Decreasing von Willebrand Factor Levels Upon Nonselective Beta Blocker Therapy Indicate a Decreased Risk of Further Decompensation, Acute-on-chronic Liver Failure, and Death

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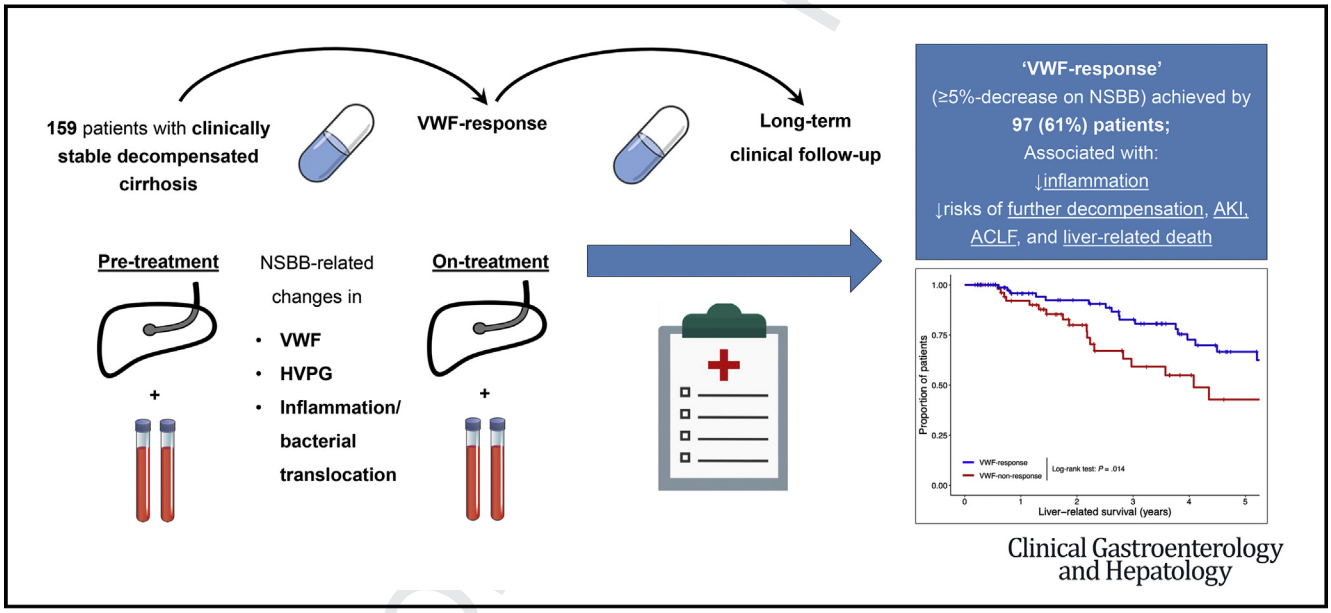

BACKGROUND & AIMS: Nonselective beta blockers (NSBBs) exert beneficial effects beyond lowering hepatic venous pressure gradient (HVPG), which may be particularly relevant in patients with decompensated cirrhosis (DC), in whom bacterial translocation and bacterial-induced systemic inflammation drive the development of complications such as acute-on-chronic liver failure (ACLF). We evaluated whether NSBB-related changes in von Willebrand factor (VWF) may serve as a biomarker for these effects.

METHODS: In this retrospective analysis, 159 prospectively characterized patients with clinically stable DC (ie, without acute decompensation) who underwent paired HVPG/VWF assessments before/on

Abbreviations used in this paper: ACLF, Acute-on-chronic liver failure; aHR, adjusted hazard ratio; AKI, acute kidney injury; AUROC, area under the receiver operating characteristic curve; BL, baseline; BT, bacterial translocation; CI, confidence interval; CRP, C-reactive protein; CSPH, clinically significant portal hypertension; DC, decompensated cirrhosis; FU, follow-up; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; IL-6, interleukin-6; IQR, interquartile range; LBP, lipopolysaccharide-binding protein; MAP, mean arterial pressure; NIT, noninvasive test; NSBB, nonselective beta blocker; OLT, orthotopic liver transplantation; PCT, procalcitonin; SBP, spontaneous bacterial peritonitis; SI, systemic inflammation; TIPS, transjugular intrahepatic portosystemic shunt; VWF, von Willebrand factor.

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NSBB therapy were classified as 'VWF responders' (as defined by a ≥5% decrease in VWF) versus 'VWF nonresponders.'

RESULTS: **There were no major differences in baseline characteristics between VWF responders (61%) and VWF nonresponders. VWF responders showed more pronounced decreases in inflammation (procalcitonin), whereas rates of HVPG response were similar. In line, NSBB-related changes in VWF correlated with the dynamics of bacterial translocation/inflammation (lipopolysaccharide-binding protein, C-reactive protein, and procalcitonin), rather than those of HVPG. Interestingly, VWF responders also showed less pronounced NSBB-related decreases in mean arterial pressure, suggesting an amelioration of systemic vasodilatation. Finally, VWF response was associated with decreased risks of further decompensation (adjusted hazard ratio [aHR], 0.555; 95% confidence interval [CI], 0.337-0.912; $P = .020$), ACLF (aHR, 0.302; 95% CI, 0.126-0.721; $P = .007$), and liver-related death (aHR, 0.332; 95% CI, 0.179-0.616; $P < .001$) in Cox regression models adjusted for prognostic factors including changes in HVPG.**

CONCLUSIONS: **Decreases in VWF upon NSBB therapy reflect their anti-inflammatory activity, are accompanied by less pronounced adverse effects on systemic hemodynamics, and are independently associated with a decreased risk of further decompensation, ACLF, and death. VWF response may discriminate between decompensated patients who benefit from NSBB treatment and have a favorable prognosis versus patients with poor outcomes.**

Keywords: Acute-on-chronic Liver Failure; Cirrhosis; Nonselective Beta Blocker; Portal Hypertension; von Willebrand Factor.

Nonselective beta blockers (NSBBs) are the cornerstone in the medical treatment of portal hypertension.[1] However, they are not equally effective throughout all patients.[2] There is an ongoing debate regarding the risk/benefit-ratio of NSBBs in decompensated patients[3,4] in whom NSBB treatment achieves less pronounced decreases in hepatic venous pressure gradient (HVPG).[5] Specifically, NSBB treatment has been associated with increased mortality in patients with refractory ascites[6] and spontaneous bacterial peritonitis (SBP),[7] as it may impair cardiac function and systemic hemodynamics[7,8] in a subgroup of patients, thereby possibly worsening kidney function[8] and promoting acute kidney injury (AKI).[7] Accordingly, there is a need for novel biomarkers to assess the expectable benefits in an individual patient, because the assessment of HVPG response is invasive and only available in few academic centers.[2] Moreover, NSBB therapy exerts additional nonhemodynamic effects,[9–11] which could be the mechanisms by which NSBB treatment prevents SBP[12] and ameliorates the course of acute-on-chronic liver failure (ACLF).[13,14]

Von Willebrand factor (VWF) is a marker of endothelial dysfunction and has primarily been studied as a noninvasive test (NIT) for clinically significant portal hypertension (CSPH) in patients with compensated advanced chronic liver disease.[15] Importantly, in patients with CSPH, high VWF is linked to poor prognosis, even after adjusting for the severity of portal hypertension (ie, HVPG),[16,17] indicating that VWF is more than a NIT for portal hypertension. Pathological bacterial translocation (BT) from the gut directly worsens endothelial dysfunction via toll-like receptor 4 activation by endotoxins/lipopolysaccharides,[18] thereby triggering the release of VWF into the portal and the systemic circulation.[19] Accordingly, VWF may also serve as a marker of BT and resulting systemic inflammation (SI) – important pathophysiologic mechanisms that are particularly relevant in decompensated cirrhosis (DC) as they drive the development of further hepatic decompensation (ie, 'unstable decompensated cirrhosis') and are main determinants of ACLF development.[20]

The close association of VWF with the postulated nonhemodynamic effects of NSBB therapy on the one hand, and clinical endpoints on the other hand, indicate that VWF changes in response to NSBB therapy may serve as a surrogate for its therapeutic benefit.

Thus, we evaluated the association between NSBB-related changes in VWF and the development of further decompensation, AKI, ACLF, and mortality in thoroughly characterized patients with DC who underwent paired HVPG and VWF measurements.

Methods

Patient Cohorts and Study Design

In this retrospective analysis, we included prospectively characterized patients (ie, standardized clinical and hemodynamic evaluation) who underwent paired assessments of HVPG and VWF in the course of primary/secondary prophylaxis of variceal bleeding at the Vienna Hepatic Hemodynamic Lab of the Medical University of Vienna between 2006 and 2019 and who

fulfilled the following criteria: (1) HVPG >12 mm Hg at baseline (BL; ie, without NSBB treatment); (2) stable NSBB intake at the time of follow-up (FU) (NSBB HVPG) measurement with a maximum time interval of 90 days between BL and NSBB measurements. This time interval was chosen to minimize the impact of the natural history of the underlying liver disease on the obtained measurements. Importantly, (3) only outpatients with clinically stable DC at BL were included, as evident from a history of hepatic decompensation in the past with no evidence of acute decompensation at BL.

Patients with a history of: (1) occlusive portal vein thrombosis, (2) noncirrhotic portal hypertension, (3) hepatocellular carcinoma (HCC), (4) transjugular intrahepatic portosystemic shunt (TIPS), or (5) orthotopic liver transplantation (OLT), as well as (6) bacterial infection/antibiotic treatment except for rifaximin at the time of BL or NSBB measurement were excluded.

Information on TIPS, OLT, events indicating further hepatic decompensation, AKI, ACLF, or death were recorded. Moreover, information on risk-modifying events/treatments during FU (ie, diagnosis of HCC, alcohol abstinence in alcoholic liver disease, or initiation of antiviral therapy), was obtained.

Moreover, we recruited stable DC patients with paired VWF measurements but without NSBB treatment initiation from the prospective Vienna Cirrhosis Study (VICIS, NCT: NCT03267615). Details are provided in the Supplementary Methods.

What You Need to Know

Background

Nonselective beta blockers (NSBBs) may prevent acute-on-chronic liver failure development by modulating systemic inflammation. Biomarkers for monitoring these nonhemodynamic effects are lacking. von Willebrand factor (VWF) indicates systemic inflammation-induced endothelial dysfunction and predicts outcomes, independently of portal hypertension severity.

Findings

Decreases in VWF upon NSBB therapy reflect their anti-inflammatory activity and are accompanied by less pronounced adverse effects on systemic hemodynamics. 'VWF responders' showed lower rates of decompensation, acute-on-chronic liver failure, and liver-related death.

Implications for patient care

VWF response may discriminate between decompensated patients who benefit from NSBB treatment and have a favorable prognosis versus patients with poor outcomes.

Measurement of HVPG and VWF and Biomarkers of BT and SI

HVPG measurements were conducted following a standardized operating procedure described elsewhere.[21] Laboratory tests were performed at the ISO-certified Department of Laboratory Medicine of the Medical University of Vienna. VWF was measured by a latex agglutination assay (STA LIATEST vWF, Diagnostica Stago, Asnieres, France). Assessments of precision/intermediate precision (Supplementary Methods) yielded a coefficient of variation of approximately 3%.

Definition of DC

History of variceal bleeding or past/current ascites/hepatic encephalopathy defined DC.[22] See Supplementary Methods for details.

Definition of VWF Response

A relative change in VWF by −2% was the best cutoff for liver-related mortality during FU, as determined by Youden's index. However, due to the precision/intermediate precision of the assay and observations in 'untreated' patients, decreases in VWF ≥5% at the time of NSBB HVPG measurement identified 'VWF responders' in this proof-of-concept study.

Definition of Clinical Events During FU

Clinical events during FU that were considered in our analyses comprised variceal bleeding, development/admission due to hepatic encephalopathy, paracentesis/TIPS implantation, SBP or other major infections, ACLF, and liver-related death.[22] More detailed information is given in the Supplementary Methods.

Statistical Analysis

Statistical analysis was conducted using R 4.0.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism 8 (GraphPad Software, La Jolla, CA). To evaluate the prognostic value of relative VWF changes from BL to NSBB HVPG, time-dependent under the receiver operating characteristic (AUROC) curve analysis was performed. For time-to-event analyses, 2 different approaches were applied: (1) Kaplan-Meier method and log-rank test stratified by VWF response group status and (2) multivariate Cox regression incorporating a time-dependent variable for VWF response. A landmark of 30 days after NSBB HVPG for the assignment of VWF response status was chosen for both strategies to reduce bias from our analyses,

which is further explained in the Supplementary Methods.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of the Medical University of Vienna (Nos.1493/2016;1971/2016). No written informed consent was required for this retrospective analysis, whereas informed consent was obtained for inclusion in the VICIS study.

Results

Patient/Treatment Characteristics

One hundred fifty-nine patients were included. Detailed information on patient/treatment characteristics is provided in the Supplementary Tables 1 and 2).

The median time between BL and NSBB HVPG was 33 days (interquartile range [IQR], 28-41 days).

Of note, no patient achieved alcohol abstinence or was prescribed antiviral therapy between BL and NSBB assessments, nor was any patient treated with antibiotics besides chronic rifaximin therapy for hepatic encephalopathy (n = 11; 6.9%). Seven patients (4.4%) were on chronic statin treatment at BL, which remained unchanged from BL to NSBB measurement.

Dynamics of VWF in Stable DC Without NSBB Therapy Initiation

There were no spontaneous dynamics in VWF (median relative change, 1% [IQR, −3 to 4%]; $P = .888$), and 'VWF-response' was uncommon (n = 11/66; 16.7%) (Supplementary Methods).

NSBB Treatment-related Changes in HVPG/VWF and Systemic Hemodynamics

NSBB treatment was associated with pronounced relative changes in HVPG (median, −11.1%; 21 mm Hg [IQR, 18-24 mm Hg] at BL to 18 mm Hg [IQR, 15-21 mm Hg] at NSBB HVPG; $P < .001$), VWF (median, −8.0%; 350% [IQR, 291%-420%] at BL to 322% [IQR, 253%-398%] at NSBB HVPG; $P < .001$), and C-reactive protein (CRP) (n = 138; median, −19.8%; 0.50 mg/dL [IQR, 0.20-1.22 mg/dL] at BL to 0.44 mg/dL [IQR, 0.17-0.88 mg/dL] at NSBB HVPG; $P < .001$). Of note, the relative change in VWF clearly differed from the above-mentioned 'untreated' cohort ($P < .001$).

Information on systemic hemodynamics at NSBB HVPG and paired comparisons to BL values are shown in Supplementary Tables 1 and 2.

Comparison of Dynamics of HVPG, VWF, and Systemic Hemodynamics Between VWF Responders and VWF Nonresponders

Interestingly, relative changes in HVPG (VWF responders, −11.1% [IQR, −23.5% to −3.9%] vs VWF nonresponders, −11.5% [IQR, −24.7% to −3.5%]; $P = .973$) and the proportion of patients achieving HVPG response (VWF responders, 48 [49.5%] vs. VWF nonresponders, 29 [56.8%]; $P = .864$) (Table 1) were similar between VWF response groups.

The median relative decrease in VWF levels in the VWF response group was −14.7% (IQR, −21.4 to −10.0%), whereas VWF nonresponders showed a median relative increase of 3.2% (IQR, −0.4% to 10.3%) from BL to NSBB HVPG measurement ($P < .001$).

Interestingly, patients with VWF response showed less pronounced NSBB therapy-associated relative decreases in mean arterial pressure (MAP) (VWF responders, −8.0% [IQR, −15.0 to 0%] vs VWF nonresponders, −12.2% [IQR, −18.5% to −2.8%]; $P = .044$).

Comparison of BL Treatment Characteristics Between VWF Responders and VWF Nonresponders

NSBB treatment initiation was paralleled by ≥5% VWF decreases from BL to NSBB measurement ('VWF response') in 97 patients (61.0%). Of note, there were no significant differences in BL HVPG, severity of hepatic dysfunction, or BL levels of markers of SI (ie, CRP, procalcitonin [PCT], and interleukin-6 [IL-6]), and BT (ie, lipopolysaccharide-binding protein [LBP]) between the 2 groups (Table 1).

Notably, a higher proportion of patients with VWF response were on carvedilol (VWF responders, 75.3% vs VWF nonresponders, 54.8%; $P = .012$).

Correlates of VWF as Well as its NSBB Treatment-related Changes

BL VWF correlated positively with BL HVPG (Spearman's ρ, 0.192; $P = .016$) and BL CRP (ρ, 0.305; $P < .001$) as well as trend-wise with BL PCT (ρ, 0.312; $P = .064$) and BL IL-6 (ρ, 0.334; $P = .051$), whereas no correlation with BL LBP (ρ, 0.021; $P = .907$) was found (Table 1). A heat map of correlations between BL values of VWF, HVPG, and markers of BT/SI is shown in Figure 1.

VWF response was accompanied by stronger NSBB therapy-related relative decreases in PCT (available in n = 31; VWF responders, −20.2% [IQR, −34.1% to −3.8%] vs VWF nonresponders, 20.0% [IQR,11.7%–36.4%]; $P = .001$) and CRP (available in n = 138; VWF responders, −26.2% [IQR, −50.0% to 11.8%] vs VWF nonresponders, −3.5% [IQR, −33.1% to 10.0%]; $P = .050$), and a tendency towards stronger decreases in LBP (available in n = 32; VWF responders, −8.2% [IQR, −22.7% to 7.4%] vs VWF nonresponders, 4.6% [IQR, −8.4% to 13.0%]; $P = .111$). In

Table 1. Comparison of Patient Characteristics at BL (ie, Before NSBB Therapy), NSBB Treatment Characteristics, and Treatment-related Changes Between VWF Nonresponders (<5% Decrease in VWF Levels from BL to NSBB HVPG) and VWF Responders' (≥5% Decreasing VWF levels from BL to NSBB HVPG)

Patient characteristic	VWF nonresponders, (n = 62)	VWF responders, (n = 97)	*P*
Sex, male/female (% male)	49/13 (79.0)	69/28 (71.1)	.355
Age, *years*	55.9 ± 10.7	55.4 ± 10.4	.795
BMI, kg/m^2	25.8 (23.4–29.8)	24.7 (21.6–28.1)	.121
Etiology of ACLD			
ALD	41 (66.1)	62 (63.9)	.324
Viral	8 (12.9)	7 (7.2)	
ALD + viral	4 (6.5)	13 (13.4)	
NAFLD	4 (6.5)	3 (3.1)	
Other/cryptogenic	5 (8.1)	12 (12.4)	
Alcohol consumption			
Abstinent	42 (67.7)	65 (67.0)	.466
Below threshold[a]	6 (9.7)	5 (5.2)	
Above threshold[a]	14 (22.6)	27 (27.8)	
BL CTP score, *points*	8 (7–9)	7 (6–9)	.204
NSBB CTP score, *points*	7 (6–9)	7 (6–8)	.080
BL MELD (2016), *points*	11 (10–16)	12 (10–18)	.399
NSBB MELD (2016), *points*	12 (10–17)	11 (9–15)	.205
BL albumin, *g/L*	32.10 (29.92–35.80)	33.40 (30.20–37.80)	.271
BL bilirubin, *mg/dL*	1.59 (1.07–2.45)	1.75 (1.06–2.60)	.846
BL INR	1.3 (1.2–1.5)	1.4 (1.2–1.5)	.767
BL creatinine, *mg/dL*	0.82 (0.72–0.98)	0.76 (0.66–1.00)	.351
BL sodium, *mmol/L*	136 (134–138)	137 (133–140)	.868
Varices			
Small	25 (40.3)	29 (29.9)	.237
Large	37 (59.7)	68 (70.1)	
History of bleeding	24 (38.7)	35 (36.1)	.868
Ascites			
No	9 (14.5)	22 (22.47)	.429
Mild/moderate	42 (67.7)	61 (62.9)	
Severe/refractory	11 (17.7)	14 (14.4)	
HE	22 (35.5)	28 (28.9)	.631
Type of NSBB therapy			
Carvedilol	34 (54.8)	73 (75.3)	**.012**
Propranolol	28 (45.2)	24 (24.7)	
BL MAP, *mm Hg*	100 (91–112)	98 (90–107)	.362
BL MAP <65 mm Hg	0 (0)	0 (0)	N/A
NSBB MAP, *mm Hg*	90 (80–96)	90 (84–100)	.368
NSBB MAP <65 mm Hg	4 (6.5)	2 (2.1)	.322
ΔMAP, absolute, *mm Hg*	−13 (−19 to −3)	−8 (−15 to 0)	.064
ΔMAP, relative, %	−12.2 (−18.5 to −2.8)	−8.0 (−15.0 to 0)	**.044**
BL HVPG, *mm Hg*	21 (17–25)	21 (18–24)	.577
NSBB HVPG, *mm Hg*	18 (15–21)	18 (15–21)	.914
ΔHVPG, absolute, *mm Hg*	−2 (−5 to −1)	−2 (−5 to −1)	.960
ΔHVPG, relative, %	−11.5 (−24.7 to −3.5)	−11.1 (−23.5 to −3.9)	.973

Table 1. Continued

Patient characteristic	VWF nonresponders, (n = 62)	VWF responders, (n = 97)	*P*
HVPG decrease ≥10%	34 (54.8)	57 (58.8)	.746
HVPG decrease ≥20%	22 (35.5)	34 (35.1)	1.000
HVPG response[b]	29 (56.8)	48 (49.5)	.864
BL VWF, %	328 (260–410)	366 (304–466)	**.016**
NSBB VWF, %	361 (284–419)	305 (246–378)	**.024**
ΔVWF, absolute, %	9 (−2 to 33)	−53 (−85 to −29)	**< .001**
ΔVWF, relative, %	3.2 (−0.4 to 10.3)	−14.7 (−21.4 to −10.0)	**< .001**
BL CRP,[c] *mg/dL*	0.50 (0.17–1.21)	0.53 (0.21–1.22)	.947
NSBB CRP,[c] *mg/dL*	0.53 (0.17–1.13)	0.37 (0.18–0.84)	.172
ΔCRP, absolute, *mg/dL*	−0.02(−0.20 to 0.03)	−0.09 (−0.42 to 0.02)	.148
ΔCRP, relative, %	−3.5 (−33.1 to 10.0)	−26.2 (−50.0 to 11.8)	**.050**
BL PCT,[d] *ng/mL*	0.10 (0.06–0.16)	0.13 (0.11–0.20)	.215
NSBB PCT,[d] *ng/mL*	0.15 (0.07–0.19)	0.09 (0.06–0.14)	.125
ΔPCT, absolute, *ng/mL*	0.01 (0.01–0.04)	−0.02 (−0.04 to −0.01)	**.008**
ΔPCT, relative, %	20.0 (11.7–36.4)	−20.2 (−34.1 to −3.8)	**.001**
BL IL-6,[e] *pg/nL*	10.85 (7.88–20.49)	15.46 (7.79–33.27)	.614
NSBB IL-6,[e] *pg/nL*	14.88 (7.40–21.65)	11.83 (7.58–20.39)	.556
ΔIL-6, absolute, *pg/nL*	−2.52 (−4.19 to 0.99)	−0.26 (−10.89 to 4.95)	.858
ΔIL-6, relative,%	−13.4 (−30.0 to 7.5)	−8.3 (−43.1 to 25.4)	.921
BL LBP,[f] *μg/mL*	6.28 (5.16–8.34)	8.32 (6.48–9.63)	.129
NSBB LBP,[f] *μg/mL*	6.53 (5.02–9.76)	7.32 (5.46–8.43)	.683
ΔLBP, absolute, *μg/mL*	0.22 (−0.62 to 0.83)	−0.66 (−1.93 to 0.42)	.073
ΔLBP, relative, %	4.6 (−8.4 to 13.0)	−8.2 (−22.7 to 7.4)	.111

Note: Data are presented as number (%), mean ± standard deviation, or median (interquartile range). Boldface *P* values indicate statistical significance.
ACLD, Advanced chronic liver disease; ALD, alcoholic liver disease; BL, baseline; BMI, body mass index; CRP, C-reactive protein; CTP, Child-Turcotte-Pugh; FU, follow-up; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; IL-6, interleukin-6; INR, international normalized ratio; LBP, lipopolysaccharide-binding protein; MAP, mean arterial pressure; MELD, Model of End-stage Liver Disease; NAFLD, non-alcoholic fatty liver disease; NSBB, nonselective beta blocker; PCT, procalcitonin; VWF, von Willebrand factor
[a]>30 g/day and >20 g/day for males and females, respectively.
[b]Defined by an HVPG decrease to ≤12 mm Hg or by ≥10% in primary and ≥20% in secondary prophylaxis of variceal bleeding.
[c]CRP values available in n = 146 at BL and in n = 143 at FU.
[d]PCT values available in n = 36 at BL and in n = 36 at FU.
[e]IL-6 values available in n = 35 at BL and in n = 37 at FU.
[f]LBP values available in n = 35 at BL and in n = 38 at FU.

contrast, there was no difference in relative changes in IL-6 (available in n = 32; VWF responders, −8.3% [IQR, −43.1% to 25.4%] vs VWF nonresponders, −13.4% [IQR, −30.0% to 7.5%]; $P = .921$).

Furthermore, the magnitude of VWF decrease was linked to the dynamics of several markers of BT/SI (Figure 2).

Finally, although relative changes in VWF levels did neither correlate with relative changes in HVPG (Spearman's ρ, −0.087; $P = .278$) nor with relative changes in IL-6 (ρ, 0.092; $P = .615$), we observed direct correlations of weak (CRP: ρ, 0.257; $P = .002$; LBP: ρ, 0.352; $P = .049$) to moderate strength (PCT: ρ, 0.661; $P < .001$) with relative changes in markers of BT/SI.

Clinical FU

Patients were followed-up for a median of 25.1 months (IQR, 9.8–46.0 months). Detailed information about FU events is provided in the Supplementary Methods.

Prognostic Value of NSBB Therapy-related VWF Response for Further Decompensation, AKI Development, and ACLF Development, as Well as Liver-related Death

In time-dependent AUROC analysis, relative NSBB therapy-related changes in VWF from BL to NSBB

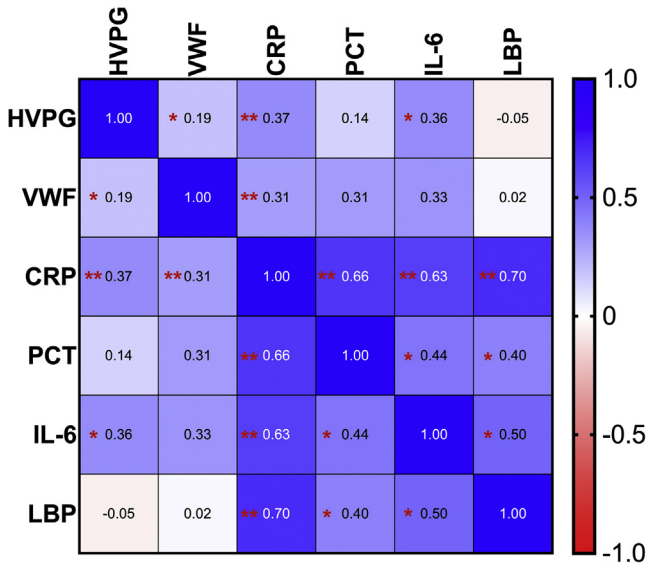

Figure 1. Correlations of BL (ie, before NSBB therapy) values of HVPG, VWF, and biomarkers of BT/SI. CRP, PCT, IL-6, and LBP values were available in n = 146, n = 36, n = 35, and n = 35 patients, respectively. *Indicates *P*-values < .05, whereas **denotes *P*-values < .001.

measurement were of superior prognostic value as compared with changes in CRP (Figure 3), which did not yield prognostic information in this context.

Nineteen patients developed events or were censored before the landmark of 30 days after NSBB HVPG (Supplementary Figure 1), and thus were excluded from Kaplan-Meier/log-rank test analyses. In the remaining 140 patients, we observed significantly lower incidences of further decompensation ($P = .046$), AKI ($P = .010$), ACLF ($P = .001$), and liver-related death ($P = .014$) in VWF responders (Figure 4).

In a multivariate Cox regression model considering VWF response upon NSBB therapy initiation as a time-dependent covariate (Supplementary Figure 1), the achievement of VWF response was independently associated with a decrease in the risks of further decompensation (adjusted hazard ratio [aHR], 0.555; 95% confidence interval [CI], 0.337–0.912; $P = .020$; adjusted for BL VWF, Child-Turcotte-Pugh stage, serum creatinine, BL HVPG, and relative HVPG change from BL to NSBB HVPG).

In addition, VWF response was found to be associated with a reduced risk of AKI (aHR, 0.367; 95% CI, 0.167–0.803; $P = .012$); adjusted for the same factors as above) and was also independently protective of ACLF development (aHR, 0.302; 95% CI, 0.126–0.721; $P = .007$; adjusted for the same factors as above).

Finally, VWF response was found to be independently associated with a profoundly decreased risk of liver-related mortality (aHR, 0.332; 95% CI, 0.179–0.616; $P < .001$; adjusted for the same factors as above).

Detailed information regarding the multivariate Cox regression models for the respective outcomes of interest are shown in Supplementary Table 3.

Discussion

We observed VWF changes following NSBB therapy initiation in clinically stable outpatients with DC, which were independent of those of HVPG. VWF changes correlated with the dynamics in biomarkers of BT/SI, confirming our previous findings obtained in a one-time assessment.[17] Importantly, patients who showed a decrease in VWF after NSBB treatment initiation (ie, 'VWF responders') had a strongly reduced risk of further decompensation, AKI development, and ACLF development, even after adjusting for other prognostic factors, including HVPG response. Finally, the risk of liver-related mortality was more than halved in VWF responders, indicating that ≥5% VWF decreases upon NSBB treatment translate into a clinically meaningful benefit.

Although NSBB therapy has recently been found to prevent the development of DC,[23,24] its beneficial effects are especially well-established and important in secondary prophylaxis and/or once DC has developed: In these patients, NSBB therapy is the key component of combination treatment, as it reduces mortality.[25,26] Moreover, NSBB therapy is particularly effective if HVPG response is obtained[2] – a finding which also extends to the subgroup of patients with ascites (ie, patients who do not necessarily have a history of bleeding).[27] However, the sequential HVPG measurements that are required to assess hemodynamic response to NSBB therapy are invasive, resource-intensive, and not broadly available. The diagnostic performance of NIT (ie, spleen stiffness measurement) for HVPG response varied considerably throughout studies,[28,29] and most importantly, NSBB-related changes in spleen stiffness measurement did not translate into improved clinical outcomes.[28] Accordingly, there is currently no NIT that may serve as a surrogate for the efficacy of NSBB therapy.[15]

NSBB therapy seems to exert additional, so-called nonhemodynamic effects, which are independent of hemodynamic response.[10] Moreover, a post-hoc analysis of the CANONIC study[13] suggested that NSBB therapy ameliorates the course of ACLF, and carvedilol treatment decreased 28-day mortality in patients with ACLF by preventing SBP/infections, AKI, and ACLF progression in a randomized controlled trial.[14] Of note, clinically applicable surrogate markers to monitor these important, likely nonhemodynamic effects of NSBB treatment have yet to be developed.

Based on previous observations on VWF that are outlined in the introduction section, we hypothesized that VWF decreases upon NSBB treatment initiation reflect beneficial nonhemodynamic effects, and thus, may be of prognostic value.

VWF decreased by ≥5% in 61% of NSBB-treated patients, a number that was profoundly different from the rate of spontaneous VWF decreases ≥5% in stable

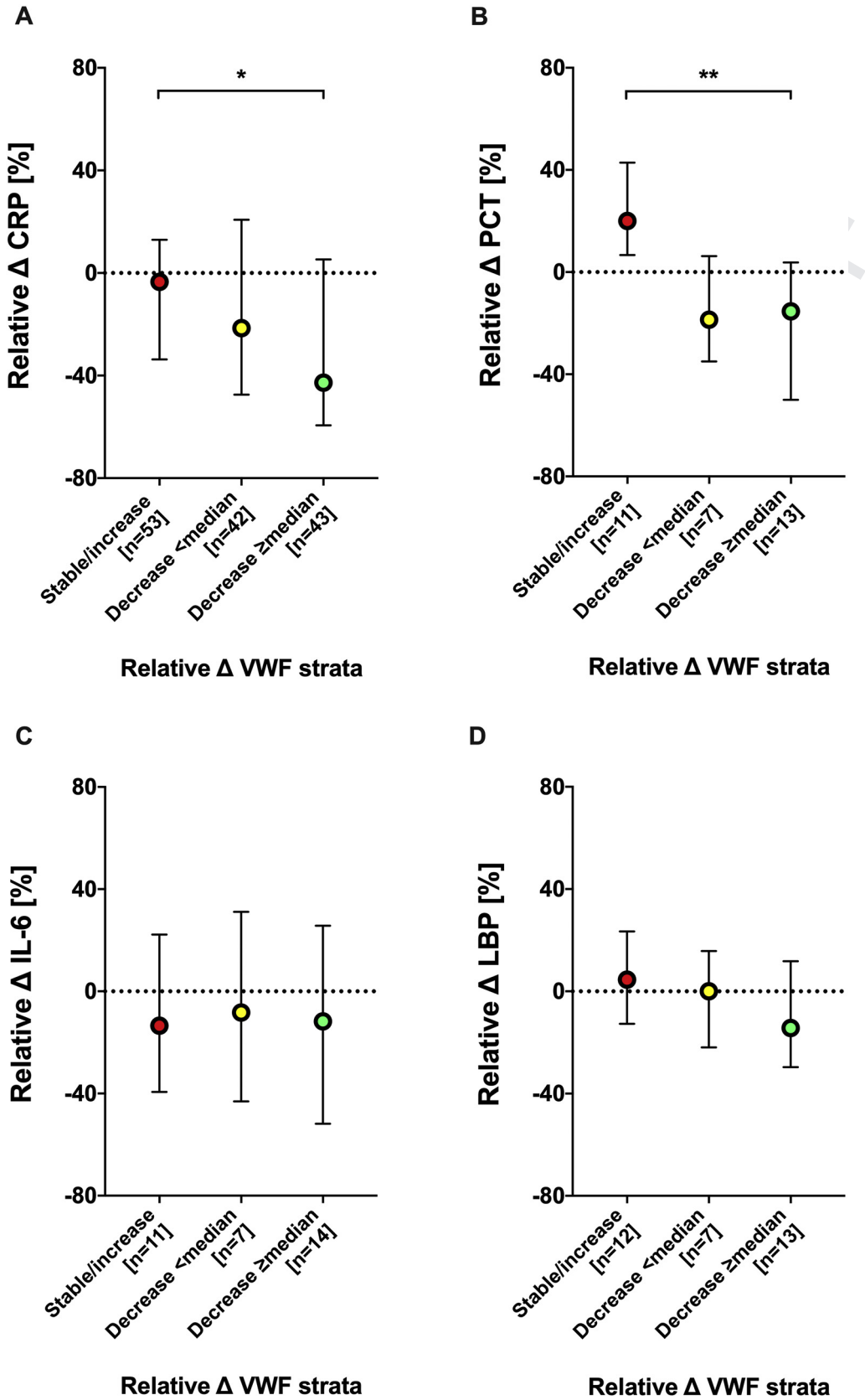

Figure 2. Comparison of relative changes in markers of bacterial translocation and BT/SI ([*A*] CRP, n = 138; [*B*] PCT, n = 31; [*C*] IL-6, n = 32; and [*D*] LBP, n = 32) upon NSBB therapy, stratified by the dynamics of VWF: Stable/increasing VWF levels 'VWF nonresponders' versus reductions below or above/equal to the median relative VWF decrease (14.7%) that was observed among 'VWF responders' (ie, the group of patients who showed NSBB treatment-related decreases in VWF).

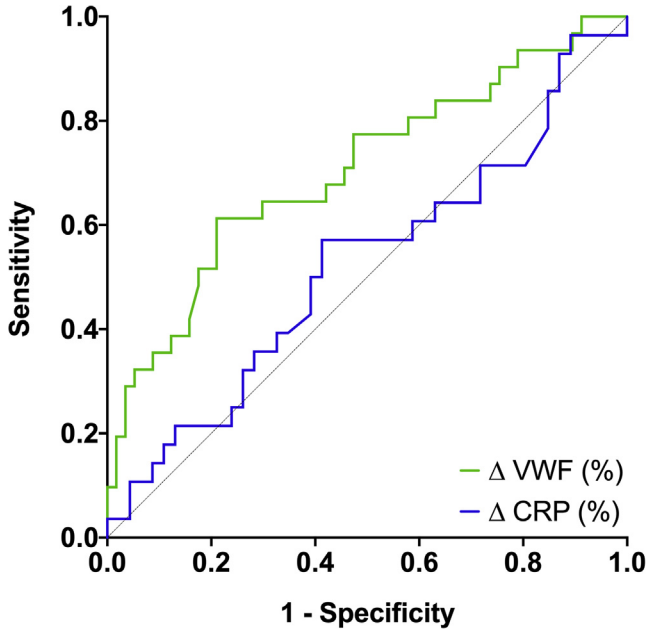

Figure 3. Time-dependent receiver operating characteristic curves for the prediction of liver-related death within 3 years of FU by relative changes in VWF (AUROC for relative Δ, 0.707; 95% CI, 0.594–0.821) and CRP (AUROC for relative Δ, 0.538; 95% CI, 0.394–0.682) upon NSBB treatment initiation.

'untreated' patients with DC and higher than the HVPG response rate in our study (48%) and previous reports.[2] Of note, the higher proportion of patients who achieved VWF response also fits the previous notion that the proportion of patients who benefit from NSBB therapy may exceed the rate of hemodynamic response.[30]

To minimize the impact of the natural history of the underlying liver disease[31,32] or intercurrent conditions[33] on VWF levels, we restricted the time interval between the assessments, evaluated only clinically stable outpatients (ie, without acute decompensation), and additionally excluded patients with bacterial infections or antibiotic treatments other than rifaximin. Although a causal relationship between NSBB treatment and changes in VWF cannot be proven due to the design of our study, we have made all reasonable effort to rule out potential confounding factors and also included a control group of stable 'untreated' DC patients, in whom the dynamics of VWF were clearly different. Moreover, this limitation is not in any way specific to our study, as it equally applies to landmark studies that established the prognostic value of chronic HVPG response to NSBB therapy – a generally accepted surrogate.[2]

Interestingly, NSBB therapy-related VWF changes were unrelated to those of HVPG, which may be explained by the weak correlation between HVPG and VWF at high values and by the increasing contribution of BT/SI in these patients. The substantially higher importance of BT/SI (vs portal hypertension) as a determinant of the dynamics of VWF is also supported by its (weak to moderate) correlations with (changes in) inflammatory markers.

Intriguingly, VWF responders also showed less pronounced NSBB therapy-related decreases in MAP, although carvedilol use was more common in this group. MAP reflects renal perfusion[8] and provides guidance for the safe use of NSBB therapy in patients with DC.[34] The observation of smaller NSBB-related decreases in MAP in VWF responders may be explained by the more pronounced amelioration of SI – and thus, systemic vasodilatation – upon NSBB therapy in these patients.

We evaluated the prognostic value of relative changes in VWF by time-dependent AUROC analysis for liver-related mortality and determined the optimal cutoff for defining VWF response by Youden's index, which was −2%. Since this is a first proof-of-concept study, we simply compared patients with or without a meaningful decrease (≥5%) in VWF in all further analyses. Of note, we also evaluated the relative changes in CRP – a readily available laboratory test for SI with profound prognostic implications in patients with CSPH[17] – as a comparator, which showed no association with liver-related mortality, highlighting the particular relevance of VWF in this context of NSBB therapy.

VWF response was consistently associated with a favourable clinical course as indicated by lower incidences/risks of further decompensation, AKI, ACLF, and liver-related death, independently of established prognostic indicators. After validation, VWF response may serve as a valuable NIT/biomarker to discriminate between patients with DC who benefit (the most) from NSBB treatment and have a favorable prognosis versus patients with poor outcomes. The latter patients may be candidates for emerging therapies that target the pathophysiologic mechanisms underlying elevated VWF levels, such as statins,[35] albumin,[36] or possibly TIPS,[37] and should preferably be evaluated early for OLT.

The lack of a validation cohort receiving NSBB therapy is a main limitation of our study. In addition, only patients undergoing paired HVPG measurements were considered, and thus, our study population may not be fully representative of the population of patients with DC treated at our and other institutions, as only 16% of patients had recurrent/refractory ascites, which may be explained by safety concerns and NSBB intolerance. However, the potential clinical relevance of NSBB-related VWF response is limited to patients who are considered eligible for or tolerate NSBB therapy. Moreover, a subset of patients lacked a strong indication for NSBB treatment according to the international recommendations that were in place at the time of treatment initiation; however, Austrian consensus recommendations were more proactive regarding the use of NSBB therapy for primary prophylaxis in patients with low-risk varices throughout the whole study period. Of note, our study was not designed to evaluate the prognostic relevance of NSBB therapy-related HVPG changes, as patients with HVPG nonresponse and large varices but without a history of bleeding were considered for additional endoscopic therapies at our center. Finally, we did not assess the

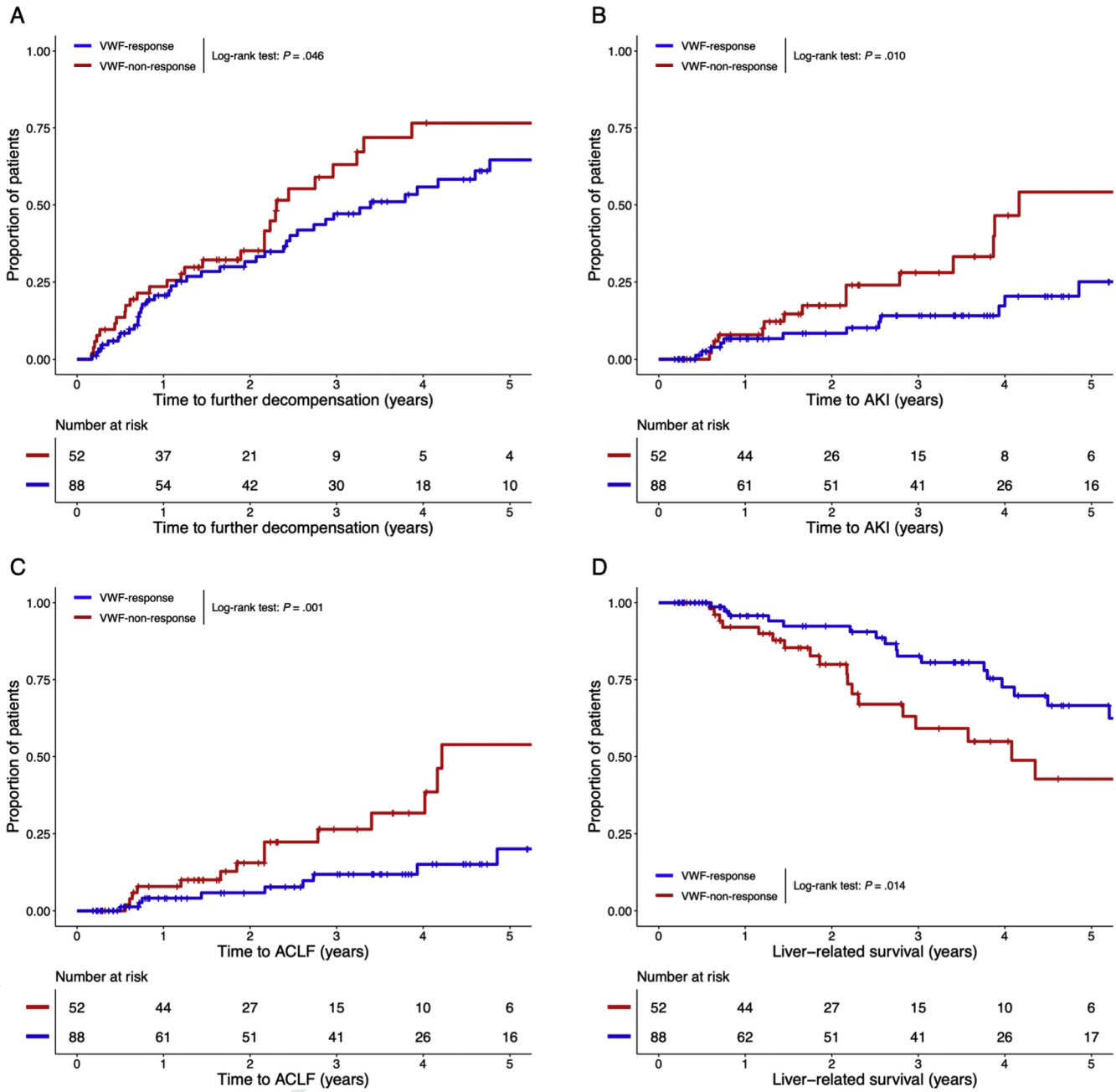

Figure 4. Landmark Kaplan-Meier analyses with further hepatic decompensation (*A*), AKI development (*B*), and ACLF development (*C*), as well as liver-related mortality (*D*) as outcomes of interest. Patients were censored upon etiologic treatments/HCC diagnosis, and transplantation (all models), as well as non-liver-related mortality (models *A* and *D*) and death (models *B* and *C*). Importantly, all patients that were censored or developed an outcome of interest before 30 days after the second measurement (ie, the defined landmark) were not considered for the analyses (n = 19 for all models).

impact of ABO blood type on VWF; however, its impact in ACLD – in particular DC – is comparatively small,[38] and it appears unlikely that ABO blood type significantly impacted the NSBB-related VWF changes.

Conclusions

In conclusion, a VWF decrease upon NSBB therapy reflects its anti-inflammatory activity and is accompanied by less pronounced adverse effects on systemic hemodynamics as well as decreased risks of further decompensation, ACLF, and death. Thus, VWF is a promising biomarker to assess the therapeutic benefit in patients with DC: Patients with decreasing VWF benefit from NSBB treatment and have a favorable prognosis – accordingly, discontinuation of NSBB therapy should be carefully scrutinized. In contrast, the absence of a VWF decrease identifies patients with poor outcomes, who may require additional treatments to prevent significant morbidity and mortality.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2021.07.012.

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Peter Quehenberger, MD (Data curation: Equal; Methodology: Equal; Writing – review & editing: Equal)
Michael Trauner, MD (Supervision: Supporting; Writing – review & editing: Equal)
Thomas Reiberger, MD (Conceptualization: Equal; Supervision: Lead; Writing – review & editing: Equal)
Mattias Mandorfer, MD, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Investigation: Equal; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)

Conflicts of interest
These authors disclose the following: Benedikt Simbrunner has received travel support from AbbVie and Gilead. David Bauer served as as speaker and/or consultant and/or advisory board member for AbbVie and received travel support from AbbVie and Gilead. Bernhard Scheiner received travel support from AbbVie and Gilead. Philipp Schwabl served as as speaker and/or consultant and/or advisory board member for Bristol-Myers Squibb and Boerhinger Ingelheim and received travel support from Falk and Gilead. Albert F. Stättermayer served as a speaker and/or consultant and/or advisory board member for Boehringer Ingelheim, Gilead, and MSD. Matthias Pinter served as a speaker and/or consultant and/or advisory board member for Bayer, Bristol-Myers Squibb, Ipsen, Eisai, Lilly, MSD, and Roche, and received travel support from Bayer and Bristol-Myers Squibb. Peter Quehenberger has served as a speaker and/or consultant and/or advisory board member for Roche and Takeda. Michael Trauner served as a speaker and/or consultant and/or advisory board member for Albireo, BiomX, Boehringer Ingelheim, Bristol-Myers Squibb, Falk, Genfit, Gilead, Intercept, Janssen, MSD, Novartis, Phenex, Regulus, and Shire and received travel support from AbbVie, Falk, Gilead, and Intercept, as well as grants/research support from Albireo, Cymabay, Falk, Gilead, Intercept, MSD, and Takeda. Moreover, he is a coinventor of patents on the medical use of 24-norursodeoxycholic acid. Thomas Reiberger served as a speaker and/or consultant and/or advisory board member for AbbVie, Bayer, Boehringer Ingelheim, Gilead, Intercept, MSD, Siemens, and W.L. Gore & Associates and received grants/research support from AbbVie, Boehringer Ingelheim, Gilead, MSD, Philips, and W.L. Gore & Associates, as well as travel support from Boehringer Ingelheim and Gilead. Mattias Mandorfer served as a speaker and/or consultant and/or advisory board member for AbbVie, Bristol-Myers Squibb, Gilead, Collective Acumen, and W. L. Gore & Associates and received travel support from AbbVie, Bristol-Myers Squibb, and Gilead. The remaining authors disclose no conflicts.

Supplementary Methods

Detailed/Additional Information on the Cohort of Stable Patients With Decompensated Cirrhosis With Paired von Willebrand Factor Measurements but Without Nonselective Beta Blocker Treatment Initiation

We have retrospectively identified all patients with decompensated cirrhosis (DC) who were included in the prospective Vienna Cirrhosis Study (VICS, IRB vote No. 1493/2016) between the first quarter of 2017 and the fourth quarter of 2020 (von Willebrand factor [VWF] assessments within extended routine blood draws in patients with advanced chronic liver disease who did not undergo hepatic venous pressure gradient (HVPG) measurements were introduced in quarter 1 of 2017 at our clinic) who (1) were seen at our outpatient clinic twice within 14–90 days (ie, within the time frame that was also applied for the inclusion in our main cohort) with paired information on VWF; (2) showed stable DC (ie, no decompensation between measurements and a maximum change in Model of End-stage Liver Disease score by 2 points); and (3) either were not on nonselective beta blocker (NSBB) treatment or were already on stable chronic NSBB intake before the first VWF assessment.

Detailed/Additional Information on Measurement of HVPG/VWF and Biomarkers of Bacterial Translocation/Systemic Inflammation

After local anesthesia, a catheter introducer sheath was placed in the right internal jugular vein. A specifically designed balloon catheter with an angled tip[1] was advanced into the inferior vena cava and placed in a large hepatic vein under fluoroscopic guidance. HVPG was calculated by subtracting the free from the wedged hepatic venous pressure. The mean of 3 measurements was used for further analyses. Chronic hemodynamic response was evaluated during the follow-up (FU). NSBB HVPG measurement and HVPG response was defined as recommended by the Baveno VI consensus (ie, HVPG reduction by $\geq$10% [primary prophylaxis], $\geq$20% [secondary prophylaxis], or to an absolute value of $\leq$12 mm Hg[2]).

All laboratory analyses were performed from central venous blood samples that were obtained at the time of baseline (BL) and NSBB HVPG measurement.

To evaluate the precision (ie, the variability in the data from replicate determinations of the same homogenous sample under stable operating conditions) of the assay at plasma VWF levels that are representative of our study population, we used a blood sample obtained from an individual patient with DC with a plasma VWF level of 330%. Thus, this sample was close to the median VWF detected in the main cohort of our study, which were 350% at BL and 322% at the second HVPG measurement (NSBB HVPG). Importantly, when conducting 10 sequential measurements, the coefficient of variation was only 3%. To evaluate intermediate precision (ie, the variability in data from replicate determinations of the same sample at different time points) we reviewed quality assurance data from our clinical laboratory service throughout the study period, which revealed a similar coefficient of variation (around 3%) that was very stable over time.

Standard laboratory methods were used for the assessment of routine laboratory tests (eg, C-reactive protein). Commercially available chemiluminescent immunometric assays were used for the measurement of procalcitonin, interleukin-6, and lipopolysaccharide-binding protein.

Detailed/Additional Information on the Definition of DC and Clinical Events

Patients' medical records were searched for the following events that defined DC: (1) History of acute variceal bleeding, as evidenced by active bleeding from varices observed during endoscopy or clinical evidence of upper gastrointestinal bleeding in patients with varices and in the absence of another source of bleeding; (2) history of large volume paracentesis and/or presence of ascites/diuretic treatment at BL; and/or (3) history of admission due to overt hepatic encephalopathy (HE) and/or presence of overt HE/anti-HE treatment at BL. Ascites and HE were graded according to current recommendations.[3]

The following events were defined as further decompensation: acute variceal bleeding, development of overt HE as evidenced by initiation of anti-HE therapies or admission due to/development of West-Haven grade III–IV HE, development of ascites as evidenced by initiation of diuretic treatment or requirement of large volume paracentesis/transjugular intrahepatic portosystemic shunt implantation for ascites control, spontaneous bacterial peritonitis or other bacterial infections, acute-on-chronic liver failure (ACLF) development, and liver-related death. Spontaneous bacterial peritonitis was diagnosed if the ascitic fluid polymorphonuclear leukocyte count was >250 cells/mL in the absence of other intra-abdominal sources of infection.[3] We also recorded episodes of acute kidney injury (AKI) stage 1b or higher, as defined by an acute increase in serum creatinine $\geq$0.3 mg/dL or by $\geq$50% to a final value of $\geq$1.5 mg/dL.[3] ACLF was diagnosed according to European Association for the Study of the Liver – ChronicLiver Failure (EASL-CLIF) criteria.[3]

Detailed/Additional Information on Statistical Analysis

Group comparisons of categorial variables were performed using the Fisher exact test. For unpaired

comparisons of continuous variables, the unpaired Student *t*-test or the Mann-Whitney *U*/Kruskal-Wallis test were applied, whereas the Wilcoxon signed-rank test was used for the comparison of paired continuous variables. Spearman's rank correlation was used to investigate associations between (changes in) VWF and HVPG as well as biomarkers of bacterial translocation/systemic inflammation.

Time-dependent area under the receiver operating characteristic curve analysis was performed using the R package timeROC,[4] and the optimal relative ΔVWF cutoff point ('VWF response') for prognostication of liver-related mortality was calculated by Youden's index using the R package cutpointr.[5]

For time-to-event analyses, 2 different approaches (Supplementary Figure 1) were used to minimize immortal time bias/inverse causality, which may have occurred due to the design of the study.

First, for comparing the incidences of clinical events between VWF responders and VWF nonresponders, Kaplan-Meier and log-rank analyses were performed. To minimize bias from immortal time and/or reverse causality, patients entered the Kaplan-Meier models 30 days after the second measurement (determination of VWF response), which was chosen as the landmark for this analysis. Accordingly, 140 patients were considered in the Kaplan-Meier outcome analyses, whereas 19 patients had developed events before the landmark or had been censored.

Second, to establish the predictive value of VWF response for further decompensation, AKI, and ACLF, as well as liver-related death, we applied multivariate Cox regression incorporating a time-dependent variable for VWF response: All patients were classified as VWF nonresponders upon entering our models at BL (ie, BL HVPG). Patients who attained VWF response at the time of NSBB HVPG measurement were reclassified as VWF responders 30 days thereafter. In all Cox regression models, we included VWF response as well as variables that were considered clinically relevant (ie, BL VWF, Child-Turcotte-Pugh stage, serum creatinine, BL HVPG, and relative HVPG change from BL to NSBB HVPG).

A P-value $\leq$ .05 was considered statistically significant.

Detailed/Additional Information on the Dynamics of VWF in Stable DC Without NSBB Therapy Initiation

We identified 66 patients who met all of the above-mentioned criteria, of whom 48 were on chronic NSBB therapy at both VWF measurements, whereas 18 were NSBB-naïve. Indeed, VWF levels remained stable in the vast majority of these subjects and did not change in paired comparison ($P = .888$) (Supplementary Figure 2). The median relative change in VWF levels was 1% (interquartile range, −3% to 4%), and thus clearly differed from our main cohort (ie, patients in whom NSBB treatment was initiated between the VWF measurements (−8% [interquartile range, −17 to 1%]; $P <$ .001). Of note, despite the between-group differences in the changes in VWF, changes in Model of End-stage Liver Disease were similar between the 2 patient groups ($P = .741$).

Detailed/Additional Information on Clinical FU

Twelve patients (overall, 7.5%; VWF responders, 9.3% vs VWF nonresponders, 4.8%) were diagnosed with hepatocellular carcinoma during FU. Moreover, 17 patients (10.7%; VWF responders, 9.3% vs VWF nonresponders, 12.9%) achieved abstinence from alcohol and 6 patients (3.8%; VWF responders, 3.1% vs VWF nonresponders, 4.8%) were prescribed antiviral therapy. Fifteen patients (9.4%; VWF responders, 8.2% vs VWF nonresponders, 11.3%) underwent orthotopic liver transplantation.

Eighty-eight patients (55.3%; VWF responders, 50.5% vs VWF nonresponders, 62.9%) developed at least 1 event of further decompensation during FU.

AKI was diagnosed in 31 patients (19.5%; VWF responders, 12.4% vs VWF nonresponders, 30.6%).

Twenty-seven patients (17.0%; VWF responders, 9.3% vs VWF nonresponders, 29.0%) developed ACLF during FU.

Finally, 48 patients (30.2%; VWF responders, 24.7% vs VWF nonresponders, 38.7%) and 6 patients (3.8%; VWF responders, 4.1% vs VWF nonresponders, 3.2%) died from liver- or non-liver-related causes, respectively.

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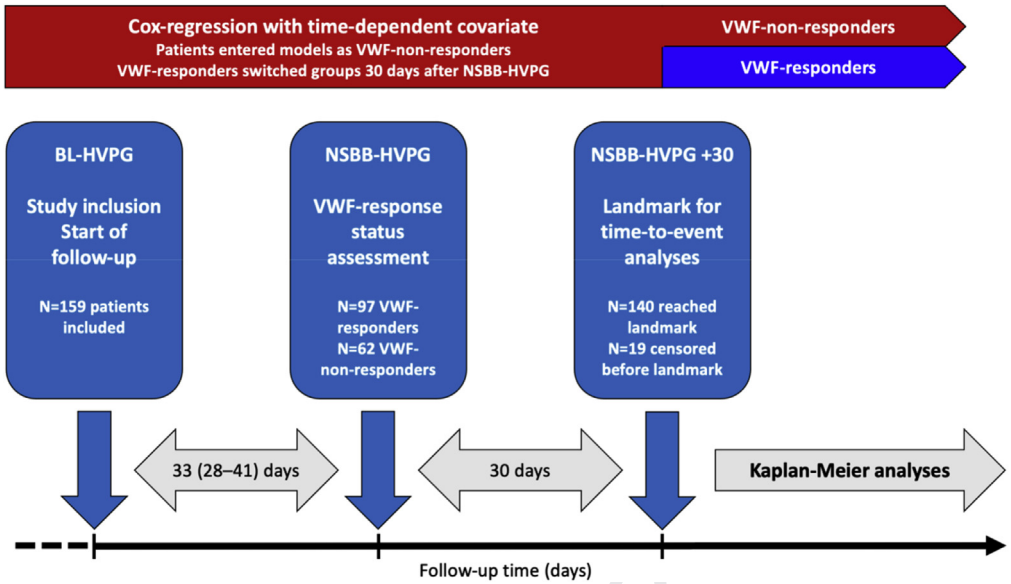

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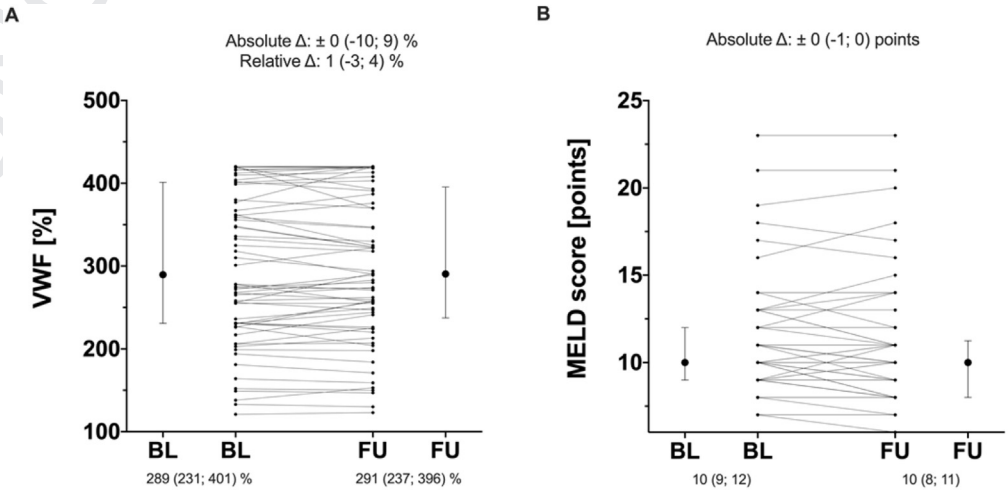
Supplementary Figure 1. A schematic summary of the most relevant time points of the study, including (1) BL measurement of HVPG and VWF; (2) the determination of VWF response under chronic NSBB intake (NSBB HVPG) after a median of 33 days (interquartile range, 28–41 days); and (3) the landmark set 30 days after NSBB HVPG for Kaplan-Meier analyses. All patients entered the Cox regression models as VWF nonresponders at study inclusion and were assigned to the VWF responder group at 30 days after NSBB HVPG measurement. A total of 140 patients were included in the landmark Kaplan-Meier/log-rank test analyses.



Supplementary Figure 2. Changes in plasma VWF levels (*A*) and Model of End-stage Liver Disease score (*B*) in patients with stable DC. BL, Baseline; FU, follow-up.

Supplementary Table 1. Patient Characteristics at BL (ie, Before NSBB Therapy), NSBB Treatment Characteristics, and Treatment-related Changes From BL to Second HVPG Measurement on NSBB Treatment

Patient characteristic	All patients, (n = 159)
Sex, male/female (% male)	118/41 (74.2)
Age, *years*	55.6 ± 10.5
BMI, *kg/m²*	25.1 (22.2–28.7)
Etiology of CLD	
ALD	103 (64.8)
Viral	15 (9.4)
ALD + viral	17 (10.7)
NAFLD	7 (4.4)
Others/cryptogenic	17 (10.7)
Alcohol consumption	
No	107 (67.3)
Below threshold[a]	11 (6.9)
Above threshold[a]	41 (25.8)
BL CTP score, *points*	8 (6–9)
NSBB CTP score, *points*	7 (6–8)
BL MELD (2016) score, *points*	12 (10–17)
NSBB MELD (2016) score, *points*	11 (10–16)
BL albumin, *g/L*	33.0 (30.2–37.3)
BL bilirubin, *mg/dL*	1.71 (1.06–2.59)
BL INR	1.4 (1.2–1.5)
BL creatinine, *mg/dL*	0.79 (0.68–1.00)
BL sodium, *mmol/L*	136 (134–139)
Varices	
Small	54 (34.0)
Large	105 (66.0)
History of bleeding	59 (37.1)
Ascites	
No	31 (19.5)
Mild/moderate	103 (64.8)
Severe/refractory	25 (15.7)
HE	50 (31.4)
Type of NSBB therapy	
Carvedilol	107 (67.3)
Propranolol	52 (32.7)
BL MAP, *mm Hg*	99 (90–109)
BL MAP <65 mm Hg	0 (0)
NSBB MAP, *mm Hg*	90 (82–99)
NSBB MAP <65 mm Hg	6 (3.8)
ΔMAP, absolute, *mm Hg*	−8 (−16 to −2)
ΔMAP, relative, %	−8.9 (−16.0 to −2.0)
BL HVPG, *mm Hg*	21 (18–24)
NSBB HVPG, *mm Hg*	18 (15–21)
ΔHVPG, absolute, *mm Hg*	−2 (−5 to −1)
ΔHVPG, relative, %	−11.1 (−23.5 to −3.6)
HVPG decrease ≥10%	91 (57.2)
HVPG decrease ≥20%	56 (35.2)
HVPG response, %[b]	77 (48.4)
BL VWF, %	350 (291–420)
NSBB VWF, %	322 (253–398)
ΔVWF, absolute, %	−26 (−60 to 2)
ΔVWF, relative, %	−8.0 (−16.8 to 0.9)
VWF response (%)[b]	
BL CRP,[c] *mg/dL*	0.50 (0.20–1.22)
NSBB CRP,[c] *mg/dL*	0.44 (0.17–0.88)
ΔCRP, absolute, *mg/dL*	−0.04 (−0.35 to 0.03)
ΔCRP, relative, %	−19.8 (−48.8 to 11.3)
BL PCT,[d] *ng/mL*	0.11 (0.07–0.20)
NSBB PCT,[d] *ng/mL*	0.12 (0.07–0.16)
ΔPCT, absolute, *ng/mL*	−0.01 (−0.03 to 0.01)
ΔPCT, relative, %	−7.1 (−26.1 to 17.4)
BL IL-6,[e] *pg/nL*	11.61 (7.81–26.28)
NSBB IL-6,[e] *pg/nL*	13.08 (7.40–21.65)
ΔIL-6, absolute, *pg/nL*	−1.55 (−6.98 to 4.48)
ΔIL-6, relative, %	−10.9 (−40.9 to 23.0)
BL LBP,[f] *μg/mL*	7.36 (5.54–9.46)
NSBB LBP,[f] *μg/mL*	6.96 (5.02–8.68)
ΔLBP, absolute, *μg/mL*	−0.16 (−1.26 to 0.64)
ΔLBP, relative, %	−2.3 (−17.8 to 9.8)

Note: Data are presented as number (%), mean ± standard deviation, or median (interquartile range).
ACLD, Advanced chronic liver disease; ALD, alcoholic liver disease; BL, baseline; BMI, body mass index; CLD, chronic liver disease; CRP, C-reactive protein; CTP, Child-Turcotte-Pugh; FU, follow-up; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; IL-6, interleukin-6; INR, international normalized ratio; LBP, lipopolysaccharide-binding protein; MAP, mean arterial pressure; MELD, Model of End-stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; NSBB, nonselective beta blocker; PCT, procalcitonin; VWF, von Willebrand factor
[a]>30 g/day and >20 g/day for males and females, respectively.[6]
[b]Defined by an HVPG decrease to ≤12 mm Hg or by ≥10% in primary and ≥20% in secondary prophylaxis of variceal bleeding.
[c]CRP values available in n = 146 at BL and in n = 143 at NSBB HVPG.
[d]PCT values available in n = 36 at BL and in n = 36 at NSBB HVPG.
[e]IL-6 values available in n = 35 at BL and in n = 37 at NSBB HVPG.
[f]LBP values available in n = 35 at BL and in n = 38 at NSBB HVPG.

Supplementary Table 2. Systemic Hemodynamics at BL (ie, Before NSBB Therapy) and Second HVPG Measurement on NSBB Treatment

Hemodynamic characteristics	BL HVPG	NSBB HVPG	*P*
Heart rate, bpm	80 (70; 93)	64 (58; 72)	< .001
Systolic arterial pressure, mm Hg	130 (119; 145)	118 (108; 131)	< .001
Diastolic arterial pressure, mm Hg	80 (74; 89)	73 (67; 82)	< .001
Mean arterial pressure, mm Hg	99 (90; 109)	90 (82; 99)	< .001

BL, Baseline; HVPG, hepatic venous pressure gradient; NSBB, nonselective beta blocker.

Supplementary table 3. Multivariate Cox Regression Analyses With Further Hepatic Decompensation, AKI Development, and ACLF Development, as Well as Liver-related Mortality as Events of Interest

		95% CI		
	Adjusted HR	Lower	Upper	*P*
Model A – further hepatic decompensation				
VWF response	0.555	0.337	0.912	**.020**
BL VWF, per 10%	1.008	0.989	1.026	.428
CTP stage				
B vs A	1.301	0.772	2.194	.323
C vs A	2.446	1.173	5.101	**.017**
Serum creatinine, per mg/dL	1.898	1.216	2.963	**.005**
BL HVPG, per mmHg	1.056	1.011	1.104	**.014**
ΔHVPG, per % change	1.005	0.991	1.019	0.480
Model B – AKI development				
VWF response	0.367	0.167	0.803	**.012**
BL VWF, per 10%	1.003	0.970	1.037	.848
CTP stage				
B vs A	5.140	1.387	19.041	**.014**
C vs A	8.797	1.792	43.188	**.007**
Serum creatinine, per mg/dL	3.636	1.874	7.052	**< .001**
BL HVPG, per mm Hg	1.022	0.956	1.092	.528
ΔHVPG, per % change	0.999	0.978	1.020	.891
Model C – ACLF development				
VWF response	0.302	0.126	0.721	**.007**
BL VWF, per 10%	0.977	0.939	1.017	.262
CTP stage				
B vs A	3,737	1.067	13.094	**.039**
C vs A	12.207	2.429	61.336	**.002**
Serum creatinine, per mg/dL	2.320	0.838	6.425	.105
BL HVPG, per mm Hg	1.035	0.962	1.113	.358
ΔHVPG, per % change	0.998	0.976	1.020	.845
Model D – Liver-related death				
VWF response	0.332	0.179	0.616	**< .001**
BL VWF, per 10%	1.018	0.992	1.045	.171
CTP stage				
B vs A	1.383	0.665	2.877	.385
C vs A	3.198	1.200	8.523	**.020**
Serum creatinine, per mg/dL	1.701	0.674	4.294	.261
BL HVPG, per mm Hg	1.051	0.993	1.113	.087
ΔHVPG, per % change	1.002	0.984	1.021	.813

Note: VWF response was considered as a time-dependent covariate. Results are presented as adjusted HRs with 95% CIs and corresponding *P*-values. All models incorporated a time-dependent variable for exposure to VWF response and were adjusted for BL VWF, CTP stage, HVPG at BL, and percentual HVPG response. Patients were censored at the time of etiological treatments/hepatocellular carcinoma diagnosis and liver transplantation (all models), as well as non-liver-related mortality (models A and D) and death (models B and C). Boldface *P* values indicate statistical significance.

ACLF, Acute-on-chronic liver failure; AKI, acute kidney injury; BL, baseline; CI, confidence interval; CTP, Child-Turcotte-Pugh; HR, hazard ratio; HVPG, hepatic venous pressure gradient, VWF, von Willebrand factor.