Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS

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Research Article
Cirrhosis and Liver Failure

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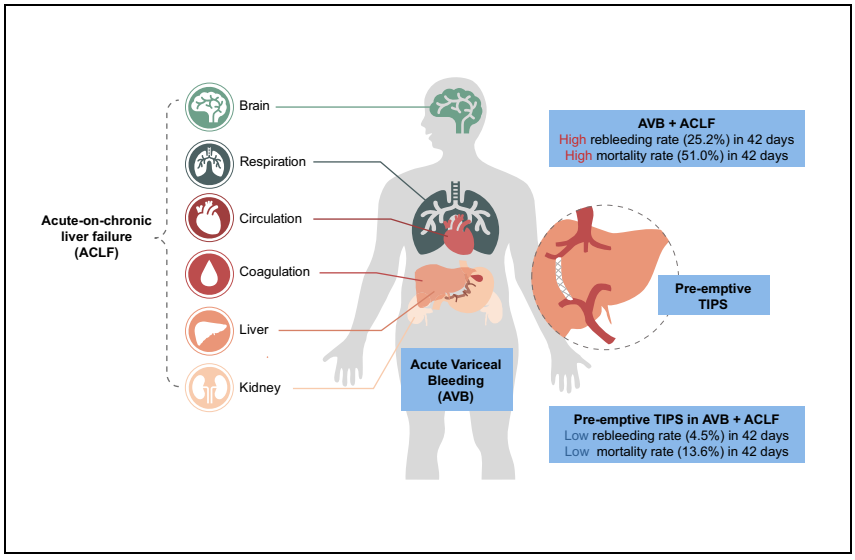
Graphical abstract



Highlights

- Variceal bleeding is frequently associated with ACLF in cirrhosis.
- ACLF is independently associated with rebleeding and mortality.
- Patients with variceal bleeding and ACLF can benefit from a pre-emptive (early) TIPS.

Authors

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Lay summary

Acute variceal bleeding is a deadly complication of liver cirrhosis that results from severe portal hypertension. This study demonstrates that the presence of acute-on-chronic liver failure (ACLF) is the strongest predictor of mortality in patients with acute variceal bleeding. Importantly, patients with ACLF and acute variceal (re)bleeding benefit from pre-emptive (early) placement of a transjugular intrahepatic portosystemic shunt.

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Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS

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Background & Aims: The relationship between acute-on-chronic liver failure (ACLF) and acute variceal bleeding (AVB) is poorly understood. Specifically, the prevalence and prognosis of ACLF in the context of AVB is unclear, while the role of transjugular intrahepatic portosystemic shunt (TIPS) in the management in patients with ACLF has not been described to date.

Methods: A multicenter, international, observational study was conducted in 2,138 patients from 34 centers between 2011 and 2015. ACLF was defined and graded according to the EASL-CLIF consortium definition. Placement of pre-emptive TIPS (pTIPS) was based on individual center policy. Patients were followed-up for 1 year, until death or liver transplantation. Cox regression and competing risk models (Gray's test) were used to identify independent predictors of rebleeding or mortality.

Results: At admission, 380/2,138 (17.8%) patients had ACLF according to EASL-CLIF criteria (grade 1: 38.7%; grade 2: 39.2%; grade 3: 22.1%). The 42-day rebleeding (19% *vs.* 10%; p <0.001) and mortality (47% *vs.* 10%; p <0.001) rates were higher in patients with ACLF and increased with ACLF grades. Of note, the presence of ACLF was independently associated with rebleeding and mortality. pTIPS placement improved survival in patients with ACLF at 42 days and 1 year. This effect was also observed in propensity score matching analysis of 66 patients with ACLF, of whom 44 received pTIPs and 22 did not.

Conclusions: This large multicenter international real-life study identified ACLF at admission as an independent predictor of rebleeding and mortality in patients with AVB. Moreover, pTIPS was associated with improved survival in patients with ACLF and AVB.

Lay summary: Acute variceal bleeding is a deadly complication of liver cirrhosis that results from severe portal hypertension. This study demonstrates that the presence of acute-on-chronic liver failure (ACLF) is the strongest predictor of mortality in patients with acute variceal bleeding. Importantly, patients with ACLF and acute variceal (re)bleeding benefit from pre-emptive (early) placement of a transjugular intrahepatic portosystemic shunt.

Introduction

Acute variceal bleeding (AVB), which accounts for 70% of all upper gastrointestinal bleeding episodes in cirrhosis,[1] has been identified as a common cause of death in patients with cirrhosis, with a 6-week mortality around 20%.[2] At present, progress has been made in the treatment of AVB, including endoscopic treatment, drug therapy, and transjugular intrahepatic portosystemic shunt (TIPS).[3,4] However, 10–20% of patients with AVB experience treatment failure after initial endoscopic and medical treatment, which is associated with a high short-term risk of further liver decompensation and death.[5]

Several factors have been proposed to identify patients with AVB who are at high risk of poor outcomes and treatment failure, such as the model for end-stage liver disease (MELD) score, renal failure, bacterial infection and active bleeding at endoscopy.[2,6,7] The Baveno VI Consensus recommends the use of pre-emptive TIPS (pTIPS) in cirrhotic patients with Child-Pugh B cirrhosis and active bleeding at endoscopy despite being on vasoactive drugs, and in patients with Child-Pugh C (<14 points).[8] Several studies have shown that pTIPS placed within 24–72 hours after admission, leads to a significant improvement in relevant clinical outcomes.[5,9–12] pTIPS prevents rebleeding and ascites without increasing the complication of hepatic encephalopathy (HE),[13] and is thus a milestone in the treatment of cirrhotic patients with AVB. The benefits of pTIPS probably rely on the prevention of further deterioration after failure of initial treatment, avoiding subsequent increase in rebleeding, organ failure and death.[14] This condition frequently meets the criteria of acute-on-chronic liver failure (ACLF), which comprises a rapidly deteriorating syndrome with extremely high short-term mortality.[15] With a prevalence of over 22%, ACLF is common in cirrhotic patients with acute decompensation.[15,16] AVB is a well-known trigger for the development of ACLF.[17,18] However, the role of ACLF in the outcome of patients with AVB has not yet been investigated.

This multicenter, international, observational study addresses 3 clinically relevant issues: i) the prevalence of ACLF at admission in patients with AVB; ii) the influence of ACLF at admission on AVB outcomes (rebleeding and mortality); iii) the impact of pTIPS on mortality of patients with ACLF and AVB.

Patients and methods

Study design and patients

This study has been conducted using the database of a multicenter, international, prospective observational study by the Baveno Cooperation to evaluate AVB in cirrhotic patients in 34 centers between October 2011 and May 2015. The study protocol (see supplementary information and CTAT table) and details were published previously.[13] All patients were managed according to the guidelines of the Baveno V consensus and the AASLD guidelines.[19] Patients at high risk of variceal rebleeding, *i.e.* with either Child-Pugh grade C cirrhosis, or grade B cirrhosis with active bleeding at endoscopy despite the use of vasoactive agents, were considered for pTIPS based on individual center policy.[5]

Patients were regularly followed-up for 1 year, until death, liver transplantation, or the end date of follow-up, whichever came first. Medical history, clinical, biochemistry and endoscopic findings, treatments and outcomes were recorded during hospitalization. The primary outcome of this study was all-cause

Table 1. Baseline characteristics of all patients and patients with or without ACLF.

Baseline characteristics	All patients (n = 2138)	ACLF (n = 380)	Non-ACLF (n = 1758)	*p* value
Male, n (%)	1,570 (73.4)	286 (75.3)	1,284 (73.1)	0.382
Age	58.0 (50.0–68.0)	57.0 (50.0–67.8)	59.0 (50.0–68.0)	0.356
Etiology of cirrhosis, n (%),	1,006/508/282/342	216/71/45/48	790/437/237/294	<0.001
Alcohol/virus/alcohol & virus/others	(47.1/23.7/13.2/15.9)	(56.8/18.7/11.9/12.6)	(45.0/24.8/13.5/16.8)	
Hepatocellular carcinoma, n (%)	129 (6.0)	24 (6.3)	105 (6.0)	0.799
Portal vein thrombosis, n (%)	33 (15.6)	273 (15.8)	60 (16.0)	0.938
Previous bleeding, n (%)	671 (31.4)	93 (24.5)	578 (32.9)	0.001
Previous episode of decompensation, n (%)				
Ascites	1013 (47.4)	237 (62.4)	776 (44.1)	<0.001
Hepatic encephalopathy	323 (15.1)	111 (29.2)	212 (12.1)	<0.001
Spontaneous bacterial peritonitis/bacteremia	123 (5.8)	52 (13.7)	71 (4.0)	<0.001
Hepatorenal syndrome	40 (1.9)	22 (5.8)	18 (1.0)	<0.001
Decompensation at admission				
Ascites	866 (40.5)	162 (42.6)	704 (40.0)	0.357
Hepatic encephalopathy	618 (28.9)	220 (57.9)	398 (22.6)	<0.001
Bacterial infection	368 (17.2)	132 (34.7)	236 (13.4)	<0.001
Laboratory tests				
Hemoglobin (g/L)	85.0 (66.0–101.0)	78.0 (65.0–93.0)	87.0 (67.0–104.0)	<0.001
Leucocytes (10^9/L)	7.7 (5.5–11.1)	9.1 (6.0–14.6)	7.5 (5.3–10.5)	<0.001
Platelet count (10^9/L)	97.0 (67.0–138.8)	90.0 (64.0–136.0)	98.0 (68.0–139.0)	0.013
Creatinine (mg/dl)	0.9 (0.7–1.2)	1.7 (1.0–2.5)	0.8 (0.7–1.0)	<0.001
Urea nitrogen (mg/dl)	49.0 (30.0–76.0)	82.0 (43.0–132.0)	46.0 (28.0–68.0)	<0.001
Na (mEq/L)	137.0 (134.0–140.0)	136.0 (131.0–140.0)	138.0 (134.0–140.0)	<0.001
Bilirubin (mg/dl)	1.7 (1.0–3.1)	2.9 (1.2–7.3)	1.6 (0.9–2.7)	<0.001
Albumin (g/L)	27.1 (23.2–31.0)	26.0 (21.1–30.0)	28.0 (24.0–32.0)	<0.001
AST (U/L)	53.0 (33.0–95.0)	66.0 (36.0–128.8)	50.0 (33.0–90.0)	<0.001
ALT (U/L)	33.0 (21.0–52.0)	36.0 (22.0–63.5)	32.0 (21.0–50.0)	0.006
INR	1.4 (1.3–1.7)	1.7 (1.4–2.4)	1.4 (1.2–1.6)	<0.001
Glucose (mg/dl)	139.0 (112.0–187.3)	140.0 (110.8–180.5)	139.0 (113.0–189.0)	0.257
Organ failures, n (%)				<0.001
Circulatory failure	233 (10.9)	202 (53.2)	31 (1.8)	
Respiratory failure	232 (10.9)	169 (44.5)	63 (3.6)	
Cerebral failure	219 (10.2)	117 (30.8)	102 (5.8)	
Renal failure	163 (7.6)	163 (42.9)	0 (0.0)	
Coagulation failure	112 (5.2)	89 (23.4)	23 (1.3)	
Liver failure	82 (3.8)	66 (17.4)	16 (0.9)	
Length of ICU stay (days) (686/227/459)	5 (2–10)	7 (3–12)	4 (2–8)	<0.001
Scores				
MELD	11.7 (7.6–16.7)	21.4 (17.0–27.4)	10.3 (6.8–14.1)	<0.001
Child-Pugh	8.0 (7.0–10.0)	10.0 (8.0–12.0)	8.0 (7.0–9.0)	<0.001
Child-Pugh class (A/B/C), n (%)	468/1,102/568 (21.9/51.5/26.6)	45/136/199 (11.8/35.8/52.4)	423/966/369 (24.1/54.9/21.0)	<0.001

ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICU, intensive care unit; INR, international normalized ratio; MELD, model for end-stage liver disease.
Mann-Whitney *U* test.

mortality or liver transplantation at day 42 and 1 year. The secondary outcome was rebleeding.

In this secondary ancillary study, we analyzed the influence of ACLF at admission in variceal bleeding evolution and the role of pTIPS on the outcomes of patients with ACLF.

For this purpose, ACLF at admission was retrospectively defined and graded according to the EASL-CLIF consortium definition (supplementary methods).[15] Briefly, liver, kidney and coagulation failure were assessed by bilirubin, creatinine and international normalized ratio (INR) levels that were specifically included in the electronic case report form (CRF). Brain failure was evaluated by HE grades (West Haven). Circulatory failure was considered when vasopressor therapy was needed to maintain blood pressure. A total of 233 patients treated with vasoactive drugs to maintain blood pressure were defined as having circulatory failure. Finally, respiratory failure (n = 232) was diagnosed when mechanical ventilation was required for reasons other than airway protection and in the absence of HE grade III or IV. Renal replacement therapy was not recorded in any patients, at least at enrollment, but renal dysfunction and failure were based on creatinine values, as defined by the EASL-CLIF ACLF definition. A total of 686 patients were admitted to the intensive care unit (ICU) and the length of ICU stay was recorded, with a median of 5 days.

For the specific analysis of the impact of the relationship between pTIPS in ACLF, patients were excluded if they were older than 75 years, had developed hepatocellular carcinoma outside the Milan criteria, had active sepsis, creatinine levels ≥3 mg/dl, heart failure or complete portal vein thrombosis. Only patients who fulfilled the prespecified criteria for pTIPS were included in the analysis on pTIPS (Fig. S1).

The ethics committees of all participating hospitals approved the study protocol and all participants included in the study provided written informed consent.

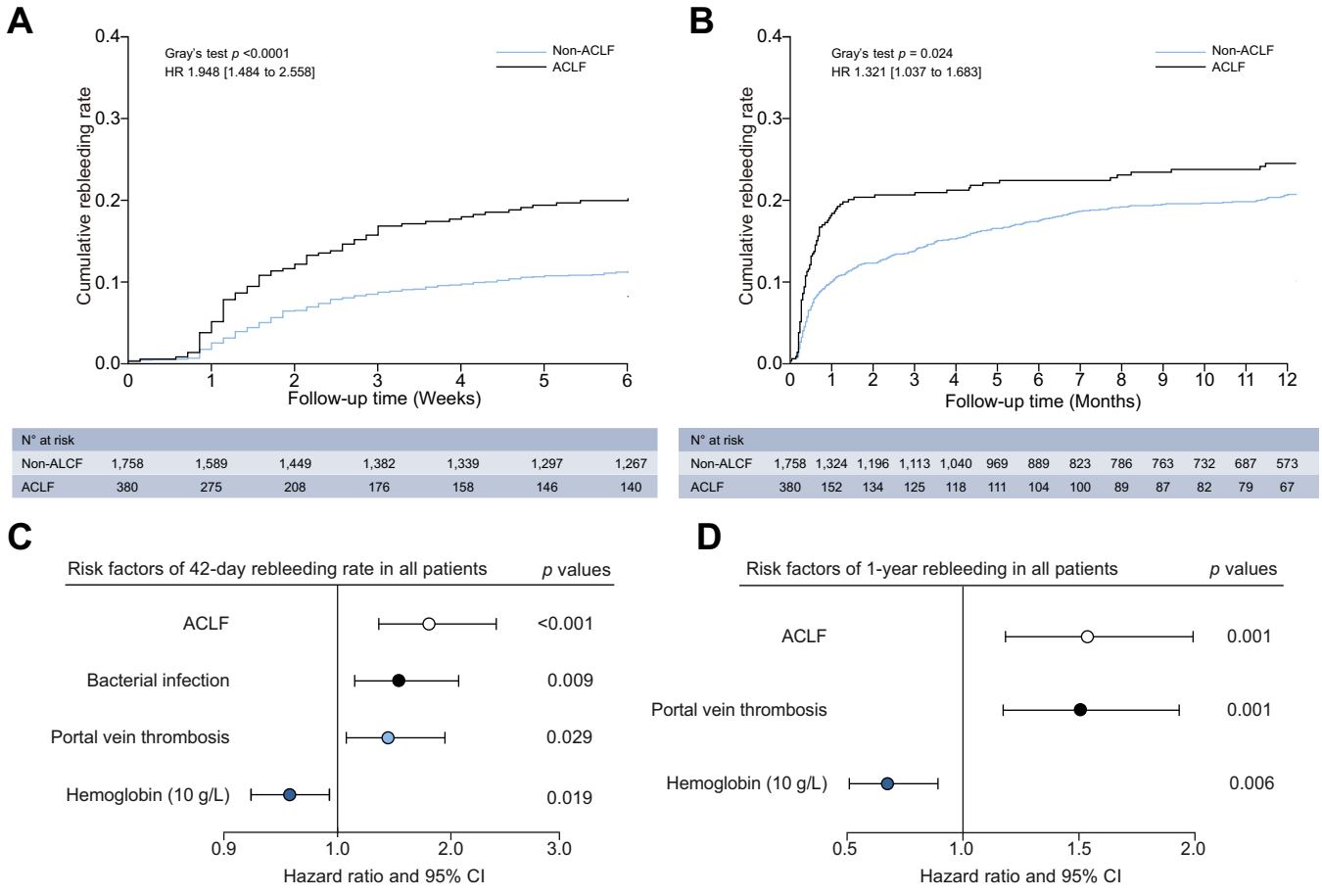

Fig. 1. ACLF and risk factors for rebleeding in patients with variceal bleeding. (A) Cumulative incidence function curve of 42-day cumulative rebleeding rate in patients with and without ACLF. Levels of significance: p <0.0001 (Gray's test). (B) Cumulative incidence function curve of 1-year cumulative rebleeding rate in patients with and without ACLF. Levels of significance: p = 0.024 (Gray's test). (C) Independent risk factors of 42-day rebleeding in all patients with acute variceal bleeding. Levels of significance of each significant covariate are marked in the figure (competitive risk Cox model). (D) Independent risk factors of 1-year rebleeding in all patients with acute variceal bleeding. Levels of significance of each significant covariate are marked in the figure (competitive risk Cox model). ACLF, acute-on-chronic liver failure.

Data management and statistical analysis

Multiple excellence control procedures were used to optimize data quality. This included the use of a unified REDCap electronic data capture system to record and manage data. Additionally, a steering committee was formed to monitor data consistency and correctness.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for reporting observational studies. Continuous variables were described as median and interquartile range, and categorical variables as frequency and percentage. Non-parametric Mann-Whitney U test or Fisher's exact test were used to compare groups of patients where appropriate. Cumulative incidence function curve with Gray's test were used for survival analysis. Univariate and multivariate competitive risk Cox regression models were used to identify independent predictors of 42-day and 1-year rebleeding (liver transplantation or death as competing risks) or mortality (with liver transplantation as competing risks). Potential risk factors that were significant (p <0.05) in the univariate competitive risk Cox regression analysis were included in a multivariate analysis to analyze the subdistribution hazard ratio (sHR). To confirm the robustness of our results, we performed a sensitivity analysis comparing patients with ACLF receiving pTIPS with those not receiving pTIPS by propensity score matching (1:2).

A 2-tailed p value of <0.05 was considered statistically significant. All statistical analyses were performed using the SAS software (version 9.4; SAS Institute Inc., Cary, NC) or SPSS (version 19.0; IBM, Chicago, IL).

Results

Baseline characteristics and the prevalence of ACLF at admission in patients with AVB

We included a total of 2,138 patients (Fig. S1). Their baseline characteristics are shown in Table 1. Patients were predominantly male (73.4%), with a median age of 58 years. Alcohol was the most common etiology of liver disease. Of all the patients included, 380 (17.8%) had ACLF at baseline (147 [38.7%], 149 [39.2%] and 84 [22.1%] had ACLF grade 1, 2 and 3, respectively). Age and gender were similar between patients with and without ACLF, but more patients with ACLF had an alcoholic etiology. As expected, patients with ACLF more frequently presented with

Table 2. Competing risk model of 42-day and 1-year rebleeding and mortality in all patients.

	42-day				1-year			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	sHR (95% CI)	*p* value	HR (95% CI)	*p* value	sHR (95% CI)	*p* value
Risk factor for rebleeding								
Age	0.998 (0.988–1.007)	0.602	0.999 (0.989–1.009)	0.818	0.994 (0.987–1.002)	0.126	0.995 (0.987–1.003)	0.195
Female	0.862 (0.645–1.151)	0.314	0.881 (0.649–1.195)	0.415	0.801 (0.633–1.014)	0.065	0.813 (0.639–1.036)	0.094
ACLF	1.946 (1.482–2.555)	<0.001	1.798 (1.336–2.418)	<0.001	1.313 (1.030–1.674)	0.028	1.535 (1.183–1.992)	0.001
Portal vein thrombosis	1.509 (1.119–2.036)	0.007	1.420 (1.036–1.945)	0.029	1.423 (1.113–1.819)	0.005	1.506 (1.173–1.932)	0.001
Hemoglobin	0.996 (0.992–0.999)	0.010	0.996 (0.992–0.999)	0.019	0.997 (0.994–0.999)	0.017	0.996 (0.993–0.999)	0.006
Infection	1.873 (1.456–2.410)	0.004	1.519 (1.113–2.072)	0.009	1.295 (1.049–1.599)	0.016	1.184 (0.946–1.481)	0.140
Leukocyte	1.014 (1.003–1.025)	0.014	1.002 (0.987–1.017)	0.792	–	–	–	–
Platelet	1.001 (1.000–1.003)	0.023	1.001 (1.000–1.003)	0.072	–	–	–	–
Risk factors for mortality								
Female	1.049 (0.832–1.324)	0.684	1.229 (0.896–1.686)	0.201	0.887 (0.737–1.068)	0.207	0.910 (0.718–1.155)	0.439
Age	1.009 (1.001–1.018)	0.028	1.016 (1.003–1.029)	0.014	1.021 (1.014–1.027)	<0.001	1.025 (1.016–1.034)	<0.001
ACLF	6.059 (4.922–7.459)	<0.001	2.716 (1.953–3.777)	<0.001	3.394 (2.844–4.052)	<0.001	1.554 (1.181–2.044)	0.002
Child-Pugh score	1.447 (1.384–1.513)	<0.001	1.278 (1.188–1.375)	<0.001	1.337 (1.290–1.386)	<0.001	1.264 (1.198–1.335)	<0.001
Bacterial infection	3.363 (2.593–4.363)	<0.001	2.256 (1.656–3.075)	<0.001	2.153 (1.798–2.579)	<0.001	1.752 (1.416–2.168)	<0.001
Hepatocellular carcinoma	2.915 (2.296 -3.703)	<0.001	3.296 (2.273–4.781)	<0.001	3.698 (3.109–4.400)	<0.001	3.308 (2.542–4.306)	<0.001
Urea nitrogen	1.009 (1.008–1.011)	<0.001	1.003 (1.000–1.005)	0.027	1.008 (1.006–1.010)	<0.001	1.003 (1.000–1.005)	0.037
Leukocyte	1.022 (1.011–1.033)	<0.001	1.012 (1.000–1.025)	0.044	1.013 (1.003–1.023)	0.012	0.995 (0.979–1.010)	0.480
Portal vein thrombosis	1.466 (1.134–1.896)	0.004	1.070 (0.747–1.534)	0.711	1.584 (1.305–1.923)	<0.001	1.200 (0.932–1.546)	0.157
Sodium	0.979 (0.966–0.992)	0.002	0.999 (0.978–1.021)	0.961	0.981 (0.968–0.993)	0.003	0.988 (0.976–1.001)	0.079

ACLF, acute-on-chronic liver failure; HR, hazard ratio; sHR, subdistribution hazard ratio.

ascites, spontaneous bacterial peritonitis, bacterial infections, HE and hepatorenal syndrome, as well as significantly higher MELD and Child-Pugh scores at baseline. However, patients with ACLF had a significantly lower rate of previous bleeding, but a similar rate of primary prophylaxis compared to patients without ACLF (27.6% *vs.* 24.4%, $p = 0.192$).

ACLF as an independent risk factor of 42-day and 1-year rebleeding and mortality in patents with AVB

Patients with ACLF had a higher rate of rebleeding compared to patients without ACLF (42-day: 19.1% *vs.* 10.1%, $p < 0.001$; 1-year: 22.9% *vs.* 17.7%, $p = 0.024$) (Fig. 1A and B). The risk of rebleeding increased in line with ACLF grade (Fig. S2A).

Presence of ACLF, bacterial infection and non-occlusive or non-tumoral portal vein thrombosis at admission were independently associated with 42-day (multivariate ACLF: sHR 1.798; 95% CI 1.336–2.418; $p < 0.001$) and 1-year rebleeding (multivariate ACLF: sHR 1.535; 95% CI 1.183–1.992; $p = 0.001$). Hemoglobin appeared as a protective factor for the risk of rebleeding at 42 days (Fig. 1C,D, Table 2).

As expected, patients with ACLF were more prone to die than patients without ACLF (42-day: 47.1% *vs.* 10.0%; $p < 0.001$, 1-year: 55.0% *vs.* 23.1%, $p < 0.001$) (Fig. 2A,B), and mortality increased in line with severity of ACLF (Fig. S2B). These effects of ACLF on survival remained independent after adjusting for confounders (Fig. 2C,D, Table 2). Other independent risk factors associated with both 42-day and 1-year mortality were age, Child-Pugh score, bacterial infection, hepatocellular carcinoma within Milan criteria and blood urea nitrogen at baseline.

Impact of pre-emptive TIPS on rebleeding rate and mortality in patients with AVB, with or without ACLF

In the subgroup analysis of patients eligible for pTIPS, a total of 66 patients underwent pTIPS, of whom 22 (33.3%) had ACLF (Fig. S1). There were more patients with ACLF Grade III, who did not receive TIPS. While patients with ACLF receiving pTIPS had lower creatinine and glucose levels at baseline than patients with ACLF who did not receive pTIPS, there were no significant differences in age, gender, Child-Pugh score and other baseline characteristics (Table 3).

pTIPS placement was independently associated with a lower 42-day rebleeding rate (HR 0.128; 95% CI 0.017–0.937; $p = 0.043$) in patients with ACLF and treatment with pTIPS in these patients reduced the risk of rebleeding due to ACLF (Fig. 3A,B and Table S1).

Regarding mortality and in cases where the analysis was restricted to patients with ACLF, patients treated with pTIPS had a significantly lower 42-day and 1-year mortality than patients receiving standard of care (Fig. 4A). Mortality was significantly lower in the pTIPS compared to the non-pTIPS group of patients with ACLF (42-day: 13.6% *vs.* 51.0%, $p = 0.002$; 1-year: 22.7% *vs.* 56.5%, $p = 0.002$). Treatment with pTIPS reduced 42-day (multivariate sHR 0.22; 95% CI 0.07–0.74; $p = 0.014$) and 1-year (multivariate sHR 0.33; 95% CI 0.12–0.92; $p = 0.034$) mortality after adjustment for confounders (Fig. 4C,D, Table S1). Similar results were observed after adjusting for CLIF-C ACLF score instead of Child-Pugh score in the competitive Cox regression model for 42-day and 1-year mortality (Table S2). When we limited our analysis to patients with bilirubin over 5 mg/dl, pTIPS significantly increased the survival rate in patients with ACLF, regardless of hyperbilirubinemia (Fig. S3).

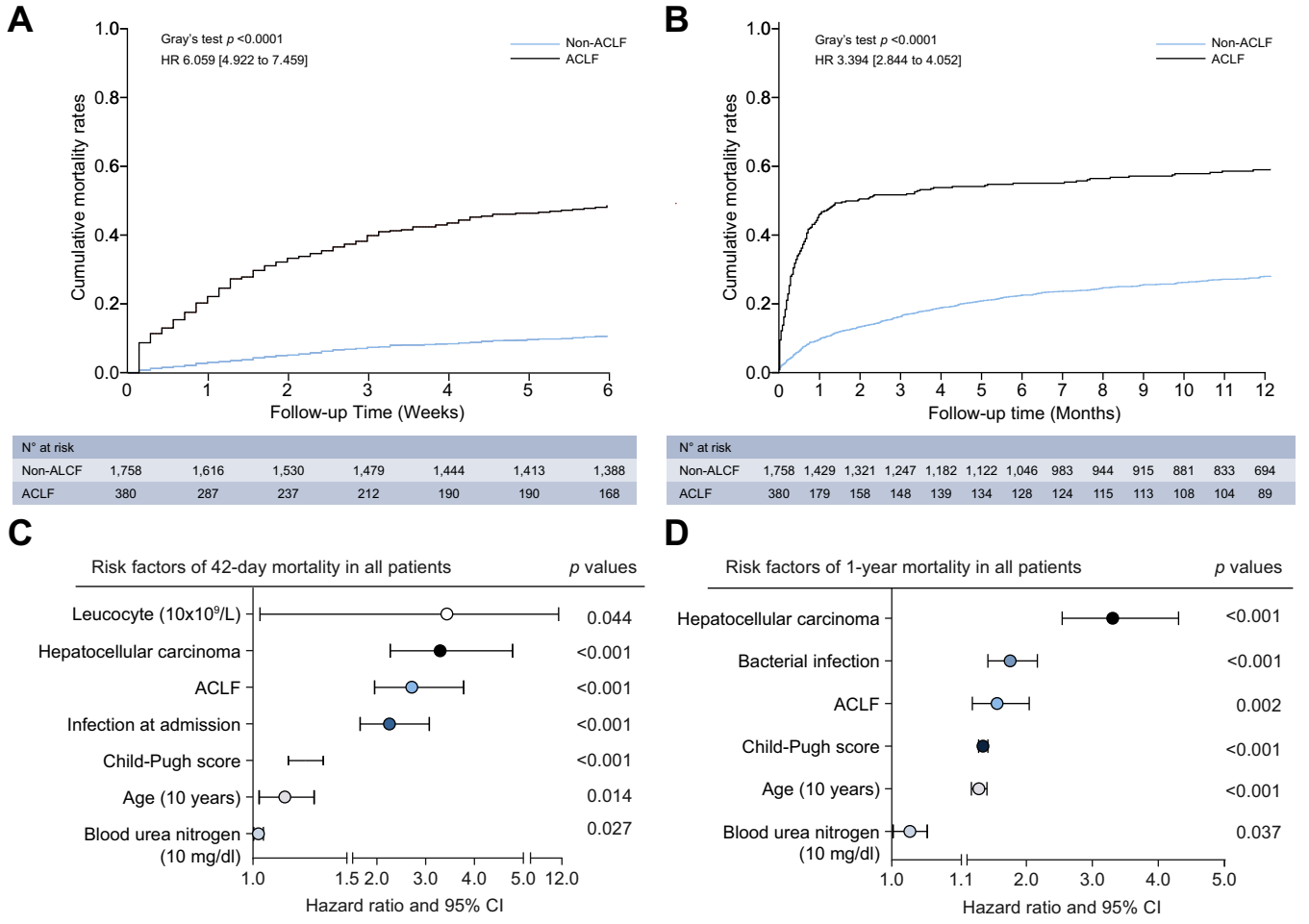

Fig. 2. ACLF and risk factors for mortality in patients with variceal bleeding. (A) Cumulative incidence function curve of 42-day mortality patients with or without ACLF. Levels of significance: p <0.0001 (Gray's test). (B) Cumulative incidence function curve of 1-year mortality patients with or without ACLF. Levels of significance: p <0.0001 (Gray's test). (C) Independent risk factors of 42-day mortality in all patients with acute variceal bleeding. Levels of significance of each significant covariate are marked in the figure (competitive risk Cox model). (D) Independent risk factors of 1-year mortality in all patients with acute variceal bleeding. Levels of significance of each significant covariate are marked in the figure (competitive risk Cox model). ACLF, acute-on-chronic liver failure.

In the absence of ACLF, patients treated with pTIPS also had lower mortality, but without reaching statistical significance (Table S3). Similar results can be seen in Fig. S4, showing the competing risk analysis. It is important to remark that the study was not designed to analyze this effect and it is underpowered for this analysis.

To control for the severity of liver and extrahepatic dysfunction, we performed a propensity score matched sensitivity analysis. The matched baseline characteristics of patients with ACLF, treated with and without pTIPS, are shown in Table S4. There were no significant differences between the 2 groups. In this matched cohort, pTIPS significantly improved survival in patients with ACLF, confirming the results observed in the unmatched cohort (Fig. 4E).

Discussion

This is the first study to describe the prevalence of ACLF and its relationship with rebleeding and mortality in patients with AVB. ACLF is an independent risk factor for rebleeding and mortality in patients with AVB. Moreover, patients with ACLF and AVB may benefit from placement of pTIPS.

ACLF is characterized by rapid deterioration of organ function leading to multiple organ failures and high short-term mortality.[15] AVB has been described as a precipitating event for ACLF,[15,20] but the role of ACLF on the outcomes associated with AVB has not been investigated to date. We found that a substantial percentage of patients with AVB present with ACLF. One in every 5–6 patients with AVB presented with or developed ACLF.

One of the most important and clinically relevant findings of this study was that ACLF almost doubled the risk of rebleeding, providing an easy identification criterion for patients with rebleeding risk. Interestingly, ACLF predicted this independently of the presence of portal vein thrombosis, which is a well-known risk factor for rebleeding described in several studies.[21,22] These facts show that our cohort data collection is consistent with the literature, while confirming that our analysis is robust, despite the limitations of the study design described below.

ACLF, not surprisingly, was associated with worse prognosis in patients with AVB. However, to date, this has not been investigated thoroughly. The CANONIC study, which characterized ACLF, demonstrated that bleeding occurs similarly in

Table 3. Comparison of baseline characteristics between patients with and without pre-emptive TIPS based on baseline ACLF status.

	ACLF			Non-ACLF		
Baseline characteristics	**pTIPS (n = 22)**	**No pTIPS (n = 147)**	***p* value**	**pTIPS (n = 44)**	**No pTIPS (n = 458)**	***p* value**
Male, n (%)	13 (59.1)	116 (78.9)	0.058	34 (77.3)	350 (76.4)	1.000
Age	53.0 (43.8–60.5)	54.0 (49.0–60.0)	0.522	53.0 (44.3–62.0)	55.0 (47.0–62.0)	0.300
Etiology of cirrhosis, n (%)			0.754			0.262
Alcohol liver disease	16 (72.7)	94 (64.0)		31 (70.5)	260 (56.8)	
Hepatotropic virus	1 (4.5)	22 (15.0)		6 (13.6)	62 (13.5)	
Alcohol and virus	3 (13.6)	23 (15.6)		5 (11.4)	80 (17.4)	
Others	2 (9.1)	18 (5.4)		2 (4.5)	56 (12.2)	
Hepatocellular carcinoma, n (%)	0 (0.0)	4 (2.7)	1.000	1 (2.3)	4 (0.9)	0.369
Previous bleeding, n (%)	6 (27.3)	34 (23.1)	0.788	11 (25.0)	156 (34.1)	0.245
Portal vein thrombosis	0 (0.0)	8 (5.5)	0.599	2 (4.5)	27 (6.0)	1.000
Previous episode of decompensation, n (%)						
Ascites	13 (59.1)	90 (61.2)	1.000	19 (43.2)	238 (52.0)	0.274
Bacterial infection	5 (22.7)	55 (37.4)	0.235	6 (13.6)	91 (19.9)	0.424
Hepatic encephalopathy	7 (31.8)	48 (32.7)	1.000	8 (18.2)	67 (14.6)	0.509
Spontaneous bacterial peritonitis/bacteremia	2 (9.1)	24 (16.3)	0.534	3 (6.8)	24 (5.2)	0.722
Hepatorenal syndrome	1 (4.5)	6 (4.1)	1.000	1 (2.3)	8 (1.7)	0.565
Laboratory test						
Hemoglobin (g/L)	87.5 (51.0–101.3)	76.0 (63.0–90.0)	0.298	77.5 (60.0–90.3)	86.0 (68.0–101.0)	0.017
Leucocytes (10^9/L)	9.1 (6.7–12.9)	8.7 (6.1–14.1)	0.900	9.5 (6.3–12.7)	8.2 (5.8–11.6)	0.337
Platelet count (10^9/L)	76.0 (64.5–97.8)	79.0 (54.0–125.0)	0.835	89.0 (73.0–112.0)	83 (58.5–122.5)	0.296
Creatinine (mg/dl)	0.9 (0.6–1.4)	1.3 (0.8–1.8)	0.070	0.8 (0.7–1.1)	0.8 (0.6–1.0)	0.193
Urea nitrogen (mg/dl)	51.0 (24.6–91.0)	59.0 (36.0–105.0)	0.227	40.0 (18.5–51.7)	40.0 (24.8–64.0)	0.883
Na (mEq/L)	135.0 (132.9–139.8)	135.2 (131.0–140.0)	0.868	138.0 (134.1–140.8)	137.0 (134.0–140.0)	0.344
Bilirubin (mg/dl)	2.4 (1.7–5.3)	4.6 (2.1–13.0)	0.020	2.3 (1.7–4.4)	2.9 (1.7–4.5)	0.337
Albumin (g/L)	22.9 (20.6–27.9)	26.0 (22.0–29.0)	0.219	25.0 (21.3–27.2)	26.0 (22.0–29.0)	0.333
AST (U/L)	71.0 (51.0–164.0)	81.0 (48.0–143.0)	0.734	54.0 (39.0–97.0)	64.0 (41.0–112.0)	0.131
ALT (U/L)	50.0 (29.0–74.5)	39.0 (25.0–65.5)	0.386	23.0 (19.0–39.0)	34.0 (22.0–55.0)	0.025
INR	1.9 (1.6–2.4)	1.9 (1.6–2.6)	0.886	1.7 (1.5–1.8)	1.6 (1.4–1.9)	0.749
Glucose (mg/dl)	153.0 (129.0–234.5)	139.5 (103.7–171.5)	0.034	150.5 (113.5–197.8)	132.0 (109.0–173.0)	0.541
Scores						
MELD	19.0 (13.0–22.0)	22.0 (17.0–26.0)	0.021	14.0 (10.0–17.0)	13.0 (10.0–17.0)	0.620
Child-Pugh	11.0 (10.0–11.0)	11.0 (10.0–12.0)	0.362	10.0 (9.0–11.0)	10.0 (8.0–11.0)	0.755
Child B, n (%)	3 (13.6)	27 (18.4)	0.769	16 (36.4)	191 (41.7)	0.525
Child C, n (%)	19 (86.4)	120 (81.6)		28 (63.6)	267 (58.3)	
ACLF grades			0.043			
1	8 (36.4)	50 (34.0)			–	
2	13 (59.1)	56 (38.1)			–	
3	1 (4.5)	41 (27.9)			–	

ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; pTIPS, pre-emptive transjugular intrahepatic portosystemic shunt.
Mann-Whitney *U* test.

patients with and without ACLF. However, the present study is the first to investigate the role of ACLF in patients with variceal bleeding. Indeed, ACLF is, together with hepatocellular carcinoma, the strongest predictor of short-term mortality in variceal bleeding, with an almost 3-fold increased risk. These data are in line with the data of the CANONIC study and, again, prove the robustness of our study.[15]

Our results showed that ACLF is a major independent risk factor for rebleeding and mortality and that it may justify or even require more aggressive treatment. pTIPS has been introduced to treat patients at high risk of treatment failure, identified either by an hepatic venous pressure gradient over 20 mmHg, either a Child-Pugh C or Child-Pugh B with active bleeding at endoscopy.[21,23,24] Previous studies using the latter criteria have shown that pTIPS can improve the prognosis of patients with AVB,[10,25] without increasing the risk of complications such as HE.[13] There are currently no related studies discussing the relationship between pTIPS and patients with ACLF. Our results suggest that pTIPS could improve the survival of patients with ACLF remarkably. Both short-term and long-term mortality could be halved in the patients who were treated with pTIPS. Therefore, and considering the marked impact of pTIPS on rebleeding and most importantly on short-term mortality, this therapeutic tool should be considered in the management of patients with ACLF and AVB, even in patients with bilirubin higher than 5 mg/dl. The consequence of this hypothesis would be to transfer the affected patients to hospitals with access to TIPS, thereby potentially reducing their mortality rate by 75%. These data are nicely supported by a recent study which showed that the higher the MELD score, the bigger the survival benefit after pTIPS.[25] Despite a reduction in mortality observed in patients without ACLF, the statistical significance was not achieved. This is because mortality in these patients is much lower and therefore the sample size needed to demonstrate a potential significant benefit is higher than the 44 patients evaluated. Further studies must dissect the role of pTIPS in high-risk patients without ACLF.

These results could be confirmed after controlling for confounders using propensity score matching. However, this study

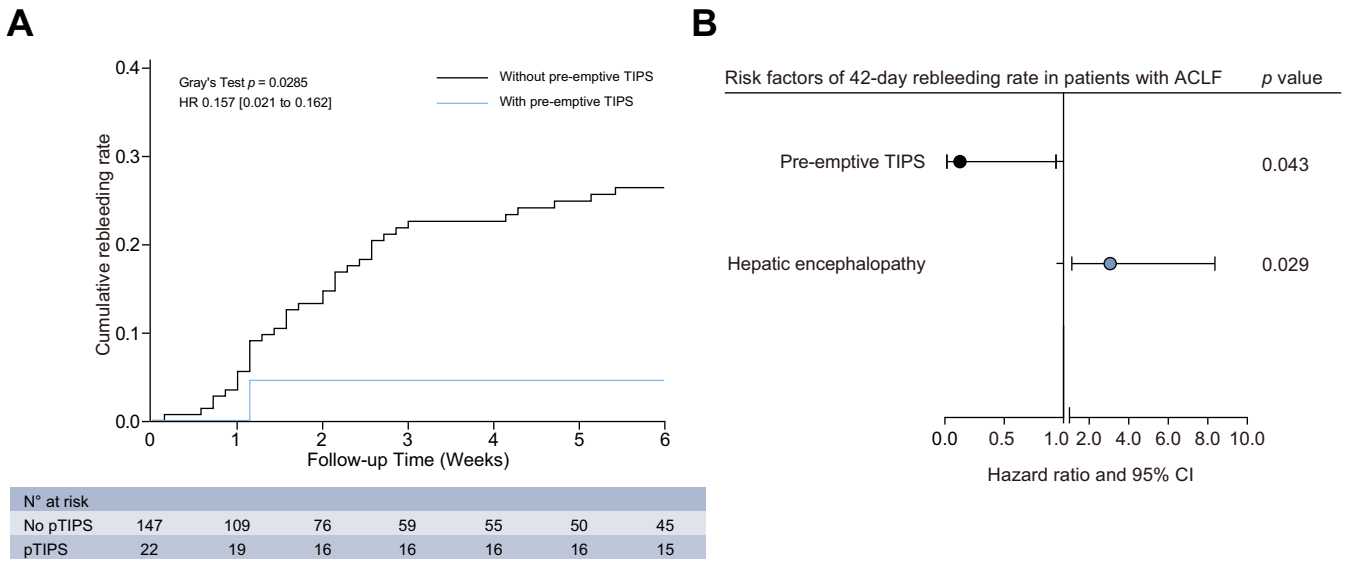

Fig. 3. Pre-emptive TIPS and risk factors for rebleeding in patients with ACLF and acute variceal bleeding. (A) Cumulative incidence function curve of 42-day rebleeding rate in patients with ACLF, with or without pre-emptive TIPS. Levels of significance: $p = 0.0285$ (Gray's test). (B) Risk factors for 42-day rebleeding in patients with ACLF, with or without pre-emptive TIPS. Levels of significance of each significant covariate are marked in the figure (competitive risk Cox model). ACLF, acute-on-chronic liver failure; TIPS, transjugular intrahepatic portosystemic shunt.

had several limitations. While the data collection process of this study is prospective, multi-centered and large-scale, it lacked the on-site monitoring visit of a randomized control trial. Moreover, ACLF was diagnosed retrospectively, since the study had been planned before publication of the EASL-ACLF criteria. The precise information on vasoactive drug use were retrieved from the CRFs, and those patients treated with vasoactive drugs to maintain blood pressure were defined as having circulatory failure. Additionally, in the database, the need for mechanical ventilation without HE grade III or IV at admission was reported as respiratory failure. However, the result was confirmed by propensity score matching and thus had a high degree of consistency. Additionally, data regarding ACLF development after variceal bleeding were not collected. Unfortunately, we cannot clarify whether bleeding was the precipitating event of ACLF. Still, we believe that the study is relevant in real clinical practice. Another limitation of this study is the limited number of patients with ACLF treated with pTIPS, even though this is the largest and first study investigating pTIPS in this population. Further studies assessing the role of pTIPS on outcomes in patients with ACLF are needed to validate these results.

This large, multicenter, international study confirms that ACLF is frequent in patients with AVB, that ACLF is an independent predictor of rebleeding and mortality, and that pTIPS could improve survival in patients with ACLF and AVB.

Abbreviations

ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AVB, acute variceal bleeding; HE, hepatic encephalopathy; HR, hazard ratio; ICU, intensive care unit; INR, international normalized ratio; MELD, model for end-stage liver disease; sHR, subdistribution HR; pTIPS, pre-emptive TIPS; TIPS, transjugular intrahepatic portosystemic shunt.

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Conflict of interest

Christophe Bureau has received speaker fees from GORE and is a board member of Alfawassemran/Norgine. Virginia Hernández - Gea, Álvaro Giráldez, Jaume Bosch, Agustin Albillos, Dominique Thabut, Michael Praktiknjo and Frederik Nevens have received speaker fees from GORE. Juan Carlos Garcia – Pagan has received consultant fees from GORE, Shionogi and Cook grants from GORE and Novartis. Jonel Trebicka has received speaking and/or consulting fees from GORE, Bayer, Alexion, MSD, Gilead, Intercept, Norgine, Grifols, Versantis, and Martin Pharmaceutical, and

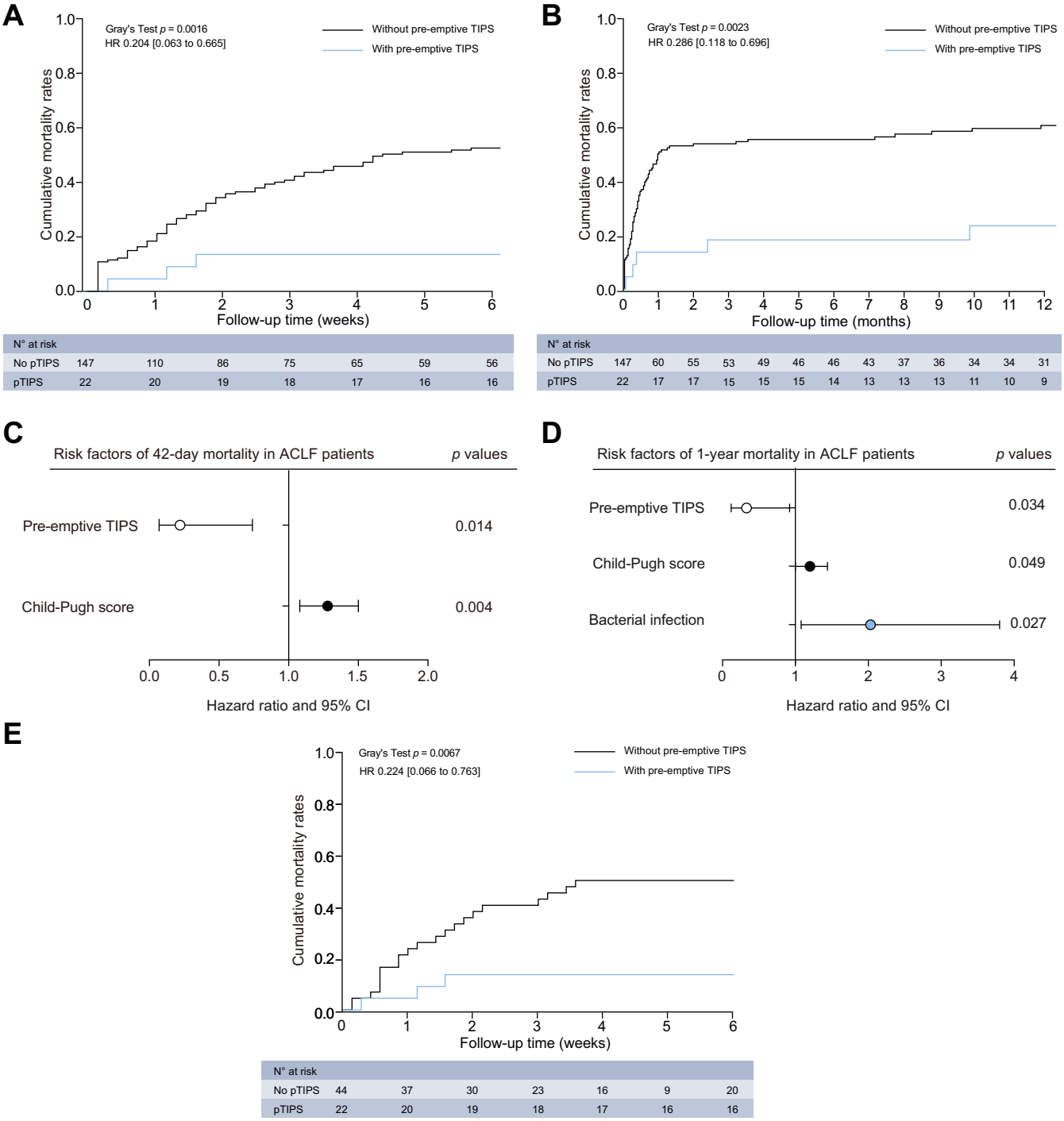

Fig. 4. Pre-emptive TIPS and risk factors for mortality in patients with ACLF and acute variceal bleeding. (A) Cumulative incidence function curve of 42-day mortality rate in patients with ACLF, with or without pre-emptive TIPS. Levels of significance: $p = 0.0016$ (Gray's test). (B) Cumulative incidence function curve of 1-year mortality rate in patients with ACLF, with or without pre-emptive TIPS. Levels of significance: $p = 0.0023$ (Gray's test). (C) Risk factors for 42-day mortality in patients with ACLF, with or without pre-emptive TIPS. Levels of significance of each significant covariate are marked in the figure (competitive risk Cox model). (D) Risk factors for 1-year mortality in patients with ACLF, with or without pre-emptive TIPS. Levels of significance of each significant covariate are marked in the figure (competitive risk Cox model). (E) Cumulative incidence function curve of 42-day mortality rate in patients with ACLF, with or without pre-emptive TIPS after propensity score matching. Levels of significance: $p = 0.0067$ (Gray's test). ACLF, acute-on-chronic liver failure; TIPS, transjugular intrahepatic portosystemic shunt.

Rafael Bañares has received speaker fees from GORE and Grifols, unrelated to the submitted work.

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

Authors' contributions

JT and RB: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content,

statistical analysis, obtained funding, technical or material support and study supervision. WG and CJ: acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, obtained funding and technical or material support. VHG, JG, JB and JCGP: acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, obtained funding, technical or material support and study supervision. CP, EG, FT and MP: analysis and interpretation of data. LI, BP, AG, LA, CV, DT, GSJ, JM, CB, EL, WL, JMP, JC, SR, LLG, CFN, RB, NC, MR, AF, JLM, HG, MHG, RS, ADE, MS, JGA, MRG, AZ, MC, HM, MP, EW, MVC, HPE, FEU, MS, MB, MP, JC, AK, FN, JLC, MAR, IC, AA, MR, EA, MAG and MT: acquisition of data and critical revision of the manuscript for important intellectual content.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.04.024.

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Author names in bold designate shared co-first authorship

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