Elective Surgery but not Transjugular Intrahepatic Portosystemic Shunt Precipitates Acute-On-Chronic Liver Failure

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Acute-on-chronic liver failure (ACLF) is a syndrome associated with organ failure and high short-term mortality. Presence of ACLF at interventions, such as surgery or transjugular intrahepatic portosystemic shunt (TIPS), has been shown to determine outcome, but those interventions have also been attributed to precipitate ACLF in different studies. However, dedicated investigation for the risk of ACLF development in these interventions, especially in elective settings, has not been conducted. Patients with cirrhosis undergoing elective surgery were propensity score matched and compared to patients receiving TIPS. The primary endpoint was ACLF development within 28 days after the respective procedure. The secondary endpoint was 3-month and 1-year mortality. In total, 190 patients were included. Within 28 days, ACLF developed in 24% of the surgery and 3% of the TIPS cohorts, with the highest ACLF incidence between 3 and 8 days. By day 28 after the procedure, ACLF improved in the TIPS cohort. In both cohorts, patients developing ACLF within 28 days after surgery or TIPS placement showed significantly worse survival than patients without ACLF development at follow-up. After 12 months, mortality was significantly higher in the surgery cohort compared to the TIPS cohort (40% vs. 23%, respectively; P = 0.031). Regression analysis showed a European Foundation Chronic Liver Failure Consortium acute decompensation (CLIF-C AD) score ≥50 and surgical procedure as independent predictors of ACLF development. CLIF-C AD score ≥50, C-reactive protein, and ACLF development within 28 days independently predicted 1-year mortality. *Conclusion:* Elective surgical interventions in patients with cirrhosis precipitate ACLF development and ultimately death, but TIPS plays a negligible role in the development of ACLF. Elective surgery in patients with CLIF-C AD ≥50 should be avoided, while the window of opportunity would be CLIF-C AD <50. (*Hepatology Communications* 2021;5:1265-1277).

Cirrhosis is the common end stage of chronic liver disease. Unstable clinical courses of disease may occur after the development of acute decompensation (AD). However, AD can progress to acute-on-chronic liver failure (ACLF), a specific syndrome characterized by the development of organ

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; AUC, area under the curve; CANONIC, European Foundation Chronic Liver Failure Consortium–Acute-on-Chronic Liver Failure in Cirrhosis; CLIF-C, European Foundation Chronic Liver Failure Consortium; CRP, C-reactive protein; CTP, Child-Turcotte-Pugh; EASL, European Association for the Study of the Liver; ERCP, endoscopic retrograde cholangiopancreatography; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; PIRO, Predisposition, Insult, Response, and Organ Failure; PREDICT, Personalized Responses to Dietary Composition Trial; ROC, receiver operating characteristic; TIPS, transjugular intrahepatic portosystemic shunt.

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failure and high short-term mortality.[1,2] Variceal hemorrhage, paracentesis without albumin substitution, excessive alcohol intake, and/or bacterial infections, among others, have been identified as precipitating events for ACLF.[3-7] Moreover, interventions, such as surgical intervention, endoscopic retrograde cholangiopancreatography (ERCP), or transjugular intrahepatic portosystemic shunt (TIPS), have been attributed to be associated with or precipitate ACLF. ACLF following ERCP has been reported to occur in significantly higher rates in patients with cirrhosis with procedure-related adverse events (AEs) than in those without post-ERCP AEs (26% vs. 8%, respectively; $P = 0.01$),[8] suggesting ERCP-related factors (and not the indication of ERCP) as precipitating factors. However, the exact role of elective surgical intervention or TIPS in ACLF development has not been studied.

Recently, we showed that the outcome in patients with cirrhosis undergoing either surgery or TIPS is mainly determined by ACLF itself.[9,10] In the case of gastrointestinal bleeding, we demonstrated that TIPS improves survival and the rebleeding rate in patients with ACLF.[10] Currently, the Child-Turcotte-Pugh (CTP) score and Model for End-stage Liver Disease (MELD), among others,[11,12] are the most commonly applied prognostic models to stratify patient outcome after surgery or TIPS.[13-15] Data on the specific role of elective surgery or TIPS implantation as a precipitating event for ACLF development is at best scarce. The European Foundation Chronic Liver Failure Consortium (CLIF-C) AD score is a prognostic score developed from the CLIF-ACLF in Cirrhosis (CANONIC) study database, including hospitalized patients with cirrhosis and AD but without ACLF. The CLIF-C AD score has been shown to more accurately predict the outcome of those patients; however, it has not yet been applied in the setting of elective surgery as a precipitant for ACLF.[16]

Because we believe that elective surgery and TIPS may have a different impact on the outcome of patients, we compared the development of ACLF in a matched cohort of patients undergoing elective surgery with patients who received TIPS to evaluate the role of elective interventions as a precipitating event for ACLF development and distinguish between TIPS and surgery as precipitating events for ACLF development. This allowed us to explore possible pathophysiologic explanations in their relationship to ACLF development.

Patients and Methods

PATIENTS AND DATA COLLECTION

In this retrospective single-center study, patients with cirrhosis undergoing surgery were compared

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to patients receiving TIPS and investigated for ACLF development. Initially, 495 patients from the Department of Internal Medicine I, University of Bonn, Germany, with liver cirrhosis and who underwent a surgical intervention between the years 2007 and 2017 were identified by a hospital database search. The search combined nonvisceral and visceral surgical codes and the diagnosis of liver cirrhosis according to the German International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. We excluded 126 patients with liver transplantation as the index surgical procedure and 10 patients who had already received TIPS before the index surgery procedure (Fig. 1). We propensity score matched 141 of the remaining patients to patients receiving TIPS from the Non-invasive Evaluation Program for TIPS and Follow Up Network (NEPTUN) cohort (clinicaltrials.gov identifier: NCT03628807).[5,6] Matching criteria were etiology of cirrhosis, sex, MELD ±3 points, CTP score ±1, elective procedure, and age ±3 years. A total of 142 patients did not meet the matching criteria or were not eligible for further matching. Besides not matching with the TIPS cohort, these included patients with hepatocellular carcinoma (HCC) outside the Milan criteria and other malignancy without curative resection or tumor operations requiring adjuvant or neoadjuvant chemotherapy. After matching, additional patients with their respective matches were excluded. These included patients with serum bilirubin above 5 mg/dL as a contraindication for TIPS placement (and potential bias not reflected by MELD) and patients with the presence of ACLF at baseline according to the European Association for the Study of the Liver (EASL)-CLIF classification (n = 92).[1] A final cohort of 190 matched patients receiving either TIPS or undergoing surgery electively were enrolled in the study (Fig. 1). Elective surgeries were defined as necessary and scheduled operations not involving any emergency indication. All emergency operations that needed to be done immediately were excluded from the study before matching (Fig. 1). Baseline was defined as 1 day before procedure (surgery or TIPS). The primary endpoint of this study was ACLF development according to the EASL-CLIF classification within 28 days after surgery or TIPS procedure. The secondary endpoints were 3-month and 1-year mortalities.

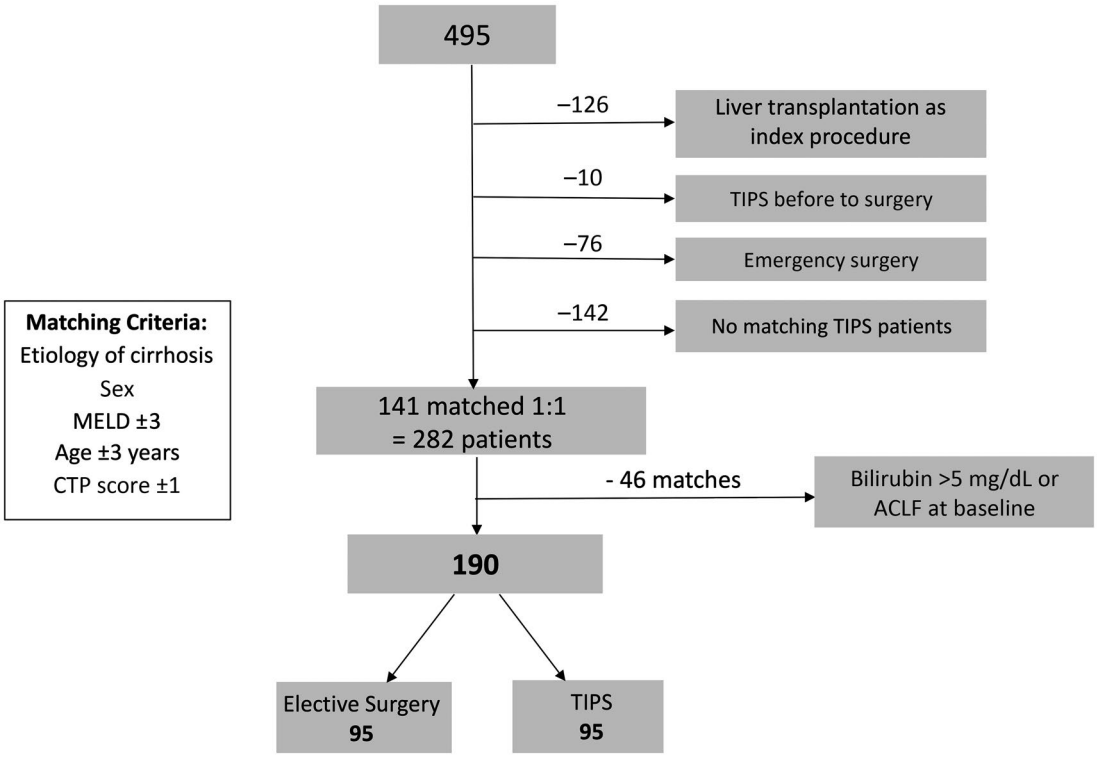

FIG. 1. The selection and matching process to define the final study cohort of patients with cirrhosis undergoing surgery versus patients receiving TIPS.

The type of surgery was established in three categories: abdominal surgery involving the liver (visceral-liver), abdominal surgery without liver involvement (visceral-nonliver), and nonabdominal surgery (nonvisceral) (Supporting Table S1). Abdominal surgery without liver involvement included all surgery types in which the liver was not touched or mobilized by the operating surgeons or surgical instruments. Surgeries were also divided into extensive and limited surgery. Limited surgery was defined as a routine surgery procedure with a duration of under 90 minutes of surgery (e.g., simple hernia surgery); extensive surgery was defined as complex surgical procedures with a duration over 90 minutes with large scale or more complex intraabdominal or extraabdominal involvement. The shift from laparoscopic to an open procedure was also categorized as extensive (Supporting Table S1). All data were obtained from detailed surgical reports and anesthesia protocols. Surgery data were obtained and classified by an individual and confirmed by another blinded individual.

Patient data were collected, including medical history, previous episodes of AD, significant clinical events, and data on surgery and anesthesia. Laboratory and clinical data were collected at baseline and follow-up visits 1-2, 3-8, and 9-28 days after surgery. The CLIF Sequential Organ Failure Assessment score[4,17] was applied to define the organ failure score after intervention. ACLF was retrospectively defined as follows according to the EASL-CLIF consortium definition[1]: renal failure when serum creatinine ≥2 mg/dL and liver failure when bilirubin ≥12 mg/dL. Cerebral failure was defined as hepatic encephalopathy (HE) grades III-IV based on West Haven criteria, coagulation failure in international normalized ratio (INR) ≥2.5 or platelets ≤20,000 per μL, and circulatory failure was defined as arterial hypotension (mean arterial pressure, <70 mm Hg) or the use of vasopressors (indication other than hepatorenal syndrome [HRS] therapy). Respiratory failure was diagnosed when mechanical ventilation was required for reasons other than airway protection and in the absence of HE grade III or IV, exceeding the standard postoperative care or in case of reintubation. Data on ACLF development were also applied to the Predisposition, Insult, Response, and Organ Failure (PIRO) concept, a concept developed in North America for the sepsis setting that has been established to distinguish between a precipitating event and an inflammatory response in the development of ACLF.[18]

STATISTICAL ANALYSIS

To compare two unpaired patient groups, the nonparametric Mann-Whitney test was used. ACLF development and survival rates were analyzed by a Kaplan-Meier curve with the log-rank test. In addition, competing risk analysis with Gray's test was performed to compare ACLF development and 1-year mortality between different groups with liver transplantation as the competing event. To predict survival probability and ACLF development, univariate and multivariate Cox regression with forward selection was performed. Clinically relevant predictors, such as age, etiology of cirrhosis, surgery at baseline, laboratory parameters, and clinically relevant scores with $P < 0.05$ in univariate analysis were selected to enter multivariate Cox regression. The multivariate models were calculated for the development of ACLF and mortality across both cohorts. Prognostic value and selection of optimal cut-off values according to the Youden Index for CLIF-C AD were analyzed using receiver-operating characteristics (ROCs) with 1-year survival and ACLF development within 28 days as endpoints. Kaplan-Meier curve analysis with the log-rank test was also performed to calculate survival rates in the surgery cohort regarding the extensiveness of surgery, involvement of the visceral cavity, and liver involvement of operation. To avoid selection bias, inverse probability of treatment weighting (IPTW) analysis was performed that included all patients undergoing surgery. Weight was calculated using logistic regression, including age, etiology of cirrhosis, MELD, CTP score, CTP class, CLIF-AD ≥50, C-reactive protein (CRP), and surgery. Data are presented as median and range. Two-tailed $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed and plotted using SPSS 26.0 (IBM. Chicago, IL), R (version 3.6.1), and/or Prism 8.4 (GraphPad Software, San Diego, CA).

Results

BASELINE CHARACTERISTICS

We included 190 patients (95 elective surgery 1:1 matched to 95 elective TIPS) in the analysis. Patients were predominantly men (72%), median age for elective surgery was 62 years (range, 30-81 years) and for elective TIPS was 62 years (range,

TABLE 1. GENERAL CHARACTERISTICS OF PATIENTS UNDERGOING ELECTIVE SURGERY AND TIPS AT BASELINE (n = 190)

	Parameters at Baseline	Surgery n = 95	TIPS n = 95	*P*
General Conditions	Age, years	62 (30-81)	62 (31-80)	0.516
	Male/female	68/27 (72%/28%)	68/27 (72%/28%)	1.000
	Etiology (alcohol/viral hepatitis/other)	55/15/25 (58%/16%/26%)	55/15/25 (58%/16%/26%)	1.000
Baseline scores	MELD score	10 (6-18)	10 (6-17)	0.700
	CTP score	6 (5-8)	7 (5-9)	0.191
	CTP class A/B	47/48 (51%/49%)	36/59 (38%/62%)	0.109
	CLIF-AD score	47 (30-62)	46 (23-61)	0.281
Baseline laboratory	Hb, g/dL	12.4 (8.0-16.3)	10.3 (6.8-15.9)	<0.001
	WBC, 10*3/μL	5.9 (2.1-27.4)	5.4 (0.2-20.7)	0.129
	Platelets, per μL	141 (34-555)	142 (34-723)	0.816
	Sodium, mEq/L	140 (123-149)	138 (126-146)	<0.001
	Creatinine, mg/dL	0.93 (0.52-1.91)	1.0 (0.6-1.9)	<0.001
	Bilirubin, mg/dL	1.0 (0.3-3.4)	0.8 (0.1-3.6)	0.132
	AST, U/L	39 (11-254)	38 (15-177)	0.558
	Albumin, g/dL	34 (21-45)	32 (20-45)	0.092
	INR	1.1 (0.9-1.6)	1.1 (0.9-1.5)	0.057
	CRP	8.3 (0.2-175)	10.5 (0.2-99.4)	0.220
Follow-up ACLF	ACLF day 1-2	9 (10%)	1 (1%)	0.010
	ACLF day 3-8	17 (18%)	3 (3%)	0.001
	ACLF day 9-28	16 (18%)	2 (2%)	<0.001
	ACLF at follow-up	23 (24%)	3 (3%)	<0.001
Preexisting	HCC within Milan criteria at baseline	6 (6%)	2 (2%)	0.150
	Ascites	68 (72%)	63 (66%)	0.469
	Varices	72 (76%)	79 (83%)	0.210
	GI bleeding	15 (16%)	46 (48%)	0.062
Transplant and median follow-up	Transplant waiting list	13 (14%)	4 (4%)	0.023
	Liver transplantation within 1 year	3 (3%)	0	0.082
	Median follow-up in months	12	12	1.000

Data are shown as median (range) or number (percent). $P < 0.05$ is significant.
Abbreviations: AST, aspartate transaminase; GI, gastrointestinal; Hb, hemoglobin; WBC, white blood cells.

31-80 years). The most frequent cause of cirrhosis was chronic alcohol consumption (58%) followed by chronic viral hepatitis (16%). Median MELD was not significantly different between the two cohorts, with a median of 10 in both groups; the median CLIF-C AD score was similar between the surgery cohort (47; range, 30-62) and the TIPS cohort (46; range, 23-61). CTP score and class were not significantly different. In the TIPS group, hemoglobin, sodium, albumin, and INR were significant lower (Table 1).

Seventy-four surgical procedures (78%) were abdominal operations, 43 (45%) of which also involved the liver (Supporting Tables S1 and S2). Operations due to HCC were all within the Milan criteria. In all, 55 (58%) patients received TIPS for refractory ascites and 40 (42%) for variceal bleeding. The number of patients with HCC in both cohorts was not significantly different ($P = 0.15$) at baseline. In total, 13 (14%) and 4 (2%) were on the transplant list in the surgery and TIPS cohort, respectively (Table 1).

General characteristics of the patients not meeting the matching criteria or not eligible for the study are shown in Supporting Table S3A. This group showed no significant difference in the distribution of the type of surgery compared to our included patients. However, those excluded surgery patients had lower MELD and CTP scores. Nevertheless, the rate of development of ACLF was similar.

POSTPROCEDURAL SURVIVAL

In total, 26 patients developed ACLF within 28 days in the elective surgery (n = 23) and TIPS cohorts (n = 3) (Fig. 2A). Patients undergoing elective surgery showed significantly higher mortality up to the 12-month follow-up compared to the TIPS cohort (40% vs. 23%, respectively; $P = 0.032$) (Fig. 3A; Supporting Fig. S1A). Patients developing ACLF showed significantly worse survival than patients without ACLF development at follow-up across both groups (Fig. 3B; Supporting Fig. S1B). Three patients received liver transplantation within 1 year in the surgery group. There were no liver transplantations within 1 year after intervention in the TIPS group.

DEVELOPMENT OF ACLF

High rates of ACLF development were observed in patients undergoing elective surgery (24%) compared to patients undergoing TIPS (3%) within 28 days (Fig. 2A). In the elective surgery cohort, the highest incidence of ACLF occurred between days 3 and 8 after surgery (Fig. 2B). Rates of AD with the presence of ascites and development of HRS increased in the surgery cohort, whereas the TIPS cohort showed

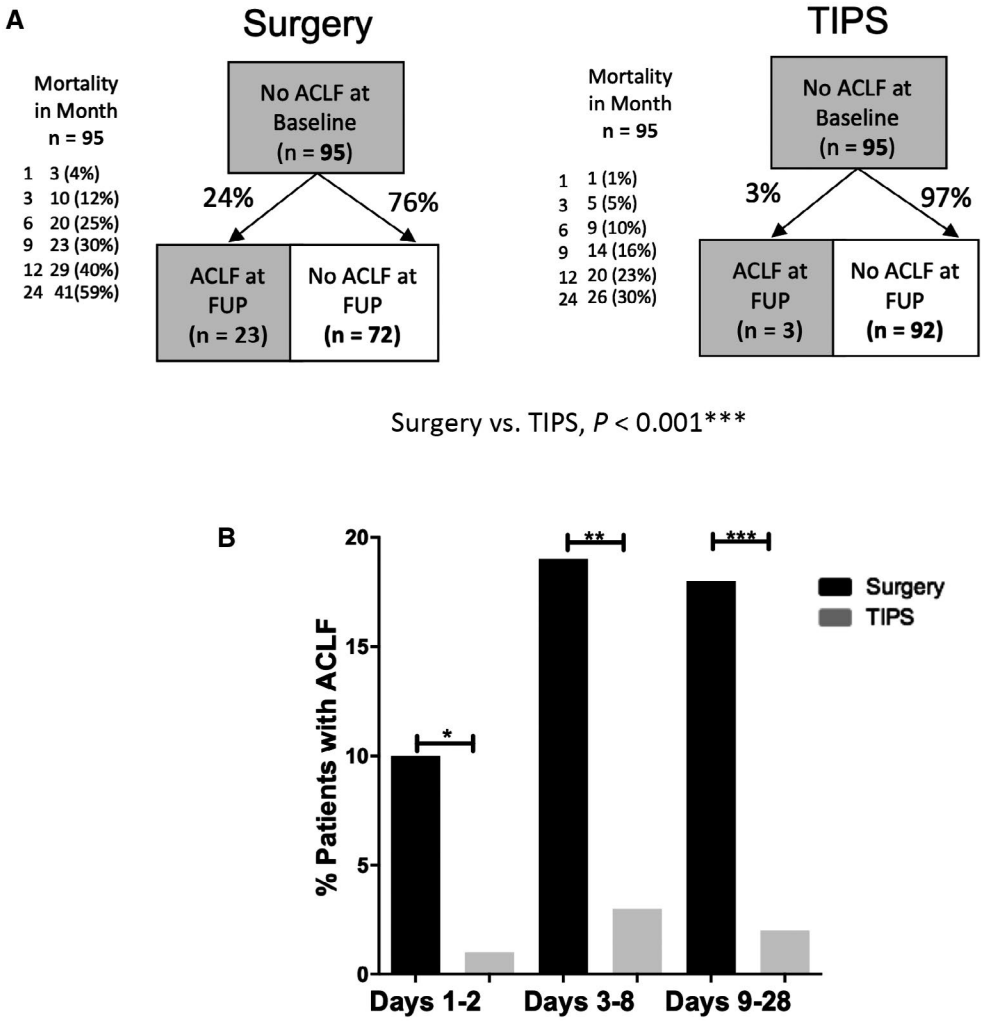

FIG. 2. Incidence of ACLF in elective surgery versus TIPS. (A) Number of patients presenting without ACLF at baseline developing ACLF within a 28-day follow-up and comparison between matched cohorts of elective surgeries (n = 95) and TIPS interventions (n = 95), ***$P < 0.001$. (B) Incidence of ACLF in elective surgery versus TIPS cohorts at three follow-up time points (days 1-2, days 3-8, days 9-28). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Abbreviation: FUP, follow-up.

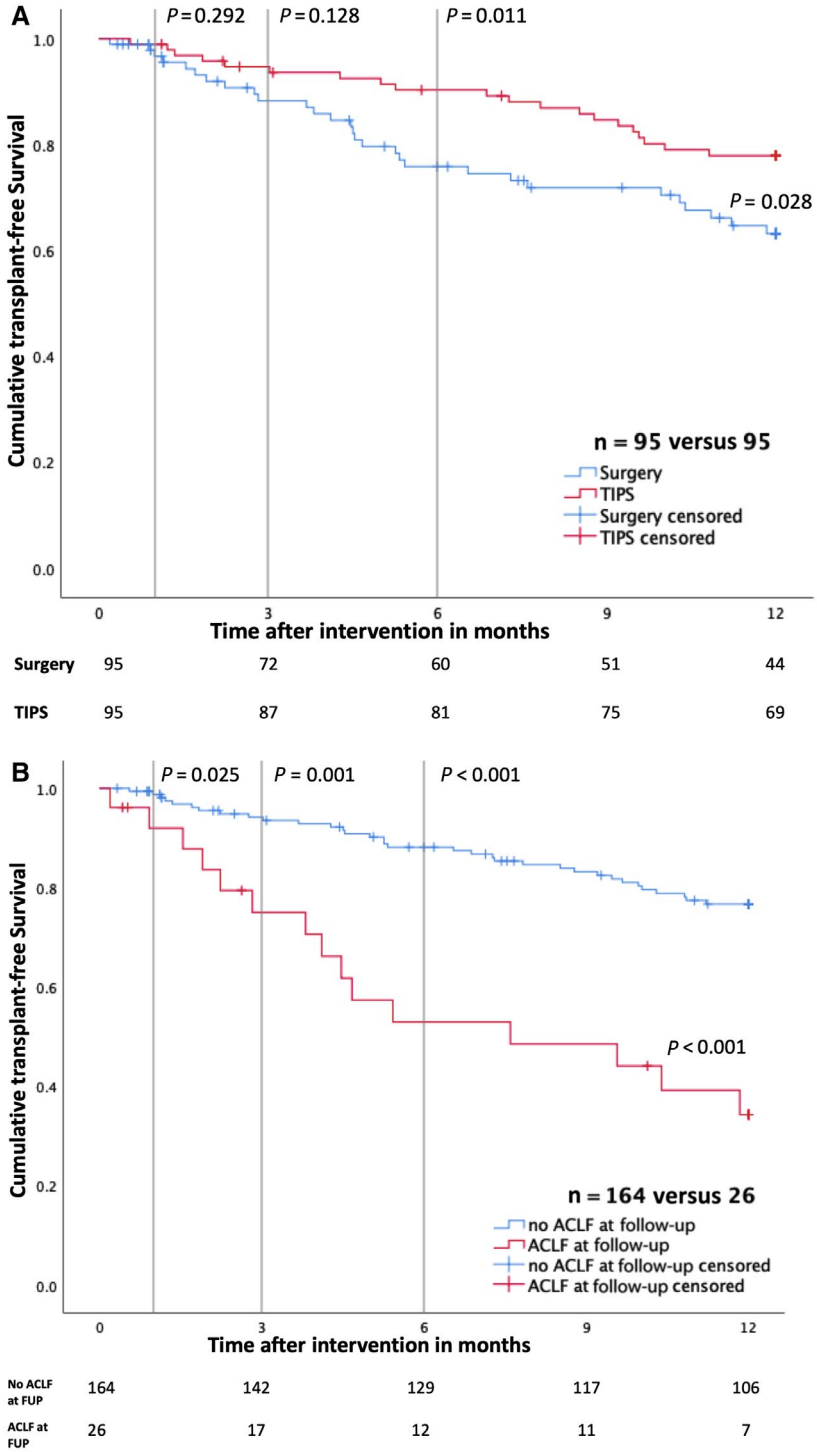

FIG. 3. Kaplan-Maier plots of patient survival. (A) A comparison of 1-year survival in patients undergoing elective surgery versus patients receiving TIPS (n = 190). (B) Survival of patients with and without ACLF development within 28 days after intervention (n = 190). Abbreviation: FUP, follow-up.

significant reduction of ascites and HRS (Supporting Fig. S2A,B). No significant difference could be found in the incidence of ACLF after surgery between categories of visceral and nonvisceral surgery (P = 0.341) (Supporting Fig. S2C). After surgery, a significant increase in leukocyte count and CRP could

be observed compared to the TIPS cohort, which showed negligible differences (Supporting Fig. S2).

PREDICTORS OF ACLF DEVELOPMENT AND MORTALITY

Univariate regression analysis for ACLF development within 28 days after surgery showed age, CLIF-C AD, and surgical procedure (vs. TIPS) as significantly associated. In multivariate analysis where these factors were calculated across both cohorts, CLIF-C AD and surgery were independent risk factors for ACLF development (Table 2A).

CLIF-C AD and CRP were independent predictors of 3-month mortality in univariate and multivariate analysis (Table 3A). For 1-year mortality, age, CLIF-C AD, CRP, and surgery were significantly associated. In multivariate regression, CLIF-C AD, CRP, and the development of ACLF within 28 days after surgery remained as independent predictors (Table 3B).

Because CLIF-C AD was an independent predictor of ACLF development and mortality, a cut-off value was defined to identify high-risk patients for elective surgery. A cut-off value of 50 for the CLIF-C-AD score was shown in the Personalized Responses to Dietary Composition Trial (PREDICT) study to identify patients at high risk of developing ACLF.[19] This cutoff was confirmed in ROC analysis in this cohort (sensitivity, 62%; specificity, 76%) (Supporting Fig. S3). Including CLIF-C AD ≥50 in the multivariate prediction models showed more than a 3-fold increase for the risk of ACLF development and a 6-fold and nearly 4-fold increase for the risk of 3-month and 1-year mortality, respectively (Tables 2B, 3B). The most common cause of death in both groups was fatal ACLF (Supporting Table S4), while the incidence of ACLF-related death was significantly higher in the surgery cohort (P = 0.017 for ACLF at 28-day follow-up; P = 0.065 for 1-year mortality).

All the above-mentioned analyses were additionally performed with CTP or MELD instead of CLIF-C AD to avoid multicollinearity, with an area under the curve (AUC) of 0.71 (P = 0.001) and AUC of 0.70 (P = 0.001), respectively (Table 2A; Supporting Table S5A-D). The CLIF-C-AD score remained as the strongest predictor in our Cox regression models, with the highest significance and AUC in ROC

TABLE 2. COX REGRESSION ANALYSIS FOR ACLF DEVELOPMENT WITHIN 28 DAYS AFTER INTERVENTION

	Univariate Regression				Multivariate Regression			
			95% CI				95% CI	
	P	B	Upper	Lower	*P*	B	Upper	Lower
(A)								
Age*	0.009	1.806	1.158	2.816				
Etiology (alcohol)	0.486	1.337	0.591	3.025				
MELD	0.001	1.260	1.094	1.452				
CTP	0.000	2.429	1.524	3.873				
CLIF-AD†,‡	0.000	1.969	1.412	2.746	0.002	1.926	1.284	2.887
CRP*	0.138	1.119	0.965	1.298				
Surgery‡	0.001	7.933	2.374	26.514	0.001	7.523	2.172	26.057
(B)								
Age*	0.009	1.806	1.158	2.816				
Etiology (alcohol)	0.486	1.337	0.591	3.025				
CLIF-AD ≥50‡	0.001	4.010	1.801	8.932	0.002	3.614	1.620	8.060
CRP*	0.138	1.119	0.965	1.298				
Surgery‡	0.001	7.933	2.374	26.514	0.001	7.633	2.281	25.545

Continuous variables in (A) include MELD, CTP, and CLIF-C-AD; binary variable in (B) is CLIF-C-AD ≥50, n = 190.
*Data shown as per increment of 10.
†Data shown as per increment of 5.
‡Parameters remaining as independent predictors in multivariate regression.
Abbreviation: CI, confidence interval.

TABLE 3. COX REGRESSION ANALYSIS FOR (A) 3-MONTH MORTALITY AND (B) 12-MONTH MORTALITY, n = 190

	Univariate Regression				Multivariate Regression			
			95% CI				95% CI	
	P	B	Upper	Lower	*P*	B	Upper	Lower
(A) 3-month mortality								
Age*	0.076	1.644	0.949	2.845				
Etiology (alcohol)	0.031	5.128	1.157	22.724				
CLIF-AD ≥50†	0.007	4.197	1.493	11.801	0.008	6.090	1.605	23.102
CRP*,†	0.007	1.255	1.064	1.480	0.005	1.271	1.076	1.502
Surgery	0.139	2.250	0.769	6.585				
ACLF at 28-day follow-up†	0.003	4.750	1.690	13.349				
(B) 1-year mortality								
Age*	0.004	1.539	1.146	2.066				
Etiology (alcohol)	0.042	1.885	1.023	3.471				
CLIF-AD ≥50†	0.000	4.309	2.432	7.636	0.000	3.830	1.904	7.705
CRP*,†	0.006	1.164	1.045	1.296	0.002	1.201	1.071	1.347
Surgery	0.048	1.786	1.006	3.173				
ACLF at 28-day follow-up†	0.000	4.076	2.214	7.506	0.003	3.142	1.471	6.713

*Data shown as per increment of 10.
†Parameters remaining as independent predictors in multivariate regression.
Abbreviation: CI, confidence interval.

analysis (AUC, 0.75; $P < 0.001$). Thus, CLIF-C-AD was chosen for further analysis.

To investigate the influence of the extensivity of the surgical procedures as well as involvement of the visceral cavity and liver involvement, these factors were included into our Cox regression models. These factors were not found to be significantly associated with ACLF development within 28 days (Supporting Table S5C). Kaplan-Meier curve analyses for 1-year survival stratified for the same categories also did not show any significant difference in 1-year survival (Supporting Fig. S4A-C).

To avoid selection bias, IPTW analysis, including the 142 patients undergoing elective surgery not meeting the matching criteria for propensity matching, was performed; we found no major changes in the results. CLIF-C AD and surgery remained as the strongest predictors for ACLF development within 28 days after intervention (Supporting Table S6).

Discussion

This study is the first to show that TIPS comprises a negligible risk of ACLF development and even suggests an inverse association. Moreover, it confirms surgical procedures as precipitating events for the development of ACLF and suggests the cutoff of the CLIF-C AD-score <50 as a window of opportunity for elective surgery.

ACLF represents a serious syndrome with rapid deteriorating organ function leading to multiple organ failure and high short-term mortality.[2,20] While some precipitating events have been identified in the CANONIC cohort, almost half of them showed no identifiable precipitating event. Surgical interventions can cause severe tissue injury, highly activated systemic inflammation, and ACLF.[11,12] Recently, we described outcomes with regard to ACLF in the context of surgery.[9] Survival in patients undergoing surgery when they already had established ACLF and of patients developing ACLF shortly after surgery were similar. Also, bacterial infections were an independent risk factor of ACLF development within 28 days after surgery. These data suggested that surgery should be avoided when bacterial infections were present and to clear infection before surgery whenever possible. However, elective and emergency surgeries were not stratified. Thus, emergency surgeries were excluded from the current study. Still, our study shows that

24% of patients undergoing elective surgical interventions developed ACLF within 28 days, filling the gap of previous study data. Thus, these results further hint at surgery itself as a precipitating event of ACLF development. Importantly, patients developing ACLF show a highly significant worse survival than patients who did not develop ACLF during follow-up. The role of systemic inflammation previously described for the development of ACLF is also confirmed in this study; CLIF-C AD score (containing surrogates of systemic inflammation) with surgery itself are independent predictors of ACLF development, while CRP is an independent predictor of mortality.[7,21,22] Our results suggest the development of only transient ACLF in patients with elective surgery, particularly in those with a CLIF-C AD score <50, and that elective surgery in patients with cirrhosis with a CLIF-C AD score of >50 is associated with high rates of fatal ACLF. It seems that surgical intervention should be avoided in these high-risk patients. Taken together, we suggest that patients with a CLIF-C AD score 50 and higher should avoid elective surgery and wait for the optimal window, although the performance of the CLIF-C AD score is only marginally superior to the MELD and CTP scores. These patients may even be evaluated for liver transplantation before surgery. However, most allocation systems are MELD or MELD-Na based.

In the present study, only 3% of the TIPS cohort, which was matched to elective surgery patients, developed ACLF, indicating that the TIPS procedure itself is not a precipitating event for ACLF development. Our observations are strengthened by a recent large, multicenter, observational study showing that even patients with ACLF with acute variceal bleeding may benefit from a preemptive TIPS (pTIPS) placement. It showed that ACLF almost doubles the risk of rebleeding and that it is a major independent risk factor for rebleeding and mortality, which can be improved by pTIPS.[10] However, patients with refractory ascites as the indication for TIPS were not included, while in the TIPS cohort of the current study, both indications (refractory ascites/variceal bleeding) are represented. Moreover, in the previous study, patients were stratified into the presence or absence of ACLF at baseline. Thus, that study would not address the issue of the TIPS procedure as a precipitant event for ACLF development, as it was viewed until recently.[10,20] In our current study, ACLF at baseline as a confounder for a worse outcome was excluded. These data alongside our study support that TIPS insertion is associated with a lower risk of ACLF development, even in patients with high systemic inflammation markers.

Patients eligible for TIPS are highly selected patients to prevent postprocedural complications. For this reason, they might be less prone to develop ACLF after a TIPS intervention. However, in non-optimally selected patients after TIPS, liver function is at risk and might show deterioration.[17,23] Thus, the TIPS procedure was considered a precipitating event for ACLF.[20] Only recently, some researchers may suggest otherwise.[10] Of note, endoscopic procedures, viewed as minimally invasive similar to TIPS, represent a potential precipitating factor for ACLF.[8] One of the main differences between TIPS and surgery is that TIPS is highly effective in treating complications of portal hypertension while portal hypertension is not ameliorated in patients undergoing surgery during the postoperative period. TIPS improves renal perfusion and therefore can resolve functional renal failure. Renal dysfunction itself is a major prognostic factor for patients with cirrhosis and therefore a hallmark of ACLF.[17] In our study cohort, liver function was similar and kidney function even worse in the TIPS group before TIPS placement. The improvement of renal function after TIPS might explain the lower incidence of postprocedural ACLF compared to surgical procedures where renal failure is aggravated in this study cohort. Thus, our results may suggest a pathophysiologic explanation of portal hypertension-driven kidney dysfunction (and HRS in particular) as a key factor in postoperative ACLF development.

Insults and tissue damage of surgery and TIPS on liver function should be taken into consideration as they seem to be pathophysiologically distinct. This is indicated by our data that show a significant difference in the evolution of leukocyte count and CRP after the respective procedure; the increase of these markers of systemic inflammation is distinctly more pronounced in patients undergoing surgery. A proinflammatory state has been shown to be associated with ACLF and complications of portal hypertension. In recent studies, the role of sterile inflammation through the degradation of extracellular matrix as a proinflammatory agent after mechanical injury during an abdominal operation has been discussed as a trigger of postoperative inflammation locally and systemically.[24-27] Sterile inflammation

might play a role for the mortality of patients with cirrhosis undergoing surgery through triggering a transient ACLF. Further prospective studies on the role of bacterial and sterile inflammation in the outcome of these patients with cirrhosis undergoing surgery are therefore needed. In this context, the PIRO concept helps in understanding the distinction between insult and response of pathophysiologic processes in ACLF. Our work shows data on development of ACLF and the progression to ACLF-related death (R and O of PIRO). Interestingly, the rate of 28-day ACLF-related death in the surgery cohort was significantly higher compared to the TIPS cohort. The development of ACLF was significantly associated with increased mortality. Moreover, Cox regression analysis showed that surgical procedure, systemic inflammation (represented by CRP), and the development of organ failure (P and I of PIRO) were significantly associated with 1-year mortality.

In addition to CLIF-C AD, CRP (a marker of systemic inflammation) at baseline is an independent predictor of mortality despite the type of intervention. This highlights and confirms the important role of an activated inflammatory state for the outcome in decompensated cirrhosis in general.[22] An enhanced inflammatory state associated with higher mortality in patients with cirrhosis was shown in the CANONIC cohort and other studies, underlining the robustness of our data.[7,22,28] Systemic inflammation has been linked to hyperdynamic circulation, which is associated with the development of ACLF.[7] Moreover, the relationship of hyperdynamic circulation and general anesthesia has been shown before. On one hand, hyperdynamic circulation, especially in patients with cirrhosis, seems to be associated with worse outcome of general anesthesia.[29,30] On the other hand, general anesthesia can cause hyperdynamic circulation,[31,32] suggesting an additional circulatory insult by general anesthesia for patients with cirrhosis undergoing surgery. Of note in our study, patients receiving TIPS generally did not undergo general anesthesia, which could present a confounder for hyperdynamic circulation compared to patients undergoing surgery.

Finally, not only preventing complications of portal hypertension but also effective reduction of portal hypertension before surgical procedures should be explored. Recently, a prospective multicenter cohort on the prognostic role of hepatic venous pressure gradient (HVPG) in elective extrahepatic surgery showed that HVPG >16 mm Hg is independently associated with mortality and HVPG ≥20 mm Hg identified a subgroup at very high risk of death (44%).[15] The concept of preoperative TIPS to lower portal pressure and thereby achieve better postoperative outcomes has been discussed.[33] No prospective trials have been performed in this setting, but these are needed. Preoperative amelioration of portal hypertension might be a key player in preventing postoperative ACLF development and mortality. Our results also indicate that optimization of portal hypertension before and after surgery and in perioperative care and management may be substantial in improving perioperative mortality.

Recently, the PREDICT study uncovered three distinct phenotypes of decompensated cirrhosis and major precipitating events for ACLF.[19,34] Our study adds further information for surgery as a precipitating event in the context of ACLF. It would be interesting to see whether these distinct phenotypes can be discovered followed by elective surgery as a precipitating event. However, patients of the PREDICT study were admitted as emergency cases to the hospital with decompensated cirrhosis and/or ACLF. These analyses, also in relationship to the type of surgery, should be done in larger cohorts in the future, but applying them in our cohort is beyond the scope of this study.

There are several limitations to this study. It is a retrospective single-center study with no external validation; this limits its generalizability even though its results are in line with and might even explain existing literature. The number of events is relatively small, which leads to wide confidence intervals and lack of precision (23 in elective surgery vs. three in the TIPS cohort), making prospective studies necessary. Despite acquiring our postsurgical data from well-documented anesthesiology records, punctual misgrading of HE grades cannot be excluded. Different types of surgery were categorized in our surgery cohort. Although our data showed no significant impact of extensivity and involvement of the visceral cavity and the liver, we acknowledge that evaluation of the impact of specific surgical procedures is beyond the scope of the study and should be investigated in further studies. Comparison to a TIPS cohort suggests an inverse association of TIPS and ACLF development. However, other obscure confounders, such as sarcopenia and a large total spontaneous portosystemic shunt area, cannot be ruled out.[5,6,35] Finally, patients with the TIPS

procedure before surgery were excluded from the analysis but should be evaluated in future studies.

In conclusion, this study shows that surgical interventions are a precipitating event for ACLF development and ultimately death in patients with cirrhosis. However, elective surgery can be performed with an acceptable outcome when the CLIF-C AD score and CRP are low. Comparatively, the TIPS procedure has a negligible effect on ACLF development.

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