

RBV ribavirin

SMV simeprevir

DCV daclatasvir

LDV ledipasvir

3D 3D regimen

Table 2

	HVPG decrease, n=48	No HVPG decrease, n=12	*P* value
Age, years	53 ±1.2	51.3 ±3.5	0.564
Sex			
Male	35 (73%)	9 (75%)	1
Female	13 (27%)	3 (25%)	
PNPLA rs738409			
C/C	22 (33%)	4 (33%)	
G/C	20 (42%)	7 (58%)	0.603
G/G	6 (13%)	1 (8%)	
HCV-genotype			
1	31 (65%)	8 (67%)	
2	0 (0%)	1 (8%)	0.291
3	13 (27%)	2 (17%)	
4	4 (8%)	1 (8%)	
BL cirrhosis	45 (94%)	11 (92%)	1
Compensated	42 (93%)	7 (64%)	0.022
Decompensated	3 (7%)	4 (36%)	
BL CP			
Stage A	41 (91%)	6 (55%)	0.01
Stage B	4 (9%)	5 (45%)	
BL MELD			
Points	8 (6.5/9)	9 (8/10)	0.123
<10 points	7 (16%)	3 (27%)	0.393
BL HVPG, mmHg	12 (9/16)	13.5 (8.5/20.5)	0.51

BL HVPG strata			
6-10mmHg	16 (33%)	3 (25%)	
10-15mmHg	18 (38%)	3 (25%)	0.389
≥16mmHg	14 (29%)	6 (50%)	
CSPH	32 (67%)	9 (75%)	0.735
BL HVPG ≥12mmHg	23 (48%)	6 (50%)	0.879
BL liver stiffness*, kPa	20.9 (15.3/28.75)	33.8 (19.8/56.5)	0.075
Absolute change in liver stiffness*, kPa	-6.04 ±1.19	-1.3 ±2.86	0.097
Relative change in liver stiffness*, %	-24.7 ±3.7	-8.38 ±6.59	0.054
BL platelet count, GxL^{-1}	104 (76-160)	100 (70/163)	0.719
Change in platelet count, GxL^{-1}	5.04 ±3.36	5.17 ±5.92	0.986

* Available in 57 patients.

Table 2. Comparison of baseline (BL) characteristics and changes after antiviral therapy between patients with a HVPG decrease, or without.

Statistics: Continuous variables were reported as mean ±standard error of the mean or median (25^{th} percentile/75^{th} percentile), while categorical variables were reported as number of patients with (proportion of patients with) the certain characteristic. Student's t-test was used for group comparisons of continuous variables when applicable. Otherwise, Mann-Whitney U test was applied. Group comparisons of categorical

variables were performed using Chi squared or Fisher's Exact test.

Abbreviations:

HVPG hepatic venous pressure gradient

MELD model for end-stage liver disease

PNPLA3 patatin-like phospholipase domain-containing protein 3

HCV hepatitis C virus

BL baseline

CP Child-Pugh score

CSPH clinically significant portal hypertension

Table 3

Patient characteristics	HVPG decrease; 1st model				HVPG decrease; final model			
	HR	95%CI lower	upper	*P* value	HR	95% CI lower	upper	*P* value
Child-Pugh stage, B vs. A	0.129	0.021	0.81	0.029	0.103	0.02	0.514	0.006
Relative change in liver stiffness, per %	0.992	0.959	1.026	0.634	-	-	-	-

Table 3. Predictors of a hepatic venous pressure gradient (HVPG) decrease.

Statistics: Binary logistic regression analysis with backward elimination (final model) was used.

Figure legends

Figure 1. Study flow chart.

Abbreviations:
ACLD advanced chronic liver disease
IFN interferon
HVPG hepatic venous pressure gradient
SVR sustained virologic response
FU follow-up
TE transient elastography

Figure 2. Hepatic venous pressure gradient (HVPG) before (baseline [BL]) and after (follow-up [FU]) antiviral therapy.

(A) Evolution of HVPG in all patients included in group A. Patients with a decrease in HVPG are shown in blue, while patients in whom HVPG remained unchanged or increased are shown in red. Subgroups of patients with **(B)** subclinical portal hypertension (6-9mmHg), **(C)** 10-15mmHg, and **(D)** pronounced portal hypertension (≥16mmHg) at BL.

Statistics: Symbols indicate mean HVPG at BL, HVPG of individual patients, and mean HVPG at FU, from left to right. The error bars show the standard error of the mean. Intraindividual comparisons were performed using Student's t-test for

paired samples.

Figure 3. Receiver operating characteristic curves for the prediction of follow-up clinically significant portal hypertension (CSPH) by transient elastography.

(A) All patients included in group A. **(B)** Subgroup of patients with baseline CSPH.

Figure 1

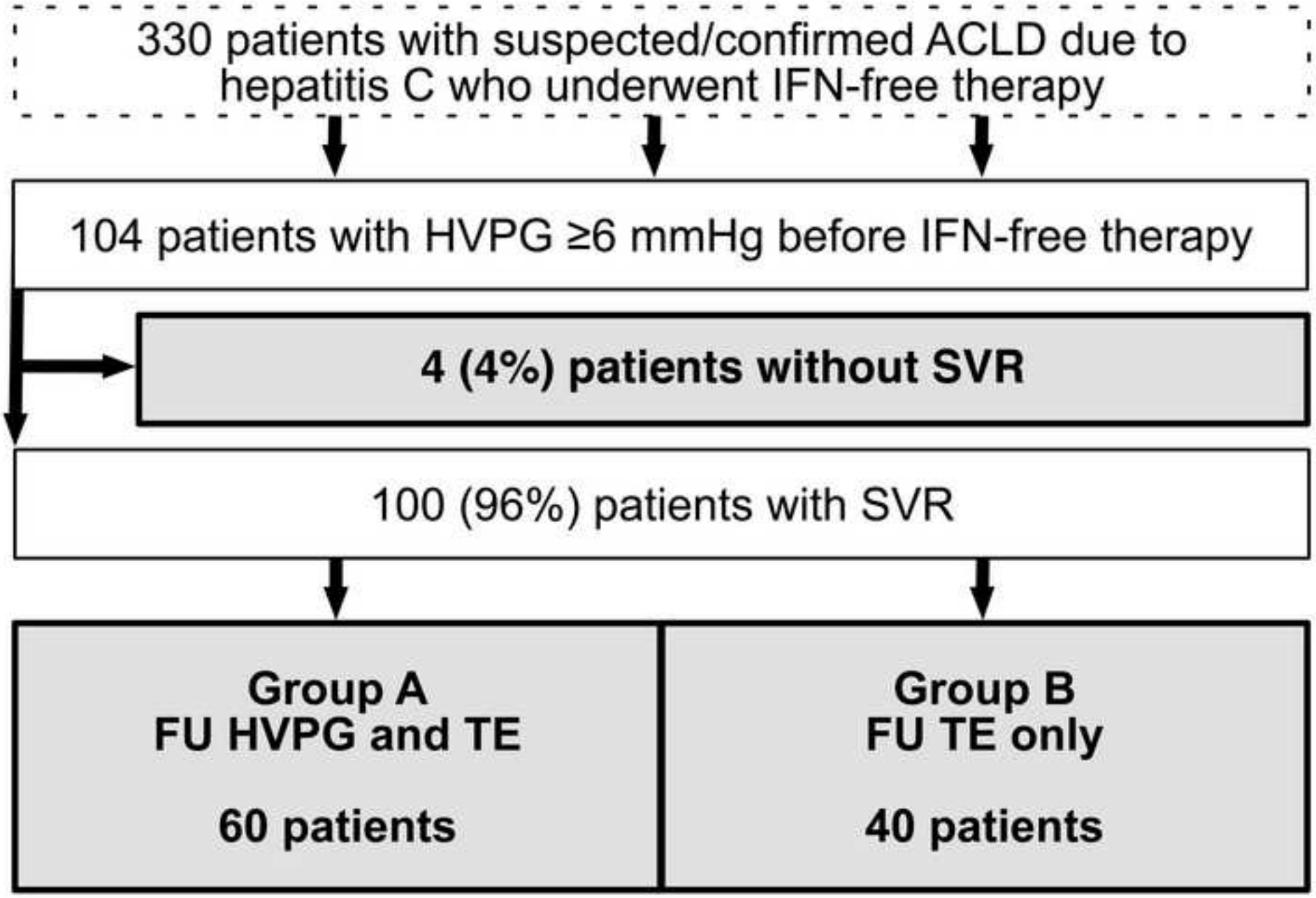
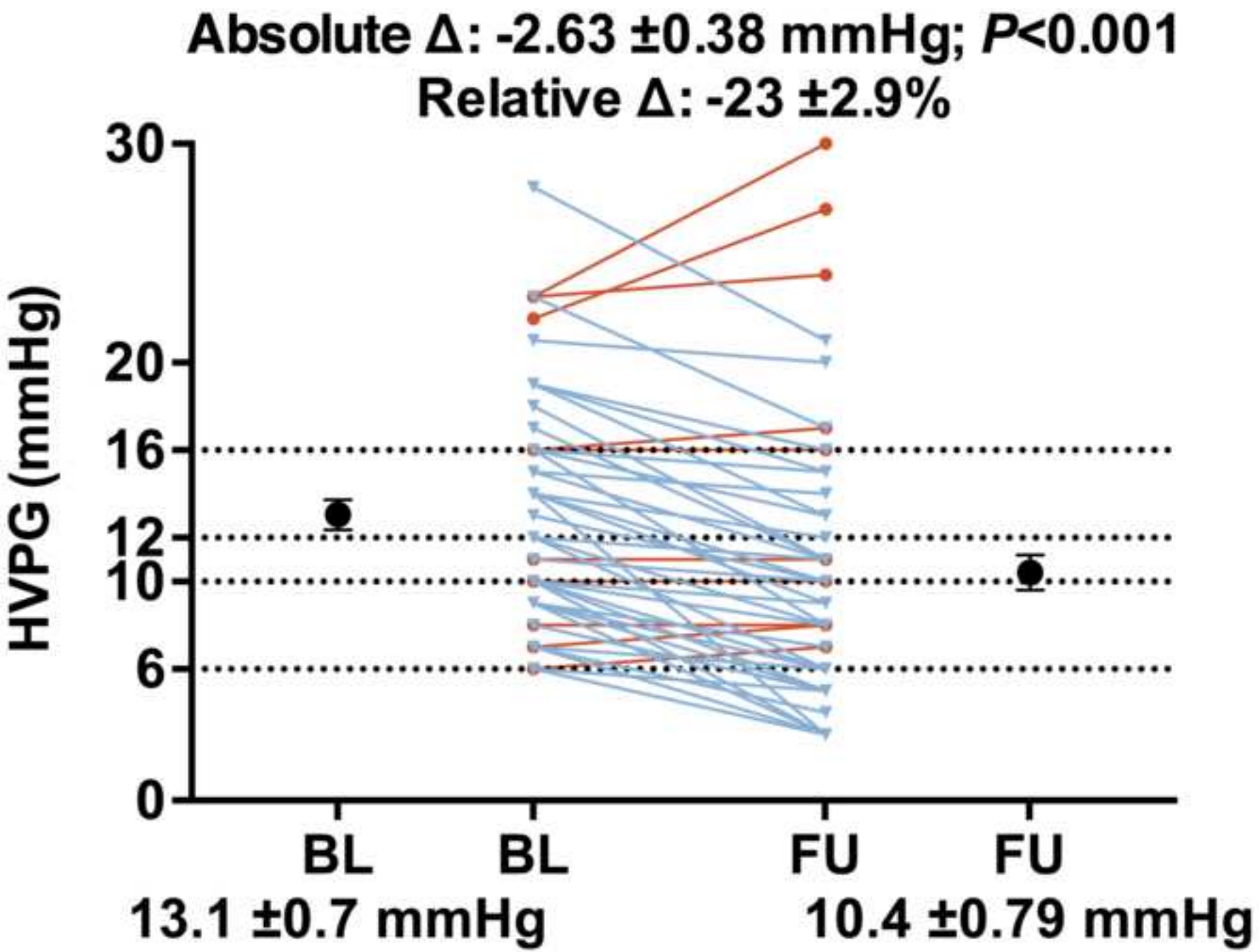


Figure 2A



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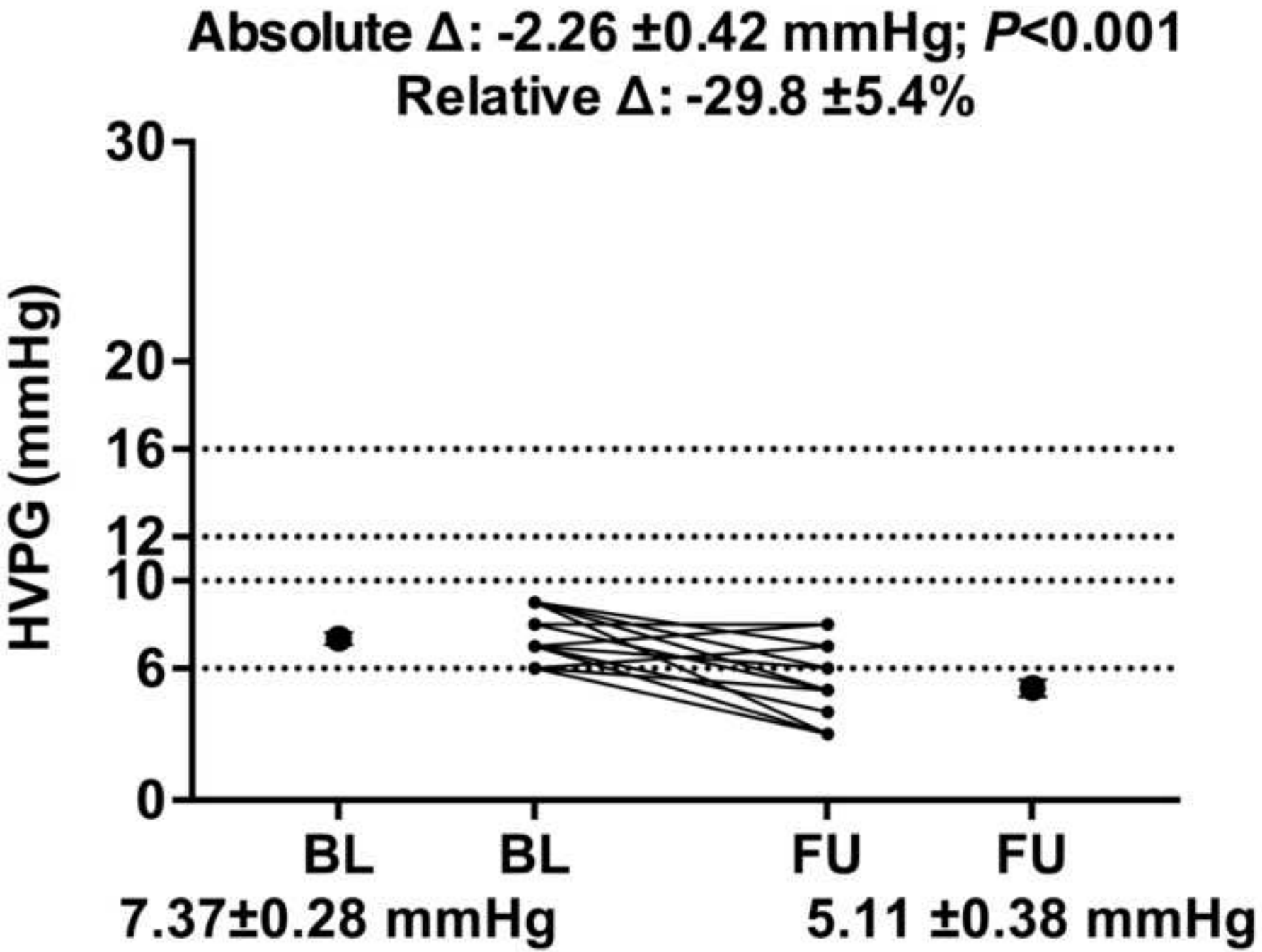

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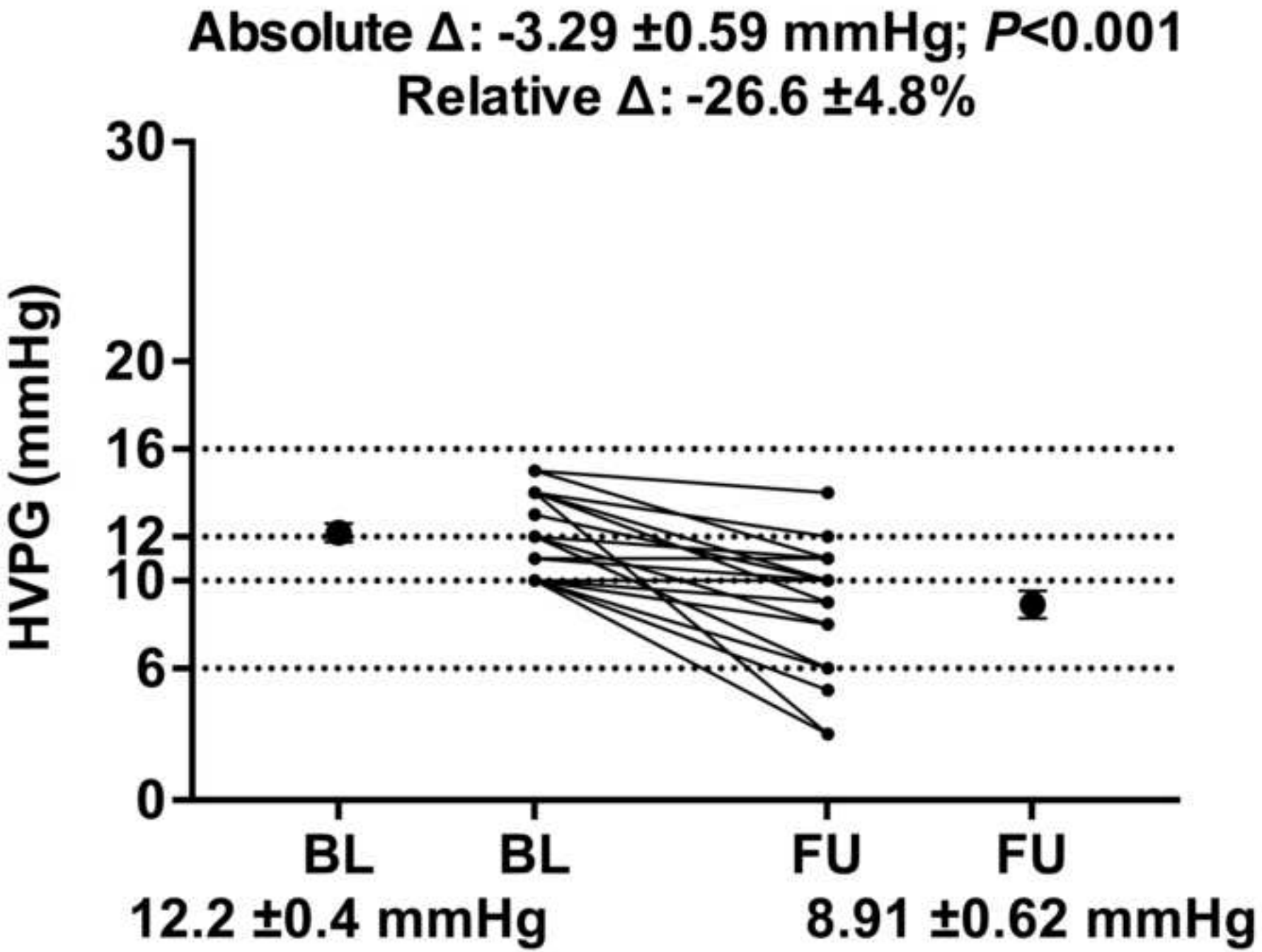

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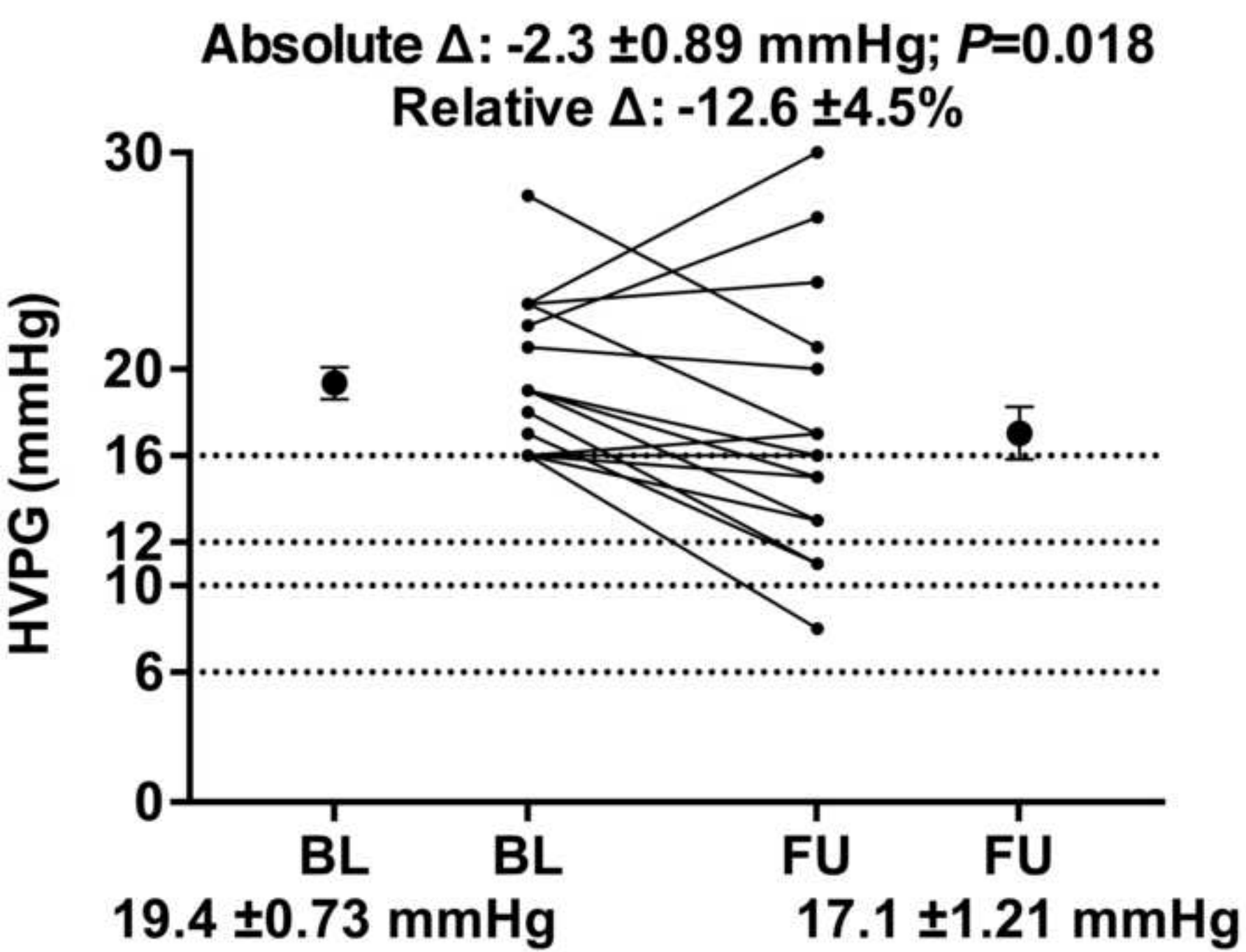


Figure 3A

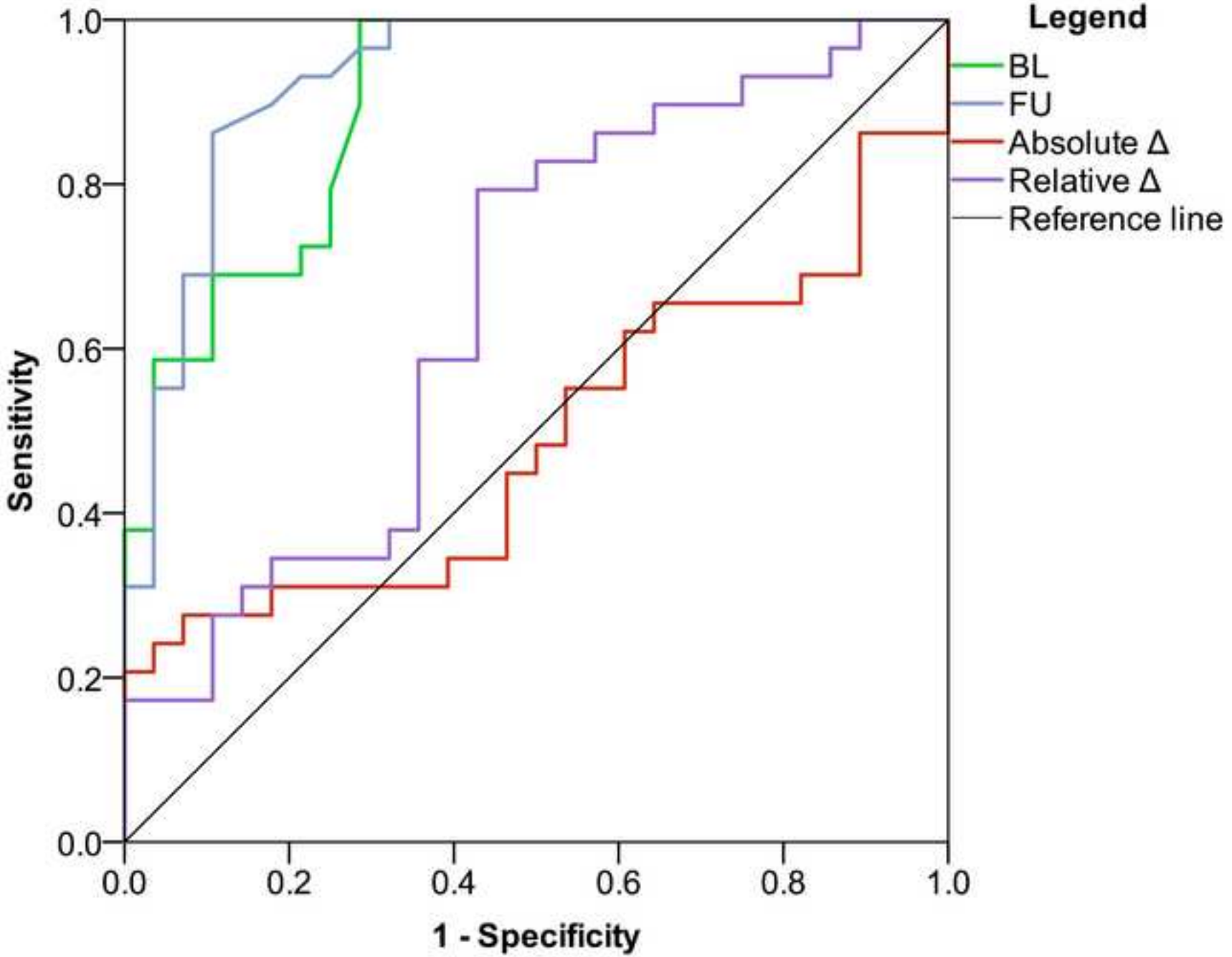
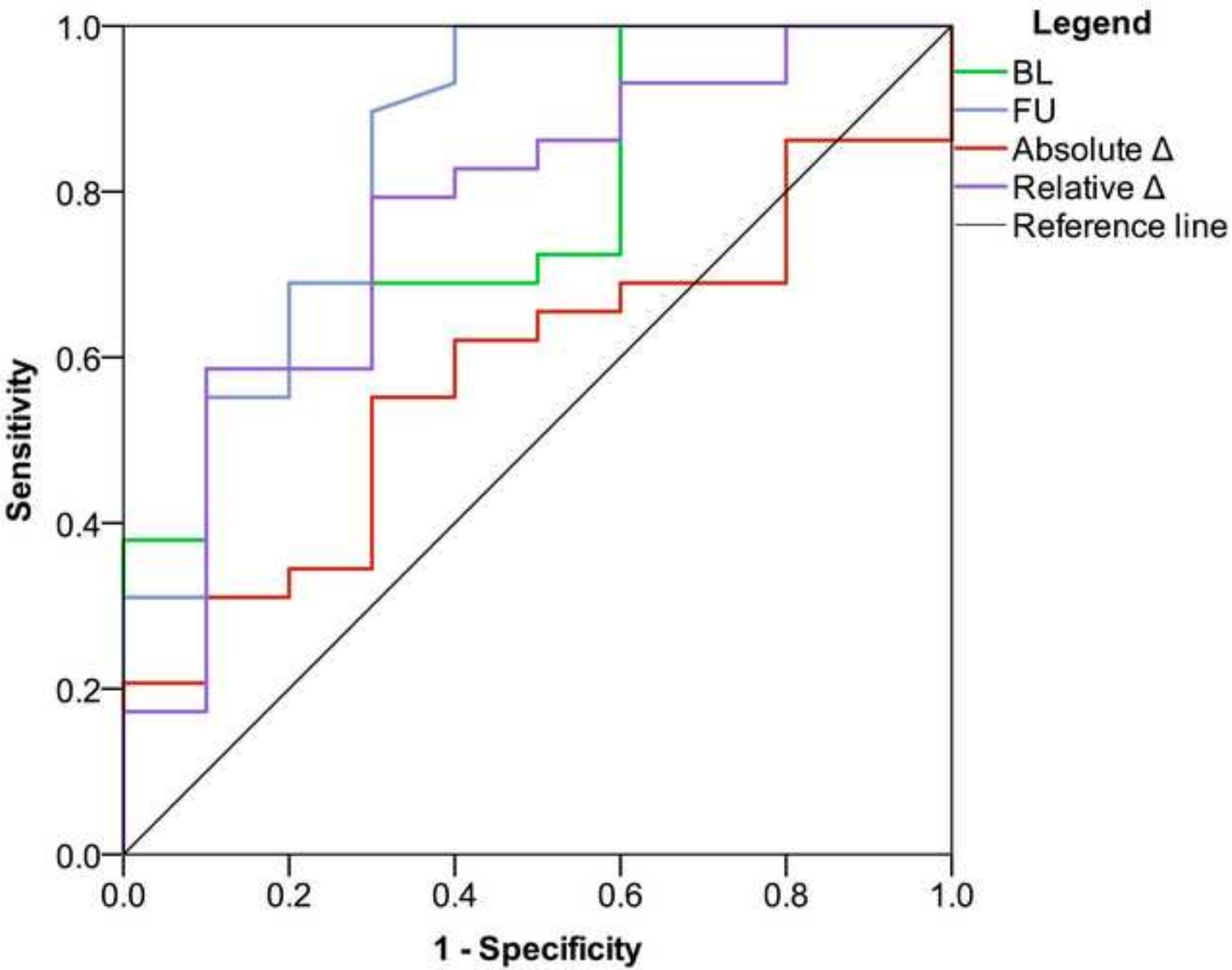


Figure 3B



Graphical Abstract