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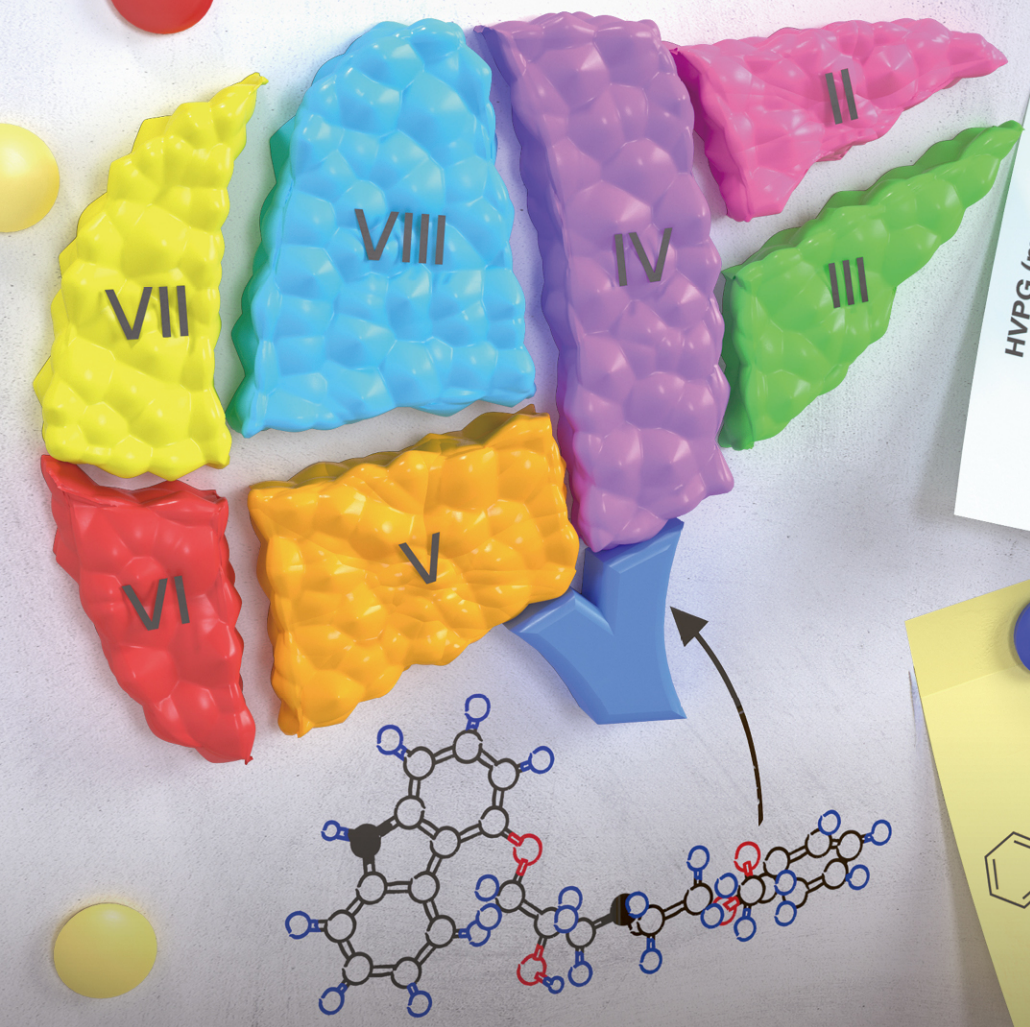

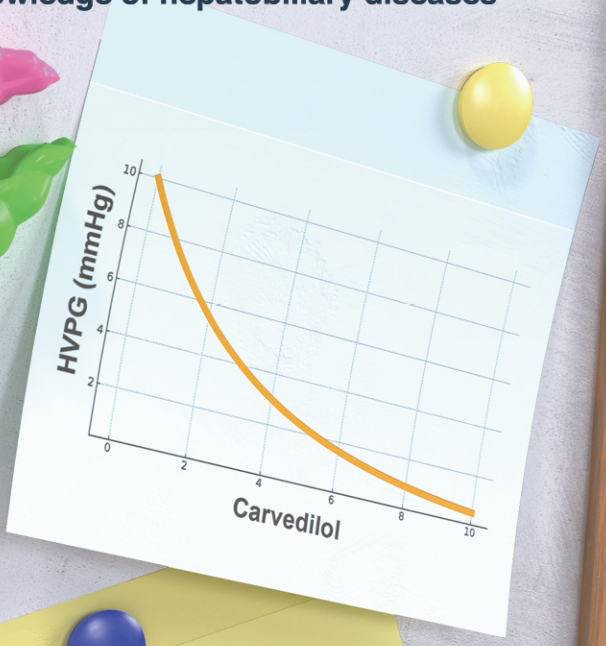

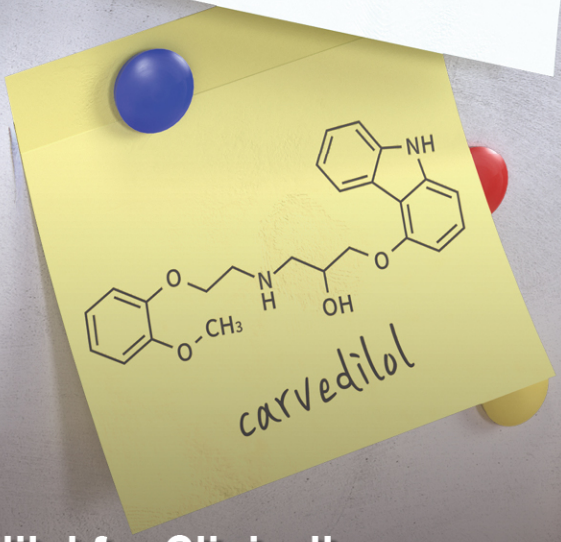

Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

Intrapatient variability of tacrolimus on CKD in LT
HCV self-testing and disease burden reduction
MASLD and microbiota
Bariatric surgery for metabolic cirrhosis

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CLINICAL and MOLECULAR HEPATOLOGY

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Clinical and Molecular Hepatology 2025;31:240-255

Original Article

Insertion of a transjugular intrahepatic portosystemic shunt leads to sustained reversal of systemic inflammation in patients with decompensated liver cirrhosis

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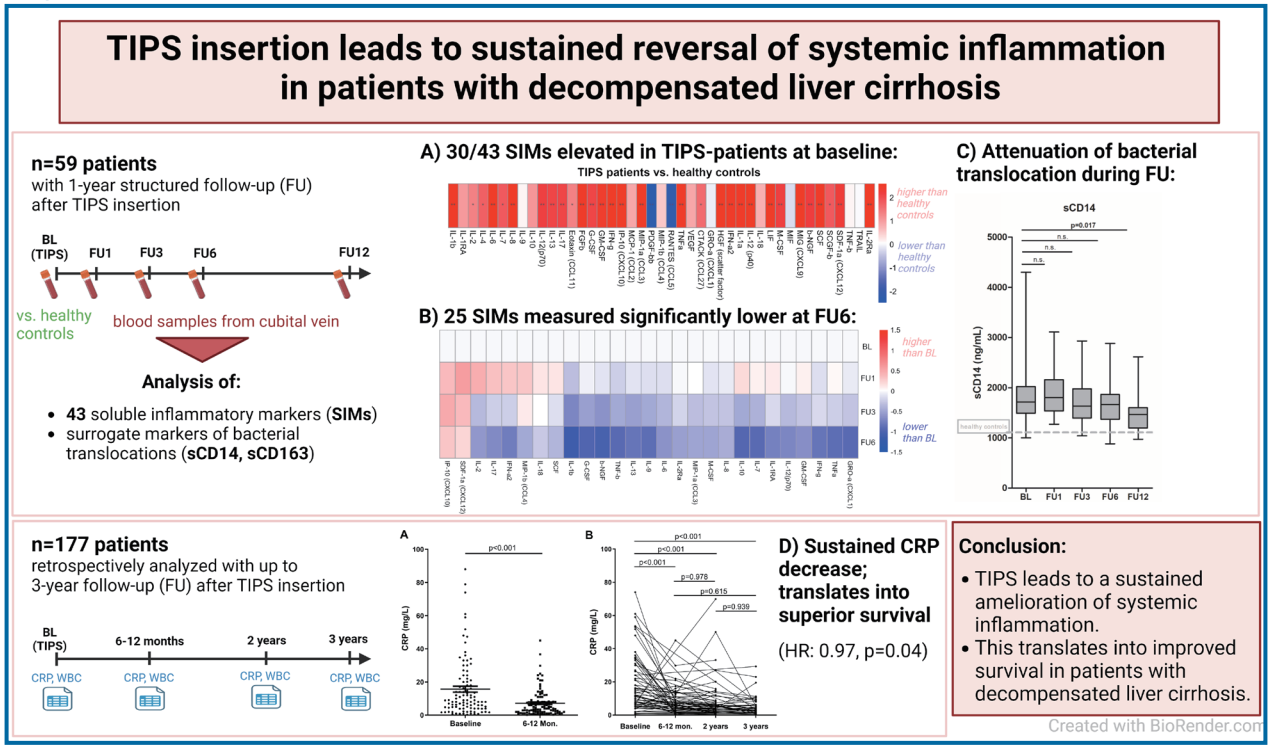
Graphical Abstract



Study Highlights

- Patients with decompensated liver cirrhosis are characterized by a state of systemic inflammation: 30/43 SIMs and surrogate markers of bacterial translocation (sCD14, sCD163) were found elevated pre-TIPS.
- TIPS-insertion significantly reduces systemic inflammation, with 25 SIMs and sCD14 decreasing at 6 months post-TIPS.
- Long-term follow-up data of CRP indicates this alleviation of systemic inflammation is sustained, translating into improved survival in TIPS patients.
- Interestingly, particularly elevated levels of IL-6 in patients with TIPS-indication refractory ascites decreased to levels seen in patients with variceal bleeding, pointing toward a potential reversal of liver disease stage.

Background/Aims: Systemic Inflammation (SI) is considered a key mechanism in disease progression and development of complications in decompensated liver cirrhosis. SI is mainly driven by portal hypertension and bacterial translocation. Transjugular intrahepatic portosystemic shunt (TIPS) insertion represents an effective treatment for portal hypertension. This study aims to investigate the impact of TIPS insertion on SI and bacterial translocation.

Methods: We prospectively included 59 cirrhotic patients undergoing TIPS insertion. Blood samples were collected at TIPS insertion and follow-up (FU) 1, 3, 6, and 12 months thereafter. At all time points, we performed a comprehensive analysis of SI including 43 soluble inflammatory markers (SIMs), and surrogates of bacterial translocation (sCD14, sCD163). To investigate long-term kinetics of SI, C-reactive protein (CRP) and white blood cells (WBC) were retrospectively analyzed in a cohort of 177 patients up to 3 years after TIPS insertion.

Results: At TIPS insertion, 30/43 SIMs, sCD14, and sCD163 measured significantly higher in cirrhotic patients compared to healthy controls. By FU6 25 SIMs and sCD14 measured at significantly lower levels compared to baseline. Interestingly, in patients with TIPS indication of refractory ascites, IL-6 decreased to levels documented in earlier stages of cirrhosis. In long-term follow-up, CRP levels significantly decreased after TIPS insertion, which translated into lower mortality in Cox regression analysis (HR 0.968, P=0.042). Notably, patients with residual ascites post-TIPS showed significantly higher CRP and IL-6 levels across all follow-ups compared to patients with resolved ascites.

Conclusions: Decreasing portal hypertension via TIPS insertion leads to a significant attenuation of SI and bacterial translocation over time. **(Clin Mol Hepatol 2025;31:240-255)**

Keywords: Transjugular intrahepatic portosystemic shunt insertion; Systemic inflammation; Liver cirrhosis; Portal hypertension; Bacterial translocation

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Abbreviations:

ACLD, advanced chronic liver disease; CV, cubital vein; CRP, C-reactive protein; dACLD, decompensated advanced chronic liver disease; DAMPs, damage-associated molecular patterns; IL, Interleukin; FDR, false discovery rate; FIPS, Freiburg index of post-TIPS survival; LTx, liver transplantation; LV, liver vein; MELD, model for end-stage liver disease; NSBB, non-selective beta blocker; PSG, portosystemic pressure gradient; PV, portal vein; RA, refractory ascites; SI, systemic inflammation; SIM, soluble inflammatory marker; TIPS, transjugular intrahepatic portosystemic shunt; WBC, white blood cells

INTRODUCTION

In advanced chronic liver disease (ACLD), the clinical trajectory generally transitions from a clinically compensated to decompensated (dACLD) stage upon development of portal hypertension driven complications, e.g., variceal bleeding or ascites.[1,2] This progression of disease stage is accompanied by a marked increase in mortality.[1] In the past decade, the pathophysiology of dACLD has been extensively investigated. Today, it is widely accepted that dACLD, in particular at later stages, represents a multi-inflammatory disease.[1-3] Patients are characterized by a 'leaky gut', which causes increased bacterial translocation from the gut lumen to the systemic circulation.[4,5] As a consequence, the innate immune system is activated, resulting in a state of systemic inflammation (SI) with elevated concentrations of inflammatory mediators in the systemic circulation.[5] The severity of SI has been described to progress across stages of ACLD, reaching its peak in patients with refractory ascites (RA).[3,6] SI is generally associated with worse clinical outcomes as it is thought to be the main driver for acute decompensation of liver cirrhosis as well as for the development of acute-on-chronic liver failure with high short-term mortality.[6,7] Therefore, a therapeutic approach to attenuate SI and thus to prevent organ failure would be highly valuable for patients with dACLD.

Transjugular intrahepatic portosystemic shunt (TIPS) insertion represents an effective and standardized treatment strategy for patients with dACLD and portal hypertension-related complications such as RA or variceal bleeding.[8] After TIPS implantation, the risk for variceal bleeding, further decompensation, as well as the need for large volume paracenteses is significantly reduced. Moreover, TIPS has been linked to a superior survival in these patients.[9-11] Besides liver transplantation (LTx), TIPS insertion constitutes the most effective tool to alleviate portal hypertension, since establishing the portosystemic bypass leads to an immediate decrease of portal pressure.[12] As portal hypertension is considered a central driver of bacterial translocation and SI,[13] one might hypothesize that SI may be attenuated after TIPS insertion. Indeed, some studies reported that portal pressure reduction through non-selective beta-

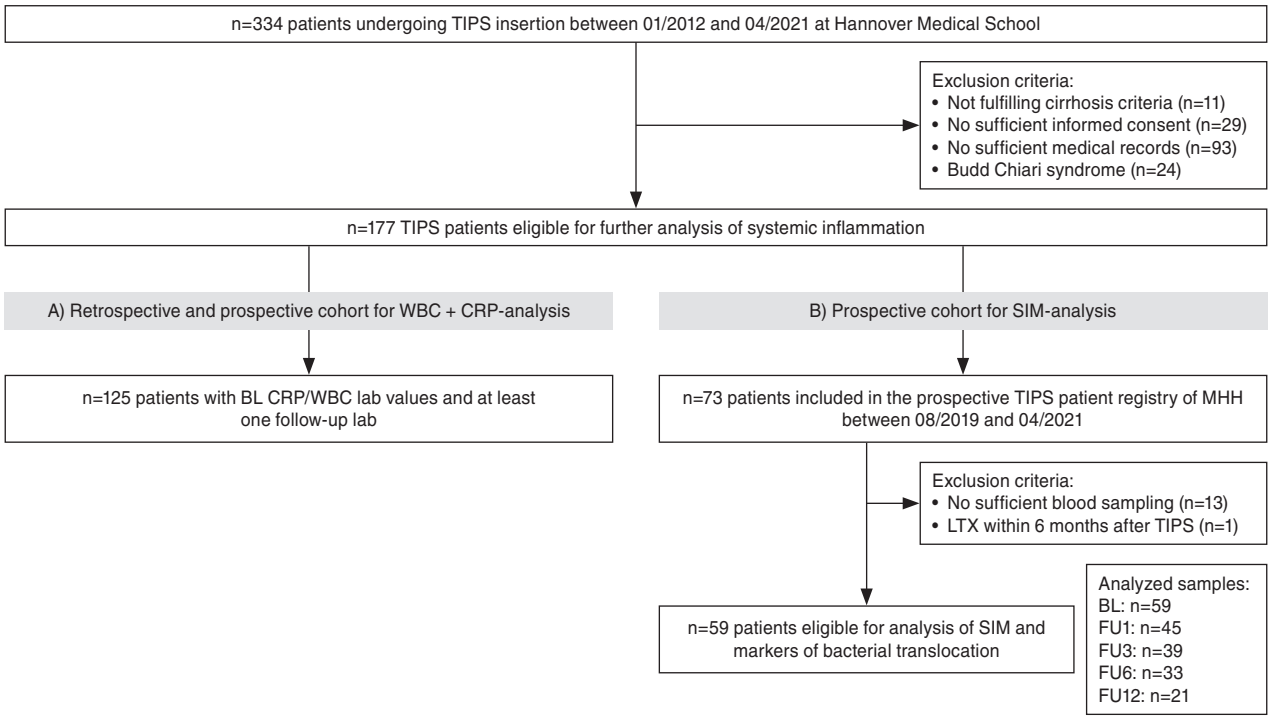

Figure 1. Selection algorithm for TIPS patients from Hannover Medical School. Shown is the selection algorithm for the TIPS patients included in the analysis of systemic inflammation based on CRP levels and WBC, as well as the subgroup of patients prospectively enrolled in the Hannover TIPS patient registry with detailed SIM analysis. TIPS, transjugular intrahepatic portosystemic shunt; CRP, C-reactive protein; WBC, white blood cells; SIM, soluble inflammatory marker.

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blockers (NSBB) leads to decreased levels of C-reactive protein (CRP), white blood cells (WBCs) and interleukin-6 (IL-6), which translated into improved outcomes.[14,15] However, detailed analyses as well as long-term kinetics of SI after TIPS insertion are lacking, so far.

Therefore, the aim of this study was to comprehensively investigate the impact of TIPS insertion on SI and bacterial translocation in patients with dACLD.

MATERIALS AND METHODS

Study population

All consecutive patients receiving an elective TIPS at Hannover Medical School (Germany) between January 2012 and April 2021 were considered for this study. Patients without liver cirrhosis (n=11), with Budd Chiari syndrome (n=24) or without written informed consent (n=29) were excluded from analysis. Overall, 177 TIPS patients were eligible for further analysis (Fig. 1). Patients receiving an early, preemptive, or rescue TIPS due to otherwise uncontrollable variceal bleeding were not considered.

Additionally, we started enrolling TIPS patients into the prospective Hannover TIPS patient registry of Hannover Medical School in August 2019 (trial number: NCT04801290). In these patients, a predefined, structured clinical assessment, as well as blood sampling from different compartments, was performed before as well as at different time points during one year follow-up after TIPS insertion. A number of 73 patients with liver cirrhosis receiving a TIPS at Hannover Medical School were included in this patient registry between August 2019 and April 2021. Patients with no sufficient blood sampling due to loss of follow-up or death (n=13) as well as one patient, who underwent LTx within 6 months after TIPS, were excluded from analysis. Overall, samples of 59 patients were eligible for a detailed analysis of 48 soluble inflammatory markers (SIM) and surrogate markers of bacterial translocation, e.g. soluble CD14 (sCD14) and CD163 (sCD163) (Fig. 1). For the comparison of SI with healthy controls, 5 healthy individuals (3 females, 2 males, median age of 44 years [IQR 36–48 years]) gave written informed consent for blood sample analysis and use of their data in this study.

Data assessment

The clinical, laboratory and TIPS procedure-related data were extracted from the patients' medical records. Laboratory values for CRP and WBC at predetermined time points during follow-up (6–12 months, 2 years, and 3 years after TIPS) were automatically identified by the Enterprise Clinical Research Data Warehouse.[16] The time-variations for the aforementioned assessments are displayed in Supplementary Table 1.

Diagnosis of liver cirrhosis was based on non-invasive methods, i.e., liver ultrasound, elastography, biochemical results and/or liver biopsy.[2] Baseline was set on the day of TIPS insertion. Only patients without ongoing active infection received a TIPS and were included in the analyses.

In clinical follow-up of up to 3 years, we retrieved the numbers of rehospitalizations due to liver-related causes, infections (per diagnosis of treating physician), and further hepatic decompensation following Baveno VII criteria,[2] from patients' medical records.

Status of ascites during follow-up was assessed based on sonography findings at 3 months (+/- 45 days) post TIPS insertion, categorizing patients with ascites prior to TIPS into groups of no, minimal and severe ascites (Supplementary Fig. 1).

Liver transplantation or permanent TIPS occlusion/thrombosis constituted the end of clinical and laboratory follow-up.

TIPS placement and blood sampling

TIPS insertion was performed according to institutional standard operating procedures by interventional radiologists with long-term clinical experience in TIPS implantation.[17] Polytetrafluorethylene (PTFE)-covered stent grafts (Viatorr®; Gore, Flagstaff, AZ, USA) were used in all patients with stent diameters of 10 mm (n=14), 8 mm (n=158) or 6 mm (n=5). The TIPS procedure was conducted under general anesthesia with continuous monitoring of the patients' vital parameters. After successful TIPS insertion, all patients were monitored in the intensive care unit for at least 24 hours. TIPS patency and adequate flow were confirmed by ultrasound measurements conducted by an experienced physician prior to discharge as well as in every outpatient follow-up visit. TIPS revisions (reductions and dilatations) during follow-up are displayed in Supplementary Table 2.

Table 1. Baseline characteristics of TIPS patients

Characteristic	All patients	Subgroup for SIM analysis
Patients (n, %)	177 (100)	59 (33)
Age (y)	56 (49–63)	57 (50–65)
Male/female (n, %)	108 (61)/ 69 (39)	34 (58)/ 25 (42)
TIPS indication*		
Refractory ascites (n, %)	134 (76)	46 (78)
Bleeding (n, %)	50 (28)	13 (22)
Hepatic hydrothorax (n, %)	2 (1)	0 (0)
Etiology of cirrhosis*		
ALD (n, %)	71 (40)	26 (44)
MetALD (n, %)	17 (10)	6 (10)
MASLD (n, %)	14 (8)	6 (10)
Viral (n, %)	21 (12)	5 (9)
Cryptogen (n, %)	21 (12)	4 (7)
Other (n, %)	34 (19)	13 (22)
MELD	12 (10–15)	11 (9–14)
FIPS	–0.22 (–0.85 to 0.14)	–0.20 (–0.63 to 0.05)
Child Pugh		
A (n, %)	25 (14)	12 (20)
B (n, %)	136 (77)	44 (75)
C (n, %)	16 (9)	3 (5)
Stent diameter (mm)		
10 (n, %)	14 (8)	3 (5)
8 (n, %)	158 (89)	51 (86)
6 (n, %)	5 (3)	5 (8)
PSG before TIPS (mmHg)	16.0 (13.1–19.0)	15.0 (13.0–17.5)
PSG after TIPS (mmHg)	5.2 (4.0–7.4)	5.0 (4.0–8.0)
% reduction of PSG	65 (56–73)	67 (52–71)
CHE (kU/L)	2.52 (1.82–3.82)	2.36 (1.69–3.77)
Bilirubin (μmol/L)	18 (11–28)	16 (9–27)
Creatinine (μmol/L)	97 (75–130)	97 (80–130)
Platelets (10^3/μL)	105 (72–171)	115 (67–212)
White blood cells (10^3/μL)	5.0 (3.7–7.7)	5.1 (3.5–7.5)
CRP (mg/L)	9.2 (4.0–21.9)	11.3 (3.4–22.0)
Albumin (g/L)	29 (26–35)	30 (27–36)
AST (U/L)	42 (32–53)	37 (30–48)
ALT (U/L)	26 (16–38)	24 (16–33)
γ-GT (U/L)	106 (64–186)	114 (57–203)
Antibiotic co-medication pre-TIPS		
Rifaximin	21 (12)	11 (19)
Norfloxacin	23 (14)	8 (14)
Either	42 (25)	18 (31)

Data are presented as median with IQR or numbers with percentages. Patients with missing data: PSG in n=6 (2 of which in SIM cohort); Co-medication in n=8 (0); CHE in n=2 (0).
SIM, soluble inflammatory marker; CHE, cholinesterase; ALD, alcohol related liver disease; MetALD, MASLD and increased alcohol intake; MASLD, metabolic dysfunction-associated steatotic liver disease; PSG, portosystemic pressure gradient; MELD, model for end-stage liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, gamma glutamyl transferase.
*Some patients have mixed TIPS indication and etiology of cirrhosis, resulting in a summation of percentages >100% in these columns.

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For 59 patients, blood samples were collected from the cubital vein (CV) at TIPS insertion and during structured follow-up (FU) at 1, 3, 6, and 12 months (FU1 through FU12) after TIPS insertion. Invasive blood sampling (EDTA plasma and Serum) during the TIPS procedure was conducted from the liver vein (LV) as well as from the portal vein (PV). PV samples were collected directly upon cannulating the right branch of the PV. Immediately after collection, all blood samples were centrifuged for 10 minutes at 3,000 rotations per minute followed by storage of the supernatants at –80°C until the measurements were conducted.

Laboratory assays

Plasma concentrations of 48 cytokines and chemokines were measured using the Luminex-based multiplex bead assay (Bio-Plex Pro™ Human Cytokine Assays, catalog no. 12007283, BioRad Laboratories, Hercules, CA, USA) following the manufacturer's instructions. Subsequently, samples were acquired using the BioPlex Manager™ software. For samples in which the concentrations were below the range of detection, the value was replaced by the lower limit of quantification divided by two. 5 of the 48 SIMs were excluded from analysis since >50% of samples were measured out of the range of the standard curve (IL-3, IL-5, IL-15, IL-16, MCP-3; Supplementary Table 3).

For quantitative determination of serum concentrations of sCD14 and sCD163, we utilized an enzyme-linked immunosorbent assay (ELISA) (Quantikine® ELISA Human CD163 and sCD14, Immunoassay [R&D Systems, Catalog Number DC 1630 and DC140]), adhering to the manufacturer's instructions, to measure the levels of sCD163 and sCD14 from the supernatant of serum samples.

Statistics

All statistical analyses were performed using SPSS (IBM SPSS Statistics, Version 26), GraphPad Prism (GraphPad Software, Version 5), and R Statistical Software (Version 4.2.0 with packages "cmprsk", "RCmdr", "rcmr.EZR plug-in", as well as "fsmb" R package version 0.7.6). Continuous variables are presented as median with interquartile range (IQR) or mean with standard deviation, as appropriate. Categorical variables are shown as numbers with percentages. Wilcoxon signed-rank test was used for comparison of paired continuous data. Chi-squared test or Fisher's exact test was used for comparison of categorical data, as required. Mann-Whitney U test was used for comparison of unpaired continuous data. For correlation analyses, we utilized Pearson correlation. SIM values were rank transformed and a mixed effect model was conducted to assess SIM changes over time after TIPS insertion with sample ID as the random effect. For the correlation analysis of association between portosystemic pressure gradient (PSG) and SIMs, we utilized the Spearman method. All analyses investigating multiple SIMs were adjusted for multiple testing employing the Benjamini & Hochberg method, yielding the false discovery rate (FDR), unless specifically stated otherwise.

To evaluate the effect of a CRP decrease from TIPS to 6–12 months thereafter on mortality, patients (n=98) were followed for further 365 days after the time point of the latter CRP value (Supplementary Fig. 2). In order to account for varying lengths of follow-up, we also integrated the decrease divided by months of follow-up into another analysis.

We conducted a cox regression analysis of the combined endpoint mortality and LTx during the previously described 1-year-follow-up. For enhanced readability, "mortality" will be used throughout the manuscript, though considering both endpoints. Due to a low number of events, we only adjusted for MELD in multivariable analysis. In competing risk analyses of clinical events undertaking the same aforementioned approach, LTx and death were treated as competing events.

In all analyses $P<0.05$ and FDR<0.05 were considered as statistically significant, with FDR<0.05 indicating significance after multiple testing correction.

Ethics

This study was approved by the local ethics committee of Hannover Medical School (vote: Hannover: 8498_BO_S_2019) and followed the principles outlined in the Declaration of Helsinki. All included patients provided written informed consent for the use of their clinical data and biosamples for research purposes. The prospective Hannover TIPS patient registry of Hannover Medical School is registered at ClinicalTrials.gov (trial number: NCT04801290). We confirm that all authors had access to the study data and have received and approved the final manuscript.

RESULTS

Baseline characteristics of the study cohort

Overall, 177 patients undergoing TIPS insertion at Hannover Medical School were included in this study. The median MELD score was 12, median age was 56 years and 61% of the patients were males. The median pre-interventional PSG was 16.0 mmHg and median post-interventional PSG was 5.2 mmHg, resulting in a median PSG reduction of 65%. The most frequent etiology of liver cirrhosis was alcohol-related liver disease (41%). RA was the predominant TIPS indication (76%, n=134) (Table 1). Baseline characteristics of the subgroup of patients, who were prospectively

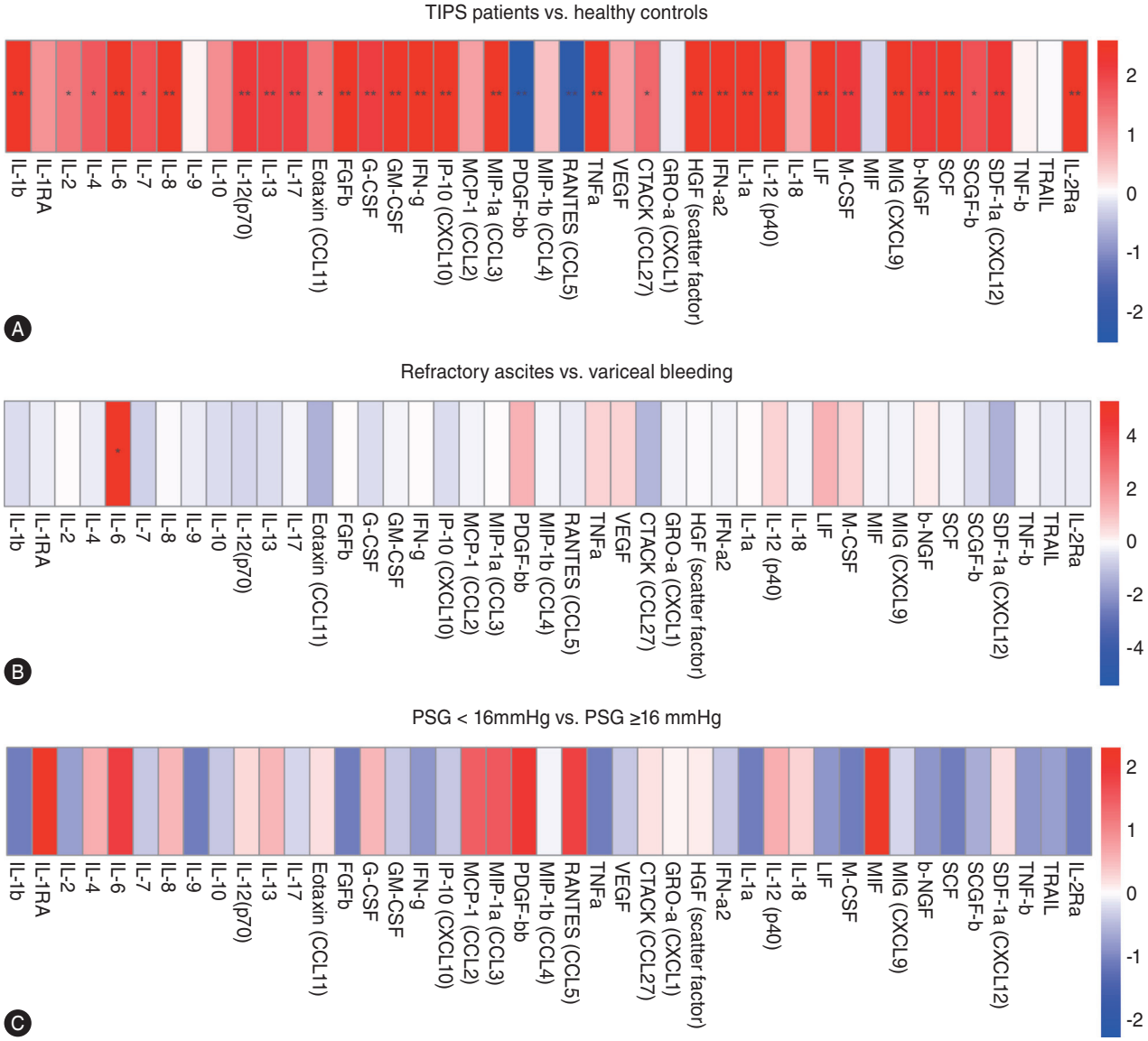

Figure 2. Comparison of SIM levels in the peripheral blood (A) of patients with decompensated liver cirrhosis compared to healthy controls and (B) in patients receiving a TIPS for RA compared to those receiving a TIPS for secondary prophylaxis of variceal bleeding and (C) in patients with a pre-TIPS PSG <16 mmHg compared to those with a pre-TIPS PSG ≥16mmHg. (A) n=5 healthy controls vs. n=58 baseline values of TIPS-patients; (B) n=45 TIPS indication RA vs. n=13 TIPS for variceal bleeding. (C) n=31 (PSG<16 mmHg) vs. n=26 (PSG≥16 mmHg); n=2 patients with missing PSG data were excluded. The color of the bar represents $-\log_{10}$(FDR)*(fold change between two groups). *FDR <0.05; **FDR <0.01. TIPS, transjugular intrahepatic portosystemic shunt; PSG: portosystemic gradient; SIM, soluble inflammatory marker.

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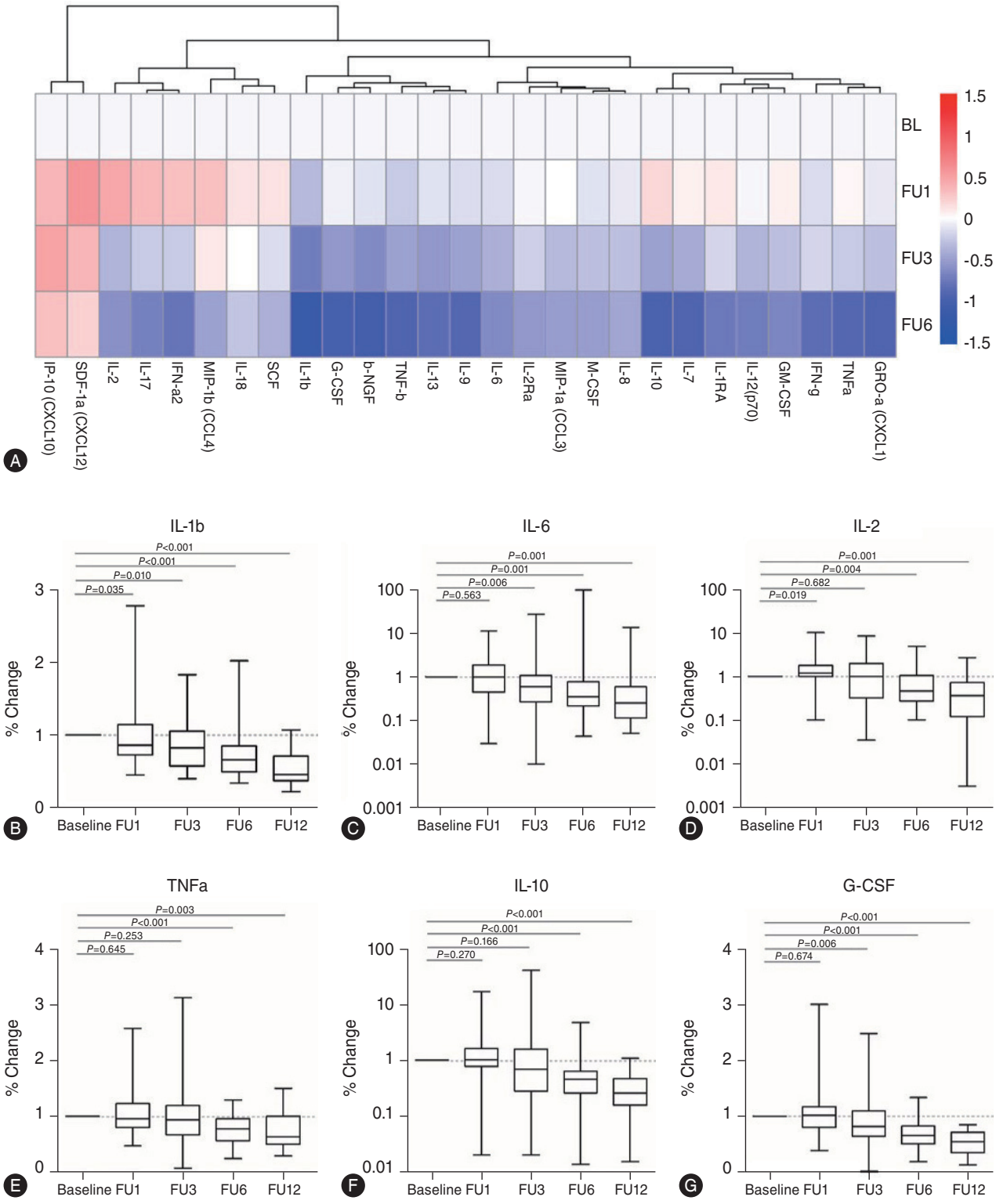

Figure 3. Course of systemic inflammation after TIPS insertion. (A) Heatmap shows SIMs with significant changes after TIPS insertion (FDR <0.05). Mixed effects model was used to assess the SIM changes after TIPS insertion with sample ID as random effect. The color of the bars represents the difference of the respective time point and baseline (FUX-BL). (B–G) shows courses of six representative SIMs. Wilcoxon signed rank test was used for comparisons. Whiskers visualize min to max. TIPS, transjugular intrahepatic portosystemic shunt; SIM, soluble inflammatory marker; BL, baseline; FU, follow-up.

enrolled in our TIPS patient registry and for whom a detailed SI analysis was performed, were similar to those of the entire cohort (Table 1).

Phenotype of systemic inflammation in different patient subgroups

Initially, baseline SIM levels were compared between patients with decompensated liver cirrhosis and healthy controls. As expected, the vast majority of SIM levels were significantly higher in the cirrhotic patients as compared to the healthy controls, affecting 30 of 43 SIMs (Fig. 2A). In contrast, the SIMs PDGF-bb (platelet-derived growth factor) and RANTES (CCL5) measured significantly higher in the control samples (FDR<0.01; Fig. 2A).

We then analyzed SI in patients receiving a TIPS for RA compared to those with secondary prophylaxis of variceal bleeding as TIPS indication. Interestingly, the pattern of SI did not differ between the two groups except for IL-6, which was significantly higher in patients with RA with a median of 7.35 pg/mL (IQR 3.8–14.9 pg/mL) vs. 2.73 pg/mL (IQR 1.1–4.4 pg/mL) than in those receiving a TIPS for variceal bleeding (FDR<0.05; Figs. 2B, 4; comparison of patient characteristics in Supplementary Table 4).

Lastly, we investigated the impact of PSG on SIM levels. When stratifying between patients with a lower degree of portal hypertension (PSG <16 mmHg) and those with a higher portal pressure (PSG ≥16 mmHg) prior to TIPS, we documented no statistically significant differences in the SIM pattern in patients with a lower compared to higher degree of clinically significant portal hypertension (Fig. 2C). A correlation analysis of PSG pre-TIPS and SIM levels also did not reveal any significant correlations after adjusting for multiple testing (Supplementary Fig. 3). Antibiotic co-medication (Rifaximin and Norfloxacin) was not found to influence SIM levels at baseline or during follow-up (Supplementary Tables 6, 7).

In addition to the measurement of SIM levels in the peripheral blood of the patients, we also analyzed the SI in the compartments PV and LV at the time of TIPS insertion. In this regard, we found significantly higher levels of IL-6, hepatocyte growth factor (HGF; scatter factor) and IL-12 (subunit p40) in the PV compared to the LV, suggesting an extrahepatic origin of these three SIMs (Supplementary Fig. 4).

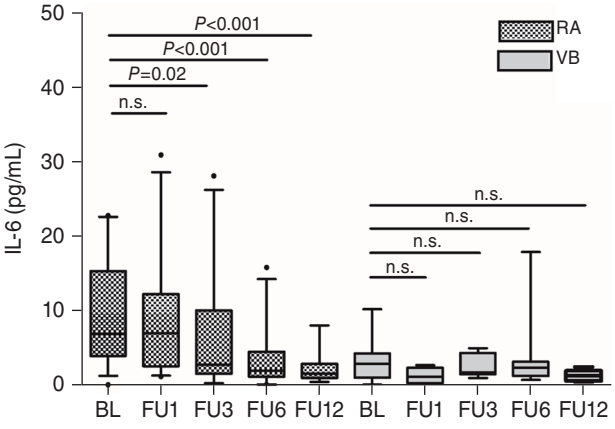

Figure 4. IL-6 levels before and after TIPS insertion in patients with TIPS indication refractory ascites and variceal bleeding. Shown is the course of IL-6 during 12-month follow-up after TIPS, stratified by TIPS indication (RA n=46 vs. VB n=13). Wilcoxon signed rank test was used for comparison. Whiskers show 95% CI with outliers as dots, the line within boxplots depicts the mean. IL-6, Interleukin 6; BL, baseline; FU, follow-up; RA, refractory ascites; VB, variceal bleeding; n.s., not statistically significant.

Distinct changes in systemic inflammation after TIPS insertion

Next, we conducted an in-depth analysis of the course of SI after TIPS insertion. Notably, at one month after TIPS insertion, most SIMs were still measured at levels comparable to baseline, with some, e.g., IL-2, even increasing (Fig. 3A). Interestingly, this finding was associated with MELD at FU1, which was significantly higher than pre-TIPS (12 vs. 11, P=0.039) (Supplementary Fig. 5).

However, during further follow-up, we documented a continuous decrease in the majority of SIMs. 25 SIMs, including IL-6 and IL-2, measured significantly lower at month 6 after TIPS compared to baseline (FDR<0.05; Fig. 3A). Seven SIMs had decreased to levels not significantly different from healthy controls by month 6 (Supplementary Fig. 6). SIM levels remained at lowered levels thereafter, indicating a sustained decrease. Interestingly, the two chemokines IP-10 (CXCL10) and SDF-1a (CXCL12) increased significantly shortly after TIPS implantation and remained at an elevated level until 6 months after TIPS insertion (FDR<0.05; Fig. 3A). The individual courses of six selected SIMs (IL-1β, IL-6, IL-2, TNFα, IL-10, and G-CSF) are shown in Figure 3B–G. The courses of the remaining SIMs are depicted in Supplementary Figures 7 and 8. We found no sig-

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nificant correlation between changes of SIM (BL to FU6) and the extent of TIPS-mediated PSG-reduction (Supplementary Figure 3). Of note, in patients with RA, the initially markedly elevated baseline IL-6 levels had dropped significantly at FU3 and reached the initially much lower IL-6 levels of patients without ascites at FU6 (BL 7.35 pg/mL to FU6 2.21 pg/mL (RA), vs. 2.48 pg/mL (VB) at FU6; Fig. 4).

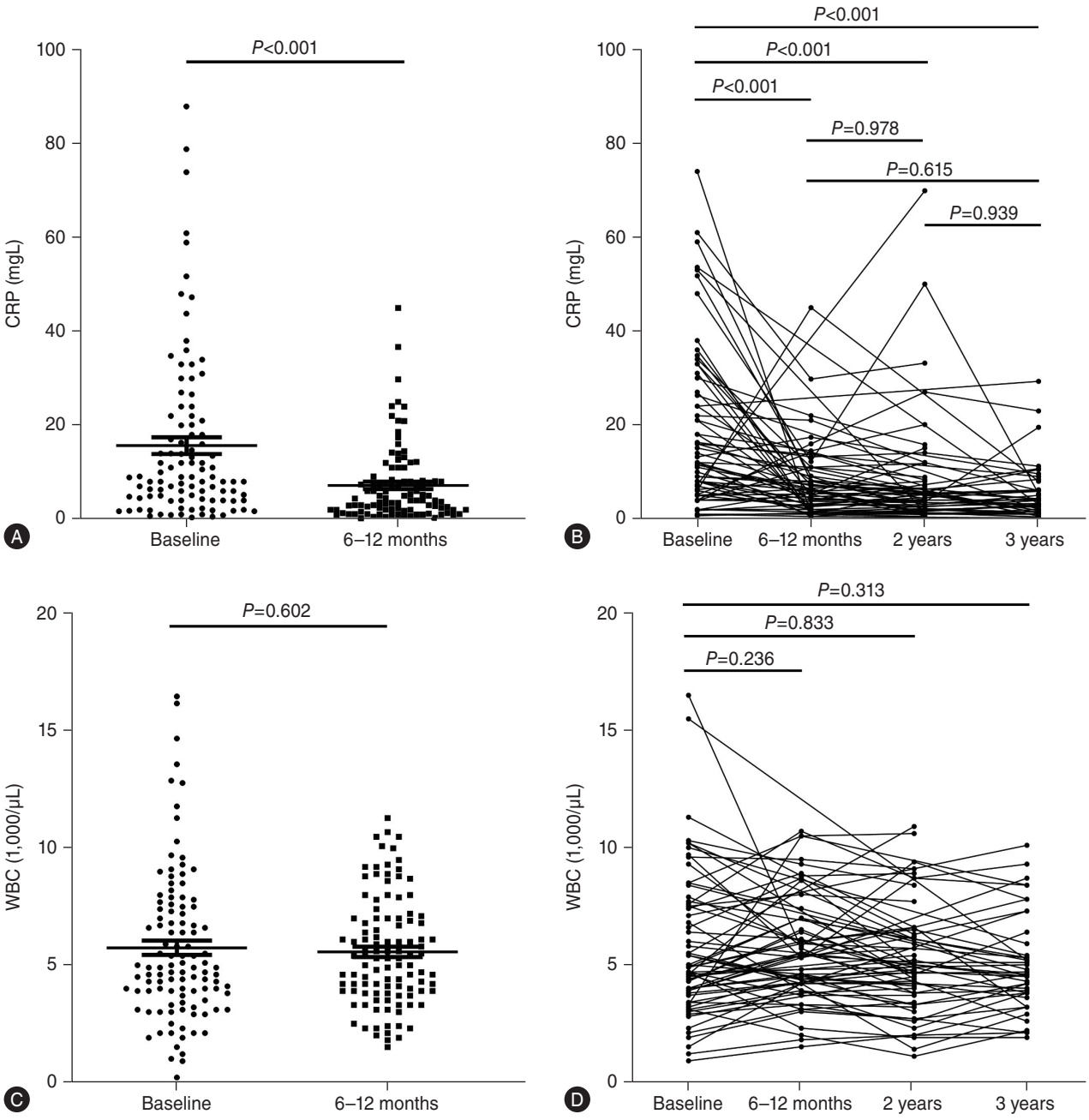

Figure 5. Course of CRP levels and white blood cells (WBC) in the long-term follow-up after TIPS insertion. Shown is the course of CRP levels from (A) baseline to 6–12 months after TIPS insertion (n=98) and (B) 2 and 3 years after TIPS implantation (n=65) as well as the course of WBC from (C) baseline to 6–12 months after TIPS insertion (n=109) and (D) 2 and 3 years after TIPS (n=68). Patients were included in the 2-3-year analysis if at least one of these long-term follow-ups was available. P-values were obtained using the Wilcoxon signed-rank test. CRP, C-reactive protein; WBC, white blood cells.

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Long-term kinetics of SI after TIPS insertion

For the analysis of SI during long-term follow-up after TIPS, we then analyzed the course of CRP and WBC levels for up to three years following TIPS insertion. Median CRP concentration at the time of TIPS insertion of patients with at least one follow-up was 9.0 mg/L (4.2–21.0 mg/L). CRP levels significantly decreased from baseline to 6–12 months after TIPS insertion (P<0.001; Fig. 5A). During further 1-year follow-up thereafter, 13 (13.3%) patients died and 5 (5.1%) patients underwent LTx. Of note, a higher absolute decrease in CRP levels per month from baseline to 6–12 months after TIPS insertion was associated with a significantly lower mortality in univariable Cox regression analysis (HR 0.847, 95% CI 0.726–0.988, P=0.035), barely missing statistical significance in multivariable analysis adjusting for MELD (HR 0.853, 95% CI 0.727–1.002, P=0.053) (Supplementary Tables 8, 9).

Furthermore, the course of CRP was analyzed in a subgroup of 65 patients, for whom data on CRP levels in the long-term follow-up after TIPS insertion were available. As shown in Figure 5B, CRP levels continued to decline from baseline to 2 and 3 years after TIPS insertion (2 years: 4.4 [1.7–8.6] mg/L, 3 years: 3.6 [1.8–6.7] mg/L). However, a further decline after 6–12 months was not statistically significant (6–12 M to 2 Y: P=0.978; to 3 Y: P=0.615), pointing towards a sustained reduction of CRP levels following TIPS. Intake of antibiotic co-medication did not impact CRP levels at baseline or during follow-up (Supplementary Fig. 9).

As WBC might also reflect SI, the course of WBC after TIPS insertion was examined in an additional analysis. The

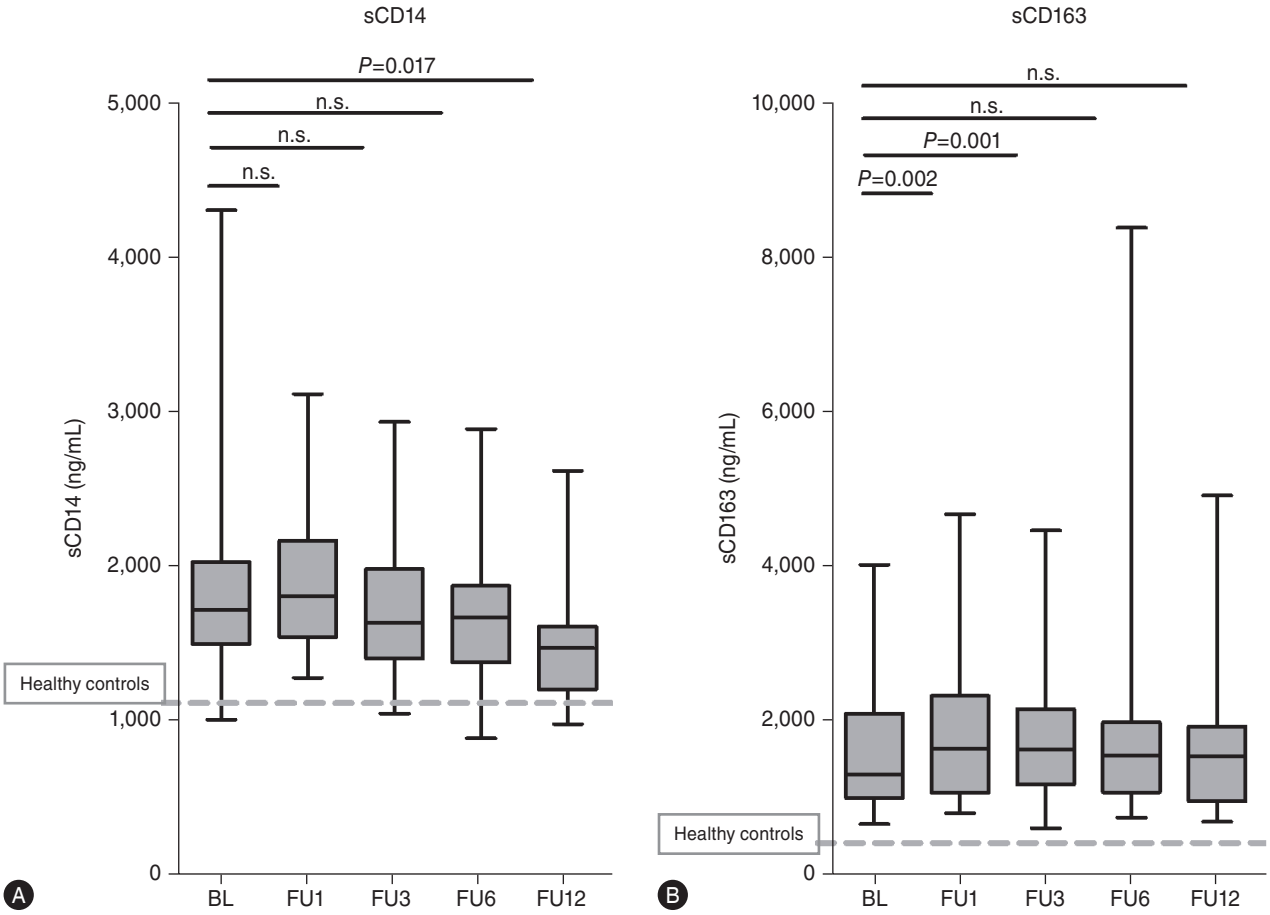

Figure 6. Course of sCD14 (A) and sCD163 (B) after TIPS insertion. Shown is the course of two surrogate markers of bacterial translocation, sCD14 (A) and sCD163 (B), at baseline and during follow-up after TIPS insertion. Whiskers show Maximum to Minimum, the line within boxplots depicts the mean. The grey dashed line on graphs indicates the mean level of respective sCD in healthy patients. sCD, soluble CD Receptor; BL, baseline; FU, follow-up; RA, refractory ascites; VB, variceal bleeding; n.s., not statistically significant.

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median WBC at the time of TIPS insertion was 5.0 10^3/μL (3.9–7.7 10^3/μL). WBC neither changed from baseline to 6–12 months nor from baseline to 2 and 3 years after TIPS insertion (Fig. 5C, D). Similarly, we did not find an association between a decrease of WBC per month from baseline to 6–12 months after TIPS insertion and a lower 1-year mortality (HR 1.051, 95% CI 0.212–5.216, *P*=0.95; Supplementary Table 8).

All aforementioned analyses were also performed in the subgroup of patients receiving a TIPS for RA. In this regard, similar results as documented in the overall cohort were obtained with respect to the course of CRP levels as well as the course of WBC after TIPS insertion (Supplementary Fig. 10). However, the link between CRP decrease per month during follow-up and LTx-free survival closely failed to reach statistical significance in this subgroup (HR 0.881, 95% CI 0.758–1.024, *P*=0.098; Supplementary Table 8).

Surrogate markers of bacterial translocation: sCD163 and sCD14

At baseline, both sCD14 and sCD163-levels were significantly higher in patients' blood as compared to healthy controls (sCD14: 1,714 [1,490–4,300] ng/mL vs. 1,174 [1,012–1,199] ng/mL, *P*<0.001; sCD163 1,292 [985–2,074] ng/mL vs. 388 [359–507] ng/mL, *P*<0.001; Fig. 6). Neither TIPS indication nor severity of PSG was found to significantly impact both markers. Measurements in LV and PV yielded comparable results for both markers, regardless of TIPS indication (Supplementary Fig. 11).

During follow-up, we demonstrated a statistically significant decrease of sCD14 to FU12 (BL: 1,714 [1,490–4,300] ng/mL vs. FU12: 1,465 [1,197–1,603] ng/mL; *P*=0.017). In contrast, sCD163 levels increased significantly to FU1 and FU3 after TIPS, before returning to levels similar to baseline (Fig. 6). Interestingly, this increase correlated with levels of IL-6 at FU1 and FU3 (FU1: Pearson r=0.501, *P*<0.001, FU3: r=0.525, *P*<0.001; Supplementary Fig. 12). Neither marker of bacterial translocation normalized to the level of healthy controls during follow-up.

Clinical course of patients and the interplay with systemic inflammation

We first assessed the impact of ascites post-TIPS on the investigated inflammatory markers. The majority of patients who had ascites pre-TIPS showed residual ascites at 3 months post TIPS, which was stratified into no, minimal and severe ascites in both the CRP- (no ascites n=9, minimal n=27, severe n=15) and SIM-cohort (no ascites n=15, minimal n=11, severe n=7; Supplementary Fig. 1) as assessed by sonography.

In our prospective cohort, IL-6 levels were found to be significantly increased in patients with severe ascites across all follow-ups compared to no ascites (FU1: 13.8 vs. 4.0 pg/mL; FU3: 8.5 vs. 1.6 pg/mL; FU6: 8.2 vs. 2.0 pg/mL; Supplementary Fig. 13). Notably, we also observed elevated CRP for as long as 2 years post TIPS insertion when comparing severe residual ascites with patients with resolved ascites (6–12 M: 7.5 vs. 2.9 mg/L; 2 Y: 6.4 vs. 0.95 mg/L), despite levels in these groups being comparable at baseline (Supplementary Fig. 14).

Having observed the significant association of CRP decrease with lower mortality, we also investigated further clinical events during follow-up (Supplementary Table 10). Interestingly, patients who showed a CRP decrease (n=70, 71.4%) between TIPS insertion and 6–12 months had a significantly lower incidence of both rehospitalizations and hepatic decompensations per month than patients that did not (hospitalizations: 0.14 vs. 0.24, *P*=0.017; hepatic decompensations: 0.20 vs. 0.31, *P*=0.026; Supplementary Table 11). In the other follow-up periods, the incidences did not differ significantly. Likewise, a competing risk analysis investigating CRP decrease to 6–12 months and the occurrence of clinical events during consecutive 1-year follow-up did not yield any significant results regarding any of the investigated endpoints (Supplementary Table 12).

DISCUSSION

In the present study, we investigated the course of SI and bacterial translocation after TIPS implantation. In this regard, we particularly focused on the detailed kinetics of 43 SIMs and surrogate markers of bacterial translocation (sCD14, sCD163) after TIPS insertion, as well as on the general course of SI in long-term follow-up after TIPS.

We first confirmed that SI and underlying bacterial translocation are unique characteristics of patients with decompensated liver cirrhosis,[18] since the majority (30/43) of SIMs

and both sCD14 and sCD163 were significantly elevated in the patients' blood compared to healthy controls. Interestingly, we did not find a significant impact of the severity of portal hypertension before TIPS on the investigated SIMs in our cohort. This finding is well in line with a study by Costa and colleagues, who analyzed the extent of portal hypertension (based on PSG) and SI (based on IL-6 and CRP levels) across distinct stages of ACLD.[3] The authors found that in decompensated liver cirrhosis, there is no strict linear correlation between SI levels and the degree of portal hypertension. IL-6 levels show a distinctly high increase across dACLD stages with IL-6 levels in stage 6 (patients with RA) being almost 6 times higher than in stage 3 (variceal bleeding as first decompensation).[3] When comparing the pattern of SI between patients with RA as TIPS indication with those receiving a TIPS for variceal bleeding, we found a similar pattern of SI except for a nearly threefold increase of IL-6 in patients with RA, thereby confirming the aforementioned findings.

While it is well established that SI is a chronic condition in patients with dACLD,[5,18] only a few studies have investigated the link between portal hypertension, and the possible attenuation thereof, on SI. Jachs et al. reported that a reduction in portal pressure via NSBB led to a decrease in WBC, CRP, and procalcitonin (PCT).[14] However, no detailed analyses of other SIMs were available and it remained uncertain whether results can be transferred to the post-TIPS setting. We did not document a significant change of WBC, which might be explained by non-hemodynamic, anti-inflammatory properties of NSBB.[15,19] Moreover, WBC were not relevantly elevated in our cohort at baseline. However, and in line with the data by Jachs and colleagues, we demonstrated a significant decrease in CRP levels. Interestingly, CRP levels seem to also be influenced by the course of ascites following TIPS insertion. Patients with resolved ascites, determined at 3 months post TIPS, showed significantly lower levels of CRP during subsequent follow-ups compared to patients with evidence of severe ascites. This is well in line with the aforementioned findings by Costa and colleagues, as patients with unresolved, severe ascites would remain to be characterized as stage 6 with high CRP, while others may transition to lower stages both in clinical (resolved ascites) and inflammatory phenotype (low CRP levels).

To date, only very limited data has been published on the effects of TIPS on a small number of selected SIMs and during short-term follow-up.[20-22] A study conducted by the group of Trebicka and colleagues investigated the kinetics of three SIM (CXCL9, CXCL10 and CXCL11) during 14 days of longitudinal sampling after TIPS.[20] Although the authors reported a prognostic value of declining CXCL10 and CXCL11 levels, they did not demonstrate a general significant decrease in this short-term study comprising mainly uncovered stents. Here, our study provides novel comprehensive insights into the dynamic changes to the inflammatory phenotype after TIPS insertion as characterized by 43 SIMs during 12 months of follow-up. Notably, we demonstrate that TIPS insertion in fact attenuates the chronic underlying SI in decompensated cirrhotic patients, evidenced by a significant decrease in the majority of SIMs, including the proinflammatory IL-6, IL-1β, TNFα and IFN-γ. Seven SIMs even decreased to levels not significantly different from those of healthy controls at FU6 after TIPS. Importantly, IL-6 levels of RA patients (stage 6 ACLD) showed a substantial decline six months after TIPS to levels documented in patients with variceal bleeding (stage 3 ACLD). Hence, we were able to demonstrate that TIPS not only reduces SI, but may lead to a reversal of ACLD stages. Importantly, our data on CRP levels indicate that this SI reversal is sustained even during longer follow-up, and that an attenuation of SI is linked to an improved survival. These findings are very well in line with recent clinical data demonstrating an overall improved outcome and an alleviated risk of further hepatic decompensation after TIPS.[11]

Despite reporting an overall decrease of SI after TIPS, we observed that some SIMs, e.g., IL-2, SDF-1a and IP-10, increased shortly after TIPS implantation (FU1). SDF-1a and IP-10 are pleiotropic chemokines that are described to be involved in tissue regeneration and angiogenesis upon liver injury,[23,24] which might explain the upregulation in the first month following the parenchymal damage caused by TIPS insertion. Additionally, the traumatic shunt insertion through already chronically damaged liver parenchyma may lead to an increased release of damage-associated molecular patterns (DAMPs) from necrotic hepatocytes, which might also trigger an inflammatory response.[18] This inflammatory response may provide an explanation for the significant increase in MELD in our study and the higher rate of clinical complications, i.e., hepatic encephalopathy and hydropic decompensation documented in previous

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studies within the first month following TIPS insertion.[25,26]

Finally, we analyzed the impact of TIPS on bacterial translocation indicated by sCD163 and sCD14. sCD163 is a specific marker of macrophage, specifically Kupffer cell, activation upon exposure to gut-derived pathogen-associated molecular patterns (PAMPs).[27,28] Levels of sCD163 correlate with the severity of portal hypertension and are chronically elevated in patients with liver cirrhosis,[27] which we confirmed in our study. One study has previously reported on the effect of TIPS on sCD163 and found neither a statistically significant decrease nor a normalization of sCD163 levels during 26-week follow-up, despite reporting a normalization of lipoprotein-binding protein (LBP) in the sense of an alleviation of bacterial translocation.[28] Our findings regarding the lack of decrease and normalization of sCD163 levels are similar to those of Holland-Fisher et al., who hypothesized a constitutive change in Kupffer cell phenotype, not requiring constant stimulation by endotoxins, as the reason for the persistent upregulation of sCD163.[28] However, the initial increase of sCD163 during short-term follow-up in our patients might be interpreted as a reaction to the DAMP release and subsequent SI response during TIPS insertion, as any acute phase response stimulates the expression of the cell surface receptor CD163 on Kupffer cells and macrophages.[28]

To further understand the role of bacterial translocation and associated endotoxemia, we analyzed sCD14. The CD14 receptor is vital for the detection of LPS in the liver and consequently for the activation of circulating neutrophils, including the induction of systemic inflammatory reaction.[18,29] Soluble CD14 (sCD14) has been shown to significantly increase upon LPS administration, indicating its role as an acute-phase reactant released by hepatocytes upon bacterial translocation.[18,29] Of note, sCD14 levels significantly decreased from TIPS insertion to 12 months thereafter, pointing towards an attenuation of bacterial translocation and restoration of gut barrier. We also found a statistically significant correlation between sCD14 levels and IL-6 during follow-up, backing the mechanism of SI stimulation through CD14 in the liver. Interestingly, sCD14 did not increase shortly after TIPS, unlike sCD163, which might be related to the new shunt. Consequently, a large proportion of blood bypasses the liver tissue and thereby also the Kupffer cells with CD14 receptors, which we hypothesize might result in an at least transiently, relatively lowered sCD14 secretion despite the systemic inflammatory reaction shortly after TIPS implantation.

Our study also has some important limitations to consider. The cohort size of patients with SIM measurements limited the analysis of clinical endpoints, despite our cohort constituting the largest comprehensive study on SI after TIPS to date. However, the superior survival associated with CRP decrease suggests a translation into improved outcomes warranting larger prospective studies. Due to the aforementioned sample size, we also did not perform extensive subgroup analyses for the course of individual SIM after TIPS insertion, except for the significantly different levels of IL-6 between the respective TIPS indications. Yet, a subgroup analysis in the larger retrospectively investigated cohort for the course of CRP and WBC after TIPS, in which we only included patients receiving their TIPS for RA, confirmed the results obtained for the entire cohort.

Due to low numbers of TIPS revisions and large time variations thereof, the impact of alterations of TIPS diameter on subsequent inflammatory markers remains of interest for further studies. Lastly, the scope of this manuscript did not allow for a detailed analysis of all co-medications and their effects on SI; however, we could demonstrate that antibiotic co-medication did not impact markers, and a recently published study reported no impact of NSBB post-TIPS on SI or clinical events.[30]

In summary, our study demonstrates that decreasing portal hypertension via TIPS implantation leads to a significant improvement of SI as measured by SIMs, CRP and WBC over time. Declining sCD14 levels point towards an attenuated bacterial translocation as one mechanism behind this amelioration of SI. This TIPS-mediated amelioration of SI may ultimately lead to a better clinical outcome, as we found CRP decrease to translate into a superior survival. However, larger studies are needed to determine the prognostic value of individual SIMs.

Authors' contribution

Guarantor of the article: Anja Tiede. AT and LS: Study concept and design, data acquisition, analysis, interpretation of the data, drafting of the manuscript and critical revision thereof for important intellectual content. ZL and CJX: Data analysis, critical revision of the manuscript for important intellectual content. JBH and BCM: TIPS insertion and data acquisition, critical revision of important intellectual

content. HR, JBM, VO, BB and JW: Data acquisition, critical revision of the manuscript for important intellectual content. AK, MC, HW and CSF: Interpretation of the data, critical revision of the manuscript for important intellectual content. BM: Supervision, study concept and design, interpretation of the data, drafting the manuscript, critical revision of the manuscript for important intellectual content. All authors approved the final version of this manuscript including the authorship list.

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Conflicts of Interest

BM: Lecture and/or consultant fees from AbbVIe, Fujirebio, Gilead, Luvos, MSD, Norgine, Roche, W.L. Gore & Associates. Research support from Altona, EWIMED, Fujirebio and Roche.

HW: Lecture and/or consultant fees from Abbott, Bristol-MyersSquibb, Hoffmann-La Roche, Roche, Gilead, GlaxoSmithKline, Janssen, Vir Biotechnology. Research support from Abbott and Biotest. MC: Lecture and/or consultant fees from AbbVie, AiCuris, Falk, Gilead, GlaxoSmithKline (GSK), Janssen, Merck/MSD, Novartis, Roche, Swedish Orphan Biovitrum (SOBI). All other authors declare that they do not have any relevant conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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