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Cardiodynamic state is associated with systemic inflammation and fatal acute-on-chronic liver failure

Michael Praktiknjo[1] | Sofia Monteiro[1,2] | Josephine Grandt[3] | Nina Kimer[3] | Jan L. Madsen[4] | Mikkel P. Werge[3] | Peter William[3] | Maximilian J. Brol[1] | Laura Turco[5] | Robert Schierwagen[6] | Johannes Chang[1] | Sabine Klein[6] | Frank E. Uschner[6] | Christoph Welsch[6] | Richard Moreau[7,8] | Filippo Schepis[5] | Flemming Bendtsen[3] | Lise L. Gluud[3] | Søren Møller[4] | Jonel Trebicka[6,9,10,11]

[1]Department of Internal Medicine I, University of Bonn, Bonn, Germany

[2]Department of Medicine, Hospital Pedro Hispano, Matosinhos, Portugal

[3]Gastrounit Medical Division, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark

[4]Department of Clinical Physiology and Nuclear Medicine, 239 Center for Functional and Diagnostic Imaging and Research, Faculty of Health Sciences Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark

[5]Division of Gastroenterology, Azienda Ospedaliero-Universitaria di Modena and University of Modena and Reggio Emilia, Modena, Italy

[6]Department of Internal Medicine I, J.W.Goethe University Hospital, Frankfurt, Germany

[7]Assistance Publique-Hôpitaux de Paris, Hôpital Beaujon, Département Hospitalo-Universitaire UNITY, Clichy, France

[8]Centre de Recherche sur l'Inflammation, Unité Mixte de Recherche, Institut National de la Santé et de la Recherche Médicale and Université Paris Diderot, Paris, France

[9]European Foundation for Study of Chronic Liver Failure, Barcelona, Spain

Abstract

Background & Aims: Acute-on-chronic liver failure (ACLF) is characterized by high short-term mortality and systemic inflammation (SI). Recently, different cardiodynamic states were shown to independently predict outcomes in cirrhosis. The relationship between cardiodynamic states, SI, and portal hypertension and their impact on ACLF development remains unclear. The aim of this study was therefore to evaluate the interplay of cardiodynamic state and SI on fatal ACLF development in cirrhosis.

Results: At inclusion, hemodynamic measures including cardiac index (CI) and hepatic venous pressure gradient of 208 patients were measured. Patients were followed prospectively for fatal ACLF development (primary endpoint). SI was assessed by proinflammatory markers such as interleukins (ILs) 6 and 8 and soluble IL-33 receptor (sIL-33R). Patients were divided according to CI (<3.2; 3.2-4.2; >4.2 L/min/m^2) in hypo- (n = 84), normo- (n = 69) and hyperdynamic group (n = 55). After a median follow-up of 3 years, the highest risk of fatal ACLF was seen in hyperdynamic (35%) and hypodynamic patients (25%) compared with normodynamic (14%) (P = .011). Hyperdynamic patients showed the highest rate of SI. The detectable level of IL-6 was an independent predictor of fatal ACLF development.

Conclusions: Cirrhotic patients with hyperdynamic and hypodynamic circulation have a higher risk of fatal ACLF. Therefore, the cardiodynamic state is strongly associated with SI, which is an independent predictor of development of fatal ACLF.

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALT, alanine transaminase; BSA, body surface area; CI, cardiac index; CLIF-C, European Foundation for the study of chronic liver failure consortium; CO, cardiac output; CRP, C-reactive protein; CSPH, clinically significant portal hypertension; Hb, haemoglobin; HR, heart rate; HVPG, hepatic venous pressure gradient; IL, interleukin; ILs, interleukins; MAP, mean arterial pressure; MELD, model of end-stage liver disease; NSBB, non-selective beta blockers; p, p-value; PC, principal component; RAP, right atrial pressure; ROC, Receiver Operating Characteristic; SI, systemic inflammation; sIL-33R, soluble interleukin-33 receptor; SVR, systemic vascular resistances; SVRI, systemic vascular resistance index.

Michael Praktiknjo and Sofia Monteiro have contributed equally as first authors.

Lise Lotte Gluud, Søren Møller and Jonel Trebicka have contributed equally as last authors.

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[10]Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

[11]Institute of Bioengineering Catalunya, Barcelona, Spain

Correspondence
Jonel Trebicka, Department of Internal Medicine I, University of Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany.
Email: jonel.trebicka@kgu.de

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KEYWORDS
acute-on-chronic liver failure, circulation, cirrhosis, hemodynamic, inflammation

1 | INTRODUCTION

In the natural history of cirrhosis, acute decompensations (AD) are frequent and often lead to development of acute-on-chronic liver failure (ACLF),[1,2] a syndrome characterized by organ failure and high short-term mortality.[2,3] The pathophysiological pathways leading to this syndrome are only partly understood but systemic inflammation (SI) seems to play a crucial role.[4] SI can occur in the setting of chronic inflammation via translocated proinflammatory signals from the intestinal lumen to the systemic circulation.[5-8] A full-blown burst of proinflammatory mediators has been found in patients with ACLF.[9] Portal hypertension is a prerequisite for AD and can be quantified by measurement of the hepatic venous pressure gradient (HVPG).[10,11]

In patients with clinically significant portal hypertension (CSPH), SI measured by C-reactive protein (CRP) and hypodynamic [defined by cardiac index (CI) <3.2 L/min/m^2] and hyperdynamic (defined by CI >4.2 L/min/m^2) cardiodynamic states have been independently associated with an increased risk of first ascites development and mortality.[12] In addition, SI as assessed by IL-6 and IL-8 plays a crucial role in AD.[4,9] In outpatients with cirrhosis, arterial hypotension, as an element of cardiocirculatory dysfunction, has also been identified as an independent risk factor for ACLF development.[13]

To date, neither the interplay between cardiodynamic states or markers of SI, other than CRP, nor their relation with ACLF development have been studied.[14]

The aim of this study was therefore to evaluate the risk of fatal ACLF development in different cardiodynamic states and their association with SI. We hypothesize that a hypo- as well a hyperdynamic circulatory state represents a risk factor for the development of ACLF.

Key points

- Acute-on-chronic liver failure (ACLF) is suggested to be associated with systemic inflammation (SI).
- The impact of systemic circulation (cardiodynamic state) and SI on ACLF development is not fully elucidated.
- This study shows that cirrhotic patients with hyperdynamic and hypodynamic circulatory state have a higher risk of fatal ACLF.
- Hyperdynamic state is strongly associated with SI, which independently predicts fatal ACLF development.

2 | PATIENTS AND METHODS

2.1 | Patients and data collection

In this retrospective analysis of a prospectively observed patient cohort from a single centre study, 224 outpatients with cirrhosis were referred to the Department of Clinical Physiology and Gastro Unit Hvidovre Hospital, Denmark, between 2002 and 2016 for per protocol hemodynamic assessment. Inclusion criteria were as follows: age above 18 years; diagnosis of cirrhosis based on histological findings or clinical, biochemical, ultrasonographic and/or endoscopic findings; and hemodynamic evaluation including HVPG and cardiac output (CO). Exclusion criteria were as follows: age under 18 years; variceal bleeding, refractory ascites, hepatorenal syndrome, bacterial infection, at time of inclusion and malignancy. Cardiovascular disease was ruled out. Fulfilment of ACLF criteria was not evaluated at

inclusion and records of non-fatal ACLF were therefore not primarily recorded.[3]

Blood samples were collected at the time of the enrolment and patients were followed until October 2017. Primary endpoint was fatal ACLF defined as ACLF leading to death. The ACLF definition according to the CLIF consortium was established in 2013 and the ACLF diagnosis was therefore established retrospectively.[3] Causes of death that were recorded as liver failure, sepsis and multiorgan failure were classified as fatal ACLF. Non-specified shock, cardiovascular disease, malignancy and unknown causes were classified as non-ACLF deaths.

Biochemical blood analyses were performed using standard tests.

Written informed consent was obtained from included patients; the study was approved by the local ethics committee and Data Protection Agency (J-No.2008-41-2020 and HVH-2011-02).

2.2 | Assessment of circulating levels of biomarkers

After collection, blood samples were centrifuged at 4°C and serum samples were stored at −80°C. Serum concentrations of interleukins (ILs) IL-6, IL-8 and the soluble IL-33 receptor (sIL-33R) were assessed. The analyses were performed with DuoSet® Elisa kits (R&D Systems) according to the manufacturer's instructions (Table S1), at the Department of Internal Medicine I, Bonn, Germany. The ILs and sIL-33R levels were quantified in undiluted serum samples. On all ELISA plates, two patient serum samples were used as controls accessing variability within plates. CRP as a common marker of SI was not part of the routine analysis in this study.

Undetectable levels were assigned a value equal to lower limit of detection,[4,15] whereas for values higher than the upper limit of detection concentrations were extrapolated using GraphPad Prism version 5.00 (GraphPad Prism Software) according to the plotted standard curve.

2.3 | Assessment of hemodynamic parameters

All patients underwent a hemodynamic investigation in the morning after an overnight fast and at least 1-hour rest in the supine position under local analgesia. None of the patients received diuretics or beta blockers in the 24 hours preceding investigations.

Catheterization of the hepatic veins and right atrium was performed as previously described.[16] A Swan-Ganz catheter, size 7F, was guided to the hepatic veins and right atrium via the femoral route under fluoroscopy control. Pressures were measured by a capacitance transducer (Simonsen & Weel, Copenhagen, Denmark) in the wedged and free hepatic vein position in at least three different vessels, the midaxillary line being zero pressure level. Mean values of repetitive measurements were used. HVPG was determined as wedged minus free hepatic venous pressure. Right atrial pressure (RAP) was measured directly.

A small indwelling polyethylene catheter was placed in the femoral artery by the Seldinger technique and advanced to the aortic bifurcation, and the systolic, diastolic and mean arterial (MAP) blood pressures were measured directly. All the pressures were expressed in millimetres of mercury.

Cardiac output (expressed in L/min) was measured by the indicator dilution technique after a bolus injection of 150 kBq of ^{125}I-labeled human serum albumin (IFE IT. 205, Institute of Energy Technique) into the right atrium, followed by arterial sampling. CI was calculated as CO/body surface area (BSA) and expressed in L/min/m^2.

Systemic vascular resistance [SVR = ((MAP − RAP)/CO) × 80; expressed in dynes·s/cm^{-5}], and systemic vascular resistance index [SVRI = ((MAP − RAP)/CI) × 80; expressed in dynes·s/cm^{-5}/m^2] were also calculated. Heart rate was determined by electrocardiography.

2.4 | Statistical analysis

Data are presented as median and ranges or absolute frequency and percentage, if not otherwise specified.

Mann-Whitney, Kruskal-Wallis and Chi-square tests were used for unpaired comparisons. Receiver operating characteristic (ROC) analysis was used to calculate cut-off values. Kaplan-Meier curves and log-rank tests were used to analyse rates of fatal ACLF development and all-cause mortality. Spearman's correlation was used to evaluate the relationship between inflammatory markers and hemodynamic parameters. Univariate Cox regression was used to identify predictors of ACLF. Parameters with a P value < .05 (P-in) and P-out value of .1 entered the multivariate, forward step-wise regression model. To avoid multicollinearity in multivariate regression, model of end-stage liver disease (MELD) and European Foundation for the study of chronic liver failure consortium (CLIF-C AD) scores and their included variables, main systemic hemodynamic parameters and their dependent parameters (such as the calculated systemic vascular resistance) were included separately. Principal components analysis was performed to reduce number of variables that influence regression analysis. In principal component analysis, linear combinations of all available variables were created. Patients were then plotted according to the created principal components.

The significance level for all tests was set at P-value < .05. Statistical analyses were performed using SPSS V25 (IBM SPSS Statistics for Macintosh, Version 25.0: IBM Corp). Principal components analysis was performed using R (R core team, Version 3.6.0).

3 | RESULTS

3.1 | General characteristics of patients

In total, 208 patients (73% male, 77% alcoholic cirrhosis and median age 60 years) were included in the final analyses (Table 1). Median Child-Pugh, MELD and CLIF-C AD scores were 7, 11 and 50 points. At inclusion, none of the patients with alcoholic cirrhosis had acute alcoholic liver injury according to NIAAA criteria (at least 3 of the following: active alcoholism of 6 months >40 g/d for female or >60 g/d for male, bilirubin >3 mg/dL, AST >50IE, AST/alanine transaminase (ALT)

TABLE 1 General characteristics of all patients and stratified by cardiodynamic state

	Parameter median (range) or absolute (%)	All patients (n = 208)	Hypodynamic CI <3.2 (n = 84)	Normodynamic CI 3.2-4.2 (n = 69)	Hyperdynamic CI >4.2 (n = 55)
General Condition	Age [years]	60 (31-81)***	62 (34-81)§	60 (31-75)	57 (35-74)$^{\#\#\#}$
	Gender [male/female]	151 (73)/57 (27)	64 (76)/20 (24)	51 (74)/18 (26)	36 (64)/19 (35)
	Aetiology of cirrhosis [alcohol/viral/other]	171 (77)/21 (10)/26 (13)	63 (75)/7 (8)/14 (17)	52 (75)/12 (18)/5 (7)	46 (84)/2 (4)/7 (13)
	BMI [kg/m^2]	25 (13-45)	25 (13-45)	25 (16-37)	26 (16-41)
	All Beta blockers	47 (23)	23 (27)	14 (20)	10 (18)
	Non-selective Beta blockers	39 (19)	18 (21)	13 (19)	8 (15)
	Diuretics	118 (57)	48 (57)	34 (49)	36 (65)
Baseline Scores	MELD$^{\Delta}$	11 (6-25)***	10 (6-20)	10 (6-21)¶¶¶	12 (6-25)$^{\#\#\#}$
	Child-Pugh [A/B/C]	76 (37)/61 (29)/71 (34)	28 (33)/27 (32)/29 (35)	29 (42)/21 (30)/19 (28)	19 (35)/13 (24)/23 (42)
	Child-Pugh	7 (5-12)	7 (5-12)	6 (5-11)	7 (5-12)
	CLIF-C AD$^{¥}$	50 (33-67)	49 (38-67)	50 (34-66)	50 (33-64)
Baseline Laboratory	Hb [g/dL]	12.2 (6.8-16.9)**	12.6 (7.6-16.9)	12.4 (6.8-16.3)¶¶	11.3 (6.9-14.7)$^{\#\#}$**
	WBC [G/L]$^{¥}$	7.0 (1.8-23.3)	6.7 (2.4-17.5)	7.0 (1.8-23.3)	7.3 (2.0-21.9)
	Platelets [G/L]†	145 (29-647)	154 (29-647)	145 (39-495)	132 (47-448)
	Sodium [mmol/L]	137 (114-145)	137 (114-143)	137 (125-145)	137 (117-145)
	Creatinine [mg/dL]	0.9 (0.4-2.7)	0.9 (0.5-2.2)	0.8 (0.4-1.8)	0.8 (0.4-2.7)
	Bilirubin [mg/dL]$^{\Delta}$	1.0 (0.1-12.7)***	0.8 (0.1-6.4)	0.8 (0.2-6.4)¶¶¶	1.4 (0.4-12.7)$^{\#\#\#}$
	ALT [U/L]$^{\Delta}$	31 (7-41)	32 (7-104)	29 (8-240)	31 (13-136)
	Albumin [g/L]$^{\Delta}$	31 (15-45)***	33 (17-44)	33 (18-45)¶¶¶	29 (15-40)$^{\#\#}$
	INR	1.3 (1.0-2.6)***	1.3 (1.0-2.6)	1.3 (1.0-2.5)¶¶	1.5 (1.0-2.2)$^{\#\#\#}$
Hemodynamics	MAP [mmHg]	90 (57-146)**	89 (57-130)§§	97 (71-122)¶¶	88 (64-146)
	HR [/min]	74 (47-117)***	69.5 (47-101)	72 (51-103)¶¶¶	80 (51-117)$^{\#\#\#}$
	HVPG [mmHg]	16 (6-33)***	15 (6-26)	15 (6-33)¶¶¶	18 (8-26)$^{\#\#\#}$
	CO [L/min]	6.5 (2.9-12.3)***	5.1 (2.9-7.5)§§§	7.1 (5.0-9.3)¶¶¶	9.0 (6.3-12.3)$^{\#\#\#}$
	CI [L/min/m^2]	3.4 (1.6-6.3)***	2.7 (1.6-3.1)§§§	3.5 (3.2-4.2)¶¶¶	4.7 (4.3-6.3)$^{\#\#\#}$
	SVR [dynes·s·cm^{-5}]$^{\Omega}$	1048 (444-2658)***	1334 (865-2658)§§§	1033 (720-1657)¶¶¶	706 (444-1349)$^{\#\#\#}$
	SVRI [dynes·s/cm^{-5}/m^2]	2020 (911-4715)***	2500 (1598-4715)§§§	2018 (1408-2727)¶¶¶	1338 (911-2639)$^{\#\#\#}$
Baseline Clinical	Ascites [no/grade 1/2/3]	101 (49)/41 (20)/36 (17)/30 (14)***	42 (50)/17 (20)/9 (10)/16 (19)	44 (64)/8 (12)/12 (17)/5 (7)¶¶¶	15 (27)/16 (27)/15 (27)/9 (16)$^{\#\#}$
	Oesophageal Varices [no—grade I/grade II-III]	159 (76)/49 (24)	68 (81)/16 (19)	51 (74)/18 (26)	40 (73)/15 (27)
Outcome	Mortality 1-year/overall	35 (17)**/82 (39)	11 (13)/32 (38)	7 (10)¶¶/22 (32)¶	17 (31)$^{\#}$/28 (51)
	Fatal ACLF development 1-year/overall	20 (10)**/50 (24)*	7 (8)/21 (25)	2 (3)¶¶/10 (14)¶¶	11 (20)$^{\#}$/19 (35)
	Time to ACLF development [months]	17 (0-137)	18 (0-92)	26 (1-88)	10 (0-137)
	Follow-Up time [years]	3 (0-15)	3 (0-11)	3 (0-15)¶¶	2 (0-14)$^{\#*}$

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALT, alanine transaminase; AP, alkaline phosphatase; BMI, body mass index; CI, cardiac index; CLIF-C, European Foundation for the study of chronic liver failure consortium; CO, cardiac output; Hb, haemoglobin; HR, heart rate; HVPG, hepatic venous pressure gradient; IL, interleukin; INR, international normalized ratio; MAP, mean arterial pressure; MELD, Model for end-stage liver disease; sIL-33R, soluble interleukin-33 receptor; SVR, systemic vascular resistances; WBC, white blood cells. Data are expressed as median (range) or absolute frequency (percentage).

$^{\Delta}$Data available in 205 patients, †Data available in 204 patients, $^{\Omega}$Data available in 200 patients, $^{¥}$Data available in 191 patients.

***P < .001, **P < .01, *P < .05, comparison of all three groups.

$^{\S\S\S}P$ < .001, $^{\S\S}P$ < .01, $^{\S}P$ < .05, for Hypodynamic vs Normodynamic.

$^{\P\P\P}P$ < .001, $^{\P\P}P$ < .01, $^{\P}P$ < .05, for Normodynamic vs Hyperdynamic.

$^{\#\#\#}P$ < .001, $^{\#\#}P$ < .01, $^{\#}P$ < .05, for Hypodynamic vs Hyperdynamic.

>1.4, AST or ALT >400 IE). Patients with viral hepatitis were untreated at inclusion.

Regarding comorbidities 44 patients (21%) were diabetic and 115 (55%) had arterial hypertension. Overweight and obesity were found in 69 (33%) and 38 (18%) patients respectively.

The median MAP was 90 mmHg (57-146), HVPG was 16 mmHg (6-33), CI was 3.4 L/min/m^2 (1.6-6.3) and median systemic vascular resistance index (SVRI) was 2020 dynes·s·cm^{-5}·m^2 (911-4715).

At inclusion, no patient had ACLF. Eighty-two patients died (39%) and 50 (24%) developed fatal ACLF. Median time to all-cause mortality was 18 months (0-137) and fatal ACLF was 17 months (0-137). None of the patients underwent liver transplantation or transjugular intrahepatic portosystemic shunt placement.

Plasma levels of IL-6, IL-8 and sIL-33R were detectable in 66 (32%), 74 (36%) and 208 (100%) patients as shown in Table 2. There was no significant difference in the levels of IL-6, IL-8 and sIL-33R between the time eras (2002-2011 vs 2012-2016), suggesting stability of the measured cytokines in the blood samples stored over the years of the study (Table S2).

3.2 | Characteristics of patients stratified by cardiodynamic state

Based on cut-offs of CI as previously applied,[12] 84 (40%) patients showed hypodynamic (<3.2 L/min/m^2), 69 (33%) patients normodynamic (3.2-4.2 L/min/m^2) and 55 patients (27%) hyperdynamic (>4.2 L/min/m^2) cardiodynamic state (Table 1).

Hypodynamic patients were significantly older compared with hyperdynamic patients. In comparison with hypo- and normodynamic patients, the hyperdynamic patients had significantly higher MELD, as well as lower blood haemoglobin (Hb) and lower plasma albumin concentrations and higher rate of ascites.

In total, 39 patients (19%) were treated with non-selective beta blockers (NSBB) and 8 patients (4%) received other beta blockers. The proportion of patients treated with NSBB was highest in the hypodynamic group (n = 18, 21%) and lowest in the hyperdynamic group (n = 8, 15%). There was no significant difference between the three cardiodynamic groups with respect to NSBB treatment.

The hypo- and hyperdynamic patients had similar level of arterial blood pressure, but MAP was lower than in the normodynamic patients. The SVRI was normal in 33%, 39% and 0% in hypodynamic, normodynamic and hyperdynamic patients. Hyperdynamic patients had higher HVPG (median 18 mmHg), than the remaining patients (median 15 mmHg).

ACLF was the cause of death in 68%, 66% and 45% of hyperdynamic, hypodynamic and normodynamic patients respectively (Table 3). The cumulative probability of fatal ACLF in the three groups was 35%, 25% and 14% (P = .006, Figure 1A). After 1 year, the numbers were 20%, 8% and 3% (P < .01) respectively. The all-cause mortality at the end of follow-up and after 1 year was also higher in the hyperdynamic group and lowest in the normodynamic group (Figure 1B, Table 1).

Most common known trigger of fatal ACLF was infection in 20%. There were no differences between ACLF triggers within cardiodynamic groups but a trend showing higher rates of infection-triggered ACLF in patients with hyperdynamic circulation (Table S3).

In other settings, normodynamic circulation has been defined as CI of 2.5-4.2 L/min/m^2.[17] We therefore stratified our patients

TABLE 2 Levels of inflammatory cytokines of all patients and stratified by cardiodynamic state

	Parameter		All patients n = 208	Hypodynamic CI <3.2 n = 84	Normodynamic CI 3.2-4.2 n = 69	Hyperdynamic CI >4.2 n = 55
Biomarkers	IL-6	[undetectable/ detectable]	142 (68)/66 (32)*	60 (71)/24 (29)	52 (75)/17 (25)¶	30 (55)/25 (45)#
		[pg/mL]	9.4 (9.4-1248.2)	9.4 (9.4-645.8)	9.4 (9.4-1248.2)¶	9.4 (9.4-890.5)
		[pg/mL] detectable	48.7 (10.2-1248.2)	44.5 (10.2-645.8)	63.5 (11.0-1248.2)	32.3 (11.0-890.5)
	IL-8	[undetectable/ detectable]	134 (64)/74 (36)*	58 (59)/26 (31)	49 (71)/20 (29)¶	27 (49)/28 (51)#
		[pg/mL]	31.2 (31.2-1464.4)*	31.2 (31.2-1464.4)	31.2 (31.2-880.3)¶¶	33.2 (31.2-926.6)#
		[pg/mL] detectable	79.8 (32.4-1464.4)	114.4 (32.6-1464.4)	61.6 (32.4-880.3)	76.4 (33.3-926.6)
	sIL-33R	[<7380.2/≥7380.2]Ψ	85 (41)/121 (59)*	38 (45)/46 (55)	33 (49)/35 (51)¶	14 (30)/40 (74)#
		[pg/mL]Ψ	15 917.2 (1430.6-15917.2)	15 917.2 (1430.6-15917.2)	7967.6 (2528.7-15917.2)¶	15 917.2 (1506.0-15917.2)

Abbreviations: IL, interleukin; sIL-33R, soluble interleukin-33 receptor.

ΨData available in 206 patients.

*P < .05, comparison of all three groups.

¶¶P < .01, ¶P < .05, for Normodynamic vs Hyperdynamic.

##P < .01, #P < .05, for Hypodynamic vs Hyperdynamic.

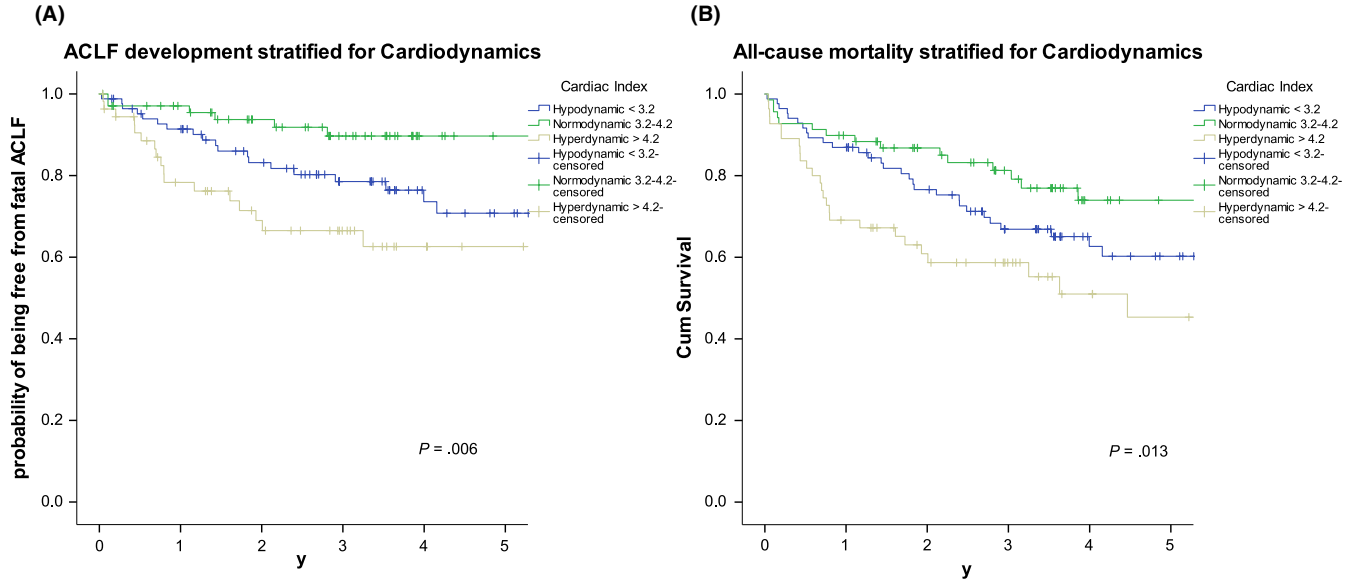

FIGURE 1 A, Kaplan-Meier survival curve with log rank test for development of fatal acute-on-chronic liver failure (ACLF) stratified by cardiodynamic state (hypodynamic <3.2 L/min/m^2 (blue line), normodynamic 3.2-4.2 L/min/m^2 (green line) and hyperdynamic >4.2 L/min/m^2 (yellow line)). B, Kaplan-Meier survival curve with log rank test for all-cause mortality stratified by cardiodynamic state (hypodynamic <3.2 L/min/m^2 (blue line), normodynamic 3.2-4.2 L/min/m^2 (green line) and hyperdynamic >4.2 L/min/m^2 (yellow line)). CI, cardiac index

according to those cut-offs as well. Kaplan-Meier plot for fatal ACLF development that hypodynamic circulation shows similar results with even worse outcome for patients with hypodynamic circulation. Normodynamic patients had the lowest while hyperdynamic patients the highest rate of fatal ACLF development (Figure S1).

3.3 | Inflammatory markers in different cardiodynamic states

In the assessment of the SI,[18-21] patients were divided into those with detectable and undetectable levels of IL-6 and IL-8 (Figure 2A,B). Among those with detectable levels, the IL-6 was 48.7 (10.2-1248.2) and IL-8 was 79.8 (32.4-1464.4) pg/mL (Table 2). The hyperdynamic group showed the highest rate of detection of inflammatory biomarkers, but no difference in detection rate was seen between the hypo- and normodynamic groups (Table 2). Similar results were obtained, when the patients were stratified for the 2.5-4.2 L/min/m^2 cut-offs (Table S4). sIL-33R levels were detectable in all patients 15 917.2 pg/ml (1430.6-15917.2). A cut-off of 7380.2 pg/ml was chosen based on the ROC analysis (Figure 2C). Across all cardiodynamic states patients, with ascites showed higher rates of detectable SI markers compared with patients without ascites (Figure 2D).

Looking at the concentrations of the inflammatory markers, in the hyperdynamic patients, levels of IL-8 and sIL-33R were higher compared with normodynamic patients, but the difference was not statistically significant. In hyperdynamic patients, levels of IL-8 were significantly higher compared with hypodynamic patients (Table 2).

IL-6, IL-8 and sIL-33R showed highly significant correlation with HVPG, whereas IL-8 was significantly correlated with CO. Inversely, SVR and MAP showed a negative correlation with IL-6 and IL-8 and sIL-33R respectively (Figure 2E).

To minimize confounding factors, we performed a principal component analysis and created linear combinations of all available variables for the presence of hypo- and hyperdynamic states. Inflammatory cytokines IL-6 and IL-8 transformed into principal component 1 (PC1 in Figure 2F). Hemodynamic parameters CO and SVR transformed with Hb into principal component 2 (PC2 in Figure 2F). Plotting of patients clearly showed that hyperdynamic patients cluster with each other as well as hypodynamic patients. The clusters are separated mostly on the axis representing the principal component 1 (x-axis). These results suggest a main contribution of inflammatory cytokines to distinguish between hypo- and hyperdynamic patients. By definition, hypo- and hyperdynamic patients are distinguished on the axis of principal component 2, which is consists of cardiodynamic parameters (CO and SVR) (Figure 2F).

3.4 | SI predicts development of fatal ACLF

Among the univariate analyses, predictors of fatal ACLF included age, MELD, Child-Pugh and CLIF-C AD scores, Hb, bilirubin, albumin, MAP, hyperdynamic state, SVRI, HVPG ≥16 mmHg (median), ascites, sIL-33R and IL-6 (Table 4). Owing to relatively long inclusion period we analysed time effects on survival, but time era of inclusion (2002-2011 vs 2012-2016) was not a significant predictor. Multivariate analysis including all significant factors from univariate analysis identified age, low albumin and detectable IL-6 as independent predictors of fatal ACLF. NSBB therapy was not significant in either analysis.

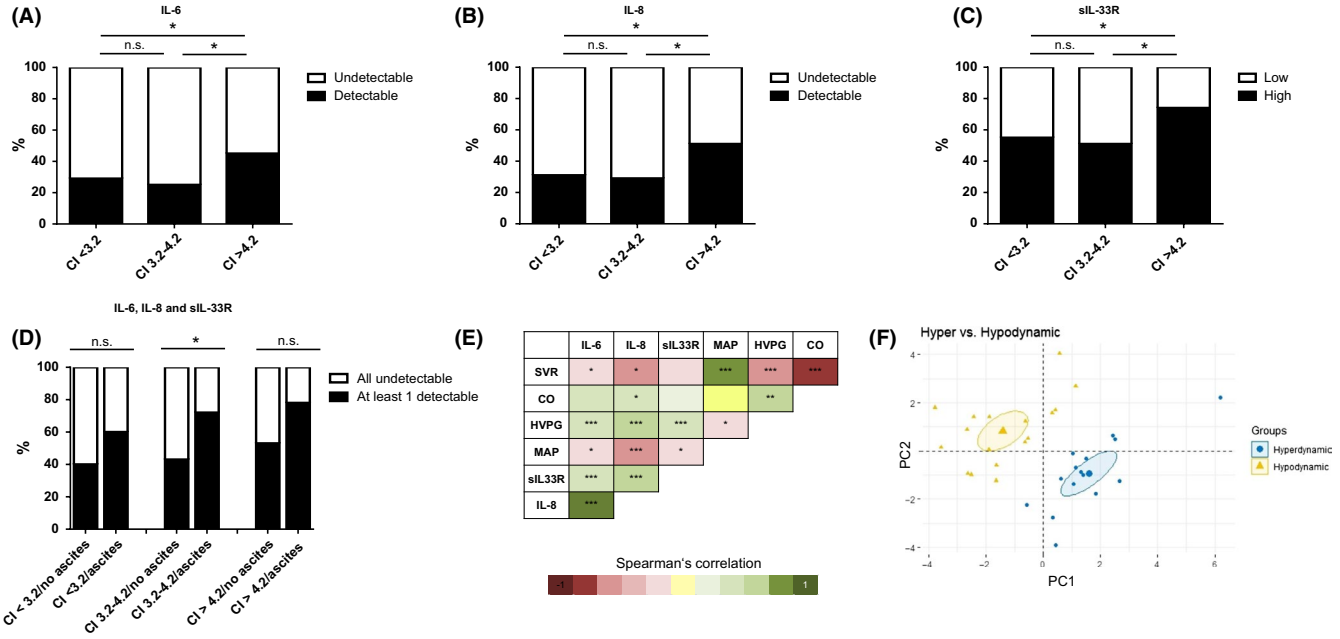

FIGURE 2 A, Percentage of patients with detectable (black fraction, lower limit detection of ELISA kit (9.38 pg/mL)) and undetectable (white fraction) levels of interleukin-6 stratified for cardiodynamic state (hypodynamic <3.2 L/min/m^2 (left column), normodynamic 3.2-4.2 L/min/m^2 (centre column) and hyperdynamic >4.2 L/min/m^2 (right column)). Highest fraction of detectable levels of interleukine-6 is found in hyperdynamic patients (right column). B, Percentage of patients with detectable (black fraction, lower limit detection of ELISA kit (31.2 pg/mL)) and undetectable (white fraction) levels of interleukin-8 stratified for cardiodynamic state (hypodynamic <3.2 L/min/m^2 (left column), normodynamic 3.2-4.2 L/min/m^2 (centre column) and hyperdynamic >4.2 L/min/m^2 (right column)). Highest fraction of detectable levels of interleukine-8 is found in hyperdynamic patients (right column). C, Percentage of patients with high (black fraction, >7380.2 pg/mL) and low (white fraction) levels of soluble IL-33 receptor—sIL-33R—stratified for cardiodynamic state (hypodynamic <3.2 L/min/m^2 (left column), normodynamic 3.2-4.2 L/min/m^2 (centre column) and hyperdynamic >4.2 L/min/m^2 (right column)). Highest fraction of high levels of soluble IL-33 receptor—sIL-33R—is found in hyperdynamic patients (right column). D, Percentage of patients with at least one detectable/high levels (black fraction) and undetectable/low (white fraction) levels of interleukine-6, -8 or soluble IL-33 receptor—sIL-33R—stratified for cardiodynamic state (hypodynamic <3.2 L/min/m^2 (left column), normodynamic 3.2-4.2 L/min/m^2 (centre column) and hyperdynamic >4.2 L/min/m^2 (right column)). Highest fraction of detectable/high levels of interleukine-6, -8 or soluble IL-33 receptor—sIL-33R—is found in hyperdynamic patients (right column). E, Spearman's correlation of inflammatory markers interleukine-6, -8 and soluble IL-33 receptor—sIL-33R—with hemodynamic parameters systemic vascular resistance (SVR), mean arterial pressure (MAP) and hepatic venous pressure gradient (HVPG). Correlation coefficient is colour coded (dark red—1, dark green—1). F, Plotting of patients and clustering according to principal components (PC) 1 and 2. Hypodynamic patients are coded in yellow and hyperdynamic patients are coded in blue. PC1 main variables: IL-6 and IL-8; PC2 main variables: CO, SVR and haemoglobin

4 | DISCUSSION

The main findings of our study are that in patients with cirrhosis the prevalence of fatal ACLF is high, significantly relating to all-cause mortality in hypo- and hyperdynamic states. The findings support the previous study by Turco et al showing that the cardiodynamic state is associated with the development of ascites and death. Moreover, the risk of developing of fatal ACLF seems related to both the type of cardiodynamic state and degree of SI.[12]

We found a strong circuital correlation among plasma ILs, HVPG and CO. Moreover, we showed that patients with a CI >4.2 L/min/m^2 had significantly higher rate of detectable circulating IL-6/-8 in comparison to patients with lower CI at baseline. This adds further granularity to previous findings that extreme cardiodynamic states and SI as determined by circulating CRP are independent predictors of outcomes in compensated patients and in those with ascites.[12] Indeed, CRP did not capture the differences in the degree of SI among cardiodynamic states.[12] This underlines the need for more specific markers of SI in this setting. Detectable levels of IL-6, which has been selected as an independent predictor of fatal ACLF development in our cohort, may be an appropriate candidate for such a purpose.

The interrelation between degree of portal hypertension and CO has been pivotal in the classical vasodilation hypothesis of portal hypertension in cirrhosis.[5-8] Moreover, this pathophysiological view represents the rational basis for the use of NSBB in the treatment and prevention of portal hypertensive complications.[22-24] Nevertheless, considering that CI >4.2 L/min/m^2 is found almost only in patients with CSPH, it is tempting to hypothesize that inflammation may be a main pathogenetic driver of disease progression in hyperdynamic cirrhotic patients.[25-29] As this study demonstrates the relationship between SI and cardiodynamic state, it points to the need of a better stratification of patients at risk for development of ACLF and delineation of potential therapeutic targets.

TABLE 3 Detailed cause mortality in different Hemodynamic states

Cause of death n (%)	All patients n = 82	Hypodynamic CI <3.2 n = 32	Normodynamic CI 3.2-4.2 n = 22	Hyperdynamic CI >4.2 n = 28
ACLF	50 (61)	21 (66)	10 (45)	19 (68)
HCC	5 (6)	2 (6)	2 (9)	1 (4)
Other cancer	5 (6)	2 (6)	2 (9)	1 (4)
Bleeding/shock	6 (7)	3 (9)	1 (5)	2 (7)
Cardiovascular disease	4 (5)	0 (0)	2 (9)	2 (7)
Unknown/ other	12 (15)	4 (13)	5 (23)	3 (11)

Abbreviations: ACLF, acute-on-chronic liver failure; HCC, hepatocellular carcinoma.

TABLE 4 Uni- and Multivariate Cox regression for fatal ACLF development

	Univariate Cox Regression			Multivariate Cox Regression		
Parameter	*p*	Hazard Ratio	95%-Confidence Interval	*p*	Hazard Ratio	95%-Confidence Interval
Age	.010	1.257	1.057-1.494	.024	1.044	1.006-1.083
Era (cat)	.211					
NSBB	.519					
Child-Pugh	.011	1.179	1.039-1.337			
MELD	.004	1.104	1.032-1.181			
CLIF-C AD	.000	1.096	1.049-1.145			
Hb	.013	0.835	0.725-0.962			
Bilirubin	.026	1.201	1.022-1.411			
Albumin	.000	0.903	0.860-0.948	.001	0.907	0.857-0.961
INR	.050	2.293	1.001-5.255			
MAP	.023	0.975	0.954-0.996			
CI	.157					
Hypodynamic (cat)	.845					
Hyperdynamic (cat)	.017	2.014	1.135-3.576			
HVPG ≥ 16 (cat)	.005	2.484	1.320-4.677			
SVRI	.028	0.999	0.999-1.000			
IL-6 (cat)	.000	3.093	1.768-5.411	.006	2.428	1.295-4.553
IL-8 (cat)	.090					
sIL-33R (cat)	.011	2.336	1.217-4.484			
Ascites (cat)	.002	2.727	1.462-5.088			

Note: Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; AP, alkaline phosphatase; cat, categorical; CI, cardiac index; CLIF-C, European Foundation for the study of chronic liver failure consortium; Hb, haemoglobin; HVPG, hepatic venous pressure gradient; IL, interleukin; INR, international normalized ratio; MELD, Model for end-stage liver disease; NSBB, non-selective beta blockers; sIL-33R, soluble interleukin-33 receptor; SVRI, systemic vascular resistance index.

Categorical variables: Era (2002-2011 vs 2012-2016), Ascites: present clinically or detected by ultrasound, IL-6: equal or above lower limit of detection (9.38 pg/mL), IL-8: equal or above lower limit of detection (31.2 pg/mL), sIL-33R: level ≥7380.2 pg/mL; hyperdynamic and hypodynamic with normodynamic as reference.

Italic—included in the multivariate model, following variable were not included Child-Pugh and CLIF-C AD score (multicollinearity with MELD) and MAP (multicollinearity with hyperdynamic circulation).

It has been shown that patients with decompensated cirrhosis are those with the most pronounced circulatory dysfunction (hyperdynamic/hypodynamic circulation).[30] At the same time, patients with decompensated cirrhosis are at higher risk of developing further AD and ACLF. Importantly, neither hyperdynamic circulation nor decompensated state (AD with previous ascites) was independent predictors of fatal ACLF development in our cohort, whereas SI (measured by IL-6) was. This suggests SI as an additional crucial risk factor for fatal ACLF development despite the association with decompensated states and hyperdynamic cardiodynamic states of cirrhosis.

However, patients with ascites had higher rates of detectable SI markers compared with patients without ascites, especially significant in the normodynamic group. This finding adds to recent studies that showed levels of SI markers in compensated cirrhosis were moderately altered compared with healthy controls and markedly increased in decompensated cirrhosis without ACLF.[9] Moreover, our data are supported by recent studies showing that CRP levels progressively increase from compensated to decompensated patients.[12,26] The cause-effect relationship between AD and SI remains unclear but current data suggest that SI is a prerequisite for development of the decompensated state and further progression to ACLF. However, in the presence of a similar activation of SI, patients with a hypodynamic circulatory state may face a higher risk of developing ACLF than those patients with a normodynamic circulation. These data outline the need of further exploration of the complex circuital interaction of hepatic and cardiac hemodynamics and inflammation in determining organ damage, AD and fatal ACLF in patients with hypodynamic features.

Hemodynamic assessments and cytokine levels represent a snapshot of the patients' current status. However, by definition, CI at rest in supine position is supposed to be stable in not acutely altered patients. Transitory conditions such as sepsis have been excluded at the time of catheterization. Favourably, future studies should perform repeated cardiodynamic assessments in case of availability of experimental treatments targeting the heart function or SI.

However, in clinical routine invasive hemodynamic assessment is resource intense. Among non-invasive methods, finometer is available for evaluation of CO. Moreover, echocardiography is widely available. Especially, more sophisticated techniques, such as speckle tracking echocardiography (STE), were shown to be able to predict ACLF development in patients with TIPS.[31,32] STE therefore seems to be a promising tool for non-invasive assessment of cardiodynamics and its impact on ACLF development should be investigated in future studies.

Interestingly, IL-6 was detectable in only 32% of patients in our cohort. A recent study by Clària et al comparing cytokine levels in healthy subjects, cirrhotic inpatients without ACLF and cirrhotic inpatients with ACLF showed lower rates of undetectable levels in both cirrhotic cohorts (eg IL-6 without ACLF 7.4%, with ACLF 0.8%), while showing high rates of undetectable levels in the healthy cohort (eg IL-6 healthy 87.5%).[4] Of note, the cirrhotic inpatients without ACLF had a much higher mean MELD of 17 compared with our outpatient cohort (median MELD 11). In our cohort of cirrhotic outpatients, we found undetectable rates of IL-6 of 55%-71% depending on cardiodynamic state. These detection rates fall right between the healthy group and cirrhotic inpatients of Clària et al suggesting an association of cytokine detection rates with progression of liver disease. The detection rates in our cohort therefore seem expected and reasonable. Moreover, this simple and natural cut-off (detectable vs undetectable) would allow for semi-quantitative testing to identify patients at risk.

Our study has several limitations. First, no data on cardiovascular diseases and cirrhotic cardiomyopathy were available. In addition, no data on alcohol consumption in follow-up, episodes of AD and non-fatal ACLF were collected and no data of trigger and degree of ACLF were available, which is a major limitation. Finally, even though NSBB were paused 24 hours before hemodynamic evaluation, it might not be completely eliminated at time of evaluation. Therefore, we cannot determine the hemodynamic state of those patients without any NSBB effect. Likewise, it is equally possible that NSBB have a detrimental effect in some and a protective one in other patients in terms of fatal ACLF development. It is likely that some patients originally hyper- or normodynamic have been classified as hypodynamic after introducing NSBB. Patients who were already hypodynamic are unlikely to be "good cardiac responders" to NSBB. Patients sensitive to NSBB would develop severe hypotension and/or intolerance to incremental dosages. Patients insensitive to NSBB might have impaired cardiosystemic response to stress either way.

5 | CONCLUSION

This study shows that in patients with cirrhosis the risk of developing fatal ACLF is independently associated with the degree of SI, which is associated with cardiodynamic state. Accordingly, further stratification may help in the identification of novel therapeutic targets.

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CONFLICT OF INTEREST

No conflict of interest exists.

AUTHOR CONTRIBUTIONS

MP, SM: acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis. JG, NK, JLM, MPW, PW, MB, LT, RS, JC, SK, FEU, CW, RM, FS, FB, SM: acquisition of data, analysis and interpretation of data, critical revision of the manuscript regarding important intellectual content, funding recipient. LLG, SM, JT: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript regarding important intellectual content, funding recipient, administrative, technical and material support, study supervision.

ORCID

Michael Praktiknjo https://orcid.org/0000-0001-7033-9956
Nina Kimer https://orcid.org/0000-0002-4807-1575
Søren Møller https://orcid.org/0000-0001-9684-7764
Jonel Trebicka https://orcid.org/0000-0002-7028-3881

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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