The Development and Outcome of Acute-on-Chronic Liver Failure After Surgical Interventions

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Acute-on-chronic liver failure (ACLF) is a syndrome with high short-term mortality. Precipitating events, including hemorrhage and infections, contribute to ACLF development, but the role of surgery remains unknown. We investigated the development of ACLF in patients with cirrhosis undergoing surgery. In total, 369 patients with cirrhosis were included in the study. The clinical and laboratory data were collected prior to and on days 1-2, 3-8, and 9-28, and at 3 and 12 months after surgery. Surgery type was classified as limited or extensive, as well as liver and nonliver surgery. A total of 39 patients had baseline ACLF. Surgery was performed during acute decompensation in 35% of the rest of the 330 patients, and 81 (24.5%) developed ACLF within 28 days after surgery. Surrogate markers of systemic inflammation were similar in patients who developed ACLF or not. Age, sex, serum sodium, baseline bacterial infection, and abdominal nonliver surgery were independent predictors for the development of ACLF after surgery. Patients who developed ACLF within 28 days after surgery had a higher mortality at 3, 6, and 12 months. Survival did not differ between patients with ACLF at surgery and those developing ACLF after surgery. Development of ACLF within 28 days after surgery and elevated alkaline phosphatase and international normalized ratio were independent predictors of 90-day mortality. Independent predictors of 1-year all-cause mortality were alkaline phosphatase, Model for End-Stage Liver Disease score, and preoperative hepatic encephalopathy, whereas nonliver surgery was associated with improved survival. ACLF frequently develops in patients with cirrhosis undergoing surgery, especially in those with active bacterial infection, lower serum sodium, and kidney or coagulation dysfunction. Prognoses of ACLF both at and after surgery are similarly poor. Patients with cirrhosis should be carefully managed perioperatively.

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Cirrhosis is the common end stage of any chronic liver disease. However, patients with cirrhosis may remain stable for long periods of time despite the progression of disease.[1] Acute complications, such as sudden development or worsening of ascites, overt encephalopathy, gastrointestinal hemorrhage, nonobstructive jaundice, and/or bacterial infections, lead to acute decompensation (AD) episodes.[2] AD may progress further to acute-on-chronic liver failure (ACLF),[2] which is associated with high short-term mortality.[3] Although several predisposing factors and precipitating events for ACLF have been identified,[4,5] to date, the role of surgery in the development and prognosis of ACLF has not been adequately studied.

On the other hand, the effect of AD and the development of ACLF at surgery on the outcome of the patients have not been adequately described even though there has

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; CANONIC, CLIF-Acute-on-Chronic Liver Failure in Cirrhosis; CLIF, chronic liver failure; CRP, C-reactive protein; EASL, European Association for the Study of the Liver; FiO_2, fraction of inspired oxygen; Hb, hemoglobin; HCT, hematocrit; HE, hepatic encephalopathy; HR, hazard ratio; HRS, hepatorenal syndrome; INR, international normalized ratio; LR, likelihood ratios; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; OF, organ failure; OR, odds ratio; ROC, receiver operating characteristic; SOFA, Sequential Organ Failure Assessment; SpO2, pulse oximetric saturation; TIPS, transjugular intrahepatic portosystemic shunt; WBC, white blood cell.

been substantial progress in both hepatology and surgery in managing patients with cirrhosis.[6,7] The currently applied prognostic factors for outcomes after surgery are still the Child-Pugh and the Model for End-Stage Liver Disease (MELD) scores,[6,7] whereas the concepts of AD and ACLF have not yet been introduced in the perioperative management of patients with cirrhosis.

This large retrospective single-center study intends to fill this gap and describes risk factors for the development of ACLF and short-term mortality in a large cohort of patients with cirrhosis undergoing surgery other than liver transplantation (LT).

Patients and Methods

PATIENTS AND DATA COLLECTION

The inclusion criteria were the presence of cirrhosis, a surgery other than LT, and the absence of ACLF at surgery according to the European Association for the Study of the Liver (EASL)–Chronic Liver Failure (CLIF) classification.[2] The primary endpoint of this study was the development of ACLF according to the EASL-CLIF classification[2] within 28 days after surgery. The secondary endpoint was the 90-day, 6-month, and 1-year mortality.

In this retrospective study, 955 patients with liver disease who had surgery were screened between June 2004 and January 2017 at the Department of Internal Medicine I, University of Bonn, Bonn, Germany (Supporting Fig. 1). The local ethics committee approved the study. The study was performed in accordance with the Helsinki Declaration. Of those, 460 patients did not have established cirrhosis, and a further 126 patients received LT as the index surgery procedure. The remaining 369 patients with cirrhosis underwent a surgery other than transplantation. Of these, 39 patients fulfilled the criteria for ACLF and were excluded from the analysis of the primary endpoint, but they served as positive controls. Their surgical intervention list is shown in Supporting Table S1.

The type of surgery was used to establish 3 different categories: 157 patients received abdominal surgery involving the liver, 91 patients received abdominal surgery not involving the liver, and 82 patients received nonabdominal surgery. The extent of the surgery was classified as either limited (routine surgery with a duration of ≤1.5 hours, eg, laparoscopic cholecystectomy or simple hernia surgery) or extensive (complex surgery with a duration of >1.5 hours, eg, hemihepatectomy or Whipple surgery). A list of surgical interventions, their classification, and the number of different types of anesthesia are available in Supporting Table S2.

Patient data on medical history, including previous episodes of AD (acute development or worsening of ascites, overt encephalopathy, gastrointestinal hemorrhage, nonobstructive jaundice, and/or bacterial infections), as well as important clinical features and events, such as ascites, hepatorenal syndrome (HRS), hepatic encephalopathy (HE), and interventions, such as transjugular intrahepatic portosystemic shunt (TIPS), were collected on all patients. To calculate major scores and organ failures as defined by CLIF–Sequential Organ Failure Assessment (SOFA),[2,3] the main laboratory data were collected at the following time points: before surgery and on 3 follow-up visits after surgery and days 1-2, 3-8, and 9-28, if patients were hospitalized or were readmitted in this period.

Organ failure after surgery was defined according to the CLIF-SOFA score[2,3]: renal failure when creatinine ≥2 mg/dL; liver failure when bilirubin ≥12 mg/dL; circulatory failure as defined as arterial

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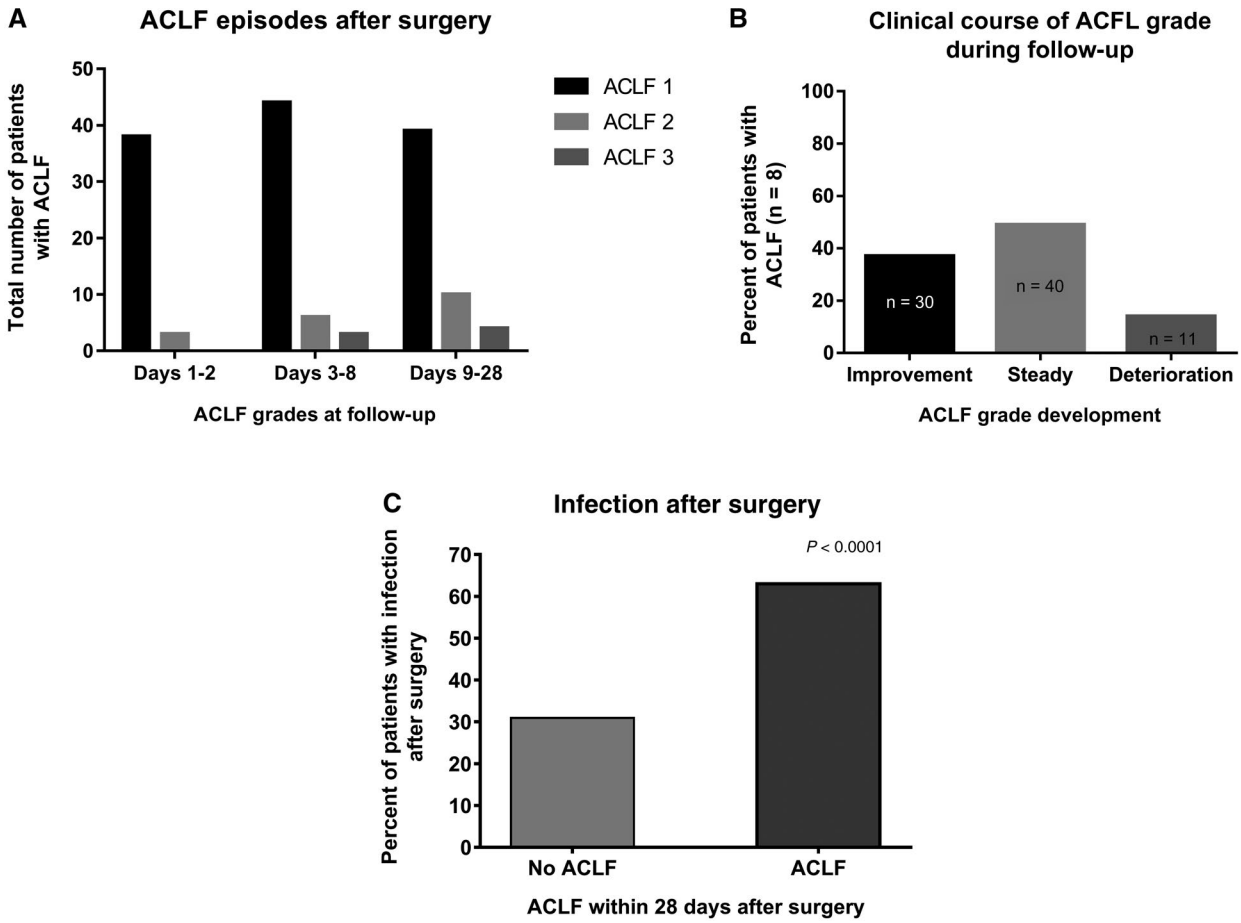

FIG. 1. (A) Evolution of ACLF in patients who developed ACLF after surgery. (B) The number of patients with different grades of ACLF at each of the time frames of follow-up after surgery. (C) Prevalence of infections in patients who developed ACLF after surgery compared with patients who did not.

hypotension or the use of vasopressors (for indications other than HRS therapy); cerebral failure when HE grade 3-4 based on West Haven criteria; coagulation failure if international normalized ratio (INR) >2 or platelets ≤20,000 G/L; and respiratory failure as defined as mechanical ventilation longer than the day of surgery (for indications other than HE) or reintubation within the follow-up period.

STATISTICAL ANALYSIS

A nonparametric Mann-Whitney U test was used to compare 2 unpaired patient groups; for the comparison of more than 2, the nonparametric Kruskal-Wallis test was used. Several regression models were performed to predict endpoints: Univariate and multivariate Cox regressions with forward selection were used for the prediction of survival probability and univariate and multivariate logistic regressions were used for the prediction of ACLF. Age, sex, and clinically relevant predictors at baseline for ACLF development with a P value of <0.1 in the univariate analysis were selected to enter the multivariate logistic regression. Variables with >20% missing values were not included in the model. Survival rates were analyzed with the log-rank test, creating a Kaplan-Meier curve. All data are presented as median and range or counts with percentages. P value levels <0.05 were considered to be statistically significant. Cutoff values were determined from the highest Youden index for each risk factor. Statistical analyses, Kaplan-Meier survival plots, and receiver operating characteristic (ROC) curves were performed and plotted by SPSS, versions 23.0/24.0 (SPSS Inc.

Chicago, IL) and GraphPad Prism 4.0 (GraphPad Software, San Diego, CA).

Results

PRESENCE AND DEVELOPMENT OF ACLF AT SURGERY AND DURING FOLLOW-UP

Table 1 shows the general characteristics of the patients receiving surgery with (n = 39) and without (n = 330) ACLF. Among the latter group, 81 (24.5%) developed ACLF within 28 days after surgery. The relationship of different types of surgery and types of organ failure before going into surgery in these patients are shown in Supporting Table S3.

Patients without ACLF at baseline were predominantly male (n = 233, 70.6%) and had a median age of 63.0 years. A total of 51.5% of the patients (n = 170) had alcoholic cirrhosis, 19.1% (n = 63) suffered from cirrhosis due to chronic virus hepatitis infection, whereas others had distinct etiologies (see Supporting Table S3). Child-Pugh class A (n = 172) was predominant, whereas the median MELD score was 9.0 points and the median CLIF-C AD score was 47.0. Importantly, surrogates of systemic inflammation at surgery were similar in patients later developing or not developing ACLF.

Patients developing ACLF within 28 days after surgery were older and had higher Child-Pugh, MELD, and CLIF-C AD scores. There was no difference between the groups regarding surgery (data not shown) and etiology of cirrhosis. Renal failure (48.1%) was the leading organ failure in patients with ACLF, followed by circulatory and respiratory failures (each 25.9%), whereas liver and cerebral failures (each 13.6%) were less prevalent (Table 1). The relationship of different types of surgery and types of organ failure before surgery in these patients is shown in Supporting Table S4.

Patients developing ACLF had experienced more than 1 AD episode prior to surgery (Table 1), including ascites, HRS, spontaneous bacterial peritonitis, HE, and variceal bleeding episodes. Only 2 of 7 patients with prior TIPS insertion, mostly due to ascites, developed ACLF.

After the development of ACLF, nearly 50% of the patients remained stable, whereas 37.0% improved and 13.6% deteriorated (Fig. 1A). Interestingly, although the prevalence of ACLF grade 1 was similar during follow-up, the prevalence of ACLF grades 2 and 3 increased over time within 28 days after surgery (Fig. 1B). As expected, infections occurred more frequently in patients developing ACLF after surgery (Fig. 1C).

DIFFERENCE IN CHARACTERISTICS BETWEEN PATIENTS WITH ACLF AT SURGERY AND DEVELOPING ACLF DURING FOLLOW-UP

As shown in Supporting Table S5, baseline parameters at surgery differed significantly between patients with ACLF at surgery and patients developing ACLF after surgery. Child-Pugh, MELD score, C-reactive protein (CRP), and creatinine were higher in patients with ACLF at surgery, whereas hemoglobin (Hb) was lower. Interestingly, patients developing ACLF after surgery underwent longer surgical procedures than patients with ACLF at surgery. Notably, the distribution of ACLF grades was similar in patients with immediate ACLF and those developing ACLF in the first 28 days after surgery during further follow-up.

TYPE OF SURGERY AND DEVELOPMENT OF ACLF

The majority of patients underwent extensive surgery (n = 206) with a median intraoperative time of 140 minutes. Abdominal surgery was performed in 248 patients, and surgery involving the liver was performed in 157 patients. Only 82 patients received nonabdominal surgery (Supporting Table S6). Median time of abdominal liver surgery was 165 minutes, which was significantly longer than that of nonliver surgery (abdominal surgery not involving the liver versus nonabdominal surgery; 118 versus 50 minutes; $P < 0.001$). Moreover, abdominal surgery, involving both liver and extrahepatic organs, was mostly extensive (complex surgery with a duration of >3 hours, eg, hemihepatectomy or Whipple surgery; see Supporting Table S2), whereas 71% of nonabdominal surgery was limited ($P < 0.001$). Patients who underwent abdominal liver surgery were less prone to develop ACLF at follow-up (22%) compared with patients who underwent nonliver abdominal surgery (35%), but these patients developed ACLF more frequently than patients with nonabdominal surgery (17%). Interestingly, the type of surgery (abdominal liver, abdominal nonliver, or nonabdominal) had no influence on 1-year mortality (Supporting Table S6).

TABLE 1. Baseline Characteristics According to ACLF Presence at Baseline and During Follow-up

Parameters at Baseline	ACLF at Baseline (n = 39)	No ACLF at Baseline (n = 330)	*P* Value*	No ACLF at Follow-up (n = 249)	ACLF at Follow-up (n = 81)	*P* Value*
Age, years	62.0 (38.0-78.0)	63.0 (0.0-84.0)	0.894	61.0 (0.0-81.0)	66.0 (28.0-84.0)	0.011
Sex			0.854			0.044
Male	27 (69.2)	233 (70.6)		183 (73.5)	50 (61.7)	
Female	12 (30.8)	97 (29.4)		66 (26.5)	31 (38.3)	
Etiology			0.368			0.486
Alcohol	25 (64.1)	170 (51.5)		131 (52.6)	39 (48.1)	
Viral hepatitis	5 (12.8)	63 (19.1)		50 (20.1)	13 (16.0)	
Other	9 (23.1)	97 (29.4)		68 (27.1)	29 (35.8)	
Scores						
Child-Pugh	7.0 (5.0-10.0)	5.0 (5.0-10.0)	<0.001	5.0 (5.0-10.0)	6.0 (5.0-9.0)	<0.001
Class			<0.001			0.012
A	12 (30.8)	172 (52.1)		135 (54.2)	37 (45.7)	
B	17 (43.6)	35 (10.6)		20 (8.0)	15 (18.5)	
C	1 (2.6)	1 (0.3)		1 (0.4)	0 (0.0)	
MELD	20.0 (8.0-29.0)	9.0 (5.0-25.0)	<0.001	9.0 (5.0-23.0)	11.0 (5.0-25.0)	<0.001
CLIF-C AD	59.0 (23.0-76.0)	47.0 (25.0-72.0)	<0.001	47.0 (25.0-72.0)	50.0 (29.0-69.0)	<0.001
CLIF-C ACLF	42.3 (30.5-53.2)	36.3 (11.6-48.7)	<0.001	36.0 (11.6-47.6)	37.2 (15.9-48.7)	0.082
Laboratory data						
Creatinine, mg/dL	3.2 (0.6-12.4)	1.0 (0.5-9.2)	<0.001	0.9 (0.5-5.8)	1.1 (0.6-9.2)	<0.001
Bilirubin, mg/dL	1.2 (0.2-16.7)	1.1 (0.2-58.0)	0.099	1.0 (0.2-58.0)	1.3 (0.3-7.4)	0.158
WBC, $\times 10^9$/L	7.1 (1.7-30.3)	6.1 (1.2-31.5)	0.026	5.8 (1.2-31.5)	6.3 (1.3-27.4)	0.879
CRP, mg/L	16.3 (5.8-330.0)	9.2 (0.2-280.0)	0.001	8.6 (0.5-280.0)	12.8 (0.2-175.0)	0.124
Alkaline phosphatase, U/L	123.0 (45.0-294.0)	119.5 (13.0-928.0)	0.745	113.5 (13.0-928.0)	128.0 (50.0-523.0)	0.068
Hb, g/L	9.7 (5.3-13.7)	12.4 (5.8-17.0)	<0.001	12.6 (6.9-16.7)	11.7 (5.8-17.0)	<0.001
INR	1.3 (0.9-2.0)	1.1 (0.9-2.8)	0.002	1.1 (0.9-2.8)	1.2 (0.9-2.2)	0.006
Albumin, g/L	32.8 (2.6-49.6)	33.6 (1.5-56.2)	0.119	34.3 (1.5-56.2)	32.3 (3.2-48.1)	0.048
Sodium, mmol/L	136.0 (123.0-145.0)	138.0 (122.0-150.0)	0.040	139.0 (124.0-147.0)	137.0 (122.0-155.0)	0.059
AD and TIPS						
Previous AD	27 (69.2)	159 (48.2)	0.017	114 (45.8)	45 (55.6)	0.127
Preoperative AD	—	116 (35.2)	—	76 (30.5)	40 (49.4)	0.002
Preoperative TIPS	1 (1.6)	7 (2.1)	0.594	5 (2.0)	2 (2.5)	0.803
Ascites, n	1	6		4	2	
Bleeding, n	0	1		1	0	
Type of surgery			0.001			0.015
Abdominal liver	8 (20.5)	157 (47.6)		122 (49.0)	35 (43.2)	
Abdominal nonliver	12 (30.8)	91 (27.6)		59 (23.7)	32 (39.5)	
Nonabdominal	19 (48.7)	82 (24.8)		68 (27.3)	14 (17.3)	
LT	4 (10.3)	19 (5.8)	0.286	11 (4.4)	8 (9.9)	0.067
LT waiting list	8 (20.5)	44 (13.3)	0.226	27 (10.8)	17 (21.0)	0.020
Organ failure	39 (100.0)	119 (36.1)	—	53 (21.3)	66 (81.5)	<0.001
Renal failure	31 (79.5)	39 (11.8)	<0.001	0 (0.0)†	39 (48.1)	<0.001
Coagulation failure	4 (10.3)	14 (4.2)	0.110	9 (3.6)	5 (6.2)	0.322
Liver failure	8 (20.5)	24 (7.3)	0.012	13 (5.2)	11 (13.6)	0.012
Respiratory failure	9 (23.1)	47 (14.2)	0.157	26 (10.4)	21 (25.9)	0.001
Circulatory failure	0 (0.0)	29 (8.8)	—	8 (3.2)	21 (25.9)	<0.001
Cerebral failure	3 (7.7)	15 (4.5)	0.421	4 (1.6)	11 (13.6)	<0.001

TABLE 1. *Continued*

Parameters at Baseline	ACLF at Baseline (n = 39)	No ACLF at Baseline (n = 330)	*P* Value*	No ACLF at Follow-up (n = 249)	ACLF at Follow-up (n = 81)	*P* Value*
Mortality						
28 days	2 (5.1)	13 (4.0)	0.665	3 (1.3)	10 (12.3)	<0.001
3 months	7 (17.9)	33 (10.0)	0.167	15 (6.9)	18 (23.4)	<0.001
6 months	10 (25.6)	56 (19.2)	0.188	29 (13.4)	27 (36.0)	<0.001
9 months	11 (28.2)	66 (22.5)	0.296	37 (17.0)	29 (38.7)	<0.001
1 year	12 (30.8)	79 (24.0)	0.334	47 (19.0)	32 (40.0)	<0.001

NOTE: Data are given as median (ranges) and n (%).
*Mann-Whitney U test and chi-square test were used to compare patients with and without ACLF at follow-up.
†Six patients with already known chronic renal failure at baseline due to terminal renal disease were considered non-ACLF at baseline.

ROLE AND PREDICTORS OF ACLF ON OUTCOME AFTER SURGERY

A total of 19 patients received a LT with median time interval of 5 months after surgery. Although the number of LTs was not statistically different between patients developing ACLF and patients without ACLF, the number of patients on the LT list was nearly doubled in the former group ($P < 0.05$; Table 1). As expected, the survival of patients with ACLF at surgery was worse compared with patients who received surgery in the absence of ACLF (Fig. 2A; Table 1). Also, patients developing ACLF after surgery showed significantly worse survival compared with patients who did not develop ACLF during follow-up (Fig. 2B; Table 1). A comparison of patients with ACLF at surgery with patients developing ACLF after surgery revealed no significant difference in their survival (Fig. 2C; Supporting Table S5).

The factors independently associated with ACLF development within 28 days after surgery were sex, age, baseline serum sodium, and the presence of bacterial infection at baseline. Meanwhile, the presence of AD before surgery reached a marginal significance. Surprisingly, compared with nonabdominal surgery, abdominal nonliver-related surgery, rather than liver-related surgery, had a more pronounced effect on postoperative ACLF development (Table 2). When subdividing the nonabdominal surgery into head or neck surgery, upper limb surgery, lower extremity, and heart or lung surgery, almost the same results were obtained. Of all surgical types, only intra-abdominal nonliver surgery remained an independent risk factor for ACLF (Supporting Table S7). Similar results were obtained by excluding a portion of patients with potential ACLF prior to surgery, ie, only including those with a Child-Pugh grade A or a CLIF-C AD score of <60 (Table 3; Supporting Table S8).

Interestingly, the development of ACLF within 28 days after surgery together with alkaline phosphatase and INR were independently associated with 3-month mortality in the Cox regression time-to-event analysis (Table 4; Supporting Table S9). However, ACLF development after surgery was not independently associated with 1-year mortality after surgery, whereas levels of alkaline phosphatase, MELD score, and the presence of preoperative HE were all independently associated (Table 4; Supporting Table S10). Interestingly, nonliver surgery was independently associated with better survival (Table 4). The ROC curves for Child-Pugh, MELD, and CLIF-C AD score to predict 3-month and 1-year mortality after surgery demonstrated the cutoff value for each score with the highest sensitivity and specificity: 5.5, 9.5, and 51.5, respectively, for 3-month mortality; and 5.5, 9.5, and 47.5, respectively, for 1-year mortality (Supporting Fig. S1).

CLINICAL PATHWAY OF PATIENTS UNDERGOING SURGERY

To construct a flow diagram for the clinical pathway of patients with surgery, we found the risk factors for the development of ACLF (Fig. 3A) and for 1-year mortality. If the patient had undergone an abdominal surgery that did not include the liver and had a bacterial infection at baseline, more than half of the patients developed ACLF (54.5%). However, for patients who underwent a liver or a nonabdominal surgery and had a bacterial infection on admission, women had a significantly higher risk of developing ACLF than men (51.9% versus 27.9%; Fig. 3A).

Cutoff values for alkaline phosphatase and MELD score were determined from ROC curves. Patients who underwent liver-related surgery with alkaline

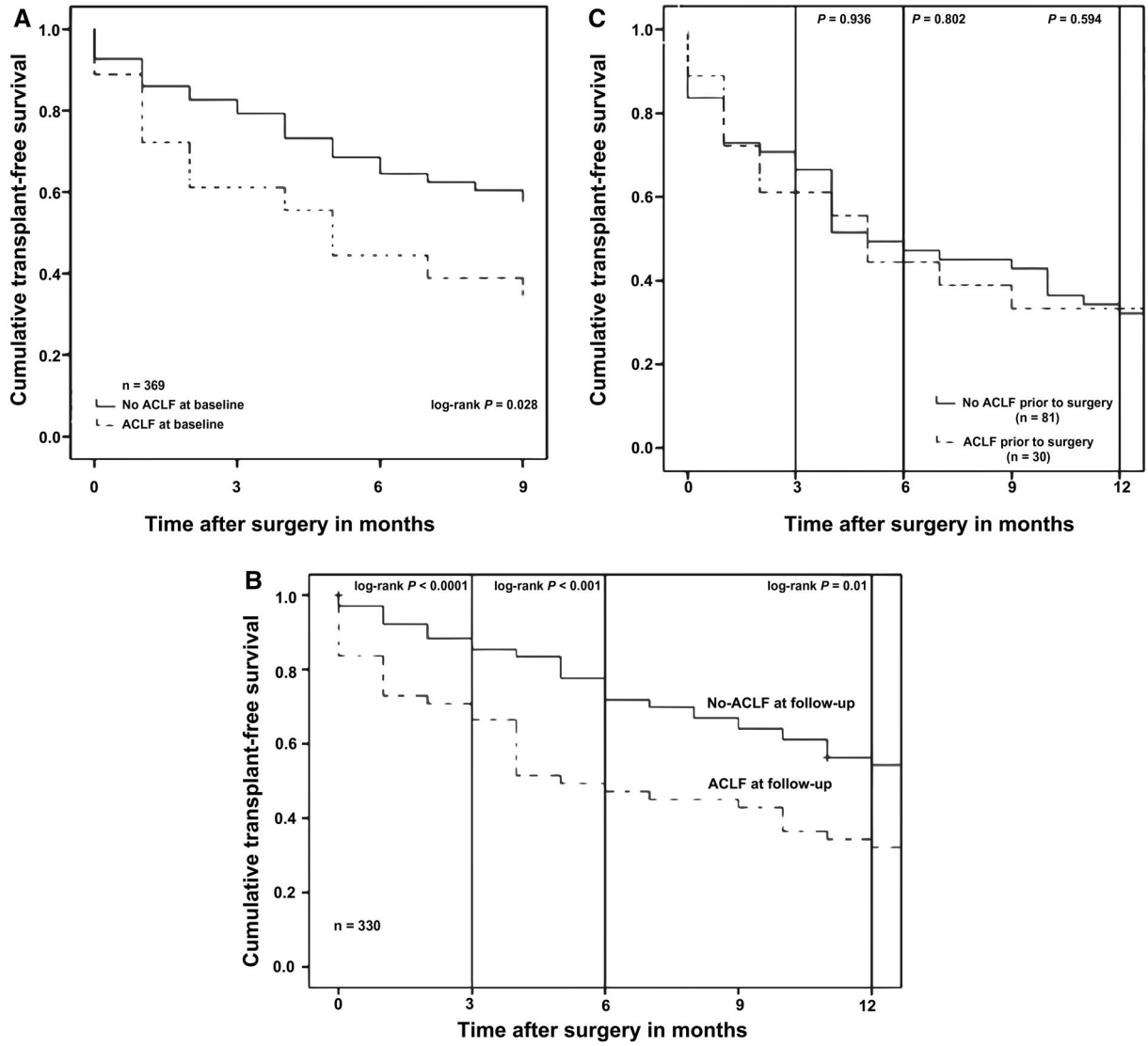

FIG. 2. (A) Kaplan-Meier plot comparing transplant-free survival of patients with ACLF at surgery with patients who underwent surgery without ACLF. (B) Kaplan-Meier plot comparing transplant-free survival of patients who developed ACLF after surgery with patients who did not. (C) Kaplan-Meier plot comparing transplant-free survival of patients with ACLF at surgery with patients who developed ACLF after surgery.

phosphatase ≥164 U/L and MELD score ≥10 carried the highest mortality risk. Their 1-year mortality rate was nearly 6 times higher than the low-risk patients (69.6% versus 11.8%, Fig. 3B).

Discussion

This study describes for the first time the risk of developing ACLF in the context of surgery. Importantly, the presence of AD at surgery was associated with the development of ACLF shortly after surgery and, therefore, heralded a worse prognosis for the patients. Notably, survival in patients who underwent surgery when they had already established ACLF was similar to that of patients developing ACLF shortly after surgery.

ACLF was first comprehensively characterized by the CLIF-Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study[3] and has recently become integrated in clinical practice guidelines.[2] The very high short-term mortality[3] renders this syndrome highly

TABLE 2. Parameters Correlating With ACLF After Surgery Within 28 Days After Surgery in the Univariate and Multivariate Logistic Regressions of All Patients Without ACLF at Baseline (n = 330)

	Univariate Analysis			Multivariate Analysis		
Parameters	*P* Value	OR	95% CI	*P* Value	OR	95% CI
Sex, female	0.045	1.719	1.013-2.918	0.043	1.925	1.020-3.634
Age	0.011	1.032	1.007-1.057	0.003	1.045	1.015-1.075
AD at baseline	0.002	2.221	1.330-3.707	0.082*	1.752*	0.932-3.294*
Bacterial infection at baseline	<0.001	3.797	2.246-6.419	<0.001	3.920	2.163-7.103
Sodium at baseline	0.035	0.934	0.876-0.995	0.047	0.928	0.862-0.999
HCT at baseline	<0.001	0.920	0.882-0.961	0.731*	0.968*	0.804-1.166*
Hb at baseline	<0.001	0.805	0.717-0.903	0.716*	0.913*	0.559-1.492*
Surgery location						
Nonabdominal	Reference					
Abdominal, not including the liver	0.008	2.634	1.284-5.403	0.003	3.628	1.528-8.614
Abdominal, including the liver	0.344*	1.393*	0.701-2.770*	0.249*	1.636*	0.709-3.776*

NOTE: Age, sex, and clinically relevant predictors at baseline significantly ($P < 0.1$) associated with ACLF development during follow-up were selected for the multivariate logistic regression analysis. Parameters in the CLIF-C OF score system, including bilirubin, creatinine, INR, HE, pulse oximetric saturation (SpO2)/fraction of inspired oxygen (FiO_2) and mean arterial pressure, were excluded from the candidates of multivariate analysis.
*Values were not significant.

TABLE 3. Parameters Correlating With ACLF After Surgery Within 28 Days After Surgery in the Univariate and Multivariate Logistic Regressions of All Child-Pugh Grade A Patients Without ACLF at Baseline (n = 172)

	Univariate Analysis			Multivariate Analysis		
Parameters	*P* Value	OR	95% CI	*P* Value	OR	95% CI
Sex, female	0.379*	1.426*	0.647-3.143*	0.024	4.599	1.224-17.286
Age	0.039	1.041	1.002-1.081	0.041	1.061	1.002-1.122
AD at baseline	0.038	2.183	1.043-4.568	0.049	3.410	1.005-11.576
Bacterial infection at baseline	0.011	2.605	1.240-5.472	0.065*	3.001*	0.934-9.645*
INR at baseline	0.031	10.498	1.240-88.905	0.006	216.621	4.826-9723.504
Creatinine at baseline	0.002	5.599	1.869-16.774	0.002	17.334	2.589-116.034
Sodium at baseline	0.008	0.866	0.778-0.963	0.027	0.839	0.719-0.980
Albumin at baseline	0.092*	0.962*	0.919-1.006*	0.625*	1.019*	0.945-1.099*
Hb at baseline	0.045	0.837	0.703-0.996	0.366*	0.965*	0.716-1.301*
HCT at baseline	0.029	0.929	0.869-0.993	0.248*	0.819*	0.583-1.149*
Surgery location						
Nonabdominal	Reference					
Abdominal, not including the liver	0.111*	2.555*	0.807-8.091*	0.024	9.379	1.350-65.161
Abdominal, including the liver	0.253*	1.859*	0.642-5.385*	0.003	19.449	2.785-135.814

NOTE: Age, sex, and objective clinically relevant predictors at baseline significantly ($P < 0.1$) associated with ACLF development during follow-up were selected for the multivariate logistic regression analysis.
*Values were not significant.

relevant for therapeutic decisions. The development of the syndrome is not yet completely understood.[1] A number of predisposing factors have been described for the development of the syndrome as well as various precipitating events, which can lead to ACLF.[4,5] In a number of patients (40%), no precipitating event was identified, whereas in others, more than 1 precipitating event occurred.[5] Surgical interventions, in particular, have been considered to be responsible for deterioration in patients with cirrhosis.[6,7] However, to date, there are no reports on the prevalence and risk factors for the development of ACLF after surgery. This study

TABLE 4. Parameters Correlating With 3-Month and 1-Year Survival in the Multivariate Cox Regression Time-to-Event Analysis (n = 330)

	Multivariate Analysis of 3-Month Survival			Multivariate Analysis of 1-Year Survival		
Parameters	*P* Value	HR	95% CI	*P* Value	HR	95% CI
Alkaline phosphatase at baseline	0.006	1.003	1.001-1.004	0.022	1.002	1.000-1.003
INR at baseline	0.010	3.580	1.362-9.413	*	*	*
Postoperative ACLF	0.005	3.318	1.442-7.634	*	*	*
MELD score at baseline	*	*	*	<0.001	1.156	1.074-1.245
Preoperative HE	*	*	*	0.020	4.401	1.257-15.413
Surgery not including the liver	*	*	*	0.005	0.390	0.201-0.757

NOTE: Analysis method: forward likelihood ratios (LR) of all patients without ACLF at baseline. Parameters that were significantly associated with 3-month and 1-year survival in the univariate Cox regression were included in multivariate Cox regression analysis. Baseline values of alkaline phosphatase, INR, CLIF-C AD score, and MELD score and postoperative ACLF and organ failure were included in the 3-month survival multivariate Cox regression time-to-event analysis. Baseline values for aspartate aminotransferase, Hb, alkaline phosphatase, Child-Pugh class, MELD score; preoperative decompensation, spontaneous bacterial peritonitis, ascites, and HE; postoperative ACLF; and nonliver surgery were included in the 1-year survival multivariate Cox regression time-to-event analysis (see Supporting Tables).
*Values were not significant.

demonstrates that 1 out of 4 patients with cirrhosis undergoing surgery develops ACLF. This figure is exceedingly high when compared with the CANONIC study, where approximately 13% of patients admitted to the hospital with AD also developed ACLF.[3]

In our study, 50% of the patients with AD at surgery developed ACLF. Thus, the presence of AD, but not previous AD, especially bacterial infection, is an independent risk factor for the development of ACLF within 28 days after surgery. Surgery represents a severe injury and can thereby induce ACLF; thus, the actual data are extremely important for the management of these patients. Above all, this study confirms once more that surgery should be avoided in patients with AD whenever possible. Instead, an alternative approach targeted at control or even treatment of the present AD and an effective control of bacterial infections prior to surgery should be preferred because previous episodes of AD were not associated with the development of ACLF when they were controlled at the time of surgery.

Not surprisingly, renal dysfunction and coagulation dysfunction seem to be highly associated with the development of ACLF after surgery in patients with Child-Pugh grade A. This is in line with previous findings, which attribute a special role to renal and coagulation function in the development of ACLF.[3,8]

The grade of ACLF seems to increase with the time after surgery. While in the first days, we only observed ACLF grades 1 and 2, presumably reflecting transient organ failures due to surgical injury. At 1 week after surgery, the severity of ACLF increased, with more patients presenting with the more advanced grades 2 and 3.[9] In fact, 50% of the patients developing ACLF remained stable, whereas 15% worsened. This suggests that ACLF induced by surgery has a worse clinical outcome than ACLF without surgery, although 50% of the patients could reverse their deterioration.[9] Detailed analysis of the patients with ACLF after surgery revealed infections as the leading complication, which is in line with other reports.[10] This finding further underlines the robustness of our data.

Apparently, etiology does not appear to play a major role for the development of ACLF after surgery, although it was strongly associated with ACLF in the CANONIC study.[3] Moreover, surrogate markers of systemic inflammation at surgery, such as serum CRP and white blood cell counts, were not significantly different between patients developing ACLF and those who did not, which is a finding that is also not in line with the CANONIC study.[11] The underlying mechanism might be that surgery likely triggers a systemic inflammatory response leading to ACLF, in which case surgery itself is a pivotal precipitating event. In line with this concept, CRP levels as well as white blood cell counts were elevated in the patients with ACLF at surgery as compared with patients who developed ACLF later on after surgery. Notably, however, survival was similar in both groups of patients, which probably reflects the fact that the severity of ACLF after surgery or, alternatively, the systemic inflammatory response, was already highly elevated but was not apparent by routine markers,

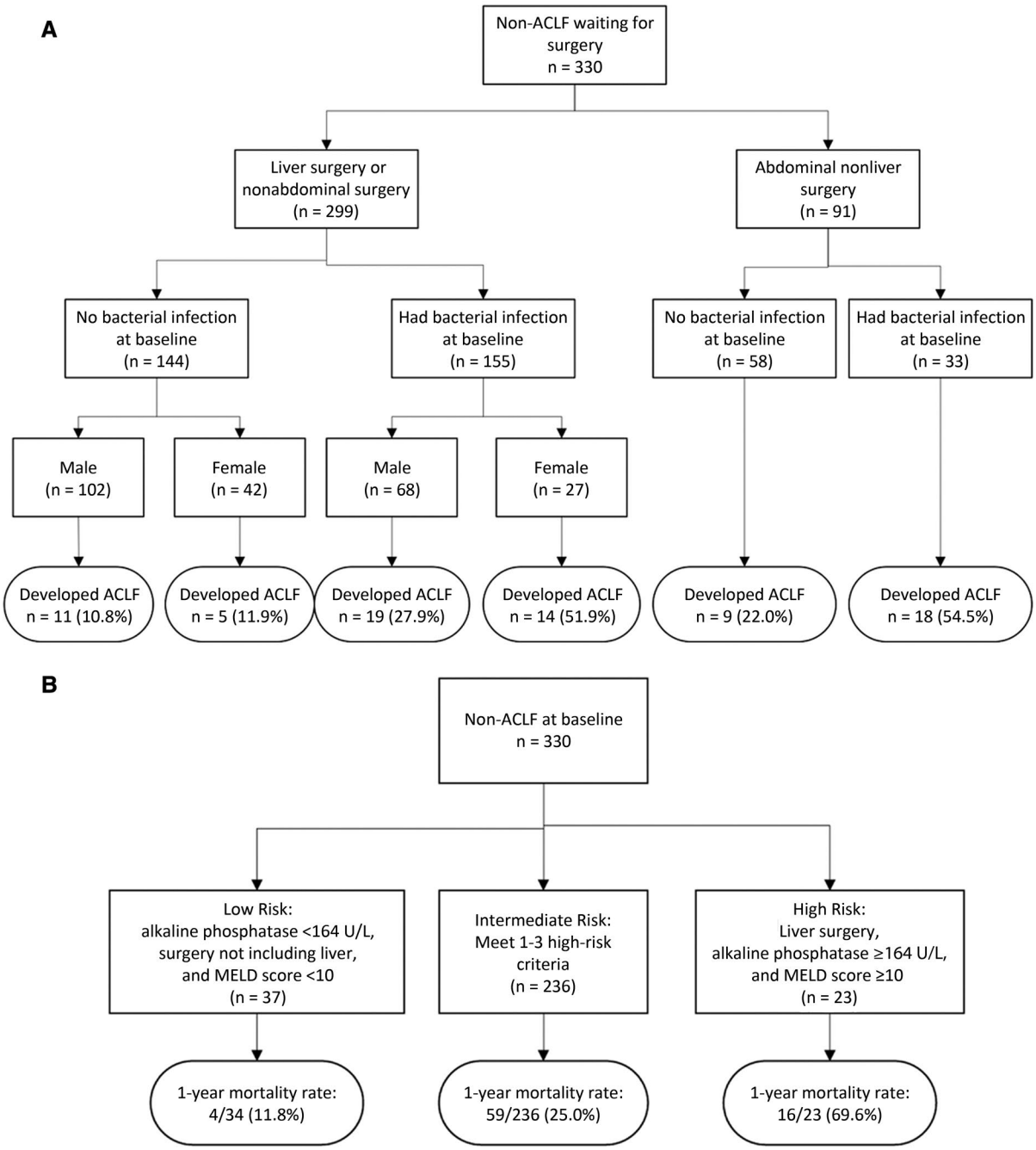

FIG. 3. (A) Flow diagram of 330 patients without ACLF at baseline and developed ACLF during 28 days with different risk factors. (B) Flow diagram of 330 patients non-ACLF at baseline and 1-year mortality rate with different independent risk factors.

such as CRP and WBC, as recently demonstrated in patients receiving TIPS.[12]

Notably, the development of ACLF within 28 days after surgery was independently correlated to 3-month mortality, together with levels of alkaline phosphatase and INR. The role of alkaline phosphatase in the prognosis of these patients with cirrhosis after surgery remains unknown, and further study is needed to demonstrate its mechanism for the impact of mid-term and longterm prognoses. The results clearly demonstrate that ACLF development in patients with cirrhosis undergoing surgery should be seen as a particularly

unfavorable prognostic sign. Although prognosis of the critical 3-month phase after surgery was influenced by postoperative ACLF development, in the longer follow-up, the development of ACLF was no longer an independent predictor of survival, suggesting that detection and therapeutic intervention is needed at an early phase after surgery.

Finally, we made the reassuring observation that surgery not including the liver was associated with better longterm outcome, was independent of the severity of the liver disease, and was unrelated to MELD or the presence of HE. Neither type nor duration of surgery had an impact on the outcome in our patient groups, possibly because the effects of AD and ACLF were so strong that they overrode the effects of the surgery. Nevertheless, for the longterm outcome, the type of surgery seems to play an important role.

Our study has several limitations that are mainly due to the retrospective design of the data collection. The lack of surgery detail makes the stratification for the type and extent of surgery to some extent arbitrary and not standardized. However, we classified diverse surgeries into extensive or limited ones based on time of surgery and type of anesthesia, which is currently the clearest stratification method. In addition, in patients with ACLF, it could not be excluded that many of these patients underwent emergency surgery, which undoubtedly has a significant impact on the prognosis of ACLF. Future studies should evaluate the impact of emergency or elective surgery on ACLF outcomes. Nevertheless, the findings of this study are of immense clinical importance and should stimulate new research in the field.

In summary, surgery during an ACLF episode is associated with high mortality, while future studies may be able to distinguish the role of elective or emergency procedures. Importantly, surgery may induce ACLF in a substantial number of patients, especially when receiving surgery during a bacterial infection episode, with lower serum sodium and with renal or coagulation dysfunction. The prognosis of patients developing ACLF after surgery is as poor as the prognosis for patients receiving surgery during an ACLF episode. The patients with a high risk of developing ACLF and undergoing inevitable surgery should be managed carefully during the perioperative period.

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