Research Article
Cirrhosis and Liver Failure

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Systemic inflammation increases across distinct stages of advanced chronic liver disease and correlates with decompensation and mortality

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Background & Aims: Distinct prognostic stages of advanced chronic liver disease (ACLD) are defined by severity of portal hypertension (PH) and the presence/absence of clinical complications. We characterised the degree of liver dysfunction, PH, and systemic inflammation across the distinct prognostic stages and assessed their relative impact on decompensation and mortality.

Methods: A single-centre, prospective cohort of ACLD patients undergoing hepatic venous pressure gradient (HVPG) measurement between 01/2017 and 08/2019 were classified into 6 prognostic stages: mild PH (HVPG 6–9 mmHg, S0), clinically significant PH (HVPG ≥10 mmHg without varices, S1), presence of varices (S2), history of variceal bleeding (S3), first non-bleeding decompensation (S4), and further decompensation (S5). The model for end-stage liver disease (MELD), C-reactive protein (CRP), and IL-6 levels were assessed in relation to their predictive value for decompensation and death.

Results: Among 168 ACLD patients 78 had compensated (cACLD, S0 = 13; S1 = 21; S2 = 44) and 90 had decompensated (dACLD, S3 = 10; S4 = 58; S5 = 22) disease. MELD increased across all stages (p <0.001), whereas HVPG mostly increased within cACLD substages. Significant increases in CRP and IL-6 levels were only noted across dACLD substages. IL-6 was an independent predictor of decompensation at 1-year follow-up in cACLD (hazard ratio [HR] 1.06, 95% CI 1.01–1.10; p = 0.013). In dACLD patients, IL-6 levels predicted death/transplantation after 1-year of follow-up (HR 1.02, 95% CI 1.01–1.03; p = 0.004).

Conclusion: HVPG progression occurs mostly in cACLD patients, whereas systemic inflammation, as reflected by IL-6 levels, only increases substantially across dACLD stages. IL-6 levels correlate with the risk of first decompensation in cACLD and of death/transplantation in dACLD patients.

Lay summary: Patients with advanced chronic liver disease (ACLD; *i.e.* liver cirrhosis) have a certain risk of mortality according to their stage of disease. Progression of disease is greatly influenced by increased pressure in the portal venous system (*i.e.* portal hypertension) and occurrence of clinical complications (*i.e.* decompensation). Our study demonstrates that systemic inflammation markedly increases across highest disease stages, and the inflammation biomarker IL-6 in blood may specifically indicate risk of disease progression in patients with ACLD.

Clinical Trials registration: The study is registered at ClinicalTrials.gov (NCT03267615).

Introduction

The clinical course of advanced chronic liver disease (ACLD) is characterised by a transition from a clinically compensated state (cACLD) to a symptomatic decompensated state (dACLD) which indicates a considerably increased risk for mortality.[1,2] Portal hypertension (PH) represents a key driver of decompensation and mortality in ACLD patients.[3] Moreover, patients with ACLD are at risk of developing acute-on-chronic liver failure (ACLF), a systemic inflammatory syndrome associated with multi-organ dysfunction.[4,5] Considering the different risks of disease progression and mortality, growing evidence suggests that the natural history of cirrhosis, i.e. ACLD, should be described by a multistate model.[2,6] The Baveno IV consensus conference[7] redefined cirrhosis in 4 substages, however, more recently, compensated cirrhosis has been subdivided into mild portal hypertension (hepatic venous pressure gradient [HVPG] of 6–9 mmHg), clinically significant PH (CSPH; HVPG ≥10 mmHg but without varices), and presence of gastroesophageal varices

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(GEV).[2,8] Three substages with increasing risk of mortality have been proposed for dACLD, defined by the occurrence of variceal bleeding alone, any first non-bleeding decompensating event (mostly frequently ascites) and any further decompensating event.[2]

This multistate model enables a prognostic classification of patients regarding their distinct risks for different clinical outcomes.[2,6] The Child-Pugh[9] and model for end-stage liver disease (MELD)[10,11] scores are currently used to define prognosis by assessing liver dysfunction, but do not necessarily reflect the dynamic clinical state of patients with cirrhosis.[6] Measurement of HVPG provides an accurate assessment of portal pressure and is the best predictor of the development of GEV[12] and decompensation.[3] In addition to the severity of PH, systemic hemodynamic derangements play an important role in the development of further decompensating events such as refractory ascites and hepatorenal syndrome (HRS).[3,6,13] More recently, is has been recognised that systemic inflammation (SI) increases with severity of PH and circulatory dysfunction and may be a key driver of clinical detoriation.[14,15] Abnormal translocation of bacteria and pathogen-associated molecular patterns from the intestinal lumen into the portal and systemic circulation is considered the main pathophysiological mechanism of SI in cirrhosis,[15,16] highlighting the central role of the gut–liver axis.[17] Although acute decompensation may be triggered by significant SI, the exact chronological relationship between bacterial translocation, SI, and decompensation currently remains elusive.[16]

A better understanding of the pathophysiological factors driving the transition across ACLD stages is necessary to redefine therapeutic strategies. To this end, a comprehensive characterisation of the interplay between hepatic dysfunction, severity of PH, and SI is required. Thus, this study was designed (i) to characterise the progression of liver dysfunction, PH and SI across distinct prognostic clinical stages of ACLD and (ii) to evaluate their relative impact on the risk for decompensation and mortality.

Patients and methods

Study design and patients

We performed a prospective, observational, single-centre cohort study in consecutively recruited patients with ACLD undergoing HVPG measurement at the Vienna General Hospital of the Medical University of Vienna between January 2017 and August 2019. Inclusion criteria were (i) confirmed diagnosis of ACLD (based on clinical, biochemical, imaging, and/or histological criteria) and (ii) HVPG >5 mmHg confirming the presence of PH. Patients meeting any of the following criteria were excluded: age <18 years, HVPG measurement while on non-selective beta-blockers (NSBBs), ACLF, active bacterial infection at evaluation, hepatocellular carcinoma, active alcohol abuse, previous transjugular intrahepatic portosystemic shunt (TIPS) insertion, occlusive portal vein thrombosis, or liver transplantation (LT), and chronic kidney disease. The study was conducted in accordance with the principles of the Declaration of Helsinki, was approved by the local ethics committee and registered at www.clinicaltrials.org (NCT03267615). All patients gave written informed consent for participation in this study.

Clinical stages of ACLD

Patients were classified according to the recently defined clinical prognostic stages, adapted from D'Amico *et al.*[2] Compensated ACLD (cACLD) was defined as absence of any decompensation event and cACLD was further divided into 3 substages: stage (S) S0: subclinical PH with HVPG 6–9 mmHg; S1: CSPH with HVPG ≥10 mmHg without GEV; S2: presence of GEV. Decompensated ACLD (dACLD) was defined by the presence or history of at least 1 decompensating event, that is ascites, variceal bleeding, and overt hepatic encephalopathy (HE). Importantly, overt HE was not observed in the absence of other decompensating events in our cohort. Moreover, as diagnosis of covert HE is challenging and its prognostic value remains to be defined,[2] covert HE was not considered as a decompensation event in this study. Patients with dACLD were subclassified into 3 substages: S3: history of acute variceal bleeding; S4: first non-bleeding decompensation (mostly frequently ascites); S5: further decompensation as defined by either ascites plus bleeding, refractory ascites according to International Ascites Club criteria,[18] HRS, or spontaneous bacterial peritonitis (SBP).

HVPG measurement

HVPG measurement was performed within this study to establish the diagnosis of CSPH for prognostication as supported by current guidelines.[19,20] Briefly, under local anaesthesia and ultrasound guidance, a catheter introducer sheath was inserted into the right internal jugular vein. Subsequently, a hepatic vein was cannulated, and the free and hepatic venous pressures were obtained at least as triplicate measurements using a balloon catheter,[21] according to a standardised protocol, as previously described in detail.[22]

Clinical and laboratory parameters

In addition to routine laboratory tests used to compute MELD and Child-Pugh scores as measures of liver dysfunction severity, serum levels of C-reactive protein (CRP) and interleukin-6 (IL-6) were assessed as biomarkers of SI at the time of liver vein catheterisation. Determination of CRP (upper limit of normal, ULN <0.5 mg/dl) and of IL-6 (ULN <7 ng/dl) was performed at the ISO-certified laboratory of the Vienna General Hospital following the manufacturer's instructions.

Clinical follow-up for outcomes and mortality

Patients were followed after HVPG until their last clinical visit, LT, or death. First decompensation was the main outcome parameter of interest in patients with cACLD (stages S0–S2), whereas liver-related mortality/LT was considered the main outcome parameter of interest for patients with dACLD (stages S3–S5).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 25 (IBM, New York, NY, USA) or GraphPad Prism 8 (GraphPad Software, CA, USA). Categorical variables were reported as absolute frequencies (n) and relative frequencies (%); continuous variables as mean ± SD or median with IQR, as appropriate. Normal distribution was assessed by Kolmogorov-Smirnov and Shapiro-Wilk tests. Kruskal-Wallis test was used to compare

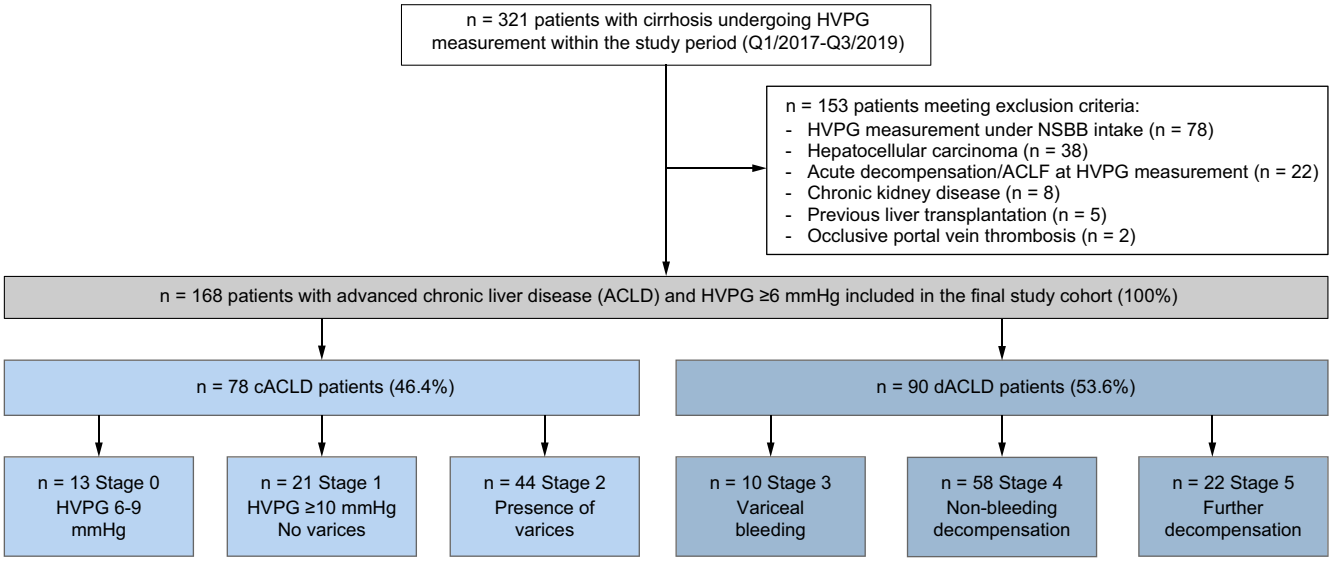

Fig. 1. Patient flow chart. ACLD, advanced chronic liver disease; ACLF, acute-on-chronic liver failure; cADLD, compensated ACLD; dACLD, decompensated ACLD; HVPG, hepatic venous pressure gradient; NSBB, Non-selective beta-blockers; Q, quartile.

non-parametric continuous variables and when significant differences were attained, Mann-Whitney U test with Bonferroni correction was applied. One-way ANOVA with Tukey *post-hoc* test was used to compare parametric continuous variables. The analyses of clinical outcomes (decompensation and liver-related mortality/transplantation) were performed separately for cACLD and dACLD patients. The time-dependent incidence rate of events of interests was obtained from Kaplan-Meier estimates and comparison of cumulative incidence curves was performed by the log-rank test. Multivariable analysis of independent predictors of the event of interest was performed by a backward stepwise Cox proportional hazards regression model considering the clinical outcome 1 year after HVPG measurement. The level of significance was set at 2-sided p value <0.05.

Results

Patients characteristics

During the study period, 321 patients with ACLD underwent HVPG measurement, of whom 168 fulfilled the inclusion and no exclusion criteria and were finally included in this study (Fig. 1 and Table 1). The median age was 57.2 years and most patients were male (n = 114, 67.9%). The main aetiologies were alcohol-related liver disease (n = 77, 45.8%) and viral hepatitis (n = 36, 21.4%). At baseline, 78 (46.4%) patients were compensated with 13 (16.7%) in substage S0 (HVPG 6–9 mmHg), 21 (26.9%) in S1 (HVPG ≥10 mmHg without GEV), and 44 (56.4%) in S2 with GEV. Representative liver biopsy specimens were available in 59 (35.1%) patients for histological confirmation of cirrhosis. Among patients with dACLD (n = 90, 53.6%), 10 (11.1%) had experienced variceal bleeding (S3); 58 (64.4%) had ascites (S4), and 22 (24.4%) had further decompensation (S5). Within decompensated substage S5, 7 patients had ascites and bleeding, 11 patients had refractory ascites, 6 had hepatorenal syndrome, 3 had SBP (some patients had more than 1 further decompensation event).

Progressive hepatic dysfunction was observed by increasing MELD across the distinct substages (median 9 in S0 to 14 in S5), with a significant difference noted in the transition from cACLD to S4 and to S5 (p <0.001; Fig. 2). Naturally, the Child-Pugh score significantly differentiated compensated from decompensated ACLD, however, it had a lower discriminative ability to distinguish the clinical substages (Table S1). HVPG progressively increased across clinical substages with most pronounced increases within the cACLD substages (median 8 mmHg in S0 to 17.5 mmHg in S2) and no significant difference was observed between S4 and S5 (Fig. 2). Regarding SI, both CRP and IL-6 increased only across the dACLD substages with IL-6 levels being significantly higher in S4 (median 10.6 pg/ml) and S5 (median 28.2 pg/ml) as compared with S0 (median 4.7 pg/ml) and to S2 (median 5.7 pg/ml; Fig. 2). The proportion of patients that showed IL-6 and CRP levels within the normal range were 70.0% and 83.3%, respectively, in cACLD, but only 29.3% and 46.7% of dACLD patients, respectively, had normal IL-6 or CRP values.

Interestingly, the degree of SI in patients with a history of variceal bleeding (S3: IL-6 median 5.7 pg/ml) was similar to the patients with cACLD (S0–S2: IL-6 median 5.8 pg/ml; p = 0.825) and SI was also significantly less pronounced as compared to the "next" dACLD substages (S4: IL-6 median 10.6 pg/ml; p = 0.009) and to the subgroup of dACLD S5 patients with a history of variceal bleeding (IL-6 median 12.3 pg/ml; 0.034). The time periods from previous variceal bleeding to the assessment of SI (*i.e.* IL-6 level determination) were a median of 18.9 months in S3 and 16.2 months in S5. Notably, there were no significant differences in IL-6 values between this subgroup of S5 patients and S4, p = 0.519 (Fig. S1). White blood cell (WBC) counts were similar between patients with cACLD and dACLD, p = 0.242 (Fig. S2).

Follow-up events and clinical outcomes

The median follow-up of the included study cohort was 12.2 months. The number of events per clinical state are displayed in Table 1 and Table S1. Among cACLD patients, 1 (1.3%) patient transitioned to S3, 8 (10.3%) patients to S4 and 1 patient (1.3%) to S5. Overall, 5 (6.4%) patients died, liver-related death was

recorded in 3 (3.8%) of patients. Among the dACLD patients, 2 (20%) patients in S3 experienced variceal re-bleeding and 4 (40%) patients progressed to substage S5 as a result of further decompensation. In substage S4 patients, 3 patients underwent LT and 10 (17.2%) patients progressed to S5 (*i.e.* experienced further decompensation. In S5, 4 (18.8%) patients underwent LT. The liver-related death rates were 10%, 10.3%, and 22.7% in the substages S3, S4, and S5, respectively.

First decompensation in cACLD

The 12-month probability of developing a decompensation event was 0%, 6%, and 16%, for substages S0, S1, and S2, respectively (Fig. 3A). Despite numerically higher risk for decompensation in stage S2 patients with varices, the difference did not attain statistical significance ($p = 0.297$). cACLD with elevated IL-6 (≥7 pg/ml) or CRP (≥0.5 mg/dl) levels did only show a non-significantly increased probability of developing a first decompensation event (Fig. 3B and C). Importantly, after adjusting for covariables using a multivariate Cox proportional hazard regression model IL-6 levels were an independent predictor of decompensation at 1-year follow-up (hazard ratio, HR: 1.06; 95% CI: 1.01–1.10; $p = 0.013$) with MELD showing a strong trend towards significance (HR 1.04; 95% CI: 1.00–1.62; $p = 0.054$; see Model 1 in Table 2). When including CRP instead of IL-6 using into the multivariate Cox regression, CRP (HR 1.90; 95% CI 0.97–3.74; $p = 0.062$) and HVPG (HR 1.13; 95% CI 1–1.28; $p = 0.059$) had a strong but non-

Table 1. Patient characteristics at baseline HVPG measurement and follow-up events in the 6 substages of ACLD.

	Compensated (n = 78 patients, 46.4%)			Decompensated (n = 90 patients, 53.6%)			
	Stage 0	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**	**Stage 5**	***p* value**
Definition	HVPG 6-9	HVPG ≥10	GEV	Bleeding	Ascites	Further decompensation[a]	
Patients, n	**13**	**21**	**44**	**10**	**58**	**22**	
Age (years)	52.3 (16.0)	55.4 (17.0)	58.8 (16.0)	52.7 (8.0)	57.2 (16.0)	60.5 (14.0)	0.142
Sex; male; n (%)	10 (76.9)	11 (52.4)	31 (70.5)	7 (70.0)	38 (65.5)	17 (77,3)	0.550
Aetiology; n (%)							
ALD	5 (38.5)	2 (9.5)	9 (20.5)	6 (60.0)	42 (72.4)	13 (59.1)	
VIRAL	4 (30.8)	9 (42.9)	14 (31.8)	3 (30.0)	3 (5.2)	3 (13.6)	
ALD+VIRAL	0 (0.0)	4 (19.0)	3 (6.8)	0 (0.0)	7 (12.1)	2 (9.1)	
NASH	1 (7.7)	3 (14.3)	11 (25.0)	0 (0.0)	1 (1.7)	2 (9.1)	
CHOL	0 (0.0)	2 (9.5)	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	
OTHER	3 (23.1)	1 (4.8)	4 (9.1)	1 (10.0)	5 (8.6)	2 (9.1)	
GEV; n (%)							
Small GEV	0 (0.0)	0 (0)	25 (56.8)	0 (0.0)	18 (31.0)	7 (31.8)	
Large GEV	0 (0.0)	0 (0)	19 (43.2)	10 (100.0)	20 (34.5)	9 (40.9)	
Child-Pugh score	5 (0.0)	5 (0.0)	5 (1.0)	5 (1.0)	8 (2.0)*†‡§	8 (2.0)*†‡§	**<0.001**
MELD	9 (5.0)	9 (2.0)	10 (4.0)	11 (3.0)	13 (6.0)*†‡	14 (4.0)*†‡	**<0.001**
MELD-Na; x (SE)	8.9 (3.0)	10.0 (2.8)	10.6 (3.6)	11.1 (2.5)	16.2 (4.8)*†‡§	16.5 (4.6)*†‡§	**<0.001**
HVPG (mmHg)	8 (3.0)	13 (3.0)*	17.5 (9.0)*	16.5 (5.0)*†	19.5 (7.0)*†‡	20 (8.0)*†	**<0.001**
Heart rate (per min)	76 (25.0)	82 (26.0)	72 (17.0)	68.5 (7.0)	80 (26.0)	81 (24.0)	0.119
MAP (mmHg)	102 (22.0)	98 (26.0)	109 (17.0)	98.5 (22.0)	98 (19.0)	96 (19.0)	0.082
Hb (g/dl)	13.9 (2.2)	13.3 (1.5)	12.2 (2.3)*†	11.4 (2.8)*†‡	11.3 (2.2)*†‡	9.7 (3.1)*†‡¶	**<0.001**
PLT (G/L)	106 (56.0)	127 (62,8)	81.5 (33)*†	63 (77.5)*†	107 (62.8)‡§	107.5 (119.3)‡§	**<0.001**
WBC (G/L)	5.2 (3.2)	6.7 (2.9)	3.5 (2.1)*†	3.2 (3.3)*†	4.9 (2.5)‡§	4.3 (2.9)	**<0.001**
Creatinine (mg/dl)	0.8 (0.3)	0.7 (0.3)	0.7 (0.3)	0.8 (0.5)	0.7 (0.3)	1.0 (1.0)	0.116
Sodium (mmol/L)	140 (3.0)	140 (3.0)	140 (4.0)	140.5 (4.3)	136 (4.0)*†‡§	137 (9.3)^	**<0.001**
Bilirubin (mg/dl)	0.8 (0.4)	1.0 (0.8)	0.9 (0.8)	1.0 (0.6)	1.6 (1.8)*†‡	1.1 (1.7)	**0.001**
Albumin (g/L)	41.9 (5.4)	39.8 (4.3)	39.7 (6.2)	39.7 (4.8)	33.8 (7.0)*†‡§	32.4 (6.8)*†‡§	**<0.001**
INR	1.2 (0.2)	1.2 (0.3)	1.3 (0.3)	1.4 (0.2)	1.5 (0.3)*†‡	1.5 (0.4)	**<0.001**
CRP (mg/dl)	0.1 (0.2)	0.2 (0.3)	0.2 (0.3)	0.1 (0.1)	0.5 (0.9)*†‡§	1.0 (2.4)*†‡§	**<0.001**
IL-6 (pg/ml)	4.7 (2.7)	7.0 (9.2)	5.7 (4.6)	5.7 (6.9)	10.6 (14.9)*‡	28.2(42.8)*†‡§¶	**<0.001**
LBP (μg/ml)	7.2 (2.7)	6.6 (2.3)	6.5 (2.5)	5.7 (2.0)	6.8 (4.4)	8.9 (6.1)	0.052
PCT (ng/ml)	0.04 (0.06)	0.08 (0.07)	0.07 (0.06)	0.05 (0.1)	0.1 (0.1)*	0.1 (0.1)*	**0.001**
FU event[b], n (%)	**0 (0)**	**2 (9.5%)**	**9 (20.5%)**	**6 (60%)**	**13 (22.4%)**	**11 (50.0%)**	
Decompensation[c]	–	2 (9.5%)	9 (20.5%)	6 (60%)	10 (17.2%)	7 (31.8%)	
Liver-related death	–	1 (4.8%)	2 (4.5%)	1 (10%)	6 (10.3%)	5 (22.7%)	
LT	–	–	–	1 (10%)	4 (6.9%)	4 (18.2%)	

Unless indicated otherwise, metric variables are presented as median (IQR).
ALD, alcohol-related liver disease; CHOL, cholestastic liver disease; CRP, C-reactive protein; FU, follow-up; GEV, gastroesophageal varices; Hb, haemoglobin; HR, heart rate; HVPG, hepatic venous pressure gradient; INR, international normalised ratio; IL-6, interleukin-6; LBP, lipopolysaccharide binding protein; LT, orthotopic liver transplantation; MAP, mean arterial pressure; MELD, model for end-stage liver disease; MELD-Na, MELD including serum sodium; NASH, non-alcoholic steatohepatitis; PCT, procalcitonin; PLT, platelet count; WBC, white blood cell count.
Statistical analysis: Kruskal-Wallis and one-way ANOVA were used to compare non-parametric and parametric variables, respectively.
[a]Stage 5 includes patients with further decompensation due to ascites and bleeding, refractory ascites, hepatorenal syndrome, or spontaneous bacterial peritonitis.
[b]Median follow-up duration was 12.2 months (max. 36.8 months).
[c]Considering first decompensation in cACLD patients, and further decompensation in dACLD patients.
*p <0.05 when compared to stage 0.
†*vs.* stage 1.
‡*vs.* stage 2.
§*vs.* stage 3.
¶*vs.* stage 4.

significant independent predictive value for first decompensation in cACLD (see Model 2 in Table 2).

Predictors of mortality and/or LT in dACLD

The 3 substages within dACLD patients were associated with a progressively increasing probability of liver-related death/LT after 1 year of 0%, 19%, and 48%, for substages S3, S4, and S5, respectively (Fig. 4A; p <0.001). Decompensated patients with high IL-6 (≥14 pg/ml, log-rank p <0.001; Fig. 4B) and CRP (≥0.5 mg/dl; log-rank p = 0.016; Fig. 4C) showed a significantly higher probability of liver-related death/LT. The Cox proportional hazard regression analysis identified IL-6 levels (HR 1.02; 95% CI 1.01–1.03; p = 0.004; see Model 1 in Table 3) and CRP levels (HR 1.51; 95% CI 1.16–1.98; p = 0.003; see Model 2 in Table 3) as independent predictors of death/LT at 1-year follow-up in dACLD patients.

Discussion

This study shows the interplay between liver function, PH and SI throughout distinct prognostic stages of ACLD. Next to the detailed clinical characterisation of our ACLD cohort, we used HVPG as the diagnostic gold-standard for assessing severity of PH, and determination of IL-6 and CRP levels as established biomarkers of SI to refine the characterisation of the complex clinical multistate ACLD model. As the outcomes and underlying pathophysiological drivers of disease procession are considerably different between patients with compensated and decompensated ACLD, prognostic indicators may be distinct or may have different weight across distinct ACLD substages.[1,2] Of note, patients in this study were electively referred to liver vein catheterisation and, thus, may not be fully representative of patients with ACLD treated at our institution, which constitutes a limitation of this study. Consequently, as patients with acute decompensation (*i.e.* non-elective admission) at the time of HVPG measurement were not included, patients were in a stable disease state to be eligible for this study. Therefore, the levels of SI in our study might not be similar to those observed in patients when sampled at the time of acute decompensation and/or pre-ACLF, as performed in the PREDICT study.[23]

In cACLD patients, a small but steady increase of MELD across indicative of progressive hepatic dysfunction was noted. However, most pronounced increases were noted in severity of PH as evident by considerable increases in HVPG across the different substages of cACLD. These results are in line with previous studies suggesting HVPG as the best predictor for the development of varices,[12] that is progression to substage S2. Most patients in compensated stages displayed normal values of IL-6 and

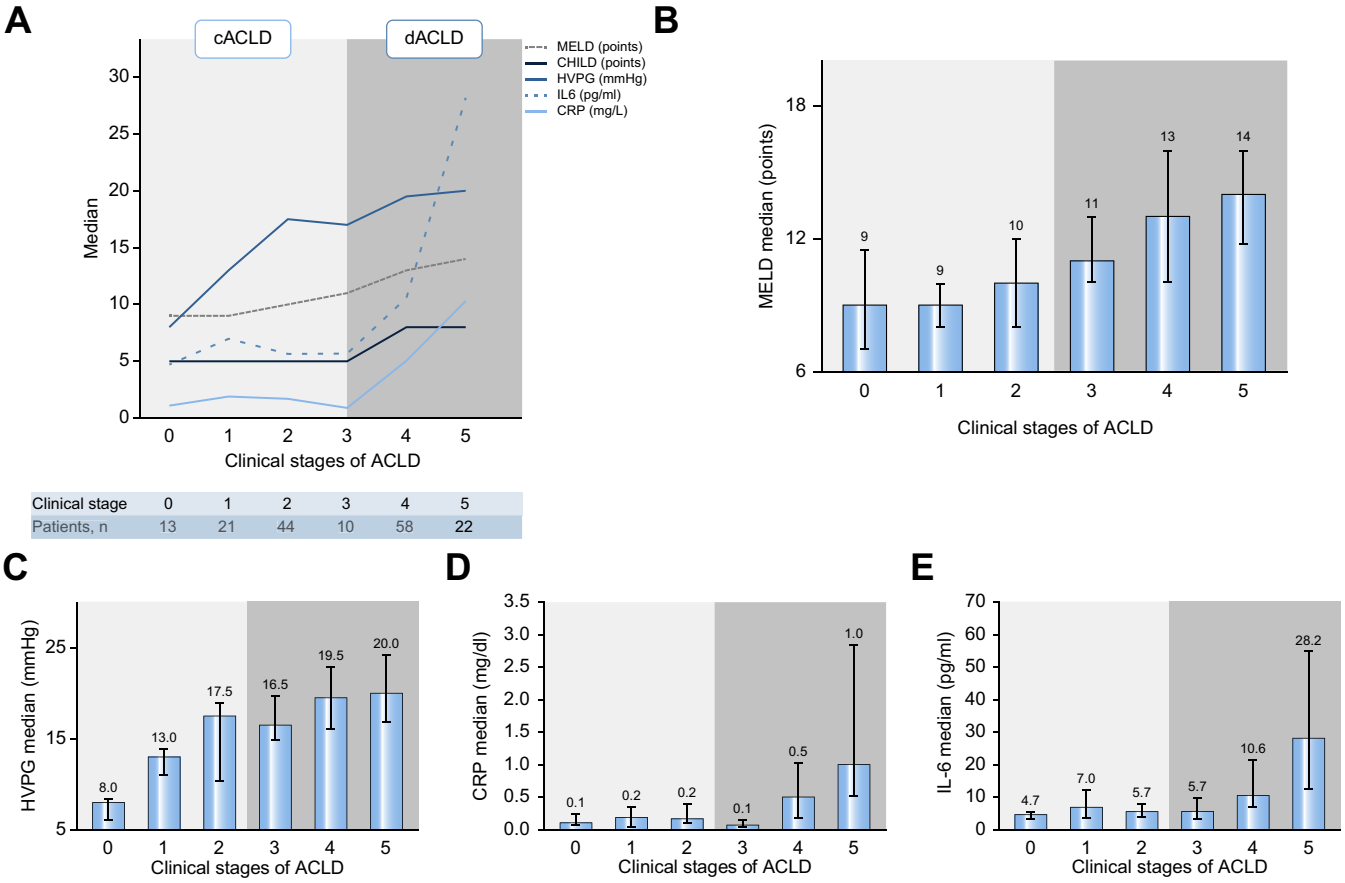

Fig. 2. Degree of hepatic dysfunction, portal pressure and systemic inflammation across ACLD substages. (A) Dynamics of median MELD, Child-Pugh score, HVPG, CRP and IL-6 serum levels across ACLD substages. (B–E) Median MELD, HVPG, CRP and IL-6 serum levels across ACLD substages (numbers indicate median levels and bars represent IQR). ACLD, advanced chronic liver disease; cACLD, compensated ACLD; CRP, C-reactive protein; dACLD, decompensated ACLD; HVPG, hepatic venous pressure gradient; IL-6, interleukin-6; MELD, model for end-stage liver disease.

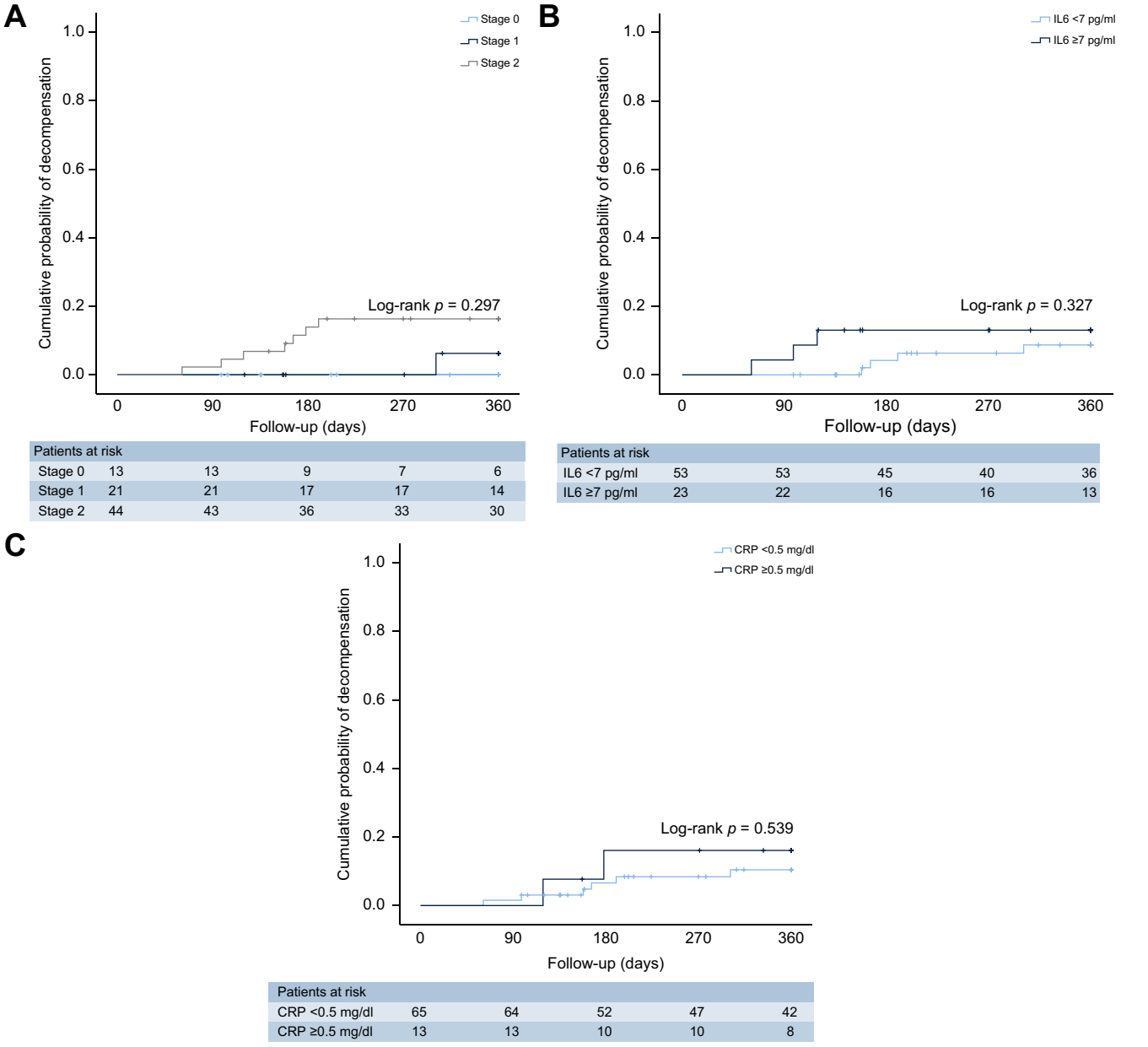

Fig. 3. Rates of first decompensation in compensated ACLD. Patients with cACLD stratified by (A) clinical substages (S0–S2), (B) IL-6 levels, and (C) CRP levels. Incidence rate of first decompensation was obtained from Kaplan-Meier estimates and compared using log-rank test (level of significance p <0.05). ACLD, advanced chronic liver disease; cACLD, compensated ACLD; CRP, C-reactive protein; IL-6, interleukin-6.

CRP, and there were no significant increases across the substages S0–S2 among cACLD patients. Recently, Turco *et al.*[13] showed a progressively higher proportion of patients with SI as defined by elevated CRP levels in the 3 compensated substages. However, other clinical and experimental studies would support the observation of increasing levels of proinflammatory cytokines and worsening of splanchnic vasodilation predominantly limited to dACLD patients with ascites.[24,25]

We observed a numerically increasing risk for decompensation across the 3 cACLD substages, supporting the key prognostic role CSPH (*i.e.* substage S1) to predict development of hepatic decompensation.[3,12] Similarly, the presence of GEV (*i.e.* cACLD substage S2) increases the risk of variceal bleeding, non-bleeding decompensation and death.[8,20] Importantly, we observed that the transition across the distinct prognostic substages is not essentially sequential, but instead cACLD patients may shift to any of the dACLD substages, most frequently to S4 because of the development of ascites as the most common first manifestation of hepatic decompensation.[26] Although we observed a clear trend for patients with abnormal IL-6 levels towards higher risk of first decompensation, this was not evident for CRP levels, which may be a less sensitive or less specific biomarker of SI. Notably, after adjusting for prognostic covariables, IL-6 remained an independent predictor of first decompensation in our cohort. When IL-6 levels were not considered in the multivariate regression model, both CRP

Table 2. Cox proportional hazard regression model assessing potential predictors of decompensation after 1 year in compensated ACLD patients (substages S0–S2).

	Univariable			Multivariable		
Model 1	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age (per year)	1.04	0.97–1.11	0.285			
MELD (per point)	1.26	1.02–1.55	0.032	1.27	1.00–1.62	0.054
HVPG (per mmHg)	1.13	0.99–1.30	0.068	1.04	0.89–1.22	0.622
Albumin (g/L)	0.90	0.79–1.02	0.100	0.98	0.82–1.18	0.832
WBC (G/L)	0.99	0.86–1.15	0.955			
IL-6 (pg/ml)	1.07	1.02–1.12	0.004	**1.06**	**1.01–1.10**	**0.013**
	Univariable			**Multivariable**		
Model 2	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age (year)	1.04	0.97–1.11	0.285			
MELD (point)	1.26	1.02–1.55	0.032	1.12	0.85–1.48	0.418
HVPG (mmHg)	1.13	0.99–1.30	0.068	1.13	1.00–1.28	0.059
Albumin (g/L)	0.90	0.79–1.02	0.100	0.93	0.80–1.08	0.331
WBC (G/L)	0.99	0.86–1.15	0.955			
CRP (mg/L)	1.79	0.93–3.46	0.082	1.90	0.97–3.74	0.062

Multivariable analysis was performed using a backward stepwise Cox proportional hazards regression model.
ACLD, advanced chronic liver disease; CRP, C-reactive protein; HVPG, hepatic venous pressure gradient; HR, hazard ratio; IL-6, interleukin-6; MELD, model for end-stage liver disease; WBC, white blood cells.

levels and HVPG had a strong, but non-significant predictive value for first decompensation in cACLD patients. Although the prognostic role of HVPG and CRP for first decompensation has been previously reported,[3,27,28] our study is the first to demonstrate the predictive power of IL-6 for first decompensation in cACLD patients.

IL-6 is a pleiotropic proinflammatory cytokine that is released by activated monocytes and macrophages activation, for example upon Toll-like receptor 4 stimulation. Subsequently, IL-6 induces an acute phase response, that may be paralleled by a CRP release in the liver.[5,16,29] Our results suggest that IL-6 is a more sensitive predictor of decompensation and represent a valuable biomarker for SI in cirrhosis. Even though these data should be further explored, our results reinforce the SI hypothesis,[16] which states that bacterial translocation and SI are key drivers of hepatic decompensation.

In dACLD patients, MELD continued to increase across the decompensated substages with most pronounced increases noted in patients with ascites (*i.e.* substage S4). Importantly, CRP and IL-6 levels considerably increased across the distinct substages of dACLD, with incremental increases of IL-6 levels noted in patients with ascites and with further decompensation, that is in substages S4 and S5.

Of note, the degree of SI in patients with a history of variceal bleeding (S3) did not differ from cACLD patients within substages S0–S2. Furthermore, dACLD patients with ascites and a history of variceal bleeding (a subgroup of S5) displayed the same levels of inflammation markers as patients with only ascites (substage S4). In both scenarios, the median time from previous variceal bleeding to HVPG measurement was longer than 1 year. One could argue that once variceal bleeding resolves, patients return to a re-compensated stage after a certain amount of time, or that the onset of significant SI is only linked to persisting ascites and/or further decompensation events. Recently published data from the PREDICT study identified 3 different courses of acute decompensation that showed different associations with PH and SI as decisive pathomechanisms.[23] In the subgroup of patients presenting with first hepatic decompensation, levels of SI were lowest in patients with gastrointestinal haemorrhage, as compared with patients with ascites or HE. These results are in line with our study, as we observed similar levels of SI in patients in S3 (after variceal bleeding) as compared with compensated patients. However, as our study cohort explicitly excluded patients with non-elective admission at the time of HVPG measurement (*e.g.* acute gastrointestinal haemorrhage), it cannot indicate whether patients with variceal bleeding have increased levels of SI at the timepoint of admission as compared with cACLD patients, or lower levels, as compared with patients with other forms of hepatic decompensation.

These observations evoke potential implications for the definition of re-compensation, which will be discussed during Baveno VII. Even though patients in S3 had a better outcome than the other decompensated substages S4/S5, these patients still experienced a considerable rate of further decompensation during the follow-up. Improved survival rates are consistently reported after acute variceal bleeding,[30,31] but the subsequent 5-year risk of further decompensation is still as high as 50%.[14,32] Therefore, it still seems reasonable to differentiate S3 patients from cACLD in terms of prognostication – especially if biomarkers of SI are high. It remains to be assessed in future studies whether the dynamics of IL-6 levels have a role for defining re-compensation after an episode of variceal bleeding.

Ascites is the most frequent first non-bleeding decompensating event[14,33] that defines dACLD substage S4. The significant increase of IL-6 and CRP levels in the transition to S4 and to S5 supports the impact of SI on the natural course of ACLD. Findings from the CANONIC study also revealed that acute decompensation occurs in the setting of SI, which is significantly more severe in patients with ACLF.[5] Similarly, the PREDICT study suggests that the longitudinal development of SI after acute decompensation greatly determines the clinical course of ACLD.[23] Finally, our results suggest that IL-6 is a strong prognostic marker associated with considerable increased risk of death if not transplanted. Potentially, IL-6 levels might be used in future studies to identify individual

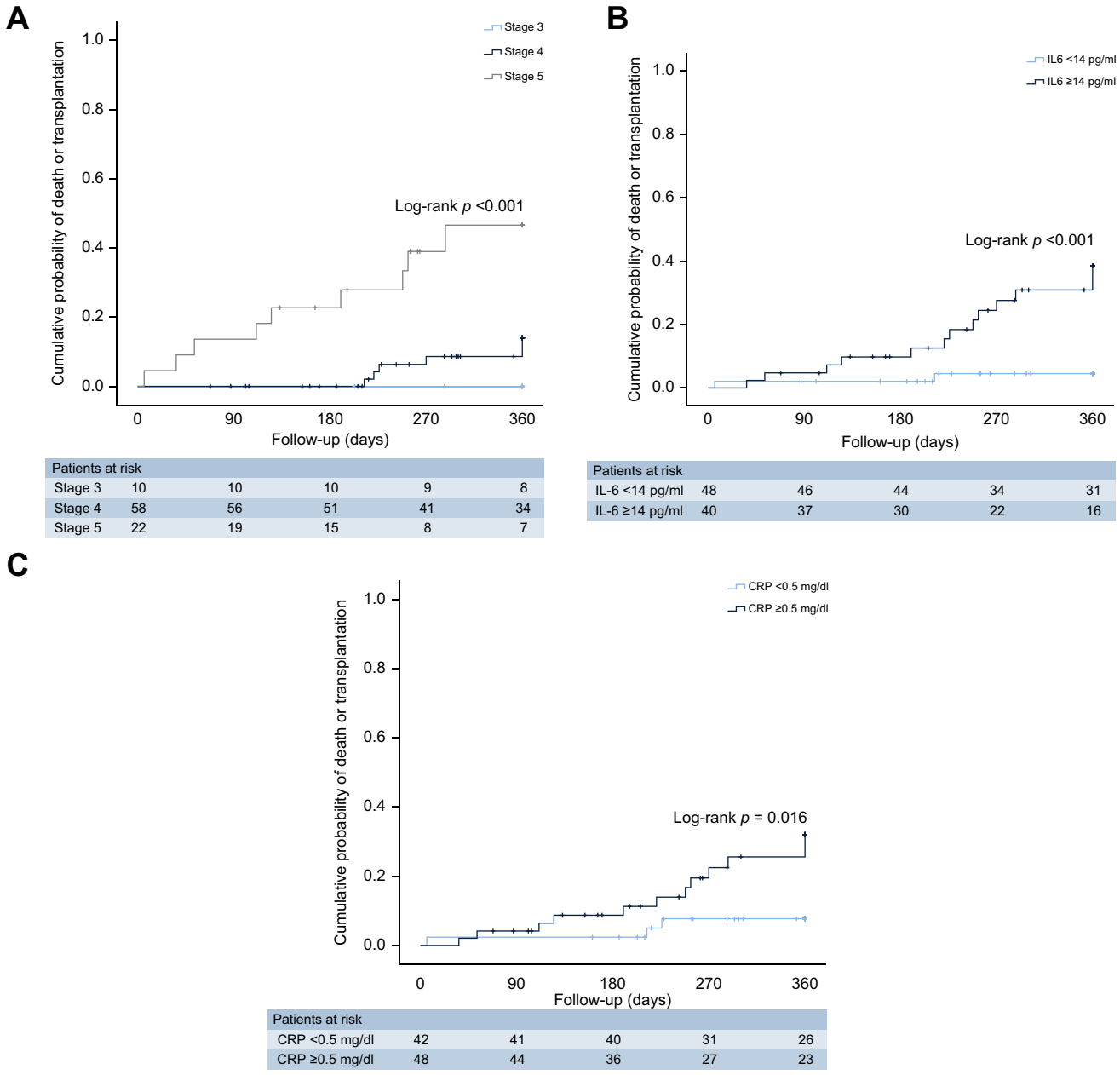

Fig. 4. Incidence of mortality or liver transplantation in decompensated ACLD. Patients with dACLD stratified by (A) clinical substages, (B) IL-6 levels or by (C) CRP levels. Incidence rate of mortality or liver transplantation was obtained from Kaplan-Meier estimates and compared using log-rank test (level of significance p <0.05). ACLD, advanced chronic liver disease; CRP, C-reactive protein; dACLD, decompensated ACLD; IL-6, interleukin-6.

dACLD patients who benefit most from therapeutic interventions targeting SI such as albumin administration[34] or NSBB intake.[35,36]

Although we confirmed increased mortality with progressive dACLD substages S3–S5, abnormal levels of CRP and IL-6 also indicated a significant and considerable increased risk for death or transplantation in dACLD patients. Both SI biomarkers IL-6 and CRP were independent predictors of liver-related death/LT, which is supported by previous studies.[5,13,27,28,37,38] Recently, Remmler *et al.*[32] showed that the prognostic value of IL-6 for predicting death after 90 days was even better than of CRP, but this superior predictive value was not observed for death at 1-year follow-up. Moreover, a recent study by Fernandez *et al.*[39] demonstrated substantial fluctuations of IL-6 levels despite an absence of a clear clinical correlate.

Finally, in contrast to reports on the predictive value of WBC counts in acutely hospitalised patients from the CANONIC study[40,41] we did not observe significant increases of WBC across ACLD stages nor predictive value of WBC for decompensation and mortality. This likely reflects the ability of WBC count to reflect short-term dynamics in patients with acute decompensation and "pre-ACLF" state (*i.e.* patients with non-elective hospitalisation). Our study population rather reflects cACLD and stable dACLD, that is disease stages that are different to "pre-

Table 3. Cox proportional hazard regression model assessing potential predictors of death or liver transplantation after 1 year in decompensated ACLD patients (substages S3–S5).

	Univariable			Multivariable		
Model 1	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age (per year)	1.05	1.00–1.10	0.075	1.05	1.00–1.11	0.055
MELD (per point)	1.09	0.97–1.22	0.161	1.04	0.89–1.21	0.625
HVPG (per mmHg)	1.09	0.99–1.19	0.072	1.05	0.95–1.17	0.326
Albumin (g/L)	0.89	0.80–0.99	0.027	0.93	0.82–1.06	0.300
WBC (G/L)	0.98	0.80–1.19	0.828			
IL-6 (pg/ml)	1.02	1.01–1.03	0.006	**1.02**	**1.01–1.03**	**0.004**
	Univariable			**Multivariable**		
Model 2	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age (per year)	1.05	1.00–1.10	0.075	1.05	0.99–1.11	0.088
MELD (per point)	1.09	0.97–1.22	0.161	1.07	0.91–1.26	0.397
HVPG (per mmHg)	1.09	0.99–1.19	0.072	1.06	0.96–1.17	0.256
Albumin (g/L)	0.89	0.80–0.99	0.027	0.95	0.83–1.09	0.465
WBC (G/L)	0.98	0.80–1.19	0.828			
CRP (mg/L)	1.53	1.12–2.00	0.002	**1.51**	**1.16–1.98**	**0.003**

Multivariable analysis was performed using a backward stepwise Cox proportional hazards regression model.
ACLD, advanced chronic liver disease; CRP, C-reactive protein; HVPG, hepatic venous pressure gradient; HR, hazard ratio; IL-6, interleukin-6; MELD, model for end-stage liver disease; WBC, white blood cells.

ACLF" and ACLF which are distinct clinical syndromes.[4] This hypothesis is also supported by the PREDICT study demonstrating significant decrease of WBC counts after 90 days in patients with a stable course of dACLD.[23]

In summary, our study, which assessed thoroughly characterised ACLD patients across distinct prognostic substages, demonstrates that the degree of SI progressively increases with severity of ACLD. Importantly, IL-6 as a biomarker of SI supported the concept of incremental increases in the degree of SI after development of ascites and/or further decompensation. Even if there was no systematic increase in the degree of SI noted among cACLD, IL-6 was an independent predictor of first decompensation. Furthermore, our results suggest IL-6 level as a valuable biomarker of ACLD progression of considerable prognostic relevance, as IL-6 predicted the risk of liver-related death or the need for LT in dACLD patients. If future studies with larger sample size confirm the prognostic value of IL-6 level across distinct ACLD stages, the incorporation of IL-6 into the clinical substage model may facilitate specific therapeutic interventions and personalised medical care for patients with complex and multistage ACLD.

Abbreviations

ACLD, advanced chronic liver disease; ACLF, acute-on-chronic liver failure; c/dACLD, compensated/decompensated advanced chronic liver disease; CRP, C-reactive protein; CSPH, clinically significant portal hypertension; GEV, gastroesophageal varices; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; IL-6, interleukin-6; LT, liver transplantation; MELD, model for end-stage liver disease; NSBB, non-selective beta-blockers; PH, portal hypertension; SBP, spontaneous bacterial peritonitis; SI, systemic inflammation; TIPS, transjugular intrahepatic portosystemic shunt; ULN, upper limit of normal; WBC, white blood cells.

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Conflict of interest

DC, MJ, LH, RP, PS, AFS declare no conflicts of interest. BeSi has received travel support from AbbVie and Gilead. DB has received travel support from AbbVie and Gilead, as well as speaker fees from AbbVie. BeSc received travel support from Abbvie, Gilead and Ipsen. MP is an investigator for Bayer, BMS, Lilly, and Roche; he received speaker honoraria from Bayer, BMS, Eisai, Lilly, and MSD; he is a consultant for Bayer, BMS, Ipsen, Eisai, Lilly, MSD, and Roche; he received travel support from Bayer and BMS. MT received grant support from Albireo, Cymabay, Falk, Gilead, Intercept, MSD, and Takeda, honoraria for consulting from BiomX, Boehringer Ingelheim, Falk, Genfit, Gilead, Intercept, Janssen, MSD, Novartis, Phenex, and Regulus, speaker fees from BMS, Falk, Gilead, Intercept and MSD, as well as travel support from Abbvie, Falk, Gilead and Intercept. MM 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. TR received grant support from Abbvie, Boehringer-Ingelheim, Gilead, MSD, Philips Healthcare, Gore; speaking honoraria from Abbvie, Gilead, Gore, Intercept, Roche, MSD; consulting/advisory board fee from Abbvie, Bayer, Boehringer-Ingelheim, Gilead, Intercept, MSD, Siemens; and travel support from Abbvie, Boehringer-Ingelheim, Gilead and Roche.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: DC, BeSi, MM, TR. Data acquisition: all authors

Analysis: DC, BeSi, MM, TR. Interpretation: all authors. Drafting the manuscript: DC, TR. Critical revision: BeSi, MJ, LH, DB, RP, PS, BeSc, AFS, MP, MT, MM

Data availability

Data are available upon reasonable request to the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.10.003.

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Author names in bold designate shared co-first authorship

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