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Combination of Model for End-Stage Liver Disease and Lactate Predicts Death in Patients Treated With Salvage Transjugular Intrahepatic Portosystemic Shunt for Refractory Variceal Bleeding

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BACKGROUND AND AIMS: Data about the prognosis of salvage transjugular intrahepatic portosystemic shunt (TIPS) using covered stents for refractory variceal bleeding caused by portal hypertension are scarce. We aimed to assess survival and to identify predictors of mortality in these patients.

APPROACH AND RESULTS: One hundred sixty-four patients with cirrhosis from five centers treated with salvage TIPS between 2007 and 2017 were retrospectively divided into a derivation cohort (83 patients) and a validation cohort (81 patients). Comparisons were performed using the Mann-Whitney and Fischer's exact test. Six-week overall survival (OS) was correlated with variables on the day of the TIPS using Kaplan-Meier curves with log-rank test and univariate/multivariate analyses using the Cox model. Eighty-three patients were included in the derivation cohort (male, 78%; age, 55 years, alcohol-associated cirrhosis, 88%; Model for End-Stage Liver Disease [MELD], 19 [15-27]; arterial lactate, 3.7 mmol/L [2.0-8.3]). Six-week OS rate was 58%. At multivariate analysis, the MELD score (OR, 1.064; 95% CI, 1.005-1.126; P = 0.028) and arterial lactate (OR, 1.063; 95% CI, 1.013-1.114; P = 0.032) were associated with 6-week OS. Six-week OS rates were 100% in patients with arterial lactate ≤2.5 mmol/L and MELD score ≤ 15 and 5% in patients with lactate ≥12 mmol/L and/or MELD score ≥ 30. The 81 patients of the validation cohort had similar MELD and arterial lactate level but lower creatinine level (94 vs 106 μmol/L, P = 0.008); 6-week OS was 67%. Six-week OS rates were 86% in patients with arterial lactate ≤2.5 mmol/L and MELD score ≤ 15 and 10% for patients with lactate ≥12 mmol/L and/or MELD score ≥ 30. In the overall cohort, rebleeding rate was 15.8% at 6 weeks, and the acute-on-chronic liver failure grade (OR, 1.699; 95% CI, 1.056-1.663; P = 0.040) was independently associated with rebleeding.

CONCLUSIONS: After salvage TIPS, 6-week mortality remains high and can be predicted by MELD score and lactate. Survival rate at 6 weeks was >85% in patients with arterial lactate ≤2.5 mmol/L and MELD score ≤ 15, while mortality was >90% for lactate ≥12 mmol/L and/or MELD score ≥ 30. (Hepatology 2021;74:2085-2101).

Gastrointestinal bleeding is a common complication of portal hypertension, and its management is currently well defined by Baveno

Abbreviations: ACLF, acute-on-chronic liver failure; CLIF-OF, Chronic Liver Failure–Organ Failure; EBL, endoscopic band ligation; HE, hepatic encephalopathy; ICU, intensive care unit; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; MRB, Multidrug-Resistant Bacteria; OS, overall survival; TIPS, transjugular intrahepatic portosystemic shunt.

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recommendations.[1-3] This strategy, by combining antibiotic prophylaxis and vasoactive drugs with endoscopic therapy, allows hemorrhagic control in >90% of cases. In case of persistent bleeding, salvage transjugular intrahepatic portosystemic shunt (TIPS) can be proposed, with a mortality rate which varies from 10.5% to 42% depending on the series.[4-16] The leading causes of death after salvage TIPS are multiorgan failure and sepsis. Severity of liver failure has been identified as a predictive factor of death.[4-16] However, most of these series considered uncovered stents and sclerotherapy as first treatment. They also included a limited number of patients and did not include an external cohort for validation of the identified prognostic factors. Over recent decades, endoscopic and radiological techniques have evolved, with progressive abandonment of sclerotherapy, in favor of endoscopic band ligation (EBL) and appearance of covered stents, thus reducing the risk of complications after TIPS placement such as thrombosis and rebleeding. To date, few data are available regarding the use of salvage TIPS according to the current recommendations of the Baveno criteria (EBL, covered-stent, medical treatment and resuscitation measures adapted to patients with cirrhosis). Updating the available data in order to identify patients who will benefit or not from TIPS placement remains a major issue. Recently, acute-on-chronic liver failure (ACLF) was identified as a major determinant of 42-day and 1-year mortality in patients with cirrhosis and failure to control variceal bleeding, and insertion of TIPS allowed improved survival in this population of patients.[17]

We assessed the survival of patients treated by salvage-covered TIPS for refractory variceal bleeding in patients with cirrhosis in a recent period, to redefine futility and to identify risk factors of early death.

Potential conflict of interest: Dr. Ganne-Carrie is on the speakers' bureau for and received grants from Gilead, Bayer, and Ipsen. Dr. Garcia-Pagan consults for Cook, Shionogi, Gore, Vifor, and Boehringer Ingelheim. He received grants from Novartis, Mallinckrodt, and Dynakin. Dr. Ollivier-Hourmand is on the speakers' bureau for and received grants from Ipsen and Bayer. She received grants from AbbVie and Gilead. Dr. Dao consults for Bayer and received grants from AbbVie, Gilead, and Ipsen. Dr. Hernandez-Gea is on the speakers' bureau for Gore. Dr. Bureau is on the speakers' bureau for Gore.

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Patients and Methods

PATIENTS

The files of all patients from four French tertiary centers (Bondy, Caen, Paris, Toulouse) and one Spanish center (Barcelona) who underwent TIPS from January 1, 2007, to December 31, 2017, were retrospectively analyzed.

All patients who fulfilled the following criteria were included: presence of cirrhosis on the association of clinicobiological, endoscopic, radiological and/or histological criteria, complicated with refractory portal hypertension bleeding (esophageal and/or gastric varices) leading to salvage TIPS placement (impossibility of performing endoscopic treatment due to massive active bleeding and refractory bleeding despite well-conducted medical and two endoscopic treatments). Patients with bleeding secondary to noncirrhotic portal hypertension were excluded, as were patients who underwent uncovered TIPS and sclerotherapy as initial endoscopic treatment. The retrospective analysis of anonymized data is allowed by French Law and all the patients were informed of their right to refuse that their results may be used for subsequent research.

TIPS PROCEDURE

TIPS was performed in all the centers by trained interventional radiologists/hepatologists under general anesthesia according to the local procedure. Early and late complications following TIPS were routinely collected (hemoperitoneum, cardiac failure, hepatic encephalopathy [HE], thrombosis, stenosis, and stent migration). Abdominal imaging (Doppler ultrasound or abdominopelvic CT scan) or TIPS catheterization was routinely performed within 48 hours of insertion to ensure good functionality and absence of TIPS thrombosis.

DATA RECORDED

Demographic data, medical history, usual treatment, and history of cirrhosis (underlying liver disease, presence of portal hypertension, and history of HE) were collected at the time of intensive care unit (ICU) admission for the bleeding episode. HE was assessed the day of the bleeding and before orotracheal intubation. Severity of HE was assessed using the West Haven criteria at the time of admission. Data about the management of bleeding (blood transfusion, vasoactive drugs, endoscopic treatment, balloon tamponade) were recorded on the day of the TIPS placement.

The variables regarding orotracheal intubation and renal replacement therapy were specified before TIPS placement, meaning that a patient identified with renal replacement therapy benefited from this treatment before the TIPS procedure and not after; a similar classification was performed for orotracheal intubation. Laboratory results (arterial lactate level, creatinine level) and liver function assessment (Model for End-Stage Liver Disease [MELD] score, ACLF grade, and Child-Pugh score) were assessed within the 24 hours before TIPS placement. Patients from a previous cohort were included when the MELD score was available within the 24 hours before TIPS. ACLF grade was calculated according to the European Foundation for the Study of Chronic Liver Failure–Organ Failure (CLIF-OF) scoring system.[18] Causes of orotracheal intubation were defined as cerebral failure, respiratory failure, or both, to perform endoscopy.

ENDPOINTS AND FOLLOW-UP

Patients were then followed regularly, and complications related to TIPS and liver disease (HE and rebleeding recurrence) within 6 weeks after the procedure were collected. Causes of death were defined as multiorgan failure, rebleeding, or sepsis-related. The primary endpoints of the study were to (1) assess the incidence of 6-week mortality as recommended by Baveno VI consensus 2 and (2) identify related prognostic factors.

STATISTICAL ANALYSES

The characteristics of the patients were presented as medians (range) for continuous variables and as numbers (percentages) for categorical data. Nonparametric Mann-Whitney U test and Fischer's exact test were used for continuous and categorical variables, respectively. Times to events were estimated from the day of the TIPS placement, and the incidence of events was estimated by the Kaplan-Meier method and compared between patient groups using the log-rank test. Association between variables and events was conducted using the univariate Cox proportional hazards regression models. All variables with $P < 0.05$ were included in a multivariate Cox regression model using a backward stepwise elimination, computing the

estimate of the HR along with the 95% CI. The cutoff value for MELD and lactate to predict 6-week survival was based on sensitivity and specificity in order to reach a better sensitivity with a specificity of almost 100%. The analyses were performed using R (1.1.456) and GraphPad Prism; a two-sided *P* value < 0.05 was considered statistically significant.

Results

Between 2007 and 2017, 164 patients with cirrhosis underwent salvage TIPS and were included in the study.

CHARACTERISTICS OF THE DERIVATION COHORT

Among the 83 patients of the derivation cohort (three centers in France: Bondy, Caen, Toulouse), 78.3% were male with a median age of 55 years (49-61), and 87.9% had alcohol-associated cirrhosis. Among them, 11.1% already experienced HE before TIPS placement (Table 1). Bleeding was related to esophageal varices in the majority of cases (79.5%) with active bleeding at first endoscopy in 67.9% (Table 2).

Balloon tamponade was used in 57.8% of cases, and no esophageal stent was used in the derivation cohort; 76.8% of patients required supportive vasoactive drugs for circulatory failure. On the day of the TIPS, 50.0% of patients were Child-Pugh C and 47.4% Child-Pugh B in the derivation cohort. Median leukocyte count was 7.2 (6.6-10.6) × 10^3/L, median neutrophil count was 4.0 (4.0-18) × 10^3/L, median C-reactive protein level was 10.0 (4.0-18.5), and 18.3% had bacterial and/or fungal infections. The median MELD score was 19 (15-27), with a median arterial lactate level of 3.7 mmol/L (2.0-8.3). Among the patients from the derivation cohort, 37.7% had ACLF grade 2, 28.6% ACLF grade 3a, and 7.8% ACLF grade 3b (Table 1). The most frequent organ failures observed were circulatory failure in 74.0%, respiratory failure in 57.1%, and coagulation failure in 29.9% of the patients (Table 1). Median intervals from last endoscopy and from balloon tamponade to TIPS placement were 4 hours (3-13) and 4 hours (2-12), respectively. TIPS placement was performed due to the impossibility of performing endoscopic treatment because of massive active variceal bleeding in 51.8% and refractory bleeding despite two endoscopic treatments in 48.2%. The TIPS procedure was performed during the night shift in 38.3%, and 55.7% of patients had variceal embolization during the procedure. Median portal pressure gradient before TIPS was 18 mm Hg (15-22) and 7 mm Hg (5-10) after TIPS placement with a portal pressure delta of 11 mm Hg (8-13 mmHg). No death was related to the TIPS procedure. Among the patients from the derivation cohort, 74.7% benefited from cardiac evaluation before TIPS placement, and 11.0% experienced cardiac failure. Among the 9 patients who suffered from cardiac failure, only 4 benefited from cardiac evaluation before the TIPS procedure; systolic function was normal, and no pulmonary hypertension was noticed. In addition, during the 6 weeks following TIPS placement, 41.0% had bacterial and/or fungal infections and 41.2% HE (30.8% of grade 3) (Table 2).

SIX-WEEK SURVIVAL IN THE DERIVATION COHORT

In the derivation cohort, overall survival (OS) was 58% at 6 weeks (Fig. 1A), 51% at 3 months (Supporting Fig. S1A), and 49% at 1 year (Fig. 1C). One patient underwent liver transplantation at day 243, and transplant-free survival (TFS) rates at 3 months and 1 year were 51% and 49%, respectively (Supporting Fig. S1C,E). Among the 36 recorded deaths at 6 weeks, 24 patients died secondary to multiple organ failure despite an adequate control of the bleeding, 6 due to rebleeding, and 6 due to sepsis. Platelet level, international normalized ratio (INR), creatinine, serum bilirubin, lactate, renal replacement therapy, ACLF grade, CLIF-OF score, MELD score, and Child-Pugh score were associated with 6-week mortality in the univariate analysis. Infections before TIPS placement or during hospitalization were not associated with mortality. In the multivariate analysis, the MELD score (OR, 1.064; 95% CI, 1.005-1.126; *P* = 0.028) and arterial lactate (OR, 1.063; 95% CI, 1.013-1.114; *P* = 0.032) were independently associated with mortality (Table 3). Six-week OS was 100% and 10% in patients with MELD score ≤ 15 (n = 23) and ≥30 (n = 11), respectively (Fig. 2A), with similar results at 3 months (Supporting Fig. S2A) and 1 year (Supporting Fig. S3A). Six-week OS was 84% and 0% when lactate was ≤2.5 mmol/L (n = 31) and ≥12 mmol/L (n = 12), respectively (Fig. 2C). Similar

TABLE 1. Baseline clinical and biological characteristics of the derivation and validation cohorts on the day of the TIPS

		Derivation Cohort		Validation Cohort		
		Available Data	Total (n = 83)	Available Data	Total (n = 81)	*P*
Gender (male)*		83	65 (78.3)	81	65 (80.2)	0.76
Age (years)†		83	55 (49-61)	81	54 (39-73)	0.95
Active alcohol consumption*		82	54 (65.8)	79	46 (58.2)	0.32
Etiology of cirrhosis	Alcohol*	83	73 (87.9)	81	57 (70.3)	**0.005**
	NASH*	83	10 (12.0)	81	3 (3.7)	0.08
	Virus*	83	8 (9.6)‡	81	19 (23.5)‖	**0.02**
	Other*	83	2 (2.4)§	81	2 (2.5)¶	0.98
Previous variceal bleeding*		83	23 (27.7)	71	30 (42.3)	0.06
Previous HE*		83	3 (3.6)	81	7 (8.6)	0.25
Treatment	Anticoagulants*	83	3 (3.6)	81	3 (3.7)	0.98
	Beta-blockers*	83	36 (43.4)	81	20 (24.7)	**0.01**
Clinical and biological characteristics	Ascites*	81	39 (48.1)	81	53 (65.4)	**0.01**
	HE*	81	9 (11.1)	78	29 (37.2)	**<0.001**
	Portal vein thrombosis*	82	4 (4.9)	81	11 (13.6)	**0.05**
	Infection before TIPS*	82	15 (18.3)	33	14 (42.4)	**0.007**
	Serum creatinine (μmol/L)†	83	106 (69-156)	81	94 (64-147)	**0.008**
	Albumin (g/L)†	82	25 (20-30)	78	26 (21-30)	0.52
	Serum bilirubin (μmol/L)†	82	44 (28-73)	81	44 (29-80)	0.42
	Platelet count ($\times 10^9$/L)†	82	73 (51-107)	81	76 (51-106)	0.54
	INR†	80	1.9 (1.4-2.5)	81	1.8 (1.4-3.0)	0.89
	Leukocyte count ($\times 10^3$/L)†	52	7.2 (6.6-10.6)	0	—	—
	C-reactive protein†	34	10.0 (4.0-18.5)	0	—	—
	Arterial lactate (mmol/L)†	74	3.7 (2.0-8.3)	70	2.7 (2.0-7.0)	0.10
Child-Pugh class	A*	78	2 (2.6)	78	4 (5.1)	0.41
	B*	78	37 (47.4)	78	35 (44.9)	0.75
	C*	78	39 (50.0)	78	39 (50.0)	1
ACLF parameters	No ACLF*	77	17 (28.6)	52	26 (50.0)	**0.001**
	ACLF grade 1*	77	3 (3.9)	52	4 (7.7)	0.43
	ACLF grade 2*	77	29 (37.7)	52	13 (25.0)	0.18
	ACLF grade 3a*	77	22 (28.6)	52	2 (3.8)	**<0.001**
	ACLF grade 3b*	77	6 (7.8)	52	7 (13.5)	0.37
	CLIF-OF score†	77	10 (9.0-12.0)	52	8 (6.0-10.0)	**0.003**
	Brain failure*	77	6 (7.8)	52	3 (5.8)	0.74
	Circulatory failure*	77	57 (74.0)	52	21 (40.4)	**<0.001**
	Coagulation failure*	77	23 (29.9)	52	11 (21.2)	0.31
	Kidney failure*	77	13 (19.5)	52	7 (13.5)	0.80
	Liver failure*	77	6 (7.8)	52	1 (1.9)	0.24
	Respiratory failure*	77	44 (57.1)	52	26 (50.0)	0.47
MELD score†		79	19 (15-27)	81	19 (15-27)	0.31

Bold indicates significance.
*Number of patients (%).
†Median (interquartile range).
‡HBV (n = 2), HCV (n = 5), HBV + HDV (n = 1).
§Other etiologies: hemochromatosis (n = 1), primary biliary cholangitis (n = 1).
‖HBV (n = 6), HCV (n = 11), HBV + HCV (n = 2).
¶Primary sclerosing cholangitis (n = 1), undetermined (n = 1).

TABLE 2. Management of variceal hemorrhage, characteristics of TIPS, and complications

		Derivation Cohort		Validation Cohort		
		Available Data	Total (n = 83)	Available Data	Total (n = 81)	*P*
Number of PRBCs during hospital stay*,†		75	11 (7-16)	74	10 (5-14)	0.84
Vasoactive drugs for hemodynamic failure†		82	63 (76.8)	78	43 (55.1)	**0.003**
Balloon tamponade†		83	48 (57.8)	33	27 (81.8)	**0.008**
Orotracheal intubation†		82	71 (86.6)	50	30 (60.0)	**<0.001**
Renal replacement therapy†		83	14 (16.9)	81	4 (4.9)	**0.01**
First endoscopy	Esophageal varices†	78	62 (79.5)	81	66 (81.5)	0.75
	Gastric varices†	78	19 (24.3)	81	17 (21.0)	0.25
	Active bleeding†	81	55 (67.9)	48	34 (70.8)	0.85
Indication for TIPS	Nonfeasible endoscopic treatment†	83	43 (51.8)	81	33 (40.7)	0.16
	Refractory bleeding†	83	40 (48.2)	81	48 (59.3)	0.16
Rebleeding within 5 days†		83	9 (10.8)	81	10 (12.3)	0.76
Infection during the in-hospital stay†		83	34 (41.0)	81	40 (49.4)	0.35
Outcomes						
≤6 weeks after TIPS	HE†	80	33 (41.2)	81	41 (50.6)	0.23
	Cardiac failure†	82	9 (11.0)	81	8 (9.8)	0.82
	Rebleeding†	83	12 (14.5)	81	14 (17.3)	0.25
	Reintervention on TIPS†	80	5 (6.2)	81	10 (12.3)	0.18

Bold indicates significance.
*Median (interquartile range).
†Number of patients (%).
Abbreviation: PRBC, packed red blood cells.

results were also observed at 3 months (Supporting Fig. S2C) and 1 year (Supporting Fig. S3C). Patients at low risk of death with lactate ≤2.5 mmol/L and MELD score ≤ 15 presented a 100% 6-week OS rate (sensitivity of 36.2%, specificity of 100.0%), 94% OS at 3 months (Supporting Fig. S2E), and 94% OS at 1 year (Supporting Fig. S3E). Six-week OS was 66% in patients at intermediate risk (lactate 2.6-11.9 mmol/L and MELD score 16-29). The only patient with a MELD score ≥ 30 still alive at 6 weeks finally died at day 48. As all the patients with a MELD score ≥ 30 or lactate ≥12 mmol/L died during the follow-up, we used these values as a cutoff (better sensitivity with a specificity of almost 100% to predict 6-week mortality) to identify patients with high risk of death. The combination of lactate ≥12 mmol/L and MELD score ≥30 had a sensitivity of 58.3% and a specificity of 97.8% to predict 6-week death. Patients at high risk of death with arterial lactate ≥12 mmol/L and/or MELD score ≥ 30 had a 5% 6-week OS rate (n = 22, 1 patient presented both lactate ≥12 mmol/L and MELD score ≥ 30) (Fig. 2E), 0% OS at 3 months (Supporting Fig. S2E), and 0% OS at 1 year (Supporting Fig. S3E). Six-week OS was similar between 2007-2010, 2011-2014, and 2015-2017 (Supporting Fig. S4A) but differed according to the center (Supporting Fig. S4B). To rule out a potential center effect (Supporting Table S1), we performed the same type of analyses in derivation cohort number 2, which included two thirds of patients of each center stratified randomly (109 patients). Characteristics of the population were similar between derivation cohort number 2 and validation cohort number 2 (Supporting Table S2). At multivariate analysis, the MELD score (OR, 1.075; 95% CI, 1.031-1.120; $P < 0.001$) and arterial lactate (OR, 1.138; 95% CI, 1.083-1.197; $P < 0.001$) were also independently associated with mortality in derivation cohort number 2 (Supporting Table S3). In derivation cohort number 2, low-risk patients presented an 88% OS rate at 6 weeks (lactate ≤2.5 mmol/L and MELD score ≤ 15) with a sensitivity of 41.2% and a specificity of 86.2%, which

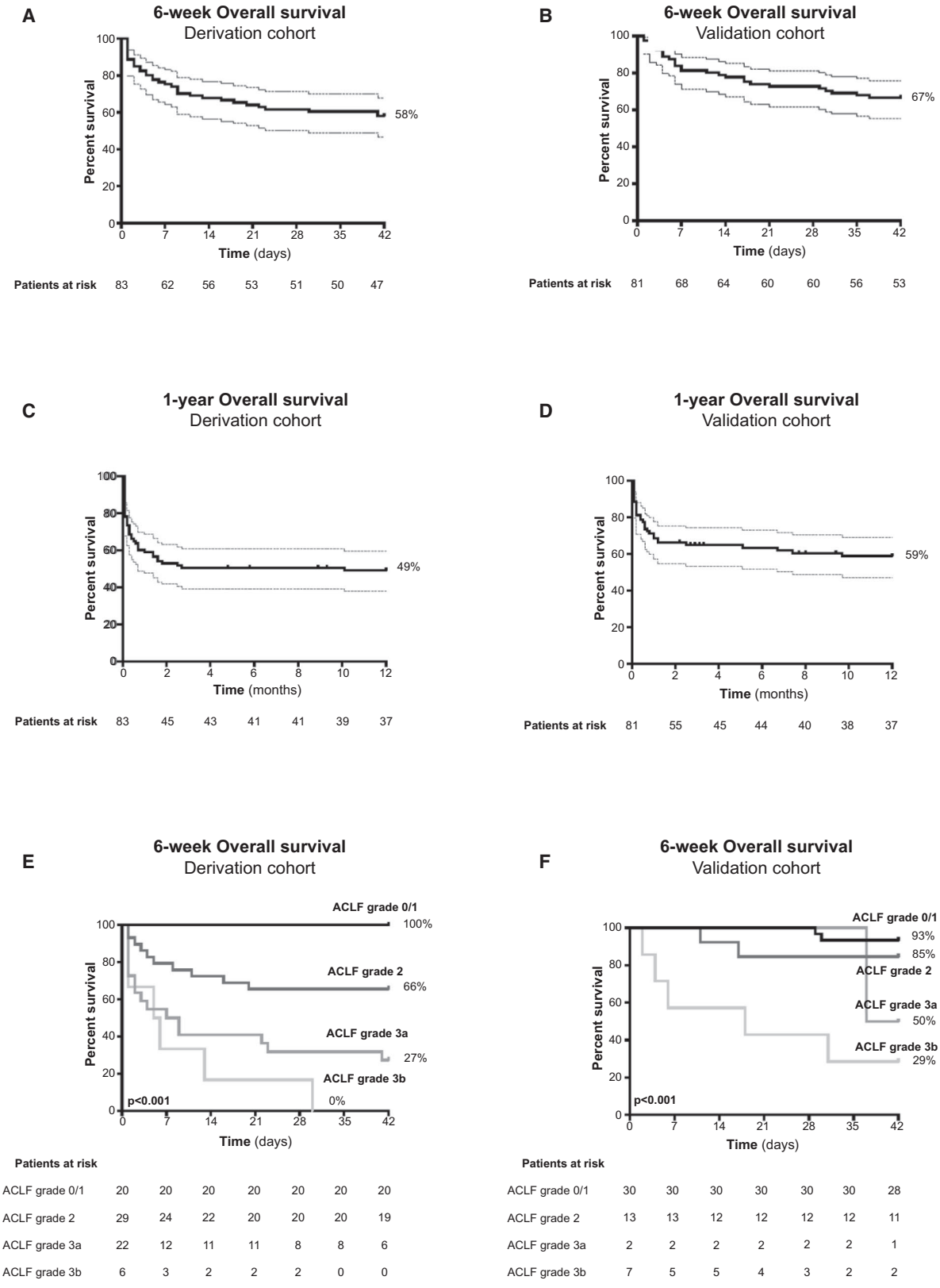

FIG. 1. 6-week and 1-year overall survival in the derivation and the validation cohort, and according to the ACLF grade.

TABLE 3. Predictors of 6-week mortality in the derivation cohort

	Available Data (n = 83)	Dead (n = 36)	Alive (n = 47)	Univariate Analysis			Multivariate Analysis		
				HR	95% CI	*P*	HR	95% CI	*P*
Age (years)*	83	54 ± 13	55 ± 8	1.004	0.963-1.030	0.810			
Gender (male)†	83	29 (80.6)	36 (76.6)	1.457	0.605-3.509	0.402			
Active alcohol consumption†	82	25 (14.3)	29 (61.7)	1.657	0.771-3.550	0.194			
Ascites†	81	20 (58.8)	19 (40.4)	1.772	0.881-3.565	0.108			
HE†	81	5 (14.7)	4 (8.5)	1.328	0.512-3.442	0.559			
Infection before TIPS†	82	13 (36.1)	8 (17.0)	1.156	0.479-2.793	0.747			
Infection during the in-hospital stay†	83	14 (38.9)	20 (42.6)	0.697	0.351-1.385	0.303			
Serum creatinine*	83	146 ± 77	80 ± 60	**1.005**	**1.001-1.009**	**0.006**			
Albumin*	82	23 ± 9	26 ± 5	0.984	0.933-1.037	0.545			
Total bilirubin*,‡	82	44 ± 104	36 ± 51	**1.003**	**1.000-1.006**	**0.036**			
INR*,‡	80	2.4 ± 0.9	1.5 ± 0.6	**2.154**	**1.532-3.028**	**<0.001**			
Leukocyte count ($\times 10^3$/L)*	52	10.6 ± 6.6	10.5 ± 10.6	0.987	0.933-1.043	0.715			
Neutrophil count ($\times 10^3$/L)*	48	6.8 ± 5.7	7.3 ± 6.5	0.984	0.915-1.058	0.715			
C-reactive protein*	34	10.0 ± 23.5	10.0 ± 14.6	1.004	0.984-1.024	0.715			
Arterial lactate*	74	8.2 ± 7.5	2.1 ± 2.7	**1.103**	**1.060-1.147**	**<0.001**	**1.063**	**1.013-1.114**	**0.032**
Child-Pugh score*,‡	78	11 ± 2	9 ± 2	**1.472**	**1.164-1.815**	**<0.001**			
MELD score*	79	25 ± 7	16 ± 6	**1.100**	**1.056-1.145**	**<0.001**	**1.064**	**1.005-1.126**	**0.028**
ACLF grade*,‡	77	3 ± 0.5	2 ± 1	**4.340**	**2.217-8.498**	**<0.001**	1.913	0.980-3.734	0.067
CLIF-OF score*,‡	77	12 ± 1.5	10 ± 2.1	**1.608**	**1.366-1.894**	**<0.001**			
Active bleeding at endoscopy†	81	26 (76.5)	29 (61.7)	1.966	0.853-4.532	0.113			
Orotracheal intubation†	82	35 (97.2)	36 (76.6)	-	-	0.997			
Renal replacement therapy†,‡	83	11 (30.6)	3 (6.4)	**4.164**	**2.025-8.559**	**<0.001**			
Use of vasopressors†	82	35 (97.2)	28 (59.6)	-	-	0.997			
Interval from last endoscopy to TIPS*	58	4 ± 6	4 ± 14	0.947	0.892-1.005	0.072			
Interval from balloon tamponade to TIPS*	31	3 ± 6	6 ± 14	0.952	0.884-1.024	0.186			
Portal pressure gradient before TIPS*	72	18 ± 6	20 ± 6	0.991	0.925-1.062	0.795			
Portal pressure gradient after TIPS*	63	6 ± 4	7 ± 4	1.039	0.938-1.151	0.467			

Bold indicates significance.
*Median (interquartile range).
†Number of patients (%).
‡Serum creatinine, total bilirubin, INR, and Child-Pugh were not entered in the multivariate analysis in order to avoid collinearity with variables included in the MELD score. CLIF-OF score was not entered in the multivariate analysis in order to avoid collinearity with variables included in the ACLF score. Renal replacement therapy was not entered in the multivariate analysis because these variables were dependent of the choice of the physician, subject to variations of indications, and not useful simple baseline biomarkers predictive of prognosis.

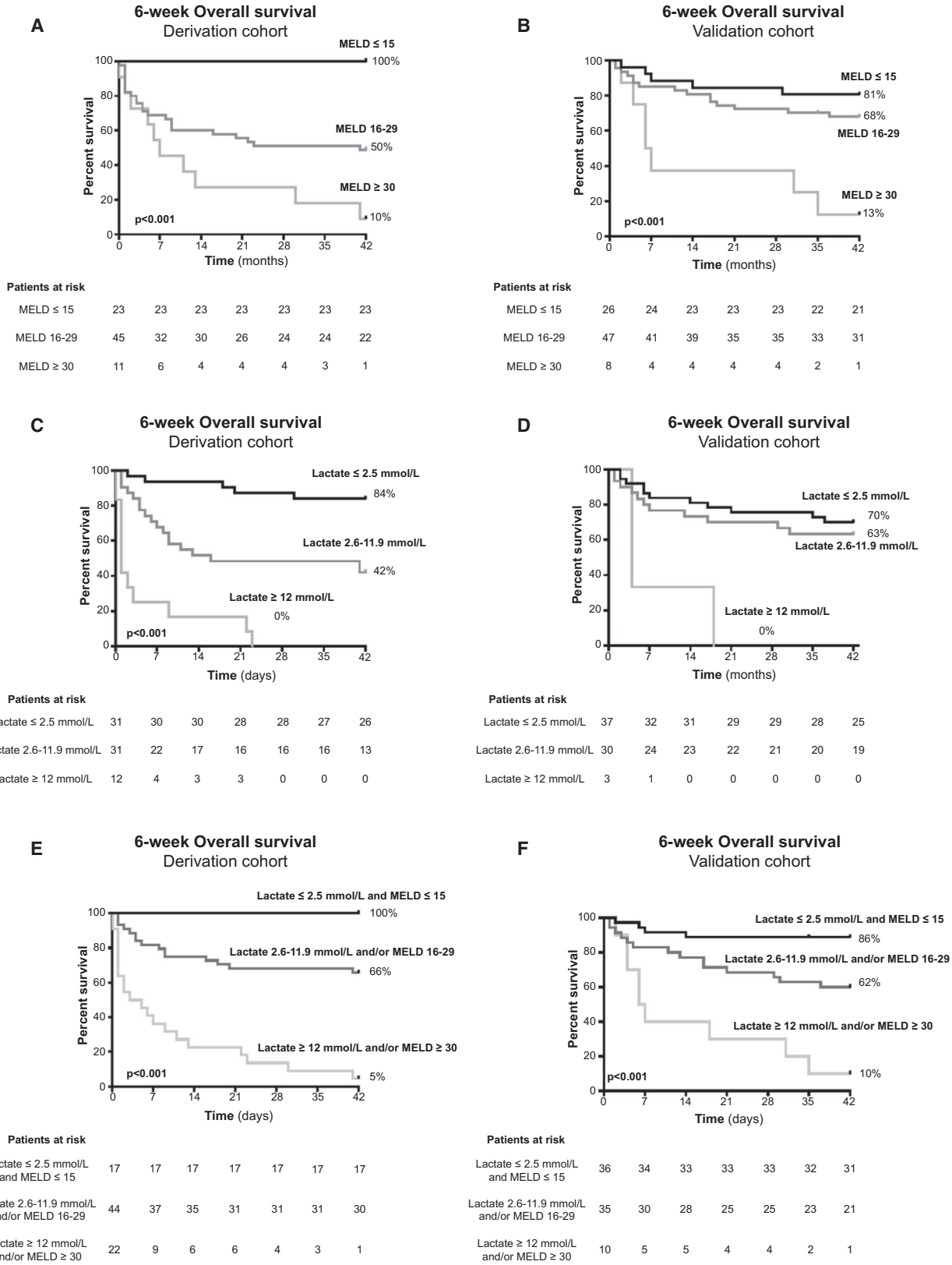

FIG. 2. 6-week overall survival in the derivation and the validation cohort according to MELD score and arterial lactate.

decreased to 10% in high-risk patients (arterial lactate ≥12 mmol/L and/or MELD score ≥ 30) with a sensitivity of 48.7% and a specificity of 97.1% (Supporting Fig. S5). Among the 43 patients with biological data available 1 week after TIPS, 15 presented an improvement in MELD score (34.5%), 4 maintained a stable MELD score (9.3%), and 24 showed aggravation of the MELD score (55.8%).

Six-week OS decreased with ACLF grade (P < 0.001) (Fig. 1E). All patients with ACLF-3b grade were dead at 6 weeks. Six-week OS was significantly higher in patients without circulatory failure, coagulation failure, kidney failure, and respiratory failure (P < 0.001) (Fig. 3).

CHARACTERISTICS OF THE VALIDATION COHORT

Among the 81 patients of the validation cohort (Pitié-Salpêtrière, France, and Barcelona, Spain), 80.2% were male, with a median age of 54 years; and the etiology of cirrhosis was alcohol in 70.3% of cases (Table 1). Compared to the derivation cohort, patients in the validation cohort presented similar Child-Pugh and MELD score (median MELD score of 19 vs. 19, P = 0.31) as well as median arterial lactate level (2.7 vs. 3.7 mmol/L, P = 0.10). However, compared to the derivation cohort, creatinine level was significantly lower (P = 0.008), as were ACLF grade 3a patients (P < 0.001) and the presence of circulatory failure (P < 0.001) (Table 1); and fewer patients required supportive pharmacological therapy (55.1% vs. 76.8%, P = 0.003), orotracheal intubation (60.0% vs. 86.6%, P < 0.001), and renal replacement therapy (4.9% vs. 16.9%, P = 0.01) (Table 2).

SIX-WEEK SURVIVAL IN THE VALIDATION COHORT

In the validation cohort, OS was 67% at 6 weeks (Fig. 1B), 64% at 3 months (Supporting Fig. S1B), and 59% at 1 year (Fig. 1D). Three patients underwent liver transplantation at 48, 91, and 132 days after the TIPS procedure. Three-month and 1-year TFS rates were 64% (Supporting Fig. S1D) and 58% (Supporting Fig. S1F), respectively. Six-week OS was 81% for patients with a MELD score ≤ 15 (n = 26) and 13% for patients with a MELD score ≥ 30 (n = 8) (Fig. 2B), 70% for arterial lactate ≤2.5 mmol/L (n = 37), and 0% for arterial lactate ≥12 mmol/L (n = 3) (Fig. 2D). Similar OS results were observed at 3 months (Supporting Fig. S2B,D) and 1 year (Supporting Fig. S3B,D). Six-week OS was 86% in patients at low risk of death (MELD < 15 and lactate ≤2.5 mmol/L), with a sensitivity of 60.0% and a specificity of 84.6%; 62% in patients at medium risk (lactate 2.6-11.9 mmol/L and MELD score 16-29); and 10% in patients at high risk of death (lactate ≥12 mmol/L and MELD score > 30), with a sensitivity of 33.3% and a specificity of 98.1% (Fig. 2F). OS rates at 3 months and 1 year were, respectively, 86% and 78% in patients with arterial lactate ≤2.5 mmol/L and MELD score ≤ 15 and 10% and 10% in patients with arterial lactate ≥12 mmol/L and/or MELD score ≥ 30 (Supporting Figs. S2F and S3F).

As for the derivation cohort, 6-week OS decreased with ACLF grade (P < 0.001) (Fig. 1F) and was significantly higher in patients without kidney failure (P = 0.003) (Fig. 4D).

PREDICTIVE FACTORS OF REBLEEDING AFTER TIPS PROCEDURE

In the overall cohort, rebleeding rates were 10.8% at 5 days and 15.8% at 6 weeks. Among the 26 patients who experienced rebleeding after the TIPS procedure, 16 died (61.5%): 11 due to multiple organ failure, 4 due to rebleeding, and 1 due to sepsis. None of the patients with rebleeding within the first 6 weeks presented TIPS thrombosis. Causes of rebleeding were ulceration post–balloon tamponade or EBL in 8 patients, secondary to portal hypertension (esophageal or gastric varices) in 12 patients, and unknown due to massive bleeding in 6 patients. Factors associated with rebleeding were HE, low albumin level, high Child-Pugh score, high ACLF grade, high CLIF-OF score, coagulation failure, and respiratory failure but not MELD score, arterial lactate level, and portal pressure gradient in univariate analysis (Table 4). Embolization of varices during the TIPS procedure was not associated with lower risk of rebleeding. Among these, ACLF grade (OR, 1.699; 95% CI, 1.056-1.663; P = 0.040) was independently associated with rebleeding at 6 weeks (Table 4).

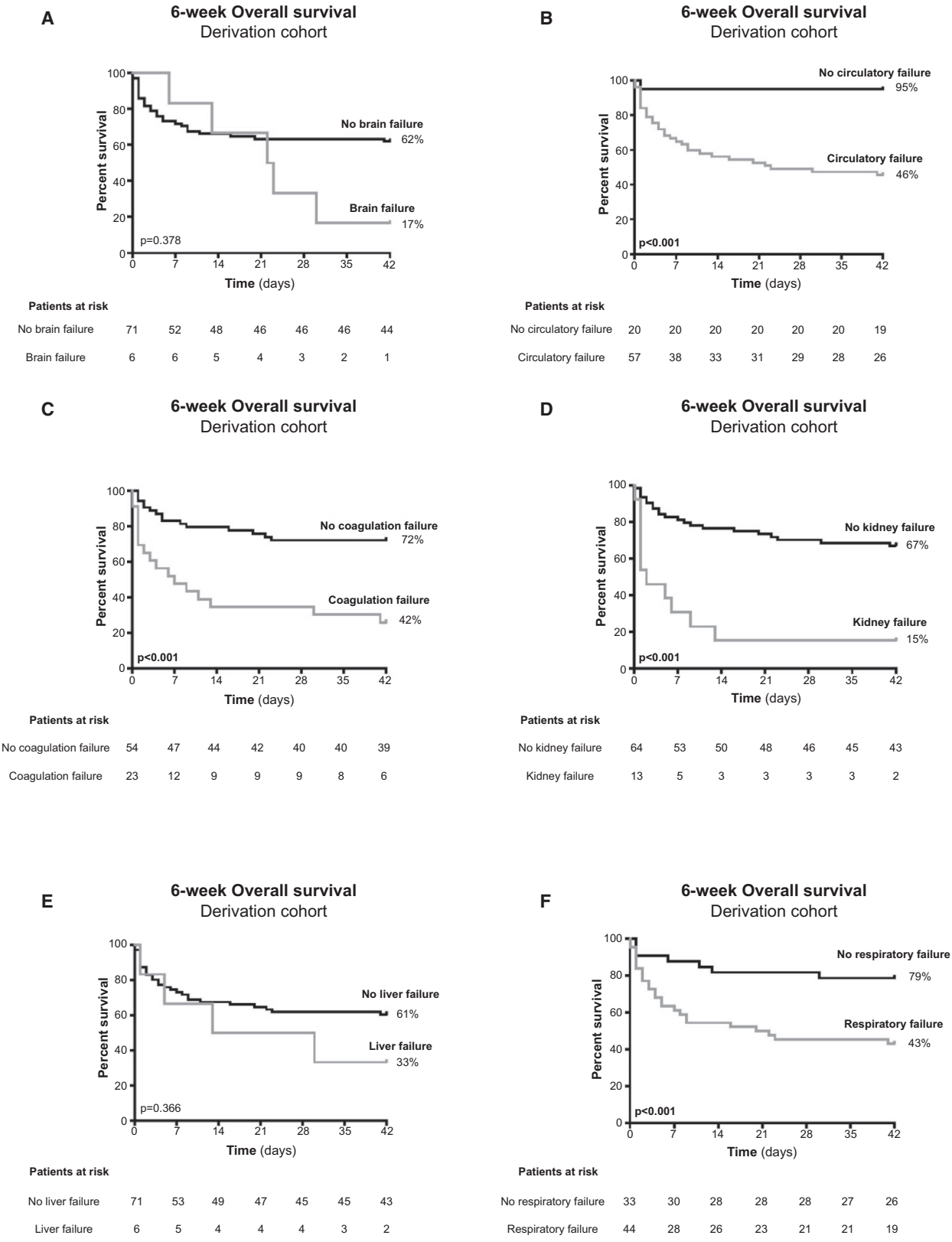

FIG. 3. 6-week overall survival in the derivation cohort according to organ failure.

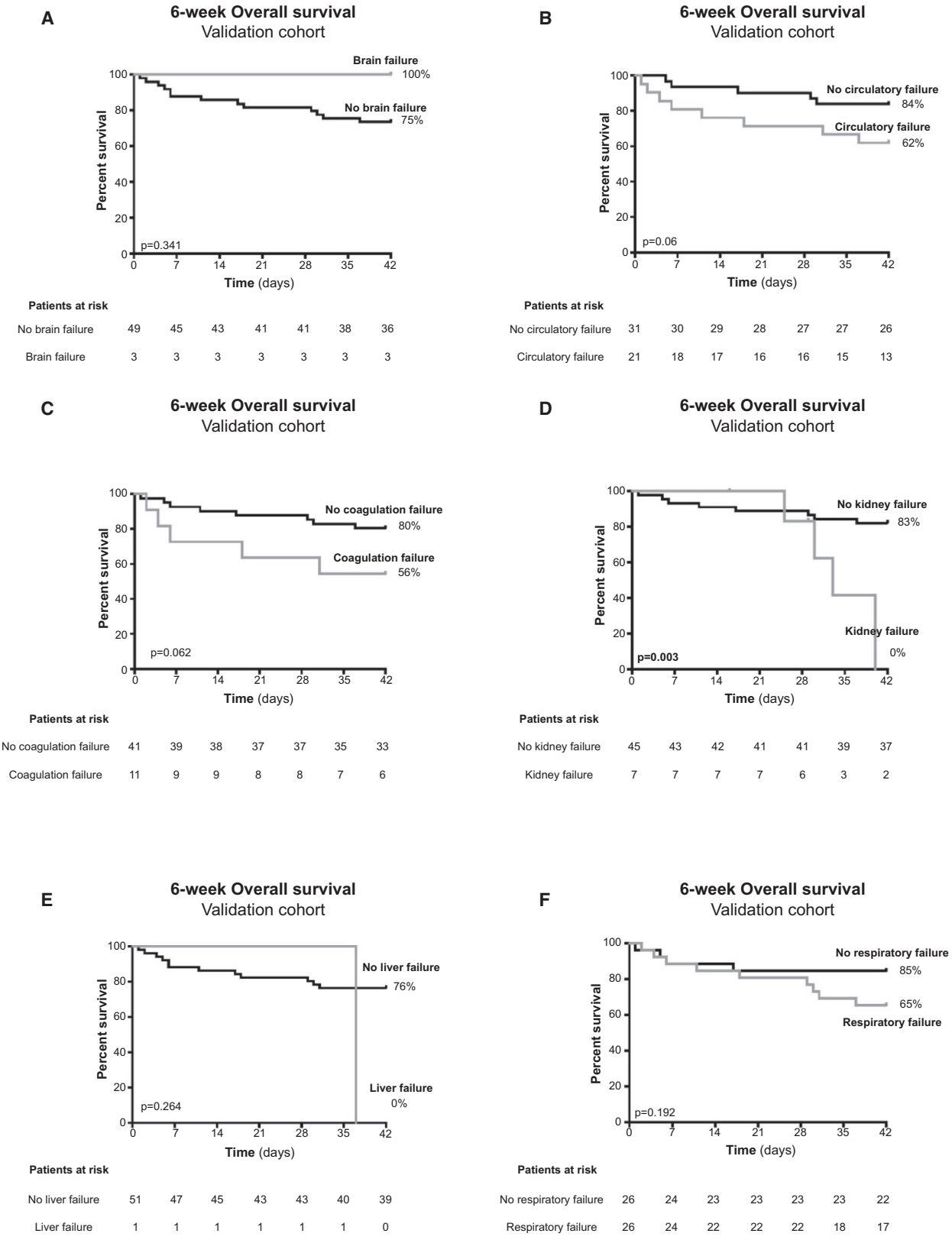

FIG. 4. 6-week overall survival in the validation cohort according to organ failure.

TABLE 4. Regression model of factors predicting rebleeding at 6 weeks in the overall cohort

	Available Data (n = 164)	Rebleeding (n = 26)	No Rebleeding (n = 138)	Univariate Analysis			Multivariate Analysis		
				HR	95% CI	*P*	HR	95% CI	*P*
Age (years)*	164	52 ± 10	55 ± 8	0.963	0.915-1.009	0.123			
Gender (male)†	164	20 (76.9)	110 (79.7)	0.848	0.326-2.496	0.748			
Active alcohol consumption†	161	19 (73.1)	81 (60.0)	1.810	0.740-4.899	0.213			
Ascites†	162	19 (73.1)	73 (53.7)	2.342	0.961-6.329	0.073			
HE†,‡	159	11 (42.3)	27 (20.3)	**2.879**	**1.169-6.971**	**0.019**			
Infection before TIPS†	115	4 (22.2)	24 (24.7)	0.869	0.230-2.98	0.819			
Infection during in-hospital stay†	147	13 (56.5)	61 (51.6)	1.343	0.550-3.355	0.519			
Serum creatinine*	164	89 ± 62	96 ± 74	1.001	0.990-41.006	0.862			
Albumin*,‡	160	22 ± 6	26 ± 6	**0.898**	**0.830-0.966**	**0.005**			
Serum bilirubin*	163	47 ± 90	45 ± 90	1.001	0.997-1.006	0.389			
INR*	161	3 ± 0.9	2 ± 0.6	1.447	0.954-2.185	0.074			
Blood lactate*	144	2 ± 1	5 ± 9.3	0.998	0.910-1.077	0.962			
Child-Pugh score*	156	11 ± 2	9 ± 2	**1.305**	**1.078-1.598**	**0.007**	1.270	1.056-2.956	0.070
MELD score*	160	22 ± 8	18 ± 8	1.047	0.994-1.103	0.080			
ACLF grade*	129	3 ± 0.6	2 ± 1	**1.980**	**1.272-3.364**	**0.005**	**1.699**	**1.056-1.663**	**0.040**
CLIF-OF score*,‡	129	12 ± 2.8	10 ± 2.6	**2.882**	**1.230-3.511**	**0.037**			
Active bleeding†	129	11 (55.0)	78 (71.6)	0.486	0.183-1.313	0.146			
Orotracheal intubation†	132	23 (88.5)	106 (78.5)	2.097	0.669-9.273	0.253			
Renal replacement therapy†	164	1 (2.4)	15 (10.1)	0.328	0.018-1.736	0.291			
Use of vasopressors†	160	12 (46.2)	85 (63.4)	2.421	0.919-7.613	0.095			
Interval from last endoscopy to TIPS*	74	5 ± 12	5 ± 20	0.959	0.875-1.051	0.375			
Interval from balloon tamponade to TIPS*	41	4 ± 5	7 ± 20	0.979	0.924-1.015	0.383			
Portal pressure gradient before TIPS*	104	17 ± 6	18 ± 5	0.927	0.820-1.033	0.195			
Portal pressure gradient after TIPS*	100	8 ± 5	8 ± 4	1.003	0.866-1.44	0.969			

Bold indicates significance.
*Median (interquartile range).
†Number of patients (%).
‡Serum albumin and HE were not entered in the multivariate analysis in order to avoid collinearity with variables included in the Child-Pugh score. CLIF-OF score was not entered in the multivariate analysis in order to avoid collinearity with variables included in the ACLF score.

INFECTION

All patients received antibiotic prophylaxis after the diagnosis of gastrointestinal bleeding (third-generation cephalosporine in 84.0%, quinolones in 8.6%, and piperacillin/tazobactam in 7.4% of cases). Bacterial or fungal infection was diagnosed in 50.3% in the whole cohort during the in-hospital stay. The occurrence of infections before or during the in-hospital stay was not associated with 6-week mortality (Table 4). No predictive factor of infection occurrence was identified in univariate analysis (Supporting Table S2).

In the derivation cohort, pneumonia was the most frequent infection, representing 32.1% of all infections, followed by bacteremia in 25.5%, urinary tract infection in 16.1%, and catheter infection in 12.5% (Supporting Table S5). The pathogenic agents involved were mostly gram-negative bacilli (46.4%), followed by gram-positive cocci (35.7%) and fungal infections (17.9%). Among them, 23.9% were multidrug-resistant bacteria. Regarding the 12 patients with Multidrug-Resistant Bacteria (MRB), 11 received third-generation cephalosporine as antibiotic prophylaxis for the gastrointestinal bleeding, and just one of them had long-term

quinolones for prevention of spontaneous bacterial peritonitis. About one third of the patients presented a severe sepsis or a septic shock. Among the 74 patients who presented infections, 36.5% died within 6 weeks after the TIPS procedure.

Discussion

Six-week survival rate after salvage TIPS for refractory bleeding was 58% in our multicentric series, close to the one available in the literature. We identified arterial lactate level and MELD score as independent predictive factors of death. In patients with low risk of death (lactate ≤2.5 mmol/L and MELD score ≤ 15), 6-week OS rates were 100.0% and 86.0% in the derivation and validation cohorts, respectively, and decreased to 5.0% and 10.0% in the derivation and validation cohorts, respectively, in patients at risk of death (lactate ≥12 mmol/L and/or a MELD score ≥ 30), which could be used as futility criteria for clinical decision-making.

Data regarding mortality after salvage TIPS are scarce in the literature, and most of the series considered uncovered stent and sclerotherapy. First, we wanted to evaluate if the improvement in the techniques used, such as covered stent as well as resuscitation measures, allowed improved survival in patients who underwent salvage TIPS. Quite surprisingly, no differences in term of survival were observed in our cohort when comparing different time periods (2007-2010 vs. 2011-2014 vs. 2015-2017), and mortality rates were similar compared to previous studies, which could be explained by a higher rate of Child-Pugh C patients in our cohort. Interestingly, the 6-week OS rate was higher in the validation cohort (67.0%) compared to the derivation cohort (58.0%), probably due to less severe disease in the validation cohort as suggested by more patients without ACLF and less use of vasoactive supportive therapy, extrarenal epuration, and orotracheal intubation. However, in view of the mortality rate which remains high after salvage TIPS, preemptive TIPS should be proposed in high-risk patients within the 72 hours after the first endoscopic treatment (Child-Pugh B cirrhosis and active bleeding or in patients with Child-Pugh C 10-13 cirrhosis) in order to prevent acute failure and rebleeding and to improve survival, as confirmed by recent multicentric series.[2,19-21]

ACLF was associated with 6-week OS and allowed us to identify a group of patients with low risk of mortality (no ACLF or ACLF-1), medium risk (ACLF-2), and high risk (ACLF-3a and 3b) in the derivation cohort and the validation cohort. Survival results were close to the one observed in the recent series of Kumar et al.[17] Conversely to this series, ACLF was associated with mortality in univariate analysis but not in multivariate analysis. However, Kumar et al. did not consider lactate in their analysis, which appears as a major predictive factor of death in such patients. But due to the high rate of deaths, ACLF-3b grade may appear as indicative of futile prognosis in patients for whom salvage TIPS is considered. Due to the implication of orotracheal intubation in the ACLF grade calculation and as orotracheal intubation is often used in refractory bleeding to protect the airways and not for acute respiratory failure, we decided to focus on MELD score and arterial lactate level, objective biological values which were independently associated with 6-week mortality. Lactate results from the metabolization of pyruvate, which is produced secondary to hypoperfusion and hypoxia to provide energy and is usually cleared by the liver.[22-24] Lactate is a well-established predictive factor of subsequent organ dysfunction and mortality in critically ill patients without cirrhosis hospitalized for diverse causes including sepsis, trauma, acute decompensated heart failure, and gastrointestinal bleeding.[25-33] Due to altered clearance and abnormal tissue oxygenation leading to an increase of its production, lactate is known to be increased in chronic liver disease.[34] However, increased lactate concentration was independently associated with death in patients with cirrhosis older than 65 years and hospitalized in an ICU[35] and in patients transplanted for acute liver failure or ACLF.[36] Nevertheless, due to the fact that liver failure is associated with altered lactate metabolism independently of acute decompensation, the use of lactate alone to predict mortality in such patients remains questionable, and combined scores appear more appropriate. The LiFe score, including arterial lactate, total bilirubin, and INR measured at ICU admission, predicted the in-hospital mortality in critically ill patients with chronic liver disease and was correlated with the ACLF grade.[34] Another score, the Asian Pacific Association for the Study of the Liver ACLF Research Consortium score, including plasmatic lactate, total bilirubin, serum creatinine, INR,

and HE, was also an independent predictor of short-term mortality in patients with chronic liver disease who had ACLF at admission.[37] In a recent series, a score combining the MELD score and lactate level at admission was an early predictor of in-hospital mortality, especially for patients with cirrhosis or patients with sepsis.[38] In our series, all of the patients with a MELD score ≥ 30 or lactate ≥12 mmol/L died during the follow-up in the derivation cohort; that is why we identify these values as cutoffs to identify patients with high risk of death. Indeed, lactate ≥12 mmol/L and/or MELD score ≥ 30 was associated with a 5.0% 6-week survival in the derivation cohort and a 10.0% 6-week survival in the validation cohort, suggesting that salvage TIPS may be futile in such a high-risk population who cannot have access to liver transplant. On the contrary, in patients with low risk of death (lactate ≤2.5 mmol/L and MELD score ≤ 15), 6-week OS rates were 100.0% and 86.0% in the derivation and validation cohorts, respectively; and patients with such criteria should definitively undergo salvage TIPS when necessary and probably will not need additional liver transplantation due to the high OS rate in this favorable group. However, selection of patients who will benefit from liver transplantation in the intermediate zone needs to be investigated. Studying the variation of MELD score dynamics 2 or 3 months after TIPS implantation may appear to be an interesting strategy. Liver transplantation should probably be proposed to patients who have a worsened MELD score during follow-up. Nevertheless, prospective multicentric studies are needed to establish a score value predicting 100% mortality to propose futility criteria and might include another parameter such as lactate clearance. Indeed, the lactate clearance within the first day was also associated with mortality in the literature,[39] but due to the retrospective design, we were not able to provide such data, which constitutes a limitation to the study.

The rebleeding rate in our series was 15.8%, in accordance with previous results. None of them was related to TIPS thrombosis, and bleeding recurrence was mostly due to esophageal or gastric variceal bleeding and ulcer because of balloon tamponade and EBL. ACLF grade but not MELD score was independently associated with the risk of rebleeding using a regression model. Interestingly, ACLF grade was also associated with 6-week rebleeding in a large cohort of patients with acute variceal bleeding.[20]

This study has some limitations, such as its retrospective design and the 10-year period of inclusion, which can be overcome by the inclusion of patients from five different hospitals, providing real-world data.

Mortality after salvage TIPS for refractory acute variceal bleeding in patients with cirrhosis remains high, as does the rebleeding rate, despite improvement in techniques. MELD score and lactate are independently associated with 6-week mortality after salvage TIPS for refractory acute variceal bleeding in patients with cirrhosis. Lactate ≥12 mmol/L and/or MELD score ≥ 30 are associated with a mortality rate >90%, which could help to identify patients who will not benefit from salvage TIPS. On the contrary, patients with lactate ≤2.5 mmol/L and MELD score ≤ 15 should undergo salvage TIPS placement as the 6-week OS rate is >85%.

Author Contributions: M.A., A.W., and J.-C.N. had full access to all data in the study, take responsibility for the integrity of the data and the accuracy of data analysis, and were responsible for the study concept and design, analysis and interpretation of data, and drafting of the manuscript. M.A., A.W., P.O., and A.B. were responsible for acquisition of data. M.R., P.O., L.M., E.T., M.A.R., I.O.-H., A.B., O.S., C.B., J.M.P., V.L.P., N.G.-C., J.C.G.-P., M.M., C.D., D.T., V.H.-G., and C.B. were responsible for critical revision of the manuscript for important intellectual content. M.A. and J.-C.N. were responsible for statistical analysis and study supervision.

Appendix

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.31913/suppinfo.