Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Hepatofugal portal flow is highly predictive of acute-on-chronic liver failure: A new hemodynamic patho-physiological hypothesis

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ARTICLE INFO

Article history:
Received 2 October 2023
Revised 22 December 2023
Accepted 10 January 2024
Available online xxx

Keywords:
Acute-on-chronic liver failure
Non-forward portal flow
Advanced liver disease

ABSTRACT

Background and aims: Acute-on-chronic liver failure (ACLF) is a severe complication of advanced liver disease. A significant number of ACLF patients have not clear precipitating factors. The aim of the study was to investigate the role of alterations in porto-hepatic hemodynamics, especially non-forward portal flow (NFPF), in ACLF and liver-related mortality.

Methods: 233 cirrhotic patients were included in the study with a median follow-up of 24 months. Color-Doppler ultrasound was used to assess portal vein patency, flow direction and significant porto-systemic collaterals (>8 mm). Patients with active cancer, both at baseline and during follow-up and severe non liver-related comorbidities were excluded. ACLF and liver-related mortality were recorded during follow-up.

Results: Fifty-six patients (24%) developed ACLF; 24 (10,3%) had baseline NFPF. In survival analysis, NFPF, but not portal vein thrombosis, was independently associated with ACLF development (HR 2.85 95% C.I. [1.49–5.42], $p = 0.001$) and liver-related mortality (HR 2.24 95% C.I. [1.16–4.28], $p = 0.015$), even after adjustment for liver disease severity scores, age and etiology of liver disease.

Conclusion: NFPF is independently associated with ACLF development and liver-related mortality, regardless of etiology, severity disease scores and portal vein thrombosis. Although there is no specific measure to reverse NFPF, patients with NFPF should receive prompt intensive management and urgent prioritization for liver transplantation.

Clinical trial number: 2730 CESC

1. Introduction

Acute on chronic liver failure (ACLF) is a complex syndrome that develops in patients with cirrhosis characterized by acute liver decompensation (new-onset or worsening of ascites, gastrointestinal bleeding or hepatic encephalopathy), organ failures (both liver and extrahepatic organs) and high short-term mortality. In Western countries, as shown in the CANONIC study [1], ACLF development is mainly due to bacterial infections and alcoholic consumption. Nevertheless, in 20–45% of cases the trigger of decompensation remains unknown [1].

The current understanding of the pathogenesis of ACLF is based on excessive and widespread systemic inflammation and worsening of cirrhosis-associated immune dysfunction, mainly related to the severity of liver disease [2]. Evidence of systemic inflammation in ACLF is supported by increased plasma levels of C-reactive protein, white blood cells, pro-inflammatory and anti-inflammatory cytokines and soluble markers of macrophage activation [3,4]. Both bacterial infections and alcoholic consumption can activate the inflammatory cascade [5]. The development of ACLF is a complex cyclic cascade of events which is self-amplifying. In this context, portal hypertension, together with the over-production of nitric oxide and reactive oxygen species due to systemic inflammation, worsen the hyperdynamic circulation with splanchnic vasodilatation, elevated cardiac output and low peripheral resistance, that can lead to multi-organ failure [6].

Non-forward portal flow (NFPF), i.e. the evidence of hepatofugal portal flow in main portal vein, has been described as a feature associated with more severe portal hypertension, advanced liver disease and liver-related mortality [7], but no data exist about its association with ACLF and, eventually, its pathogenesis. Besides being associated with the presence of large porto-systemic shunts and, consequently, a higher concentration of gut-derived toxins, we

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https://doi.org/10.1016/j.dld.2024.01.190

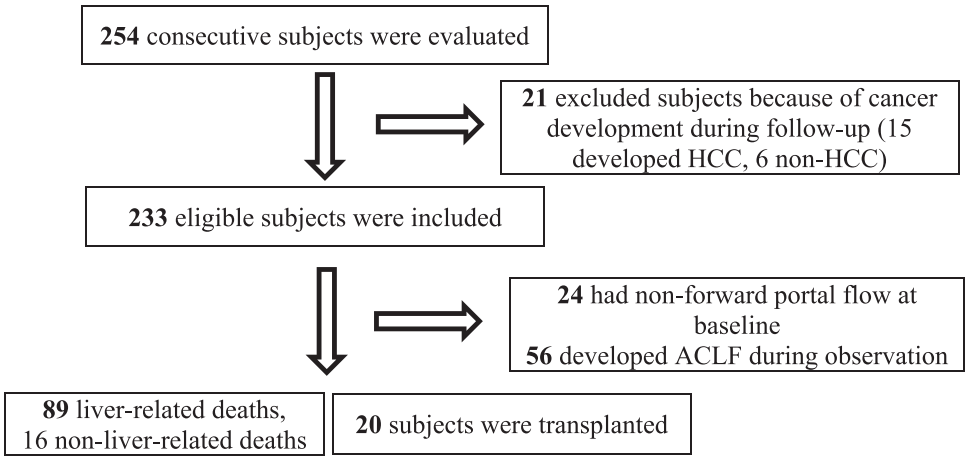

Fig. 1. Flow-chart of the study.

supposed that NFPF, differing from portal vein thrombosis, could "steal" the effective arterial perfusion of liver parenchyma and, thus, lead to a chronic hepatic ischemia and to an unstable haemodynamic status very prone to trigger ACLF and liver related death.

The aim of our prospective study was to evaluate the role of porto-hepatic hemodynamics, and in particular of NFPF, in the development of ACLF and liver-related mortality.

2. Methods

2.1. Study design, data collection and definitions (aggiungi nella discussion qlk relative a criteri di arruolamento, hcc e epatite alcolica)

This is a single centre prospective study conducted from January 2017 to November 2022. Patients were consecutively enrolled from both the outpatient and hospital setting; however, when enrolled during hospitalization, none of the patients had a severely decompensated cirrhosis (so defined for CLIF-C acute decompensation score > 60 [8], recent or active bleeding and septic shock) or ACLF.

The study protocol was approved by the Institutional Ethics Committee of Verona (Italy) and all patients provided written informed consent to be included in the study (2730CESC-VR).

The inclusion criteria were: age > 18 years and a diagnosis of liver cirrhosis of any aetiology. The diagnosis of cirrhosis was based either on histology or on compatible clinical, laboratory and radiological findings. Exclusion criteria were: pregnancy, a previous diagnosis of hepatocellular carcinoma (HCC, based on radiological findings) at enrolment or other non-HCC cancers (including hematologic malignancies), previous orthotopic liver transplantation, end-stage kidney disease and severe heart failure (NYHA classes III and IV). Patients eligible at baseline but who developed HCC and other non-HCC malignancies during follow-up were excluded; in fact, HCC, especially when with infiltrative features, is associated with massive increase in intra-hepatic resistance potentially leading to the reversal of portal blood flow. Demographic, clinical, laboratory and radiologic data of 254 consecutive cirrhotic patients admitted as inpatients or outpatients were collected; however, 25 subjects out of the total initial population were not included in the final analysis since they developed HCC (15) and non-hepatocellular tumour (6) during follow-up; 233 subjects were finally analysed (Fig. 1).

For each participant, all liver-related complications occurring during observation were recorded: ascites, acute kidney injury/hepato-renal syndrome (AKI-HRS), variceal bleeding, overt hepatic encephalopathy (HE), ACLF and death. The baseline presence of high-risk oesophageal varices, portal vein thrombosis, umbilical vein patency and intra-abdominal portosystemic shunts were also considered. Child-Pugh score (CP score), Model for End-Stage Liver Disease score (MELD, categorized as below 10 points, between 10 and 20 points and above 20 points), CLIF-C AD (Chronic Liver Failure-Consortium Acute Decompensation score) and neutrophil to lymphocyte ratio (NLR) were calculated. Death (both liver and non-liver-related) and liver transplant were considered as the end of follow-up.

Patients were evaluated by a single expert operator in order to reduce inter-observer variability [9] with Logiq S8 XD clear GE and Siemens Acuson S3000. Color and pulsed Doppler US was used to assess the direction of portal flow: forward portal flow (FPF, i.e. normo-directed portal flow) and NFPF in the main portal vein, and portal vein thrombosis. NFPF was defined as the evidence of hepatofugal portal flow in the main portal vein (Supplementary Figure 1a and 1b).

ACLF was diagnosed according to the CLIF-C ACLF (Chronic Liver Failure ACLF calculator) score [10]. Liver-related mortality was defined as the occurrence of death due to liver-related causes, such as ACLF, spontaneous bacterial peritonitis, gastrointestinal bleeding, hepatic encephalopathy and end-stage liver disease. High risk oesophageal varices were defined according to the European Society of Gastrointestinal Endoscopy guidelines: varices extending for more than 50% of the luminal diameter or touching (grade III) and/or detection of red patches [11]. Splenomegaly was defined when detecting polo-polar diameter > 12.5 cm. Intra-abdominal spontaneous portosystemic collateral shunts (SPSS) were defined as venous vessels with a diameter of at least 0,8 cm detected at baseline Color-Doppler US [12] while a calibre of 5 mm or more, as previously seen in literature, was considered to define the presence of large patent umbilical vein (PUV) [13]; however, only when associated with the inversion of right intra-hepatic portal flow, PUV was considered clinically and haemodynamically significant and, thus, similar to NFPF. Portal vein thrombosis (PVT) was defined as complete occlusion of the main trunk of portal vein with or without cavernomatous transformation or partial occlusion (<50% or ≥50%). Clinically significant HE was defined as the occurrence during follow-up of at least West-Haven grade 2 or higher HE. Clinically significant ascites was defined when requiring diuretic therapy (at least mineral-corticoid receptor antagonist at dose of 100 mg) or large-volume paracentesis.

2.2. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and as median with Inter-Quartile Range (IQR) de-

pending on the data distribution (according to the Kolmogorov-Smirnov's test); discrete variables were expressed as number and percentage. Comparison between continuous variables was performed using the Student's T test and/or the Mann-Whitney U test, depending on data distribution. Pearson's chi square test and Fisher's exact test were performed to assess differences between frequencies in groups. All tests were two-sided and a statistically significant value was considered if a $p < 0.05$.

A stepwise logistic regression analysis was performed in order to assess factors independently associated with the presence of NFPF. The risk factors for ALCF and liver-related mortality during follow-up were tested using Cox-Regression analyses and the Kaplan–Meier curve. Log-rank test was used to compare patients with NFPF and those with forward portal flow (FPF).

Univariate COX-Regression analyses were performed to assess potential factors associated with the development of ACLF and liver-related mortality (NFPF, age, sex, alcoholic etiology, portal vein thrombosis, CP class [A, B, C], baseline MELD score category (below 10 points, between 10 and 20 points and above 20 points), chronic kidney disease, diabetes mellitus). Multivariate analyses were performed with both continuous MELD score and MELD score category. Since CP and MELD score are closely collinear, each are entered in multivariate analysis separately. Only variables that resulted significantly associated with the outcome in univariate analyses ($p < 0.05$) were entered into the stepwise multivariate model. The multivariate analysis was done limiting the number of entered variables to 1/10 events to avoid the risk of overfitting models. The effect of each variable on ACLF occurrence and liver-related mortality was expressed as hazard ratio with 95% confidence interval.

Statistical package for social science (SPSS) version 22 (IBM Corp., Armonk, NY, USA) was used for all data analysis. GraphPad 5 was used for graphic design.

3. Results

3.1. Baseline characteristics of patients, ACLF development and liver-related mortality

Two-hundred and thirty-three consecutive cirrhotic patients (148 males, 63,5%; median age ± SD, 61 ± 11 years) were included in the analysis with a median follow-up of 24 months (IQR 12–39 months). The most frequent etiology was alcoholic, (alcohol-related n° 99, 42,4%; viral n° 65, 27,8%; NAFLD-related n° 33, 14,2%; autoimmune n° 19, 8,1%; mixed viral-alcoholic n° 18, 7,7%), but the vast majority (96%) had been abstinent for at least 6 months. Twenty-four (10,3%) patients had baseline NFPF at Color-Doppler US. Among them, only 2 patients had a suspect of alcoholic hepatitis (not proven by liver biopsy), mainly because recent of heavy abuse; in one patient, the inversion of portal blood flow was long-term persistent while the other, three months later, developed a fatal ALCF not allowing a long-term evaluation of the portal blood flow direction.

Almost no patients with baseline forward portal blood flow developed NFPF during the follow-up, except for 3 subjects with acute alcoholic hepatitis who developed transient NFPF that promptly resolved after recovery; however, considering these NFPFs as transient, they were not considered in final analysis as "true" NFPF.

Among patients with FPF, 26 had baseline detectable PUV (12,4%); however, in only 2 subject the presence of PUV was hemodynamically relevant, since the inversion of portal blood flow in the right brunch of portal vein was noticed. These 2 subjects were considered as NFPF in final analysis.

Fifty-six (24%) subjects developed ACLF during observation (median 5.5 months, IQR 2–13.7 months) while 89 subjects died for liver related causes (38.2%, median 12 months, IQR 5.5–24 months). Sixteen subjects (6,8%) died of non-liver related causes (5 sepsis, 4 cardiovascular events, 7 no clear causes, median 22 months) Twenty subjects (8.6%) underwent liver transplantation during follow-up.

Table 1
Comparison of baseline characteristics of patients according to portal blood flow direction.

	NFPF (10,3%)	FPF (89,7%)	p-value
	n°=24	n°=209	
Gender male, n° (%)	18 (62,5)	133 (63,6)	0,913
Age years, IQR	59 (47–70)	62 (54–70)	0,207
Alcoholic etiology, n° (%)	18 (75)	76 (36,4)	<0,001
Haemoglobin g/dL, IQR	10,2 (9,3–11,8)	12 (10,3–13,0)	0,033
Platelets /mmc, IQR	109 (61–114)	125 (74–158)	0,109
Total leukocytes / mm^3	5,4 (4,6–7,2)	5,1 (3,9–6,8)	0.143
Neutrophil/lymphocyte ratio	3,3 (1,6–5,5)	2,7 (1,7–3,9)	0.286
Creatinine mg/dL, IQR	0,8 (0,7–0,8)	0,8 (0,7–0,8)	0,520
Albumin g/L, SD	29 (26–34)	36 (30–40)	<0,001
Ferritin ng/mL, IQR	428 (208–1165)	280 (93,3–704)	0,05
Total bilirubin mg/dL, IQR	3,6 (2,2–12,2)	1,3 (0,8–2,2)	<0,001
INR, IQR	1,65 (1,2–2)	1,22 (1–1,49)	<0,001
CP score, IQR	9 (8–10)	7 (5–9)	<0,001
MELD score, IQR	19 (14,5–30,5)	11 (8–15)	<0,001
CLIF-C AD, IQR	50 (44–56)	55 (49–63)	0,009
High risk varices n° (%)	3 (12,5)	67 (32,2)	0,038
Splenomegaly n° (%)	21 (87)	161 (79)	0,230
Spleen diameter (cm)	14 (12–16)	14 (13–15)	0.900
SPSS n° (%)	21 (87,5)	96 (45,9)	<0,001
PVT n° (%)	0 (0)	28 (13,4)	0,044
<50%	–	15 (53,6)	
≥50%	–	4 (14,3)	
Totally occlusive	–	9 (32,1)	
Beta-blockers n° (%)	15 (66,7)	123 (59,1)	0,476

Legend: Values expressed as median and Interquartile Range (IQR). N.s., not significant;.
INR, International Normalized Ratio; CLIF-C AD, Chronic Liver Failure Consortium Acute Decompensation score; Splenomegaly, when >12 cm; SPSS, Porto-Systemic Shunts, defined as diameter > 8 mm; PVT, Portal Vein Thrombosis; HE, hepatic encephalopathy; AKI/HRS, acute kidney injury/hepato-renal syndrome.

NFPF patients showed significantly worse liver function tests and major complications of cirrhosis as compared to patients with FPF (Tables 1 and 2). In particular, they developed ACLF more frequently and earlier than those with FPF. The triggers of ACLF were similar in both groups and mostly related to bacterial infections. Furthermore, liver-related mortality was significantly higher in patients with NFPF (Table 2).

No NFPF patients had portal vein thrombosis (PVT) at baseline, significantly differing from those with FPF (n° 28, 13,4%; Table 1). Nevertheless, ACLF development and mortality were not significantly higher among patients with baseline PVT when compared with subjects with patent portal vein (Supplementary Table 1).

3.2. Association between NFPF and aetiology of liver disease, porto-systemic collaterals, high-risk varices and HE

Alcoholic aetiology and significant SPSS were more frequent in patients with NFPF as compared to those with FPF (for alcoholic aetiology 18 out of 24: 75% vs 77 out of 210, 36.8%, $p < 0.001$; for collaterals 21 out of 24: 87.5% vs 96 out of 209: 45.9%, $p < 0.001$). At multivariate logistic regression analysis, NFPF was found to be independently related with MELD score category and SPSS (Supplementary Table 2). High-risk varices, but not ascites and AKI/HRS, were significantly less frequent in patients with NFPF when compared with FPF patients (3 out of 24: 12.5% vs 67 out of 209: 32.2%; $p = 0.038$, Table 2). At stepwise regression analysis, the presence of high-risk varices remained significantly inversely correlated only with NFPF (OR 0.157, 95% I.C. [0.035–0.703], $p = 0.016$). HE was more frequent in subjects with NFPF (15 out of 24: 62.5% vs 63 out of 209: 30.3%, $P = 0.002$).

Table 2
Comparison of cumulative liver-related complications during follow-up according to portal blood flow direction.

	NFPF (10,3%) n°=24	FPF (89,7%) n°=209	p-value
ACLF n° (%)	14 (58,3)	44 (21,1)	<0,001
CLIF-C ACLF points, IQR	59 (55–71)	56 (54–63)	0,558
ACLF grade 1 n° (%)	2 (8,6)	12 (5,8)	0,432
grade 2 n° (%)	4 (17,4)	12 (5,8)	
grade 3 n° (%)			
	8 (34,8)	20 (9,6)	
Time to ACLF development, months median, IQR	2,5 [1–12]	10,5 [7,5–20,5]	<0,001
Triggers of ACLF n° (%)			
Bacterial infections	8 (57,1)	25 (59,5)	p = n.s.*
Alcohol	4 (28,6)	6 (14,3)	
Unknown	2 (14,3)	5 (11,9)	
Bleeding	–	6 (14,3)	
Liver-related mortality at last evaluation, n° (%)	18 (75)	71 (34)	<0,001
Ascites n° (%)	14 (58,3)	113 (54,1)	0,676
Variceal bleeding n° (%)	4 (16,7)	47 (22,5)	0,539
Hepatic encephalopathy n° (%)	15 (62,5)	64 (30,6)	0,002
AKI-HRS, n° (%)	2 (8,3)	24 (11,5)	0.481

Legend: CLIF-C ACLF, Chronic Liver Failure ACLF Calculator, AKI-HRS, Acute Kidney Injury-Hepato-Renal Syndrome. * for all alcoholic, bacterial and unknown etiologies.

Table 3a
Hazard Ratios (HR) for ACLF episodes (n° 56) occurring according to predisposing and comorbidities risk factors (including Child-Pugh class). Crude and fully adjusted values by the use of Cox-regression analysis.

	Crude HR (95% I.C.)	p-value	Fully adjusted HR (95% I.C.)*	p-value
Age (years)	1,03 [0,97–1,08]	0.038	1032 [1006–1089]	0.015
Male sex	1,42 [0,76–2,57]	0,263	–	n.s.
CKD	1,39 [0,61–3,16]	0,429	–	n.s.
DM	0,95 [0,52–1,72]	0,875	–	n.s.
Alcoholic etiology	1,63 [0,87–3,04]	0,121	–	n.s.
PVT	0,61 [0,23–1,61]	0,326	–	n.s.
NFPF	2,26 [1,15–4,43]	0,010	2,85 [1,49–5,42]	0,001
CP class**	3.05 [1,83–5,09]	0,001	1,98 [1,36–2,89]	<0,001

Legend: *: all factors included in the first column are mutually adjusted in the fully adjusted model; N.s., not significant.
Legend: CKD, Chronic kidney disease; DMII, diabetes mellitus, PVT, Portal Vein Thrombosis.

Table 3b
Hazard Ratios (HR) for ACLF episodes (n° 56) occurring according to predisposing and comorbidities risk factors (including MELD score category). Crude and fully adjusted values by the use of Cox-regression analysis.

	Crude HR (95% I.C.)	p-value	Fully adjusted HR (95% I.C.)*	p-value
Age (years)	1,03 [1,01–1,07]	0.015	1028 [1003–1055]	0.028
Male sex	1,34 [0,73–2,46]	0,352	–	n.s.
CKD	1,05 [0,44–2,31]	0,990	–	n.s.
DM	0,90 [0,49–1,65]	0,743	–	n.s.
Alcoholic etiology	1,42 [0,76–2,63]	0,263	–	n.s.
PVT	0,67 [0,62–1,76]	0,418	–	n.s.
NFPF	2,58 [1,31–5,09]	0,006	2,72 [1,42–5,28]	0,003
MELD score category	4,13 [2,51–6,79]	<0,001	4,04 [2,75–7,05]	<0,001

Legend: *: all factors included in the first column are mutually adjusted in the fully adjusted model; N.s., not significant.
Legend: CKD, Chronic kidney disease; DMII, diabetes mellitus, PVT, Portal Vein Thrombosis.

3.3. Predictors of ACLF, liver-related mortality and liver transplantation

As shown in Table 3, age, NFPF, CP class and MELD score category were significantly and independently related to the development of ACLF at both univariate analysis and multivariate stepwise Cox-regression analysis (see Table 3, Fig. 2).

Similar results were shown when considering liver-related mortality; in multivariate Cox-regression, age, CP class, MELD score category and NFPF were found to be independent predictors (Table 4, Fig. 3). These results were the same even after exclusion of patients who underwent liver transplantation. Table 4b

When considering overall mortality (105 subjects, 89 for liver-related causes, 16 for non-liver related), NFPF did not reach statistically significance in predicting the outcome (overall mortality).

During follow-up, patients with NFPF underwent liver transplantation more frequently than those with FPF (5 out of 24: 20.8% vs 15 out 209: 7.1%, p = 0.034); NFPF patients had reduced transplant-free survival compared to those with FPF (7.0 vs 21.1 months, p = 0.048). In both univariate and multivariate Cox-

Table 4a
Hazard Ratios (HR) for liver-related mortality (n°89) according to predisposing and comorbidities risk factors (including Child-Pugh class). Crude and fully adjusted values by the use of Cox-regression analysis.

	Crude OR (95% I.C.)	p-value	Fully adjusted HR (95% I.C.)*	p-value
Age (years)	1,04 [1,01–1,06]	0,005	1043 [1021–1065]	0,001
Male sex	1,01 [0,63–2,59]	0,740	–	n.s.
CKD	1,81 [0,96–3,43]	0,066	–	n.s.
DM	0,95 [0,60–1,65]	0,994	–	n.s.
Alcoholic etiology	1,12 [0,66–1,91]	0,673	–	n.s.
PVT	0,97 [0,50–1,93]	0,326	–	n.s.
NFPF	2,11 [1,09–4,13]	0,029	2,24 [1,16–4,28]	0,015
CP class**	2,52 [1,63–3,91]	< 0,001	2,06 [1,49–2,85]	<0,001

Legend: *: all factors included in the first column are mutually adjusted in the fully adjusted model; N.s., not significant.
Legend: CKD, Chronic kidney disease; DMII, diabetes mellitus, PVT, Portal Vein Thrombosis.

Table 4b
Hazard Ratios (HR) for liver-related mortality (n°89) according to predisposing and comorbidities risk factors (including MELD score category). Crude and fully adjusted values by the use of Cox-regression analysis.

	Crude OR (95% I.C.)	p-value	Fully adjusted HR (95% I.C.)*	p-value
Age (years)	1024 [1003–1046]	0,028	1025 [1006–1045]	0,011
Male sex	1,03 [0,64–1,67]	0,887	–	n.s.
CKD	1,26 [0,67–2,35]	0,470	–	n.s.
DM	0,94 [0,59–1,52]	0,822	–	n.s.
Alcoholic etiology	1,24 [0,77–2,01]	0,378	–	n.s.
PVT	1,16 [0,62–2,18]	0,631	–	n.s.
NFPF	2,96 [1,67–3,90]	<0,001	2,84 [1,62–4,96]	<0,001
MELD score category	2,68 [1,87–3,89]	<0,001	2,88 [2,05–4,06]	<0,001

Legend: *: all factors included in the first column are mutually adjusted in the fully adjusted model; N.s., not significant.
Legend: CKD, Chronic kidney disease; DMII, diabetes mellitus, PVT, Portal Vein Thrombosis.

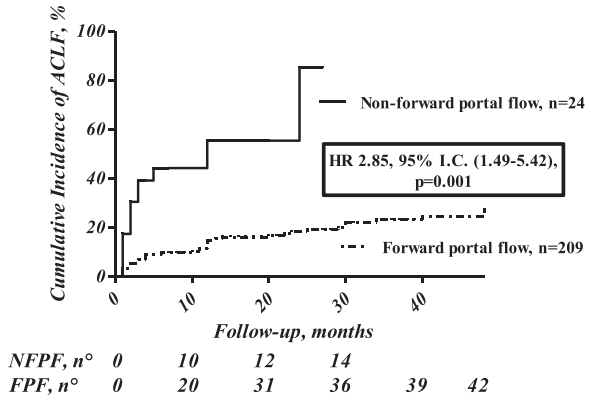

Fig. 2. Cumulative incidence of ACLF (n° total: 56 subjects) during follow-up according to the direction of portal blood flow (age, CP class and NFPF as covariates). Legend: NFPF, Non-Forward Portal Flow; FPF, Forward Portal Flow.

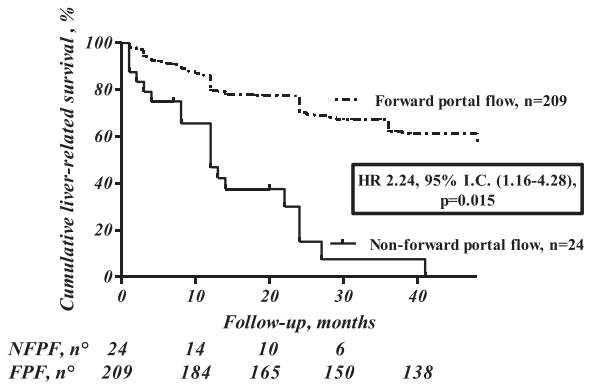

Fig. 3. Cumulative liver-related survival (n° of deaths: 89 subjects) during follow-up according to the direction of portal blood flow (age, CP class and NFPF as covariates). Legend: NFPF, Non-Forward Portal Flow; FPF, Forward Portal Flow.

regression analysis, the only predictors were shown to be either MELD score category (HR 3.88, 95% I.C. [1.90–7.91], $p < 0.001$) or CP score (HR 1.50, 95% I.C. [1.23–1.82], $p < 0.001$) and NFPF (HR 2.98, 95% I.C. [1.02–8.98], $p = 0.050$ in multivariate analysis with MELD score category, HR 3.56, 95% I.C. [1.19–10.59], $p = 0.022$ in multivariate analysis with CP score).

4. Discussion

The results of this study show that NFPF is a condition far from rare, present in nearly 10% of our cohort, and strongly associated with worse liver function and the development of liver decompensating events [7,14–16]. More importantly, patients with NFPF are at higher risk of ACLF development and liver-related mortality compared to those with FPF and this association is independent from classical risk predictors in advanced liver disease, such as Child-Pugh and MELD score. Taken together, these results point out the inversion of portal flow as a new mechanism that might contribute to clarify acute decompensation and, more interestingly, ACLF pathophysiology.

Increased resistance to portal blood flow is the main pathophysiological mechanism leading to the development of portal hypertension (PH) in patients with cirrhosis. PH has two main components: one static, due to fibrosis and regenerative nodules and the other dynamic, due to an increase in intrahepatic vascular tone [17]. PH causes SPSS, which represent an attempt to decompress the portal system but ultimately lead to variceal bleeding and hepatic encephalopathy.

NFPF is an abnormal flow pattern in which the portal venous flow comes from the periphery of the liver, i.e. from the hep-

atic parenchyma towards the *porta hepatis* and backwards along the portal vein. It is supposed that spontaneous reversal of portal vein flow in patients with cirrhosis can occur only when the hepatic outflow resistances exceeds those through SPSS and arterial blood flow partially drains into the portal vessels; this probably depicts an advanced stage of portal hypertension. In fact, the detection of a NFPF is clinically important to diagnose portal hypertension and searching for SPSS [18,19]. NFPF was shown to correlate with worsening portal hypertension and increased resistance through liver sinusoids [7]; in fact, because of sinusoidal distortion, hepatic artery inflow was shown to be impaired with an increased resistance in patients with liver cirrhosis [20]. The current understanding of NFPF also recognizes the role of the hepatic artery and the complementary phenomena of arterio-portal shunting [7]. Data regarding prevalence and clinical implications of NFPF in cirrhosis are scarce. In previous studies, NFPF was found to be present in 8.3% [14], 9% [15] and 10.8% [7] of patients. Cirrhotic patients with NFPF have been shown to have lower incidence of variceal bleeding [10] but greater hepatic dysfunction, higher incidence of hepatic encephalopathy and mortality [3–5]. However, it has not been clarified yet whether NFPF is a feature merely associated with advanced liver disease and severe PH or a determinant *per se* of worse outcome.

In recent years, a growing body of evidence clarified that ACLF is a distinct clinical syndrome from acute decompensation (AD) of cirrhosis, mainly because organ failure is associated with a much higher 28-day mortality rate [21–23]. Abnormal systemic inflammation has been shown to drive the major trajectory from compensated advanced chronic liver disease (cALD) or AD to ACLF, being supported by both exogenous and endogenous pro-inflammatory molecules [24]. In fact, as cALD progresses towards AD and ACLF, an increase in inflammatory markers (C reactive protein, interleukin-6, blood leukocytes) and prognostic score indices (Child-Pugh and MELD score) was shown, to demonstrate a *continuum* linkage explaining the progressive evolution of the disease that leads to a humoral and hemodynamic decompensation [25–27].

As recently shown, several triggers can induce the development of ACLF in both patients with cALD and those with ongoing AD, such as, bacterial infections, alcoholic consumption, gastro-intestinal haemorrhage, viral reactivation and acute hepatitis (drug-induced, autoimmune-mediated or both) [27–29]; furthermore, we recently showed that spur cells-associated disorder, i.e. spiky red blood cells typically found in alcohol-related cirrhosis, is strongly and independently associated with ACLF development and liver-related mortality [30]. However, in up to 40–50% of cases, no identifiable provoking factors can be found despite a careful history collection and an extensive screening for occult infections [29].

To date, only few studies have explored the relationship between splanchnic hemodynamics and liver decompensation and ACLF. Paraumbilical vein patency (PUV) has been shown to be a frequent finding in cirrhosis and, when haemodynamically relevant, to be related to reduced effective hepatic perfusion, CP class C, clinical decompensation (especially ascites) [31,32], more severe portal hypertension [32] but probably reduced risk of oesophageal variceal haemorrhage [13], because acting like a “spontaneous” trans-jugular intra-hepatic porto-systemic shunt. In our cohort, a modest but significant number of patients with FPF had significant PUV (defined by ≥5 mm calibre); however, in only 2 patients out of the totality of subjects with PUV and normal portal flow direction (26 out of 209) an inversion of right portal brunch flow was recorded (suggesting hemodynamic relevance) while, in the others 24, the intra-hepatic flow was normo-directed. This suggest that, at least in very few cases, PUV cannot be considered as a classical NPFP; in fact, effective liver perfusion is not significantly influenced by fugal PUV flow when in presence of normo-directed portal blood flow in right portal vein and in left portal vein distal to the shunt [33].

NFPF was shown to be strongly and independently associated with an early development of ACLF and liver-related mortality, even when adjusted for risk scores that indicate the severity of liver impairment (Child-Pugh and MELD score). Almost all patients with NFPF had alcoholic aetiology, probably suggesting it to be a major determinant. However, alcohol consumption, when considered as a trigger of ACLF, was not more prevalent in NFPF subjects compared with those with FPF. Moreover, only NFPF and liver disease severity scores, rather than alcoholic etiology, were independent predictors of outcomes. In accordance to the well-known association between alcoholic hepatitis and transient inversion of portal flow due to severe hepatic inflammation [34,35], in our cohort 3 subjects were likely to have developed alcoholic hepatitis and a transient NFPF during observation; however, since portal flow became hepatopetal after hepatitis resolution, they were not considered as “stable” NFPF subjects. On the other hand, 2 patients with NFPF at enrolment were suspected to have mild-to moderate alcoholic hepatitis, mainly because of an history of abuse and an alteration of liver biochemistry and, despite alcoholic abstinence and biochemical improvement, NFPF did not reverse during follow-up suggesting it to be “chronic”.

Interestingly, NFPF patients were shown to be protected from high risk varices even in the presence of large SPSS and higher prevalence of HE. It can be hypothesized that a higher intrahepatic resistance may cause the opening of large collateral vessels large collateral vessels draining into a low-resistance circulation in order to decompress the portal system and ultimately determining the inversion of portal flow. Thus, the higher risk of AD and ACLF could be explained by the role of NFPF in depriving the liver of an important part of the oxygenated and nutrients-rich arterial blood leading to a sort of chronic “parenchymal ischemia”. Nevertheless, the lack of invasive data, such as liver biopsies, cannot permit to confirm this hypothesis, recommending the need for further research in future.

In our cohort, the incidence of both ACLF and liver-related mortality was similar between patients with baseline PVT and those without; furthermore, PVT was not associated to liver-related complications and death. Several studies investigated the clinical impact of PVT in the natural history of cirrhosis but without unequivocal results [35–37]. However, as shown in a large randomized clinical trial involving more than 1200 cirrhotic subjects, PVT development was found to be related to liver disease severity but did not influence its further progression [37]. The findings of our study support the hypothesis that liver decompensation, ACLF, and death are not related to the reduction (when portal flow is progressively slower with worsening portal hypertension) or absence of portal inflow, but rather to NFPF, which is associated with a reduced effective arterial perfusion since its “blood stealing” behaviour. That is, ACLF develops only when “effective parenchymal hypoperfusion” is more relevant, because of the decrease of the sinusoidal arterial blood supply due to NFPF.

Our study has some limitations. First of all, no specific inflammatory markers (such as LPS or pro-inflammatory cytokines) were available, although neutrophil to lymphocyte ratio, a validated marker of systemic inflammation, was non significantly different among the study sub-groups. Furthermore, the study was not designed to have hepatic and cardio-pulmonary hemodynamics evaluated, that could have provided an insight on the degree of portal hypertension and hyperdynamic circulation. Finally, the amount of alcohol consumption during follow-up was not registered; however, only very few patients were likely to have developed mild-to-moderate alcoholic hepatitis and none of them a severe form.

However, a strong point of the study is that US evaluation of portal flow is easily available and reproducible [9], so that our findings can be replicated in other cohorts. Furthermore, we excluded patients with HCC, baseline severe liver impairment (severe alcoholic hepatitis, very advanced liver disease) and many unstable clinical conditions (severe sepsis, heart failure, bleeding) that could have had an impact in the splanchnic hemodynamic, reinforcing our results by eliminating some common selection bias.

In conclusion, NFPF was found to be strictly and independently associated with the development of ACLF and liver-related mortality. Although the exact mechanism is not clearly understood yet, the hypothesis of a chronic "ischemic" injury provided by a NFPF that deprives the liver of oxygen and nutrients could be a reasonable suggestion for new insight into ACLF pathophysiology. In this setting, the clinical *scenario* of liver cirrhosis with NFPF should be carefully considered as at very high risk of hepatic decompensation, ACLF and death and so promptly managed with both intensive care and, when possible, with liver transplantation.

Conflict of interest

This study was approved by the Ethical Committee of Verona (2730CESC-VR). We accept transfer of all copyright ownership of our manuscript to your Journal, in the event the work is published. We declare that the article is original, does not infringe upon any copyright or other proprietary right of any third party, is not under consideration by another journal, and has not been published previously. The final version of the paper has been seen and approved by the authors that are sure of the integrity of the work. No conflict of interest and financial interest exists. Furthermore, we declare that our study complies with the Declaration of Helsinki, that the locally appointed ethics committee has approved the research protocol and that informed consent has been obtained from all the recruited subjects.

Author contributions

All the authors gave a substantive contribution in the preparation of this manuscript. All the co-authors participated to the draft of the study protocol, gave a relevant contribution in the interpretation of the results, reviewed critically the manuscript and approved its final version.

Funding

No financial supports.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.01.190.

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