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Die Rolle des operativen Insultes bei der Entwicklung eines akut-auf-chronischen Leberversagens bei Patienten mit Leberzirrhose

Habilitationsschrift

zur Erlangung der Venia Legendi

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Übersicht

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1. Klein LM*, **Chang J***, Gu W, Manekeller S, Jansen C, Lingohr P, Praktiknjo M, Kalff JC, Schulz M, Spengler U, Strassburg C, Cárdenas A, Arroyo V, Trebicka J. *The Development and Outcome of Acute-on-Chronic Liver Failure After Surgical Interventions.*
Erschienen in ***Liver Transplantation.*** *2020 Feb;26(2):227-237.* *https://doi.org/10.1002/lt.25675*

2. Chang J*, Bamarni A*, Böhling N, Zhou X, Klein LM, Meinke J, Duerr GD, Lingohr P, Wehner W, Brol MJ, Rockstroh J, Kalff J, Manekeller S, Meyer C, Spengler U, Jansen C, Arroyo V, Strassburg CP, Trebicka J, Praktiknjo M. *Elective Surgery but not Transjugular Intrahepatic Portosystemic Shunt Precipitates Acute-On-Chronic Liver Failure.*
Erschienen in ***Hepatology Communications.*** *2021 Mar;5(7):1265-1277.* *https://doi.org/10.1002/hep4.1712*

3. Chang J, Höfer P, Böhling N, Lingohr P, Manekeller S, Kalff JC, Dohmen J, Kaczmarek DJ, Jansen C, Meyer C, Strassburg CP, Trebicka J, Praktiknjo M. *Preoperative TIPS prevents the development of postoperative acute-on-chronic liver failure in patients with high CLIF-C AD score.*
Erschienen in ***Journal of Hepatology Reports.*** *2022 Jan;4(3):100442.* *https://doi.org/10.1016/j.jhepr.2022.100442*

4. Chang J*, Meinke J*, Geck M, Hebest M, Böhling N, Dolscheid-Pommerich R, Stoffel-Wagner B, Kristiansen G, Overhaus M, Peyman LO, Klein S, Uschner FE, Brol MJ, Vilz TO, Lingohr P, Kalff JC, Jansen C, Strassburg CP, Wehner S, Trebicka J, Praktiknjo M. *Extrahepatic Surgery in Cirrhosis Significantly Increases Portal Pressure in Preclinical Animal Models.*
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1. Inhaltsverzeichnis

Abkürzungsverzeichnis

ACLF	Akut-auf-chronisches Leberversagen
AD	Akute Dekompensation
ASA	American Society of Anasthesiologists
BDL	Bile-duct ligation, Gallengangsligatur
CCL4	Tetrachlormethan
CLIF-C	Chronic liver failure Consortium
CRP	C-reaktives Protein
CTP	Child-Turcotte-Pugh
DAMP	Damage-associated molecular pattern
DILI	Drug induced liver injury
ERCP	Endoskopische Retrograde Cholangiopankreatikographie
HE	Hepatische Enzephalopathie
HVPG	Hepatic venous pressure gradient
IL	Interleukin
IM	Intestinale Manipulation
LAP	(Median)Laparotomie
MELD	Model for end-stage liver disease
MELD-Na	Model for end-stage liver disease-Natrium
mRNA	Messenger Ribonukleinsäure
MRS	Mayo-Risk Score
NO	Stickstoffmonoxid
OF	Organ failure
OP	Operation
PAMP	Pathogen-associated molecular pattern
PSM	Propensity Score Matching
ROC	Receiver Operating Characteristics
TGF	Transforming growth factor
TIPS	Transjugulärer intrahepatischer portosystemischer Shunt
TLR	Toll-like Rezeptor
TNF	Tumornekrosefaktor
SOFA	Sequential organ failure assessment
VOCAL	Veterans Outcomes and Costs Associated with Liver Disease

2. Einleitung

2.1 Die Leberzirrhose und ihre Komplikationen

Chronische Lebererkrankungen spielen durch ihre steigende Inzidenz in Gesundheitssystemen weltweit eine wachsende Rolle. Die Leberzirrhose wird als das gemeinsame Endstadium der meisten chronischen Lebererkrankungen angesehen. Sie ist letztlich der Ausdruck einer kontinuierlichen Schädigung der Leber, die ähnlich wie bei der Entstehung und Heilung von Wunden, zu einem fortschreitenden narbigen Umbau (Fibrogenese) des Lebergewebes führt. Die Fibrogenese beschreibt dabei den Prozess einer reaktiven Bindegewebsvermehrung bzw. der Ansammlung von Extrazellulärmatrix, welche in der Leber zur Fibrose und Zirrhose führt (Friedman, 2008). Nach Ausbildung einer Zirrhose sind die physiologischen Läppchen- und Gefäßstrukturen nicht mehr erhalten. Dies führt zu einem Funktionsverlust der Leber und den mit der Leberzirrhose assoziierten Komplikationen.

Die Leberzirrhose stellt ein zunehmendes klinisches und volkswirtschaftliches Problem dar (Pimpin et al., 2018). Rezente Daten zeigen, dass die Inzidenz von chronischen Lebererkrankungen insbesondere in Europa am höchsten ist (Global Health Data Exchange., 2020). In Deutschland sind etwa 2% der Gesamtbevölkerung von Leberzirrhose und deren Komplikationen betroffen. In den Jahren von 2000 bis 2017 stiegen die vollstationären Behandlungen aufgrund von Leberzirrhose von 79.647 bis auf 89.613 an (Gesundheitsberichterstattung des Bundes, 2019). Patienten mit Leberzirrhose weisen eine hohe Morbidität und Mortalität auf, insbesondere durch die assoziierten Komplikationen (Chirapongsathorn et al., 2016). Bei klinisch kompensierter Leberzirrhose beträgt die mittlere Überlebenszeit etwa sieben Jahre. Im Stadium der Dekompensation (Wahrscheinlichkeit einer Dekompensation beträgt bis zu 10% pro Jahr) sinkt das Zwei-Jahres-Überleben sogar auf unter 50% (Talwalkar and Kamath, 2005).

Die Komplikationen der Leberzirrhose

Bei Patienten mit Leberzirrhose besteht durch vermehrte Abgabe von Stickstoffmonoxid durch das Gefäßendothel eine arterielle Dysfunktion. Dies resultiert in einer effektiven Hypovolämie mit einem reaktiven Anstieg des vaskulären Widerstands in den

portalvenösen Gefäßen der Leber (Praktiknjo et al., 2020a). Hierdurch kommt es zur Ausbildung der sogenannten Portalen Hypertension. Das Fortschreiten der Leberzirrhose führt zu einer Aggravierung der Portalen Hypertension und dadurch zu akuten Dekompensationen. Dazu zählen vor allem die Varizenblutung, die Entwicklung von Aszites oder das Auftreten einer hepatischen Enzephalopathie (Angeli et al., 2018).

Treiber solch einer akuten Dekompensation und damit auslösend für eine erhöhte Mortalität und Morbidität sind vor allem kontinuierlich wirksame Schädigungen der Leber beispielsweise durch externe Noxen (Alkoholabusus), chronische Entzündungen, usw. mit fortschreitender Vernarbungstendenz (Bataller and Brenner, 2005; Friedman, 2008). Interessanterweise steigt das Risiko für das Auftreten weiterer Dekompensationen nach der ersten Episode einer akuten Dekompensation. Ein Pathomechanismus hierfür ist bislang noch nicht bekannt (Gustot et al., 2015). Ein Grundstein der Therapie besteht daher vor allem in der Meidung möglicher schädigender Noxen wie die Empfehlung der absoluten Alkoholkarenz bei der alkoholischen Leberzirrhose bzw. in der Behandlung der Grunderkrankung, wie beispielsweise der antiviralen Therapie bei Hepatitis B oder Hepatitis C. Die Behandlungen der Komplikationen der Leberzirrhose und der portalen Hypertension erfolgen zunächst konservativ-medikamentös oder auch endoskopisch, in fortgeschrittenen Stadien jedoch auch interventionell (Angeli et al., 2018; Gerbes et al., 2019).

Ösophagusvarizen / Varizenblutung

Ösophagusvarizen stellen sich reaktiv ausbildende portokavale Umgehungskreisläufe zur Dekompression der portalen Hypertension dar. Mit der Ausbildung solcher Umgehungskreisläufe besteht auch zunehmend die Gefahr einer Varizenblutung. Diese ist mit einer hohen Mortalitätsrate vergesellschaftet (de Franchis and Baveno VI Faculty, 2015; Götz et al., 2017). Als medikamentöse Primärprophylaxe von Varizenblutungen wird eine medikamentöse Behandlung mit nicht-selektiven Betablockern empfohlen. Diese führt zu einer Reduktion des Blutungsrisikos von 11% und der Mortalität von 9%. (Cheng et al., 2003). Alternativ kann eine primärprophylaktische endoskopische Varizenligatur-therapie erfolgen. Studien zeigten, dass die Ergebnisse der interventionellen Therapie mit denen der medikamentösen Therapie mit nicht-selektiven Betablockern vergleichbar sind (Gluud and Krag, 2012). Haben Patienten eine Varizenblutung überlebt, besteht ein hohes

Risiko einer Rezidivblutung (60%) mit letalem Ausgang (33%) (Bari and Garcia-Tsao, 2012). Daher ist für diese Patienten eine Sekundärprophylaxe unerlässlich. Diese besteht nach aktueller Datenlage aus einer Kombinationstherapie aus nicht-selektiver Beta-blockade und endoskopischer Ligaturtherapie (Puente et al., 2014; Thiele et al., 2012).

In ausgewählten Fällen, nämlich bei Patienten im Child-Turcotte-Pugh (CTP) Stadium < 14 Punkten oder CTP B mit aktiver Blutung, kann innerhalb von 72 Stunden die Implantation eines sogenannten transjugulären intrahepatischen portosystemischen Shunts (TIPS) erfolgen. Der TIPS stellt einen interventionell endovaskulär implantierten Shunt dar, der den hepatischen Ausflusstrakt mit dem Pfortadersystem verbindet (Rössle, 2013). Durch Umgehung des physiologischen hepatischen Pfortaderflusses wird der Portalhochdruck gesenkt. Dadurch werden die Varizen entlastet, die sich nach Implantation eines TIPS häufig komplett zurückbilden. Es konnte in einigen Studien gezeigt werden, dass hierdurch Rezidivblutungen praktisch nicht mehr auftreten und dadurch das Überleben erheblich verbessert wird (García-Pagán et al., 2010; Hernández-Gea et al., 2019; Lv et al., 2019).

Aszites

Der Nachweis von Aszites deutet auf ein fortgeschrittenes Stadium der Leberzirrhose bzw. der portalen Hypertension hin und ist mit einer verschlechterten Prognose vergesellschaftet (D'Amico et al., 2006; Guardiola et al., 2002; Planas et al., 2006). Dies ist vor allem durch sekundäre Ausbildungen einer spontanen bakteriellen Peritonitis und/oder eines hepatorenalen Syndroms bedingt (Ginès et al., 2004). Die Therapie besteht in erster Linie aus einem medikamentösen Therapieregime mit Diuretika; insbesondere werden Aldosteronantagonisten eingesetzt. Wird der Aszites hierdurch nur unzureichend mobilisiert, erfolgt die zusätzliche Kombination mit einem Schleifen-diuretikum (Gerbes et al., 2019). Bei fortgeschrittener Erkrankung kann ein therapie-refraktärer oder intraktabler Aszites entstehen. Als Therapieoptionen stehen hier zusätzlich zur Therapie mit Diuretika wiederholte großlumige Parazentesen oder auch die Anlage eines TIPS zur Verfügung (Bureau et al., 2017a; Solà et al., 2017; Thomas et al., 2015). Nach großvolumigen Parazentesen kann es zu hämodynamischen Veränderungen kommen, die sogenannte zirkulatorische Dysfunktion nach Parazentese (Ginès et al., 1996, 1988; Pozzi et al., 1994). Daher ist eine suffiziente Substitution mit Humanalbumin

Teil der Leitlinie (Angeli et al., 2018). Durch eine TIPS-Anlage wird der Portalhochdruck reduziert und es kommt zur verbesserten renalen Perfusion und damit einhergehend einer verbesserten Nierenfunktion (Allegretti et al., 2016; Brensing et al., 2000; Lebrec et al., 1996; Wong et al., 1995). Als relevante Komplikationen eines TIPS können durch die Umgehung der Leber und damit der Umgehung der Entgiftungsfunktion dieser, Episoden einer hepatischen Enzephalopathie auftreten. Es konnte jedoch mehrfach gezeigt werden, dass die TIPS-Anlage der wiederholten großvolumigen Parazentese bezüglich der Mortalität überlegen ist und die Lebensqualität verbessert (Allegretti et al., 2016; Bureau et al., 2017b; Gülberg et al., 2002; Rössle et al., 2000; Salerno et al., 2007).

Hepatische Enzephalopathie

Die hepatische Enzephalopathie (HE) umfasst als Syndrom die Summe aller Störungen des Zentralnervensystems, die als Komplikationen von akuten oder chronischen Lebererkrankungen und/oder portosystemischen Kollateralkreisläufen auftreten können (Ferenci et al., 2002; Vilstrup et al., 2014). Klinisch zeigt sich insgesamt ein breites Spektrum variabel auftretender intellektueller, emotionaler, kognitiver, psychischer und motorischer Störungen (Ferenci et al., 2002). Es besteht eine charakteristische zunehmende psychomotorische Verlangsamung bis hin zum Koma. Auch bei klinisch unauffälligen Patienten zeigen sich kognitive Einschränkungen, die als minimale HE bezeichnet werden (Ferenci et al., 2002; Labenz et al., 2017; Poordad, 2007; Romero-Gómez et al., 2001; Saunders et al., 1981; Vilstrup et al., 2014).

Der HE liegt pathophysiologisch liegt unter anderem eine eingeschränkte Kapazität der Leber zur Ammoniakentgiftung zugrunde. Die Skelettmuskulatur des Körpers ist in der Lage durch eine Glutamin-Synthetase-Aktivität relevante Mengen von Ammoniak in Glutamin zu konvertieren und so zu eliminieren (Jindal and Jagdish, 2019; Wright et al., 2011). Bei Patienten mit Leberzirrhose liegt jedoch überdurchschnittlich häufig eine Mangelernährung und eine damit assoziierte Sarkopenie (Muskelschwund) vor, so dass diese Möglichkeit der Ammoniakentgiftung ebenfalls einschränkt ist (Jindal and Jagdish, 2019; Lai et al., 2021; Praktiknjo et al., 2018a, 2019). Das Auftreten einer HE ist ein wichtiger Prädiktor hinsichtlich der Mortalität mit einer 1-Jahres-Mortalität von bis zu 64 % (Bustamante et al., 1999; Hartmann et al., 2000; Jepsen et al., 2010).

2.2 Das akut-auf-chronische Leberversagen (ACLF)

Das Konzept des akut-auf-chronischen Leberversagens (ACLF) wurde im Rahmen von klinischen Studien entwickelt, bei denen sich bei vielen Patienten mit akuter Dekompensation der Leberzirrhose die Entwicklung eines Syndroms, assoziiert mit systemischer Inflammation und hoher Kurzzeit-Sterblichkeit (definiert als Tod innerhalb von 28 Tagen nach ungeplanter Hospitalisation), zeigte (Moreau et al., 2013a). Das ACLF wird von der akuten Dekompensation eindeutig abgegrenzt und wird daher als eigenständige, neue Krankheitsentität betrachtet (Arroyo et al., 2015a, 2016). Die akut dekompensierte Leberzirrhose umfasst gastrointestinale Blutungen, die Bildung von Aszites, HE und jedwede Kombination dieser Komplikationen (Moreau et al., 2013a; Sarin et al., 2019). Das ACLF ist hingegen insbesondere durch drei Hauptmerkmale gekennzeichnet. Erstens tritt das ACLF in engem zeitlichen Zusammenhang mit proinflammatorischen auslösenden Ereignissen auf. Hierzu zählen vor allem bakterielle Infekte, der Alkoholabusus und die gastrointestinale Blutung (siehe Abbildung 1) (Trebicka et al., 2020a, 2020b). Zweitens tritt es im Kontext einer ausgeprägten, sogenannten systemischen Inflammation auf (Mortensen et al., 2012; Turco et al., 2018). Die systemische Inflammation kann chronisch sein oder auch durch Translokation von Signalen aus dem Intestinum in die systemische Zirkulation austreten (Albillos et al., 2014; Bernardi et al., 2015; Clària et al., 2016; Medzhitov, 2008; Úbeda et al., 2010). Es ist gezeigt worden, dass beim ACLF ein regelrechter Sturm der Ausschüttung multipler proinflammatorischer Mediatoren ausgelöst wird, was einer der Gründe für den hohen letalen Ausgang bei höhergradigem ACLF darstellt (siehe Abbildung 2) (Laleman et al., 2018; Monteiro et al., 2020; Trebicka et al., 2019). Drittens ist das ACLF mit dem Auftreten von extrahepatischen Organversagen vergesellschaftet (Arroyo et al., 2020; Trebicka et al., 2020a). Diese basieren auf dem *chronic liver failure-sequential organ failure assessment* (CLIF-SOFA)-Score, welcher auch die Grundlage des neuen CLIF-C ACLF-Scores darstellt (Moreau et al., 2013a). Auf der Anzahl der versagenden Organe beruht auch die Graduierung des ACLF, das in insgesamt drei Grade eingeteilt wird (Grad I bis Grad III) (siehe Abbildung 1 und 3). Die Kurzzeit-Mortalität des ACLF Grad III liegt bei bis zu 90% innerhalb von 90 Tagen (siehe Abbildung 4). Der CLIF-ACLF Score enthält daher auch Komponenten, die in traditionellen Scores wie dem CTP-Score oder dem *Model for*

end-stage liver disease (MELD)-Score nicht repräsentiert sind, und bildet daher die klinische Schwere beim Auftreten dieses Syndroms besser ab. Aufgrund der hohen Kurzzeit-Sterblichkeit des ACLF und den noch sehr limitierten therapeutischen Optionen mit Ausnahme der Lebertransplantation ist ein frühes Erkennen von Risikopatienten entscheidend, um der Entwicklung einer akuten Dekompensation in ein ACLF vorzubeugen (Moreau et al., 2013b).

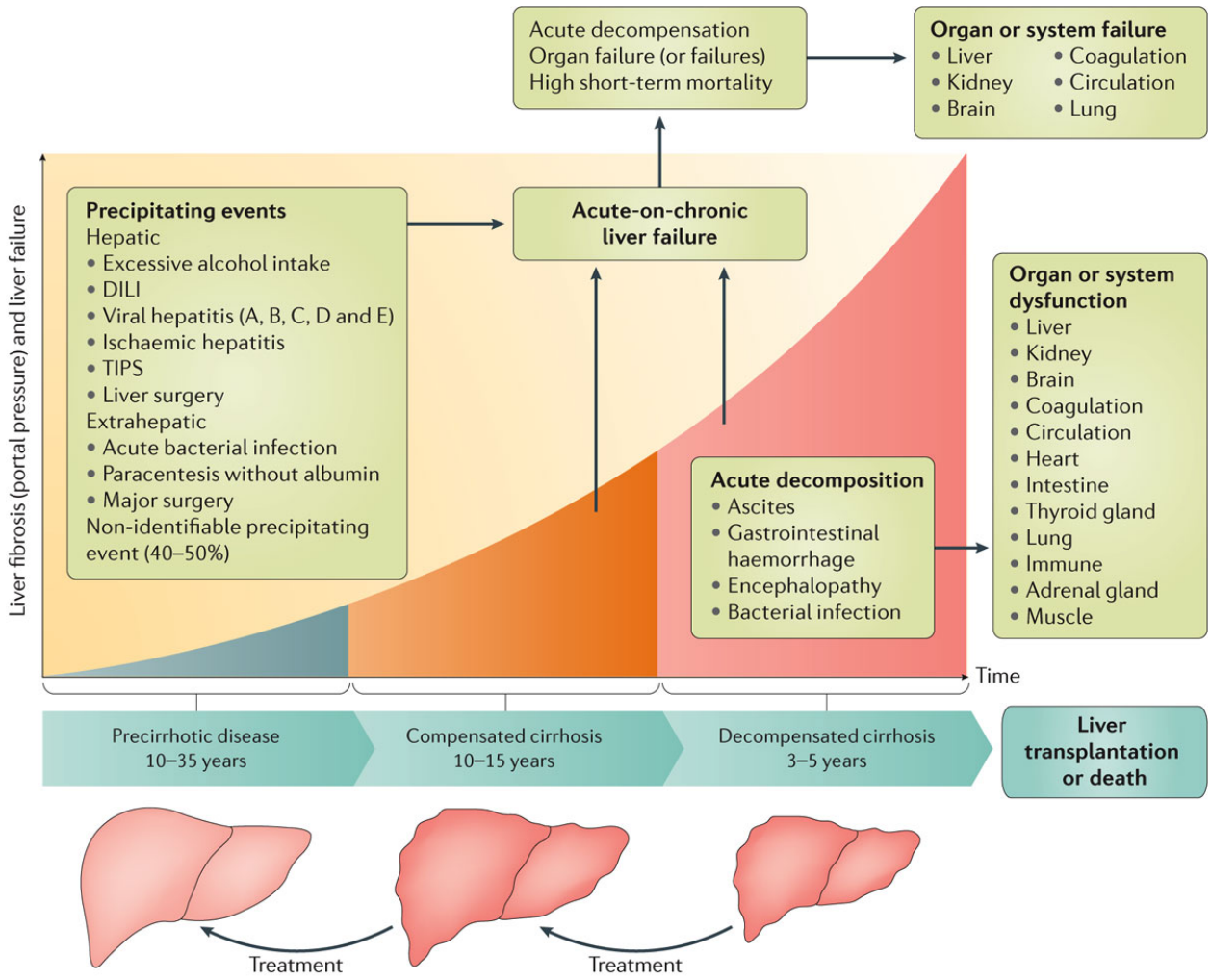

Abbildung 1: Das akut-auf-chronische Leberversagen (ACLF) kann sich aus allen Stadien der Zirrhose entwickeln, sowohl der kompensierten als auch der dekompensierten Phase. Auslösende Faktoren beziehen zum einen die Leber mit ein, wie den Alkoholabusus, virale Hepatitiden aber auch chirurgische Eingriffe. Extrahepatisch sind vor allem bakterielle Infektionen beteiligt, 40-50% der auslösenden Ereignisse sind noch nicht identifiziert. Zu den extrahepatischen Organversagen zählen das Lungenversagen, Kreislaufversagen, Koagulopathie, Nierenversagen und Gehirn-Dysfunktion. DILI, drug induced liver injury; TIPS, transjugulärer intrahepatischer portosystemischer Shunt (Arroyo et al., 2016).

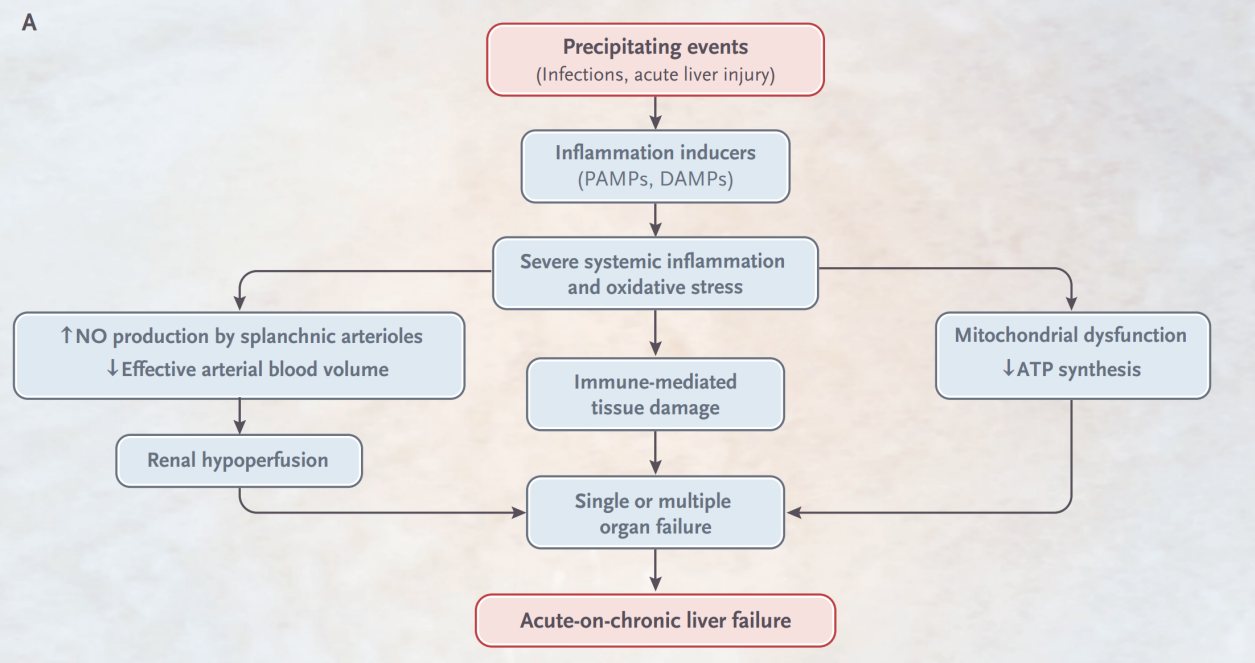

Abbildung 2: Potentielle Mechanismen der systemischen Inflammation, die zum akut-auf-chronischen Leberversagen (ACLF) führen. Ausgeprägte systemische Inflammation führt zu oxidativem Stress. Durch die Ausschüttung von Stickstoffmonoxid kommt es zur Erniedrigung des effektiven arteriellen Blutvolumens, das wiederum zur renalen Hypoperfusion führt. Dies wiederum kann ein Hepatorenales Syndrom auslösen. Das Immunversagen kann durch Mechanismen der bakteriellen oder der sterilen Inflammation unterhalten werden, die letztlich zum ACLF führen (Arroyo et al., 2020).

Organ System	1 Point	2 Points	3 Points
Liver	Bilirubin <6 mg/dl	Bilirubin 6.0–11.9 mg/dl	Bilirubin ≥12 mg/dl
Kidney	Creatinine <1.5 mg/dl Creatinine 1.5–1.9 mg/dl	Creatinine 2.0–3.4 mg/dl	Creatinine ≥3.5 mg/dl or RRT
Brain (West Haven criteria)	Grade 0	Grade 1–2	Grade 3–4
Coagulation	INR <2.0	INR 2.0–2.4	INR ≥2.5
Circulation	MAP ≥70 mm Hg	MAP <70 mm Hg	Vasopressor requirement
Respiration	Pao_2/Fio_2 >300 Spo_2/Fio_2 >357	Pao_2/Fio_2 201–300 Spo_2/Fio_2 215–357	Pao_2/Fio_2 ≤200 Spo_2/Fio_2 ≤214

Abbildung 3: Der European Association for the Study of the Liver–Chronic Liver Failure Consortium organ-failure score. Jedes Organsystem erhält 1-3 Punkte anhand der dargestellten Parameter. Dunkelgrau markiert zeigt die Definition eines Organversagens an, hellgrau die Definition einer Organdysfunktion (Moreau et al, 2013a).

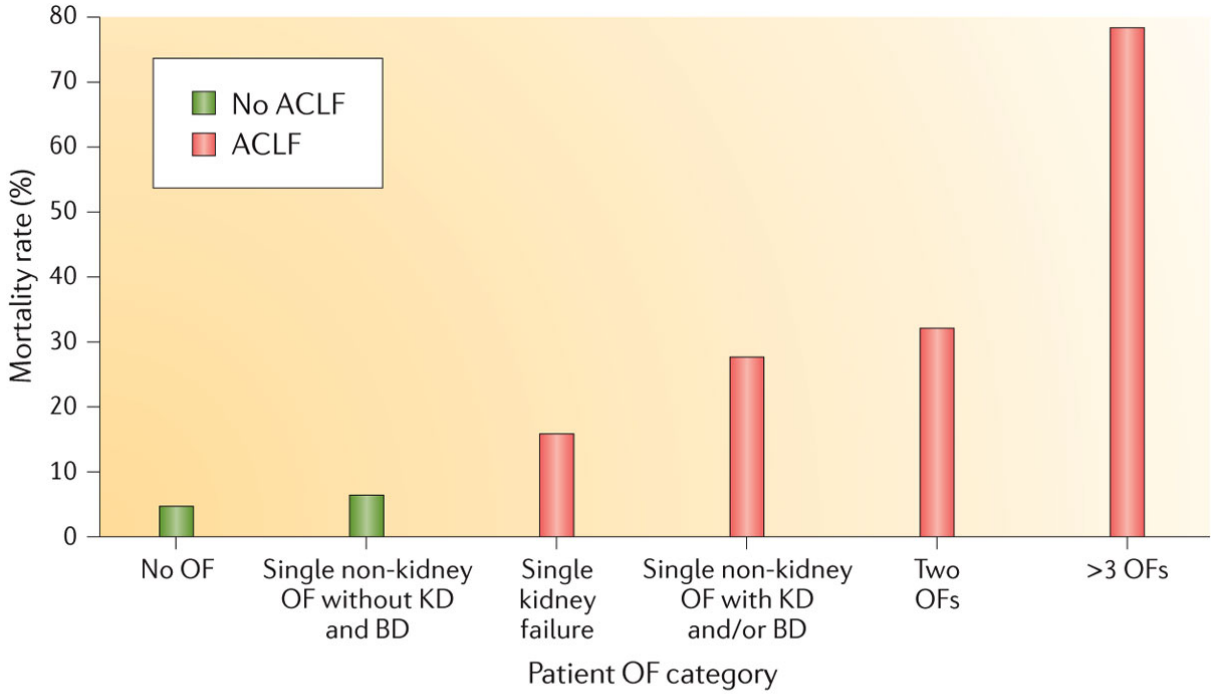

Abbildung 3: 28-Tages Mortalität von Patienten mit dekompensierter Leberzirrhose ohne (grüne Balken) und mit (rote Balken) ACLF. Die Patienten sind in die Anzahl von Organversagen klassifiziert (siehe auch Abbildung 1 und 3). Zwei Organversagen entsprechen ACLF Grad II, drei Organversagen ACLF Grad III. Eine Übersterblichkeit zeigt sich insbesondere bei Patienten mit ACLF Grad III. OF, Organ failure (Organversagen); KD, kidney dysfunction (Nierenversagen); BD, brain dysfunction (Gehirn-Dysfunktion) (Arroyo et al., 2016)

Die Erkennung von Risikopatienten sowie die Identifikation von auslösenden Ereignissen des ACLF, auch Präzipitoren (*precipitating events*) genannt, ist daher Gegenstand intensiver Forschung. Obwohl die häufigsten auslösenden Ereignisse identifiziert worden sind, bleiben 40-50% der auslösenden Ereignisse noch unerkannt. Am besten untersucht ist der Einfluss von bakterieller Infektion, der gastrointestinalen Blutung und des Alkoholabusus. Es bestehen jedoch zahlreiche weitere Auslöser, die potentiell mit der Entstehung von ACLF im Zusammenhang stehen können. Beispielsweise ist die Rolle der viralen Hepatitiden und der Einfluss weiterer Noxen wie z.B. von Medikamenten bei der Entstehung von ACLF nur unzureichend untersucht (Abbildung 1) (Arroyo et al., 2016; Trebicka et al., 2020a).

Operative Eingriffe, vor allem Eingriffe an der Leber selbst, und Interventionen sind als Auslöser von akuter Dekompensation und hoher postoperativer Sterblichkeit insbesondere in fortgeschrittenen Stadien der Leberzirrhose lange bekannt (Friedman, 2010; Mahmud et al., 2019; Teh et al., 2007). Im Bezug auf das Auftreten von postprozeduralem ACLF sind operativen Eingriffe und Interventionen zwar diskutiert worden, aber weiterführende Daten sind auf diesem Gebiet nur sehr begrenzt vorhanden. Da diese bei Patienten mit Leberzirrhose einen wichtigen und zunehmenden Stellenwert einnehmen, ist die Untersuchung ihres Einflusses auf die Entstehung von postprozeduralem ACLF und dessen Assoziation zur postoperativen Mortalität von erheblicher Wichtigkeit.

Die Evaluation des Einflusses von operativen Eingriffen auf die postoperative akute Dekompensation und auf das Risiko für die Entwicklung eines ACLF mit der Erhebung zugrundeliegender Pathomechanismen und assoziierten Prädiktoren war daher die zentrale Fragestellung dieser Habilitation. Aspekte dieser Fragestellung werden im Folgenden aufgeführt.

2.3. Die Bedeutung des operativen Insultes bei Patienten mit Leberzirrhose

Die ungünstige Prognose, hohe Dekompensationsrate, Mortalität und Morbidität bei Patienten mit Leberzirrhose nach jedweder Art von chirurgischen Eingriffen, vor allem in dekompensierten Stadien, sind weitreichend erforschte und lang bestehende Herausforderungen, die eine qualifizierte und interdisziplinäre Betreuung für dieses Patientenklientel notwendig machen (Artinyan et al., 2012; Friedman, 2010; de Goede et al., 2012; Neeff et al., 2014; Nicoll, 2012). Trotz der Signifikanz dieses klinischen Problems erfolgt die präoperative Riskostratifizierung dieser Patienten im klinischen Alltag noch weitgehend über ältere und traditionelle Scores wie den CTP-Score und den MELD-Score (Befeler et al., 2005; Northup et al., 2005). Insbesondere vom CTP-Score wird in der klinischen Routine häufig Gebrauch gemacht (Garrison et al., 1984; Mansour et al., 1997). Das CTP A-Stadium (kompensiertes Stadium der Leberzirrhose) zeigt hierbei das niedrigste postoperative Mortalitätsrisiko mit 10%, in den dekompensierten Stadien ist jedoch eine hohe Mortalitätsrate von bis zu 82% (CTP C-Stadium) beschrieben (Garrison et al., 1984). Dies führt in der klinischen Routine dazu, dass Patienten in dekompensierten Stadien der Leberzirrhose notwendige Operationen häufiger verwehrt bleiben, insbesondere, wenn diese in Gebieten leben, wo keine Maximalversorgung in Kliniken möglich ist.

In den letzten Jahrzehnten wurden jedoch sowohl in der hepatologischen Betreuung der Patienten mit Leberzirrhose als auch in den sich weiter entwickelnden minimalinvasiven Operationstechniken viele Fortschritte erreicht. Die Möglichkeiten zur Therapie der portalen Hypertension, beispielsweise durch die Implantation eines TIPS, wurden erweitert bzw. weiterentwickelt. Neuere leberrelevante Scores wurden etabliert, die wichtige Parameter wie das Patientenalter oder Parameter der Inflammation enthalten, wie der *Chronic Liver failure-Consortium Acute Decompensation* (CLIF-C AD)-Score (Jalan et al., 2015). Dieser Score wurde für die Patienten mit Leberzirrhose entwickelt, die ungeplant stationär aufgenommen werden, jedoch kein ACLF entwickelten. Er zeigte sich gegenüber den traditionellen Scores wie dem CTP- oder MELD-Score in der Vorhersage der Mortalität überlegen. Im Rahmen der postoperativen Risikostratifizierung wurde dieser Score noch nicht untersucht. Insgesamt besteht großer Bedarf an der Weiterentwicklung von operationsspezifischen Scores und zugänglichen Modellen, um das postoperative

Mortalitäts- und Dekompensationsrisiko bei Patienten mit Leberzirrhose besser voraussagen zu können und Hochrisikopatienten zu identifizieren.

Die Entwicklung operationsspezifischer Scores zur Prädiktion des postoperativen Outcomes für Patienten mit Leberzirrhose

Eine Limitation der bislang genutzten traditionellen Scores wie CTP- oder MELD-Score (MELD-Na in einigen europäischen Ländern) ist, dass sie keine operationsspezifischen Parameter enthalten, obgleich kürzlich wiederholt gezeigt werden konnte, dass das Mortalitätsrisiko abhängig von der Operationskategorie und dem Operationsgebiet differiert (Mahmud et al., 2019). Der einzige Score, der operationsspezifische Parameter inkludiert und nach der Etablierung von CTP- und MELD-Score an Patienten mit Leberzirrhose vor dem Jahr 2020 im amerikanischen Raum entwickelt wurde, ist der sogenannte Mayo-Risk Score (MRS). Dieser beinhaltet neben Alter und einigen leberspezifischen Parametern, die im CTP- oder MELD-Score enthalten sind, als operationsspezifischen Parameter zusätzlich die American Society of Anasthesiologists (ASA) Klassifikation (Teh et al., 2007). Obwohl der MRS in Nordamerika häufig genutzt wird, wird von ihm in Europa zur Risikostratifizierung nicht standardmäßig Gebrauch gemacht. Zudem scheint die Aussagekraft des MRS überholt zu sein, da sich in mehreren Studien zur Validierung des MRS zeigte, dass die Risikostratifizierung anhand des MRS häufig zur Überschätzung des Mortalitätsrisikos führt (Kim et al., 2011; Mahmud et al., 2021).

Erst kürzlich wurde in einer großen amerikanischen, retrospektiven und multizentrischen Studie der *Veterans Outcomes and Costs Associated with Liver Disease* (VOCAL)-Penn Score etabliert (Mahmud et al., 2021). Die Studie konnte an einer großen Kohorte von 3785 Patienten (VOCAL-Kohorte) zeigen, dass eine Überschätzung des Mortalitätsrisikos durch den MRS vorliegt. Außerdem zeigte der an dieser Kohorte neu etablierte VOCAL-Penn Score eine exzellente Vorhersagekraft der 30-, 60-, und 90-Tage-Mortalität, die dem CTP-, MELD-, MELD-Na- und dem MRS-Score überlegen war. Der VOCAL-Penn Score beinhaltet neben spezifischen leberassoziierten Parametern auch operationsspezifische Parameter, insbesondere die Einteilung in elektive und notfallmäßige Eingriffe und sechs

verschiedene Operationsklassen (Bauchwandchirurgie, abdominal laparoskopische-, abdominal offene-, gefäßchirurgische-, orthopädische und Herz/Thorax-Eingriffe).

Eine Limitation der Studie war, dass es sich bei der Studienkohorte um eine Veteranenkohorte handelte, die zu 97% aus Männern bestand. Außerdem zeigte sich interessanterweise ein inverses Verhältnis von Adipositas und Überleben, d.h. die adipösen Patienten zeigten ein besseres Überleben, so wie es eigentlich von Patienten mit kardialen Vorerkrankungen umgekehrt bekannt ist. Die Autoren diskutierten hier insbesondere die Körper-/Muskelmasse als einen protektiven Faktor für das Überleben im Rahmen des „Sarkopenie-Paradoxon“ (Karagozian et al., 2016; Merli et al., 2019; Schiavo et al., 2018). Daher sind weitere Studien zur Validierung dieses Scores im europäischen Kontext notwendig.

Obgleich die Rolle des operativen Insultes auf die Mortalität bei Patienten mit Leberzirrhose bereits beschrieben wurde, betonen die durchgeführten Studien die Wichtigkeit der Weiterentwicklung von neueren Modellen zur Risikostratifizierung. Die Charakterisierung des Auftretens von postoperativem ACLF bei Patienten mit Leberzirrhose und die Bedeutung etablierter Scores auf die postoperative Entwicklung von ACLF ist noch nicht untersucht und ist daher ein wichtiger Bestandteil dieser Habilitationsschrift.

Die Rolle des Portaldrucks bei operativen Eingriffen

Die postoperativ auftretenden leberassoziierten Komplikationen bestehen, wie auch bei der akuten Dekompensation der Leberzirrhose, vor allem in der Bildung von Aszites, Blutungskomplikationen mit Transfusionspflichtigkeit aufgrund kompromittierter Gerinnung, hepatischer Enzephalopathie und der Ausbildung von Infekten (Friedman, 2010; del Olmo et al., 2003). Die akute Dekompensation kann wiederum in ein ACLF übergehen. Der bereits vermutete Einfluss des Portaldrucks auf postoperatives Outcome und postoperative Komplikationen konnte kürzlich bestätigt werden. Hierzu wurde eine multizentrische, prospektive Studie durchgeführt, bei der Patienten vor einem extra-hepatischen operativen Eingriff eine Messung des *hepatic venous pressure gradient* (HVPG) zur Quantifizierung des Portaldruckes erhielten. Die Studie zeigte, dass ein erhöhter präoperativer Portaldruck mit einem signifikant erhöhten postoperativen 1-

Jahres-Mortalitätsrisiko korrelierte. Vor allem Patienten mit einem präoperativen HVPG > 16 mmHg konnten als Hochrisikopatienten identifiziert werden (Reverter et al., 2019). Die Rolle eines präoperativ implantierten TIPS zur Dekompression der portalen Hypertension vor einer Operation wurde bislang noch nicht in randomisiert kontrollierten Studien untersucht. Die Wichtigkeit solch einer Studie wird jedoch in der hepatologischen Forschung diskutiert (García-Pagán et al., 2020). In mehreren kleineren Serien wurde der vorteilhafte Einfluss eines TIPS für das postoperative Outcome beschrieben (Jain, 2018; Philip and Thornburg, 2018; Schmitz et al., 2020; Tabchouri et al., 2019; Vinet et al., 2006). Kürzlich, auch als Bestandteil dieser Habilitationsschrift, konnte durch unsere Arbeitsgruppe ein Vorteil einer präoperativen TIPS-Anlage im Bezug auf die postoperative Entwicklung von ACLF und Mortalität vor allem in viszeralen Eingriffen gezeigt werden (Chang et al., 2022). Patienten mit einem präoperativen TIPS wiesen zudem signifikant weniger häufig postoperative Komplikationen auf. Jedoch hatten diese Patienten nicht gezielt zur präoperativen Dekompression der portalen Hypertension einen TIPS erhalten, sondern aufgrund von anderen Indikationen. Daher sind diese Ergebnisse in weiteren randomisiert kontrollierten Studien zu bestätigen.

2.4 Fragestellung

In den vorangegangenen Abschnitten wurde zum einen die klinische Schwere der Komplikationen der Leberzirrhose in den dekompensierten Stadien dargelegt, insbesondere des ACLF. Für Patienten, die ein ACLF entwickeln, stehen außer der Lebertransplantation als ultima ratio kaum therapeutische Optionen zur Verfügung. Daher ist eine Identifikation von Hochrisikopatienten für die Entwicklung eines ACLF unerlässlich.

Zum anderen wurde die Bedeutung des operativen Insultes auf die postoperative Dekompensation und Mortalität und die Notwendigkeit der Entwicklung genauerer Scores zur Risikostratifizierung erörtert. Der Einfluss des operativen Insultes auf die postoperative Entwicklung der verschiedenen ACLF-Grade mit den assoziierten Prädiktoren und Pathomechanismen ist hingegen noch nicht untersucht. Auch hier besteht die Notwendigkeit der Identifikation klinischer Biomarker sowie der Validierung, Einordnung bzw. Ergänzung bestehender Scores, mit dem Anliegen einer besseren Risikostratifizierung von Patienten, die postoperativ ein ACLF entwickeln.

Zuerst erfolgt in einer monozentrischen Kohorte mit Leberzirrhose, die einen chirurgischen Eingriff erhielten, eine Erstbeschreibung von postoperativem ACLF und seinen Prädiktoren mit dem Bezug zur Mortalität. Desweiteren werden durch den Vergleich einer elektiv operierten Kohorte im Vergleich zu einer TIPS-Kohorte weitere pathophysiologische Mechanismen einer postoperativen Dekompensation untersucht und der TIPS als ein auslösendes Ereignis von ACLF evaluiert. Danach erfolgt die Untersuchung des Einflusses einer präoperativen TIPS-Anlage auf die postoperative Entwicklung von ACLF. Abschließend wird ein etabliertes Tiermodell vorgestellt, welches einen extrahepatischen Eingriff in Tiermodellen der Zirrhose simuliert und anhand dessen die postoperative Dekompensation, Inflammation und möglicherweise die Entwicklung von ACLF weiter untersucht werden kann.

3. Ergebnisse

3.1 Evaluation der Entwicklung von ACLF nach operativen Eingriffen

“The Development and Outcome of Acute-on-Chronic Liver Failure After Surgical Interventions.”
Klein LM, **Chang J**, Gu W, Manekeller S, Jansen C, Lingohr P, Praktiknjo M, Kalff JC, Schulz M, Spengler U, Strassburg C, Cárdenas A, Arroyo V, Trebicka J.
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Zielsetzung und Methoden

Ziel dieser Arbeit war die erstmalige Evaluation und Charakterisierung der Entwicklung von postoperativem ACLF. Hierzu erfolgte ein Screening von 955 Patienten mit einer chronischen Lebererkrankung, die im Zeitraum 2007 bis 2017 einen operativen Eingriff am Universitätsklinikum Bonn erhalten hatten. 460 dieser Patienten wurden aufgrund einer nicht sicher zu diagnostizierender Leberzirrhose ausgeschlossen. Bei weiteren 126 Patienten mit sicher diagnostizierter Leberzirrhose handelte es sich bei der Indexoperation um eine Lebertransplantation. Da die Lebertransplantation bei der Leberzirrrhose als einzige kurative Therapieoption in statistischen Analysen bekannterweise einen zum Tod konkurrierenden Endpunkt darstellt, wurden diese 126 Patienten ausgeschlossen. Die verbliebenen 369 Patienten (mit sicher diagnostizierter Leberzirrhose) wurden in die retrospektive Studie eingeschlossen. Von diesen wiesen 39 Patienten bereits zum Zeitpunkt der Operation ein ACLF auf und wurden daher der Positivkontrollgruppe zugeordnet. Für eine Analyse bezüglich der postoperativen Entwicklung von ACLF wurden sie jedoch ausgeschlossen, um einen statistischen Bias zu vermeiden. Die Kategorisierung der Operationen erfolgte unter anderem in die Gruppen Lokalisation, viszerale Beteiligung, Ausmaß und Länge der Operation, Zugangsweg und Beteiligung der Leber.

Ergebnisse

Charakteristika stratifiziert nach dem Auftreten von postoperativem ACLF

330 Patienten (mit Leberzirrhose) wiesen zum Zeitpunkt der Operation kein ACLF auf. Verglichen zu den 39 Patienten, die bereits zum Operationszeitpunkt ein ACLF aufwiesen, zeigten sich, wie erwartet, CTP, MELD, Kreatinin- und C-reaktives Protein (CRP)-Werte

signifikant niedriger und der Hämoglobinwert signifikant höher. Von den 330 Patienten ohne ACLF entwickelten 81 postoperativ (24,5%) ein ACLF innerhalb von 28 Tagen. Die Inzidenz von ACLF-Ereignissen war zwischen drei und acht Tagen nach der Operation am höchsten. Unter den 81 Patienten, die ein postoperatives ACLF entwickelten, zeigte sich ein statistisch signifikant höheres Alter und höhere leberassoziierte Scores wie CTP, MELD oder der CLIF-C AD zum Operationszeitpunkt. 48,1% der ACLF-Ereignisse waren mit Nierenversagen assoziiert, gefolgt von Kreislauf- und Lungenversagen (jeweils 25,9%). Zudem wiesen sie in der bekannten Krankenvorgeschichte mindestens eine Episode einer akuten Dekompensation vor dem operativen Eingriff auf. Auch traten in dieser Gruppe signifikant häufiger Infekte, sowohl zum Operationszeitpunkt als auch im postoperativen Zeitraum, auf.

Überleben stratifiziert nach ACLF

Die Patienten, die ein postoperatives ACLF entwickelten, zeigten ein signifikant verschlechtertes Überleben drei, sechs und 12 Monaten nach dem operativen Eingriff, im Vergleich zu den Patienten, die postoperativ kein ACLF entwickelten. Die verschiedenen Kategorisierungen der Operationen hatten hingegen in den Prädiktoranalysen keinen Einfluss auf die Mortalität. Zwischen der Gruppe, die postoperativ ein ACLF entwickelte, gab es keine Unterschiede bezüglich der Mortalitätsrate im Vergleich zu der Gruppe, die zum Operationszeitpunkt bereits ein ACLF aufwies. Die Entwicklung von ACLF innerhalb von 28 Tagen war mit der 3-Monats-Mortalität, jedoch nicht mit der 1-Jahres-Mortalität unabhängig assoziiert. Weitere Prädiktoren für das 1-Jahres-Überleben waren der MELD-Score, das Serumlevel der Alkalischen Phosphatase und das präoperative Bestehen einer hepatischen Enzephalopathie.

Prädiktion von postoperativem ACLF

Klinische Parameter, die unabhängig mit der Entwicklung von ACLF innerhalb von 28 Tagen nach dem operativen Eingriff assoziiert sind, waren vor allem Geschlecht, Alter, Serumnatriumwerte und das Bestehen eines Infektes zum Operationszeitpunkt. Die Entwicklung eines postoperativen ACLF war insbesondere dann sehr hoch (50%), wenn die Patienten einen Eingriff erhielten, der nicht die Leber inkludierte, und zusätzlich einen bakteriellen Infekt zum Zeitpunkt der Operation aufwiesen.

Schlussfolgerungen

Die Entwicklung von ACLF innerhalb von 28 Tagen nach dem operativen Eingriff ist sehr hoch (25%) und mit einer hohen postoperativen Sterblichkeit assoziiert. Patienten mit hohem Risiko postoperativ ein ACLF zu entwickeln, sind insbesondere ältere Patienten mit einem etablierten ACLF und/oder Infekten zum Operationszeitpunkt. Bei diesen Patienten sollte eine Optimierung der Infektsituation erfolgen und der operative Eingriff ggf. hinausgezögert werden.

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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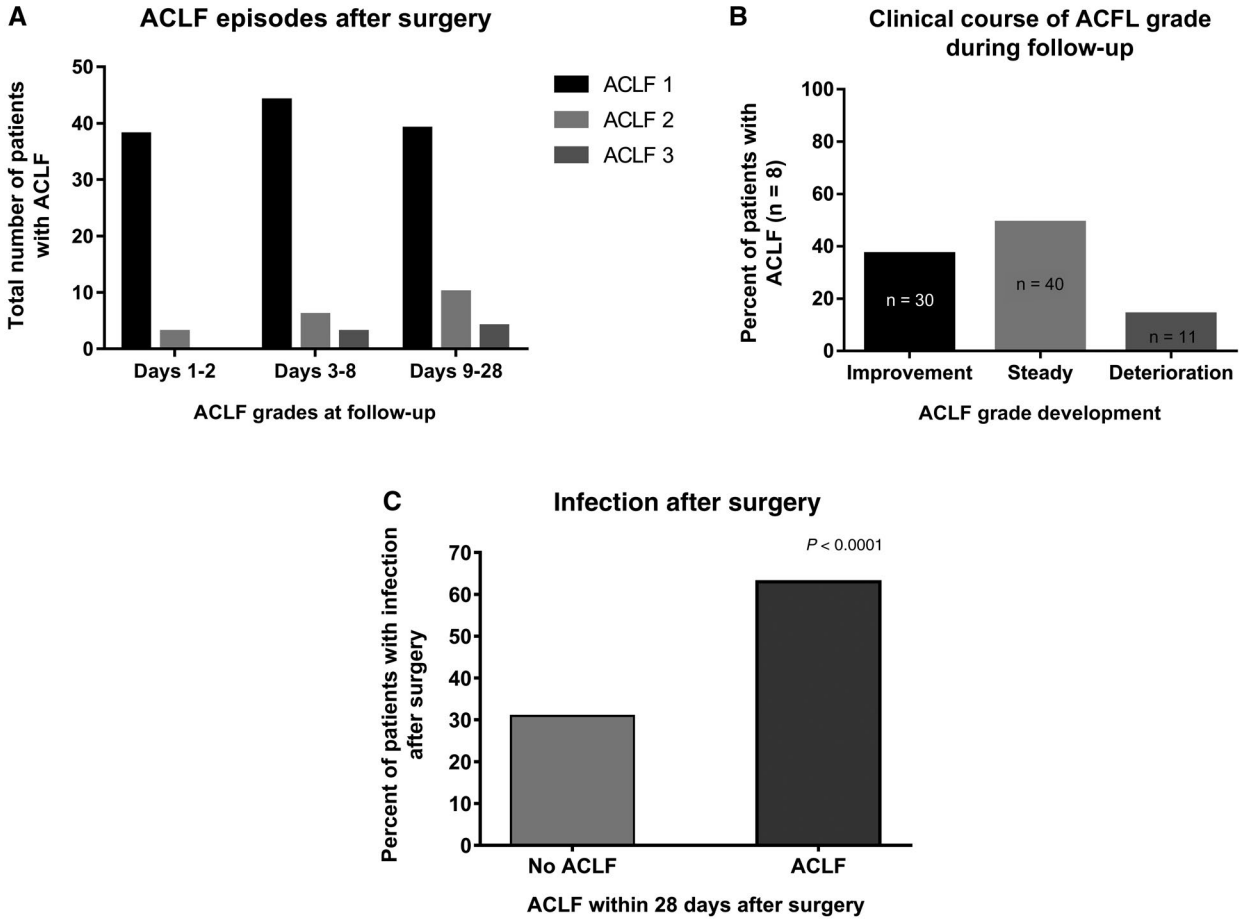

FIG. 1. (A) Evolution of ACLF in patients who developed ACLF after surgery. (B) The number of patients with different grades of ACLF at each of the time frames of follow-up after surgery. (C) Prevalence of infections in patients who developed ACLF after surgery compared with patients who did not.

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

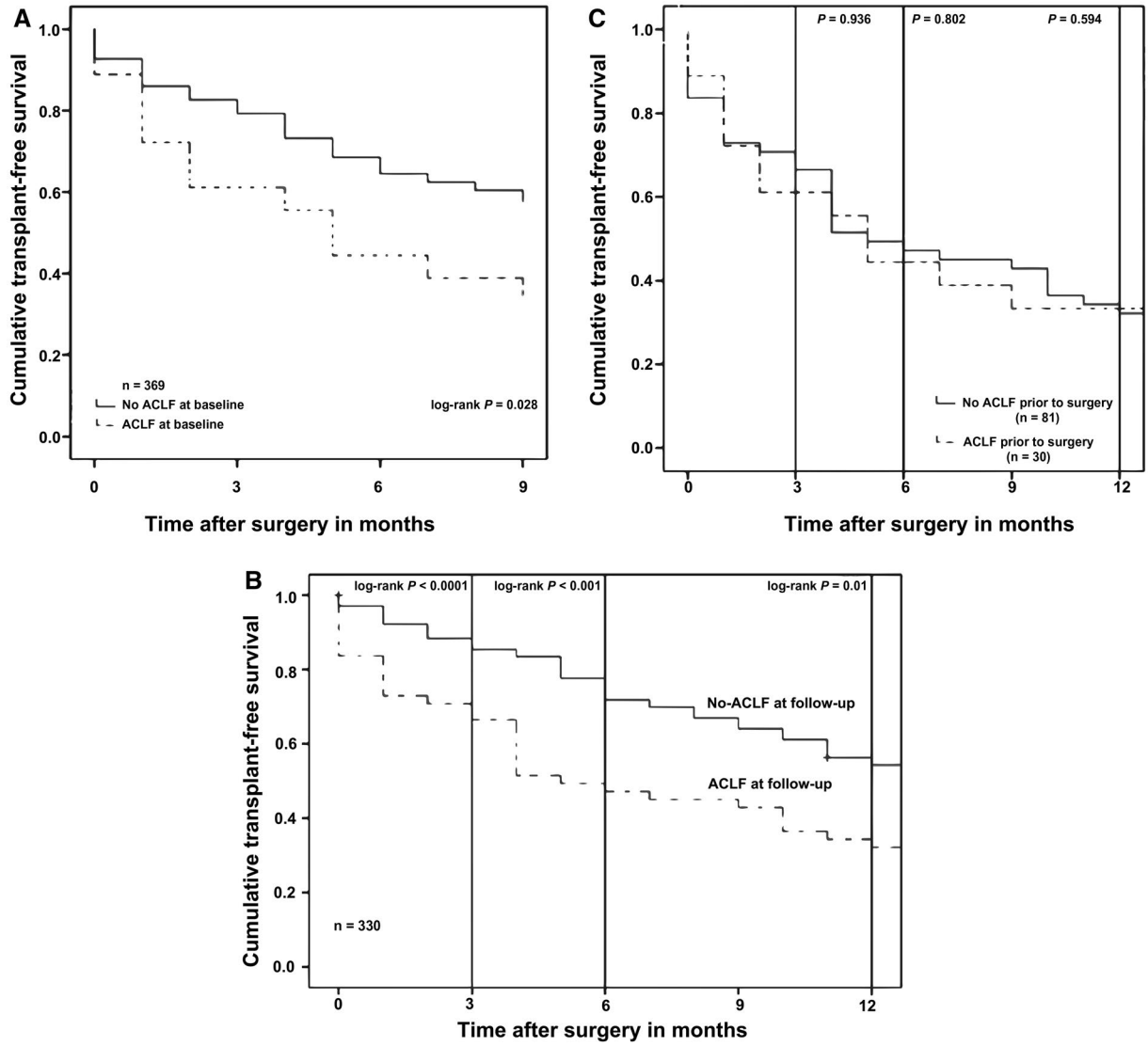

FIG. 2. (A) Kaplan-Meier plot comparing transplant-free survival of patients with ACLF at surgery with patients who underwent surgery without ACLF. (B) Kaplan-Meier plot comparing transplant-free survival of patients who developed ACLF after surgery with patients who did not. (C) Kaplan-Meier plot comparing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

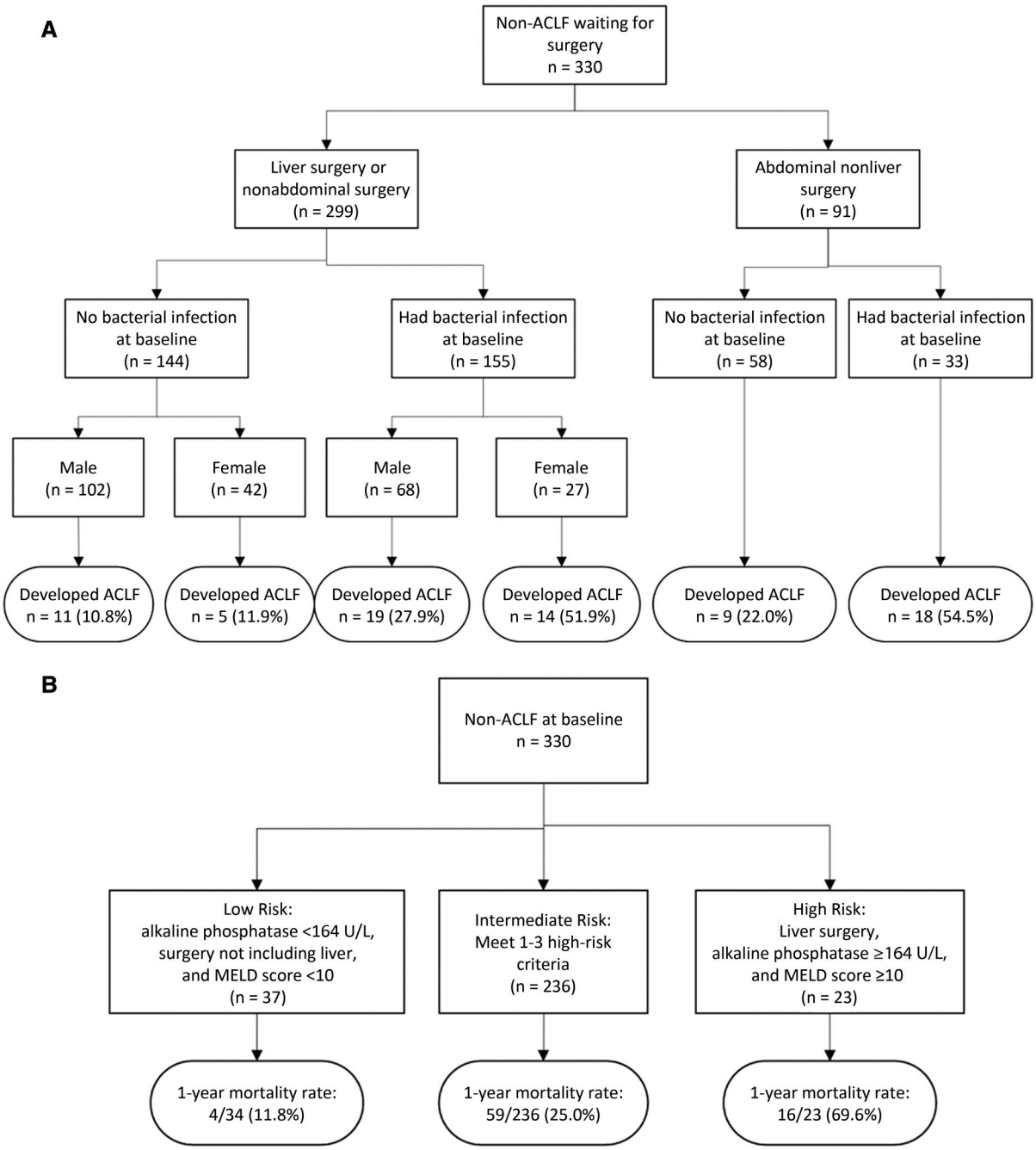

FIG. 3. (A) Flow diagram of 330 patients without ACLF at baseline and developed ACLF during 28 days with different risk factors. (B) Flow diagram of 330 patients non-ACLF at baseline and 1-year mortality rate with different independent risk factors.

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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3.2 Die Rolle von elektiven Eingriffen als Auslöser des postoperativen ACLF

“Elective Surgery but not Transjugular Intrahepatic Portosystemic Shunt Precipitates Acute-On-Chronic Liver Failure.”
Chang J, Bamarni A, Böhling N, Zhou X, Klein LM, Meinke J, Duerr GD, Lingohr P, Wehner W, Brol MJ, Rockstroh J, Kalff J, Manekeller S, Meyer C, Spengler U, Jansen C, Arroyo V, Strassburg CP, Trebicka J, Praktiknjo M.
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Zielsetzung und Methoden

In dieser Arbeit wurden Patienten, die einen elektiven operativen Eingriff erhielten, mit einer Patientenkohorte verglichen, die als Eingriff eine Intervention, nämlich die Implantation eines transjugulären intrahepatischen portosystemischen Shunts (TIPS) erhielten. Ziel dieser Studie war es, weitere pathophysiologische Hinweise für die Entwicklung eines postoperativen ACLF zu evaluieren und den TIPS als auslösendes Ereignis für ein ACLF zu untersuchen, wie es bis vor kurzem in der Literatur beschrieben wurde (Arroyo et al., 2016).

Hierzu wurde in dieser retrospektiven, monozentrischen Studie bei einer Patientenkohorte, die einen elektiven chirurgischen Eingriff erhalten hatten (OP-Gruppe) ein *Propensity Score Matching* (PSM) durchgeführt mit einer Patientenkohorte, die einen TIPS erhalten hatten (TIPS-Gruppe) und diese Kohorten verglichen. Ziel des PSM war, alle Störfaktoren für die Endpunktanalyse zu beseitigen. Die *Matching*-Kriterien beinhalteten Geschlecht, MELD-Score, Alter und CTP-Klasse.

Initial ergab die PSM-Analyse 141 Paare (282 Patienten). Weitere 92 Patienten mit einem Serumbilirubin > 5 mg/dl bzw. aufgrund eines ACLF zum Analysezeitpunkt (als Ausdruck einer schlechten Leberfunktion) mussten ausgeschlossen werden, um einen statistischen Bias zu vermeiden. 95 Paare (190 Patienten) gingen in die finalen Analysen ein. Primärer Endpunkt der Studie war die Entwicklung von ACLF innerhalb von 28 Tagen nach der Intervention bzw. des elektiven operativen Eingriffs, sekundäre Endpunkte die 3-Monats- und 1-Jahres Mortalität. Weitere Kategorisierungen der Operationen erfolgten wie bereits beschrieben (Klein et al., 2020).

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.

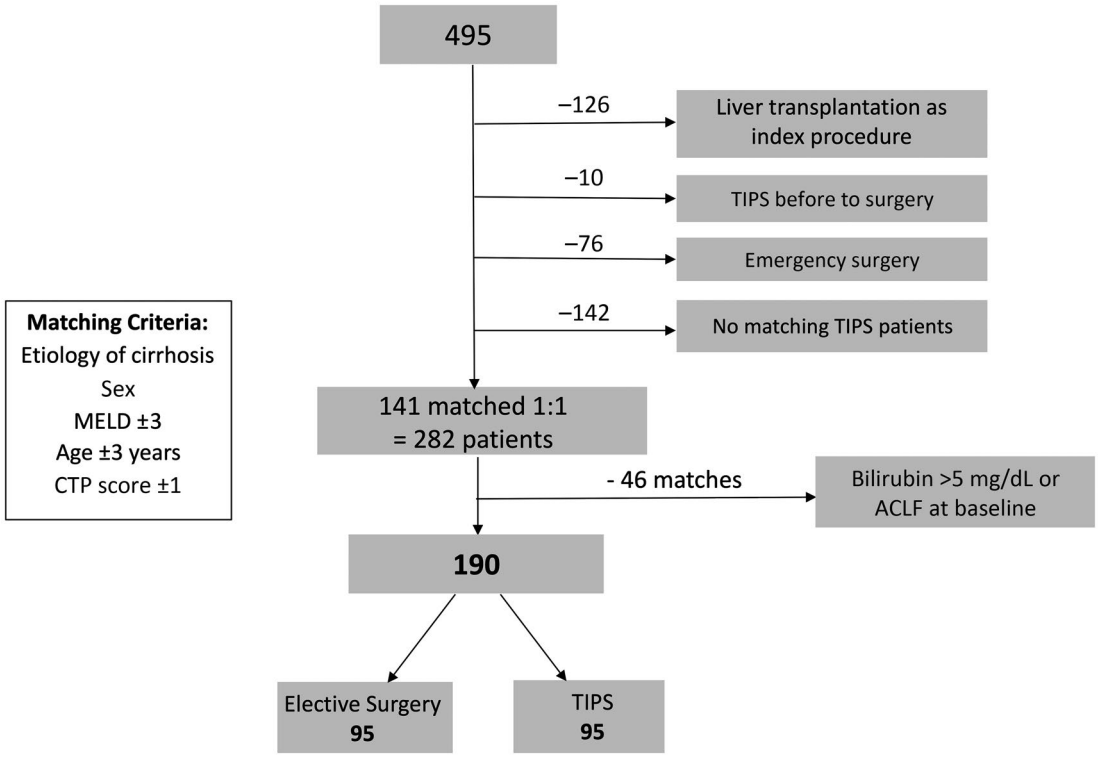

FIG. 1. The selection and matching process to define the final study cohort of patients with cirrhosis undergoing surgery versus patients receiving TIPS.

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 (non-visceral) (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 non-parametric 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

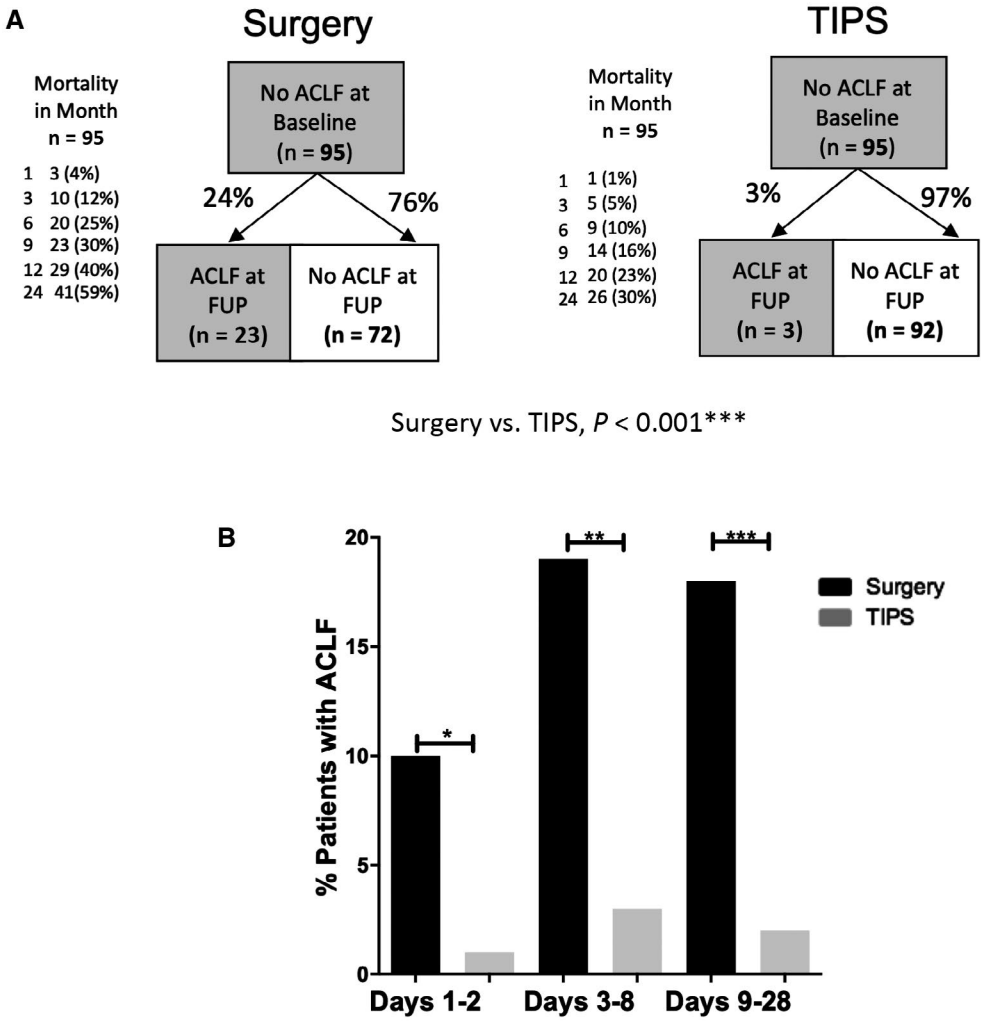

FIG. 2. Incidence of ACLF in elective surgery versus TIPS. (A) Number of patients presenting without ACLF at baseline developing ACLF within a 28-day follow-up and comparison between matched cohorts of elective surgeries (n = 95) and TIPS interventions (n = 95), ***$P < 0.001$. (B) Incidence of ACLF 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.

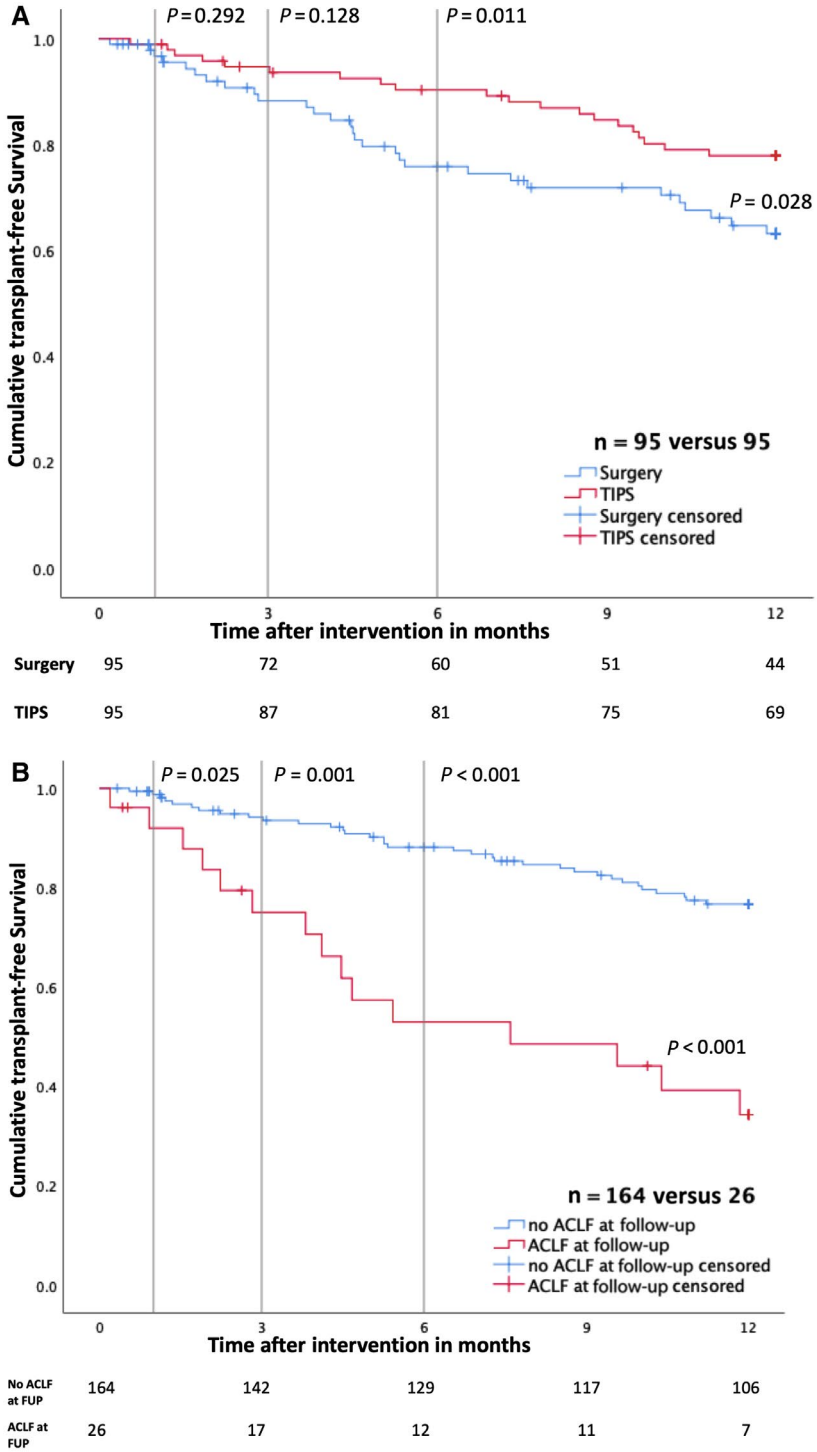

FIG. 3. Kaplan-Maier plots of patient survival. (A) A comparison of 1-year survival in patients undergoing elective surgery versus patients receiving TIPS (n = 190). (B) Survival of patients with and without ACLF development within 28 days after intervention (n = 190). Abbreviation: FUP, follow-up.

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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Author names in bold designate shared co-first authorship.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1712/suppinfo.

Ergebnisse

Überleben und ACLF-Entwicklung

In der OP-Gruppe entwickelten postprozedural 23 Patienten (24%) ein ACLF, in der TIPS-Gruppe nur 3% ($p < 0,001$). Patienten, die in der Gesamtkohorte postprozedural ein ACLF entwickelten, zeigten eine signifikant höhere Mortalität. Wie erwartet, zeigte sich eine signifikant höhere 1-Jahres Mortalität in der OP-Gruppe im Vergleich zur TIPS-Gruppe. Die höchste Inzidenz der ACLF-Ereignisse in der OP-Gruppe lag zwischen drei und acht Tagen nach dem elektiven Eingriff. Ein Unterschied in der Entwicklung von ACLF zwischen den einzelnen Operationstypen, insbesondere bezüglich der viszeralen Beteiligung konnte nicht gezeigt werden.

Der operative Eingriff und systemische Inflammation

Interessanterweise zeigte sich, dass postoperativ der CRP-Wert und die Leukozytenwerte als Surrogatparameter der systemischen Inflammation in der OP-Gruppe signifikant angestiegen waren, im Vergleich zu vor dem operativen Eingriff. In der TIPS-Gruppe dagegen bestanden keine signifikanten Unterschiede in den Inflammationsparametern vor und nach der Intervention.

Prädiktoren der ACLF-Entwicklung und Mortalität

Im univariablen Regressionsmodell für die ACLF-Entwicklung innerhalb von 28 Tagen nach der entsprechenden Prozedur waren das Alter, der CLIF-C AD-Score und der operative Eingriff selbst (vs. TIPS) die stärksten Prädiktoren. In der Multivariatanalyse verblieben der operative Eingriff (vs. TIPS) mit dem CLIF-C AD-Score als unabhängige Prädiktoren.

Für die 1-Jahres Mortalität waren das Alter, der CLIF-C AD-Score, der CRP-Wert und der operative Eingriff (vs. TIPS) in der univariaten Analyse signifikant; im multivariaten Modell blieben der CLIF-C AD-Score, der CRP-Wert und die Entwicklung von ACLF innerhalb von 28 Tagen als unabhängige Prädiktoren bestehen.

Identifikation von Hochrisikopatienten nach dem elektiven operativen Eingriff

Anhand einer Receiver Operating Characteristics (ROC)-Analyse konnte ein klarer Grenzwert des CLIF-C AD-Scores von ≥ 50 für die Entwicklung von postprozeduralem ACLF identifiziert werden. Das Ausmaß der Operation, die Leberbeteiligung oder die Beteiligung der Bauchhöhle dagegen hatten in den Regressionsmodellen keinen signifikanten Einfluss auf die postprozedurale Entwicklung von ACLF innerhalb von 28 Tagen.

Schlussfolgerungen

Auch bei elektiven operativen Eingriffen liegt der Anteil der Patienten, die postoperativ ein ACLF entwickeln, bei 25%. Der operative Eingriff selber kann sehr wahrscheinlich als ein auslösendes Ereignis für ein ACLF innerhalb von 28 Tagen diskutiert werden. Die Anlage eines TIPS hat dagegen keinen relevanten Einfluss auf eine postprozedurale Entwicklung von ACLF, so wie es bis jetzt postuliert wurde, und ist wahrscheinlich sogar invers mit der Entwicklung von ACLF assoziiert. Elektive Eingriffe bei Patienten können mit akzeptablem Outcome durchgeführt werden, wenn CLIF-C AD-Score und CRP-Werte eher niedriger sind. Der operative Insult scheint einen pathophysiologischen Mechanismus der Inflammation auszulösen, der weiter erforscht werden sollte.

3.3 Einfluss eines präoperativen TIPS auf das postoperative Auftreten von ACLF

“Preoperative TIPS prevents the development of postoperative acute-on-chronic liver failure in patients with high CLIF-C AD score.”
Chang J, Höfer P, Böhling N, Lingohr P, Manekeller S, Kalff JC, Dohmen J, Kaczmarek DJ, Jansen C, Meyer C, Strassburg CP, Trebicka J, Praktiknjo P.
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Zielsetzung und Methoden

Ziel dieser Arbeit war es, den Einfluss eines präoperativen TIPS – mit konsekutiver Dekompression der portalen Hypertension – auf die postoperative Entwicklung von ACLF und die Mortalität bei chirurgischen Eingriffen zu untersuchen. Hierfür wurde zu Patienten mit Leberzirrhose, die einen operativen Eingriff erhalten hatten und keine TIPS-Anlage in der Vorgeschichte (no-TIPS-Gruppe) aufwiesen, ein *Propensity Score Matching* (PSM) durchgeführt mit Patienten, denen vor der Operation in der Vorgeschichte ein TIPS implantiert wurde (TIPS-Gruppe). Diese Kohorten wurden miteinander verglichen.

Hierzu wurde bei 926 Patienten ein *Screening* durchgeführt. Für die no-TIPS-Gruppe verblieben von 363 Patienten nach Anwendung der Einschluss- und Ausschlusskriterien 238 Patienten ohne präoperative Anlage eines TIPS in der Vorgeschichte für das PSM. Die weiteren 563 Patienten gehörten zur NEPTUN-Kohorte (Non-invasive Evaluation Program for TIPS and Follow Up Network, clinicaltrials.gov identifier: NCT03628807), eine prospektive Beobachtungskohorte aller TIPS-Patienten am Uniklinikum Bonn. Hierunter konnten 70 Patienten identifiziert werden, bei denen die Implantation des TIPS vor einem großen chirurgischen Eingriff durchgeführt worden war.

Mit strengen 1:1 *Matching*-Kriterien (ASA-Score, MELD, CTP, Alter, OP-Klasse (viszeral vs. nicht viszeral, Notfalleingriff vs. elektiver Eingriff), Geschlecht) flossen initial 45 Vergleichspaare (90 Patienten) in die Analysen ein. Daher wurde zur internen Validierung und um die statistische Power zu erhöhen, ein erneutes PSM mit etwas permissiveren *Matching*-Kriterien durchgeführt. So konnte aus demselben Patientenpool zu 62 Patienten aus der TIPS-Gruppe zu 114 Patienten aus der no-TIPS-Gruppe ein 1:2 Matching erfolgen. Die Kohorten unterschieden sich in der nachfolgenden Analyse der klinischen Charakteristika zum Operationszeitpunkt nicht.

Ergebnisse

Die Entwicklung von ACLF innerhalb von 90 Tagen nach operativem Eingriff

In der TIPS-Gruppe war die Entwicklung von ACLF innerhalb von 90 Tagen nach dem chirurgischen Eingriff signifikant geringer als in der no-TIPS-Gruppe (für 28 Tage: n=33 (29%) vs. n=6 (10%), p=0,004 und 90 Tage: n=36 (31%) vs. n=9 (15%), p=0,016). In der no-TIPS-Gruppe waren tendenziell höhere ACLF-Grade als in der TIPS-Gruppe zu beobachten, dies war jedoch nicht statistisch signifikant. Unter fast allen Patienten, die ein ACLF entwickelten, war in beiden Gruppen die Nierenbeteiligung Bestandteil des ACLF.

Prädiktoren der Entwicklung von ACLF innerhalb von 90 Tagen nach operativem Eingriff

In der multivariaten Cox-Regressionsanalyse war der operative Eingriff ohne präoperative TIPS-Anlage ein starker Prädiktor, assoziiert mit einem mehr als 3-fachen Risiko innerhalb von 28 oder 90 Tagen postoperativ ein ACLF zu entwickeln. Der CLIF-C AD-Score war ein weiterer unabhängiger Prädiktor. Um eine Multikollinearität von CLIF-C AD-Score und MELD-Score zu vermeiden, wurden diese nicht in demselben Regressionsmodell getestet. Wurden beide Scores trotzdem in dasselbe Modell miteinbezogen, verblieb nur der CLIF-C AD-Score als Prädiktor. Das Ausmaß der Operation und die Leberbeteiligung waren keine Prädiktoren, jedoch war der viszerale Eingriff im Gegensatz zum nicht-viszeralen Eingriff signifikant mit der ACLF-Entwicklung assoziiert. Stratifziert nach viszeralen und nicht-viszeralen Eingriffen in einer Subgruppenanalyse zeigte sich, dass der operative Eingriff ohne präoperative TIPS-Anlage für die Entwicklung von ACLF innerhalb von 90 Tagen bei viszeralen Eingriffen ein signifkanter Prädiktor war, jedoch nicht bei nicht-viszeralen Eingriffen.

Identifikation von Hochrisikopatienten für die postoperative ACLF-Entwicklung

In der ROC-Analyse zeigte sich für den CLIF-C AD-Score für das Risiko einer Entwicklung von ACLF innerhalb von 90 Tagen nach operativem Eingriff ein Grenzwert von 45 in der no-TIPS-Gruppe. Patienten mit einem CLIF-C AD-Score ≤ 45 zeigten keinen signifikanten Unterschied in der Entwicklungsrate von ACLF innerhalb von 90 Tagen nach dem operativen Eingriff zwischen den beiden Gruppen. Bei Patienten mit einem CLIF-C AD-

Score > 45 war jedoch in der TIPS-Gruppe eine signifikant niedrigere Rate an ACLF innerhalb von 90 Tagen nach dem chirurgischen Eingriff zu verzeichnen.

Postoperatives Outcome in der TIPS vs. der no-TIPS-Gruppe

Patienten in der no-TIPS-Gruppe wiesen signifikant häufiger ungeplante stationäre Aufnahmen aufgrund postoperativer Komplikationen im Vergleich zur TIPS-Gruppe auf. Bei diesen Patienten wurden außerdem signifikant häufiger postoperative Bluttransfusionen durchgeführt, und es war häufiger Aszitesbildung zu verzeichnen. Patienten in der no-TIPS-Gruppe starben signifikant häufiger innerhalb eines Jahres nach der Operation. In beiden Gruppen war die Todesursache zumeist mit ACLF assoziiert. In der Cox-Regression waren der CLIF-C AD-Score und der chirurgische Eingriff ohne präoperative TIPS-Anlage unabhängige Prädiktoren der 1-Jahres-Mortalität.

Schlussfolgerungen

Patienten, die präoperativ einen TIPS zur Dekompression der portalen Hypertension erhalten haben, zeigen ein signifikant verbessertes Überleben und weniger Entwicklung von ACLF. Hochrisikopatienten bei Patienten ohne präoperative TIPS-Anlage sind Patienten mit einem CLIF-C AD-Score > 45 zum Operationszeitpunkt. Vor allem Patienten, die einen viszeralen Eingriff erhalten, scheinen von einer präoperativen TIPS-Anlage zu profitieren. Postoperatives ACLF geht vor allem mit einer eingeschränkten Nierenfunktion einher.

Preoperative TIPS prevents the development of postoperative acute-on-chronic liver failure in patients with high CLIF-C AD score

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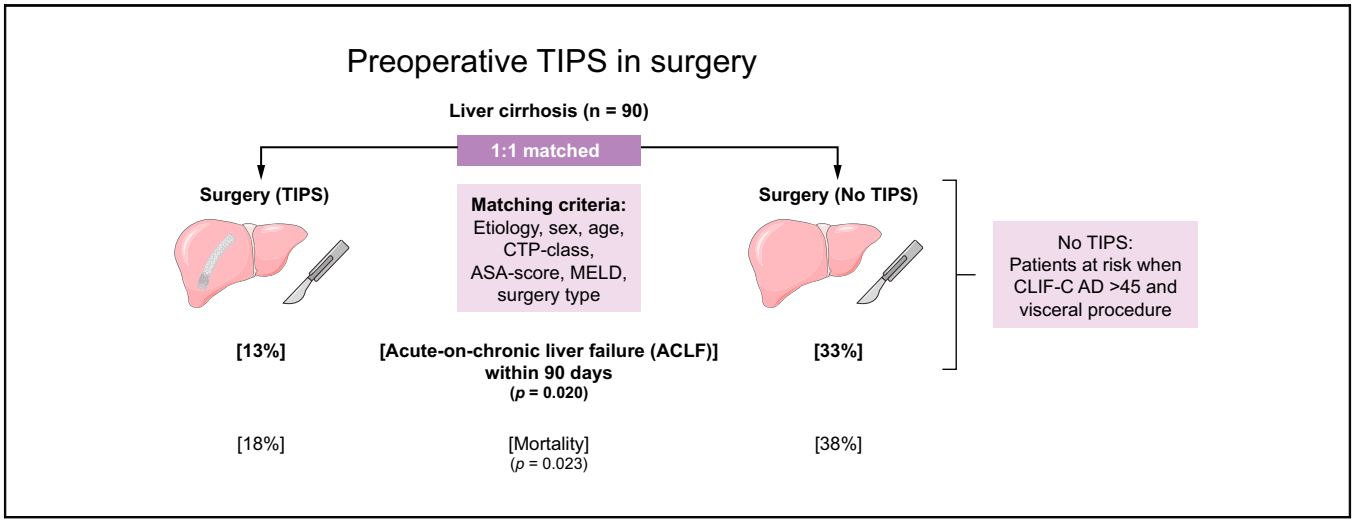
Graphical abstract



Highlights

- This study investigates the impact of preoperative TIPS on postsurgical ACLF.
- Patients with preoperative TIPS, especially before visceral surgery, develop significantly lower rates of ACLF.
- Preoperative TIPS is associated with improved postsurgical survival.
- CLIF-C AD score >45 can be used as cut-off for patients at risk for postsurgical ACLF.
- Selected patients might benefit from preoperative TIPS insertion.

Lay summary

Acute-on-chronic liver failure (ACLF) is a syndrome that is associated with high short-term mortality. Surgical procedures are a known precipitating event for ACLF. This study investigates the role of preoperative insertion of a transjugular intrahepatic portosystemic shunt (TIPS) on postoperative mortality and ACLF development. Patients with TIPS insertion before a surgical procedure exhibit improved postoperative survival and lower rates of postoperative ACLF, especially in patients undergoing visceral surgery and with a high CLIF-C AD prognostic score. Thus, this study suggests preoperative TIPS insertion in those high-risk patients.

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Preoperative TIPS prevents the development of postoperative acute-on-chronic liver failure in patients with high CLIF-C AD score

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Background & Aims: Acute-on-chronic liver failure (ACLF) is a syndrome associated with organ failure and high short-term mortality. Recently, the role of surgery as a precipitating event for ACLF has been characterised. However, the impact of preoperative transjugular intrahepatic portosystemic shunt (TIPS) placement on ACLF development in patients with cirrhosis undergoing surgery has not been investigated yet.
Methods: A total of 926 patients (363 with cirrhosis undergoing surgery and 563 patients with TIPS) were screened. Forty-five patients with preoperative TIPS (TIPS group) were 1:1 propensity matched to patients without preoperative TIPS (no-TIPS group). The primary endpoint was the development of ACLF within 28 and 90 days after surgery. The secondary endpoint was 1-year mortality. Results were confirmed by a differently 1:2 matched cohort (n = 176).
Results: Patients in the no-TIPS group had significantly higher rates of ACLF within 28 days (29 *vs.* 9%; $p = 0.016$) and 90 days (33 *vs.* 13%; $p = 0.020$) after surgery as well as significantly higher 1-year mortality (38 *vs.* 18%; $p = 0.023$) compared with those in the TIPS group. Surgery without preoperative TIPS and Chronic Liver Failure Consortium–Acute Decompensation (CLIF-C AD) score were independent predictors for 28- and 90-day ACLF development and 1-year mortality after surgery, especially in patients undergoing visceral surgery. In the no-TIPS group, a CLIF-C AD score of >45 could be identified as cut-off for patients at risk for postoperative ACLF development benefiting from TIPS.
Conclusions: This study suggests that preoperative TIPS may result in lower rates of postoperative ACLF development especially in patients undergoing visceral surgery and with a CLIF-C AD score above 45.
Lay summary: Acute-on-chronic liver failure (ACLF) is a syndrome that is associated with high short-term mortality. Surgical procedures are a known precipitating event for ACLF. This study investigates the role of preoperative insertion of a transjugular intrahepatic portosystemic shunt (TIPS) on postoperative mortality and ACLF development. Patients with TIPS insertion before a surgical procedure exhibit improved postoperative survival and lower rates of postoperative ACLF, especially in patients undergoing visceral surgery and with a high CLIF-C AD prognostic score. Thus, this study suggests preoperative TIPS insertion in those high-risk patients.

Introduction

Cirrhosis is the common end stage of chronic liver diseases and is characterised by fibrosis of liver tissue, decrease in liver function, and the development of portal hypertension.[1,2] Acute decompensation (AD) such as refractory ascites and acute variceal bleeding can be treated with placement of transjugular intrahepatic portosystemic shunt (TIPS) in selected patients.[3–6] However, AD can progress to acute-on-chronic liver failure (ACLF), a syndrome defined by the development of multi-organ failure resulting in high short-term mortality.[7–9]

Severe alcoholic hepatitis, proven bacterial infections, and variceal bleeding are the most common precipitating events for ACLF,[1,10] but many suggested precipitants have not been sufficiently studied yet. Recently, the role of surgery as a precipitating event for ACLF development has been characterised, confirming high rates of ACLF development after surgical procedures.[11]

Keywords: Surgery; Acute decompensation; TIPS; Cirrhosis; ACLF; Acute-on-chronic liver failure; Transjugular intrahepatic portosystemic shunt.
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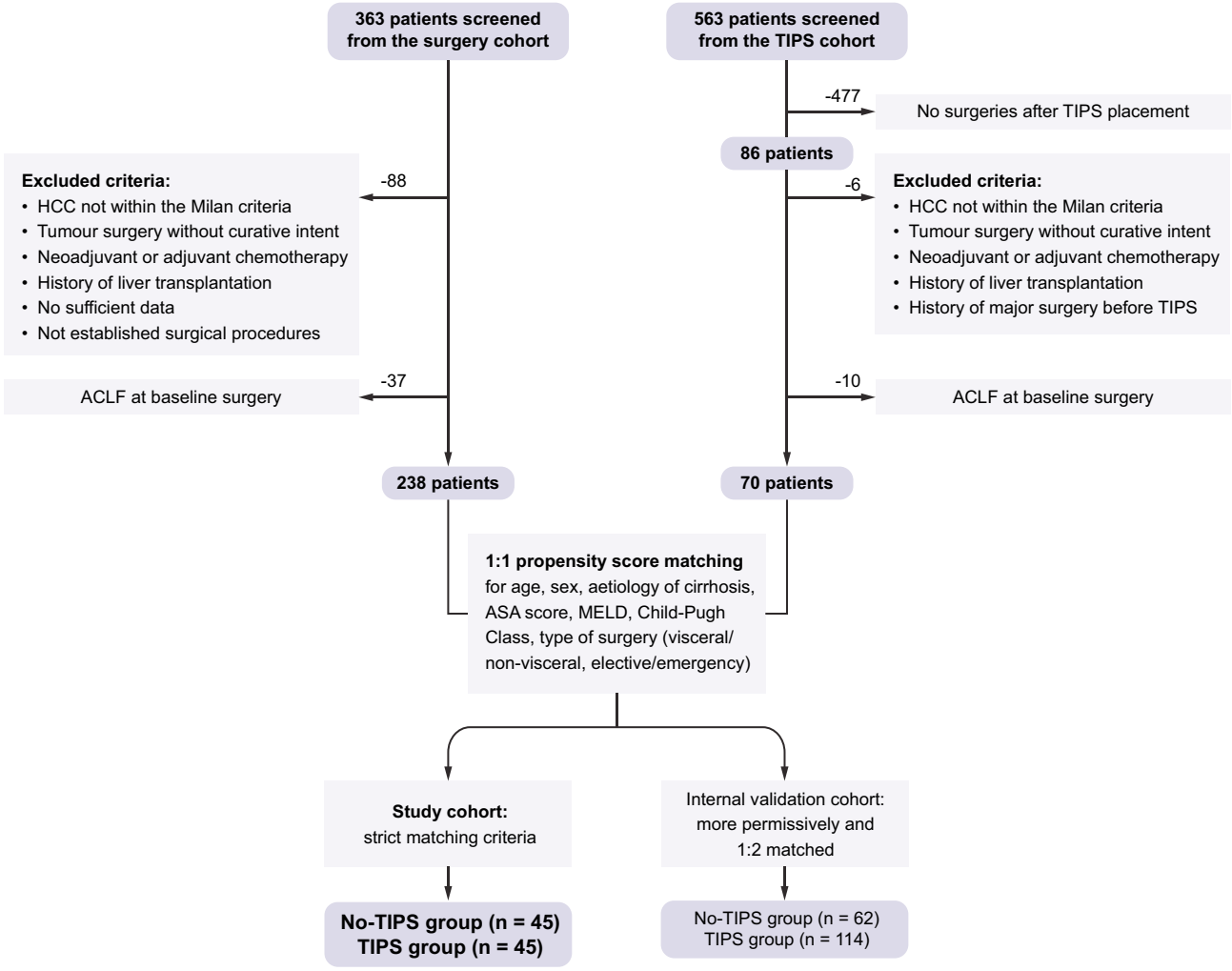

Fig. 1. Diagram depicting the selection and matching processes to define the final study cohort of patients with cirrhosis and preoperative TIPS (TIPS cohort) *vs.* patients with cirrhosis undergoing surgery without preoperative TIPS (no-TIPS cohort). ACLF, acute-on-chronic liver failure; ASA, American Society of Anesthesiologists; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt.

Until recently, TIPS placement itself has been discussed as a precipitating event for the development of ACLF.[12] However, current literature indicates that placement of TIPS in eligible patients has a rather beneficial effect concerning further development of ACLF episodes and other liver-related endpoints, probably attributed to reduction of clinically significant portal hypertension. An observational multicentre study suggested that placement of TIPS in patients with ACLF and acute variceal bleeding improves survival and rebleeding rates.[13] In the context of surgery, our group could show a negligible precipitating effect of TIPS placement for the development of ACLF compared with surgical interventions.[14]

Moreover, recent data show that high hepatic venous pressure gradients (HVPGs) of >16 and ≥20 independently predicted 90-day and 1-year mortality in patients undergoing elective extrahepatic surgery.[15] These data indicate a potential benefit of TIPS insertion before surgery by reduction of the portosystemic pressure gradient. Data concerning this hypothesis are scarce, and thus, the question of whether preoperative TIPS placement has an effect on the postoperative development of ACLF or mortality, remains unanswered. Therefore, this retrospective study aimed to investigate the impact of preoperative TIPS placement on ACLF development and mortality in patients with liver cirrhosis undergoing surgery.

Patients and methods

Patients and data collection

In this retrospective single-centre study, patients with cirrhosis undergoing surgery (no-TIPS group) were 1:1 propensity matched and compared with patients with cirrhosis undergoing surgery but with preoperative TIPS placement (TIPS group). The primary endpoint of this study was the development of ACLF within 28 and 90 days. The secondary endpoint was 1-year mortality.

For the identification of the study cohort, a total of 926 patients with liver cirrhosis between July 2006 and December 2019 of the Department of Internal Medicine I, University of Bonn, Germany, were screened. At the time of surgery, all screened patients were ≥18 years old and had clinical, radiological, or histological findings to confirm liver cirrhosis.

Table 1. General characteristics of 1:1 matched patient cohort: 45 patients with TIPS *vs.* 45 patients without TIPS (n = 90).

Parameters at baseline	TIPS (n = 45)	No TIPS (n = 45)	*p* value
General conditions			
Age (years)	63 (43–80)	64 (40–77)	0.54
Sex (male/female)	32/13 (71/29%)	32/13 (71/29%)	1.00
Aetiology (alcohol/viral hepatitis/other)	32/4/9 (71/9/20%)	32/4/9 (71/9/20%)	1.00
BMI	25.8 (17.4–34)	25.5 (18–35)	0.93
Baseline scores			
MELD score	11 (6-17)	10 (6–18)	0.32
Child-Pugh class A/B	10/35 (22/78%)	10/35 (22/78%)	1.00
CLIF-C AD score	46 (29–64)	49 (28–61)	0.74
Baseline laboratory			
Sodium (mmol/L)	140 (130–145)	139 (130–145)	0.20
Potassium (mmol/L)	4.14 (2.93–5.16)	4.07 (3.24-5.3)	0.76
Creatinine (mg/dl)	1.07 (0.49-1.76)	0.85 (0.46–1.86)	0.07
Bilirubin (mg/dl)	1.28 (0.32-4.85)	1.09 (0.24-3.85)	0.41
ALT (U/L)	24 (9–80)	23 (7-83)	0.65
AST (U/L)	38 (18-278)	39 (11–155)	0.82
Albumin (g/dl)	32 (20.8–46.2)	30 (22.4-42)	0.21
GGT (U/L)	63 (50-79)	66 (15-82)	0.83
Alkaline phosphatase (U/L)	135 (69–349)	150 (13–523)	0.72
INR	1.2 (1-1.6)	1.2 (1–2.2)	0.93
CRP (mg/L)	9.2 (0.48–58.6)	12.6 (0.7–60.3)	0.27
Hb (g/dl)	10.5 (8–16)	10.9 (7.5–16.3)	0.19
WBC (10^3/μl)	5.16 (2.25–11.77)	5.84 (1.23–11.64)	0.25
Platelets	122.5 (25–336)	137 (23–394)	0.27
Baseline clinical conditions			
Ascites	2(4%)	7(16%)	0.10
Varices before surgery (before TIPS) grade I/II/III	11/13/11 (24/29/24%)	14/13/5 (31/29/11%)	0.42
Varices before surgery (after TIPS) grade I/II/III	6/3/0 (13/7/0%)	14/13/5 (31/29/11%)	0.00
HE	0 (0%)	0 (0%)	1.00
Spleen diameter (cm)	14 (10–26)	14.5 (8.5–22.8)	0.54
Use of rifaximin	1 (2%)	2 (4%)	0.56
Surgery			
Non-visceral/visceral	21/24 (47/53%)	21/24 (47/53%)	1.00
Emergency/elective	7/38 (16/84%)	7/38 (16/84%)	1.00
ASA score (1/2/3/4)	1/4/35/5 (2/9/78/11%)	1/4/35/5 (2/9/78/11%)	1.00
Medical history			
History of ascites	35 (77.8%)	31 (68.9%)	0.34
History of GI bleeding	18 (40%)	13 (29%)	0.27
History of HE	8 (17.8%)	7 (15.6%)	0.78

Data are shown as median and ranges. Non-parametric testing was used to compare the groups, Mann-Whitney U test for comparison between continuous variables and Chi-squared test for comparison between categorical variables.
ALT, alanine transaminase; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; CLIF-C AD, Chronic Liver Failure Consortium–Acute Decompensation; CRP, C-reactive protein; GGT, gamma glutamyl-transferase; GI, gastrointestinal; Hb, haemoglobin; HE, hepatic encephalopathy; INR, international normalised ratio; MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt; WBC, white blood cells.

Identification of patients for the no-TIPS group

A total of 363 consecutive patients with cirrhosis who had undergone a surgical procedure between July 2006 and December 2017 were screened. These patients were identified using hospital database search based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), as previously described.[11] Eighty-eight patients undergoing surgical procedures owing to hepatocellular carcinoma not within the Milan criteria, non-standardised surgical procedures, and surgery with palliative intent or requiring adjuvant or neoadjuvant chemotherapy as well as patients without sufficient data or with a history of liver transplantation at the time of surgery were excluded. Further, 37 patients who presented with ACLF at the time of surgery were excluded, resulting in 238 patients eligible for propensity matching (Fig. 1).

Identification of patients for the TIPS group

Out of 563 consecutive patients from the observational NEPTUN (Non-invasive Evaluation Program for TIPS and Follow Up Network; clinicaltrials.gov identifier: NCT03628807) cohort that had undergone TIPS placement between September 2008 and December 2019, 86 patients who had a relevant surgical procedure after TIPS placement were identified. Of those, 6 patients undergoing surgical procedures owing to hepatocellular carcinoma not within the Milan criteria or surgery with palliative intent or requiring adjuvant or neoadjuvant chemotherapy and patients with a history of liver transplantation at the time of surgery or a history of major surgery before TIPS placement were excluded. Ten further patients who presented with ACLF at baseline were excluded. Thus, 70 patients were eligible for propensity matching (Fig. 1). Indications for TIPS insertion were refractory ascites or variceal bleeding. None of the TIPS insertions were performed pre-emptively to surgery.

Propensity score matching

Patients from the no-TIPS group were 1:1 propensity matched with patients from the TIPS group. Matching criteria were aetiology of cirrhosis, sex, Child-Pugh class, type of surgery (visceral/

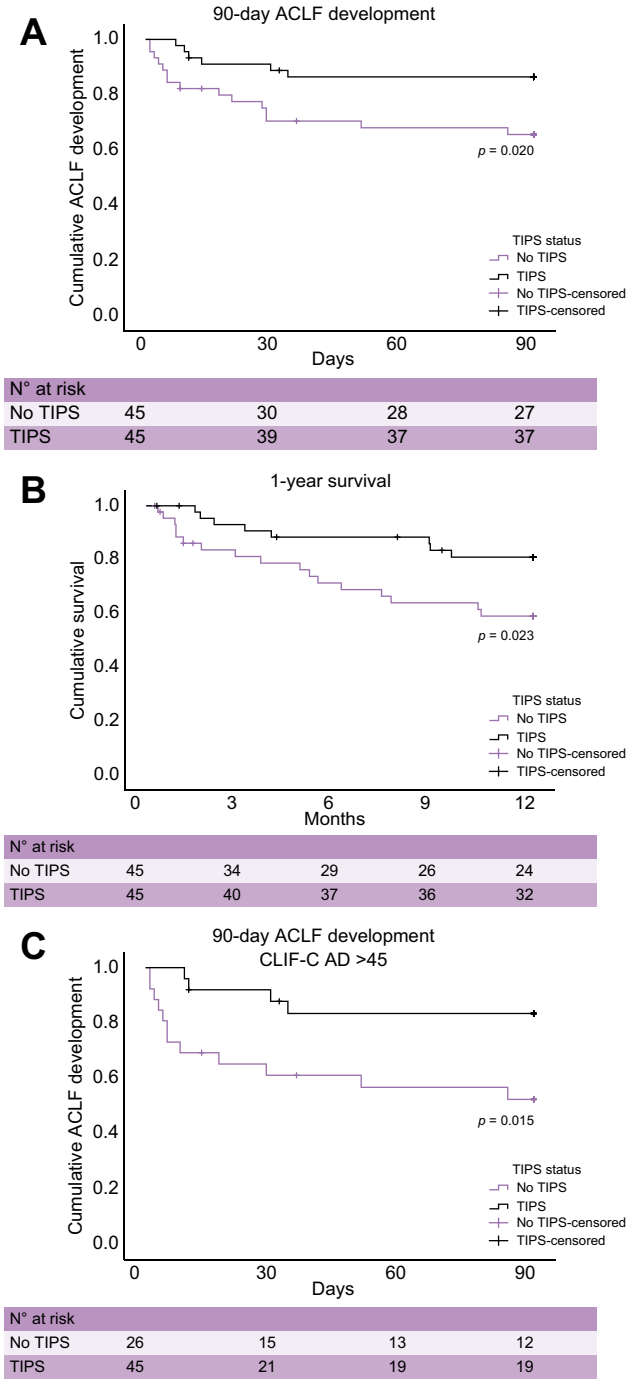

Fig. 2. Kaplan–Meier plots showing mortality and probability of 90-day ACLF development for patients undergoing surgery in the TIPS and no-TIPS groups. (A) Probability of 90-day ACLF development calculated according to the log-rank test for patients in the TIPS and no-TIPS groups (n = 90). Level of significance $p = 0.020$. (B) One-year survival calculated according to the log-rank test for patients in the TIPS and no-TIPS groups (n = 90). Level of significance $p = 0.023$. (C) Probability of 90-day ACLF development calculated according to the log-rank test for patients with a CLIF-C-AD >45 stratified to the TIPS and no-TIPS groups (n = 51). Level of significance $p = 0.015$. ACLF, acute-on-chronic liver failure; CLIF-C AD, Chronic Liver Failure Consortium–Acute Decompensation; TIPS, transjugular intrahepatic portosystemic shunt.

non-visceral and emergency/elective surgery), American Society of Anesthesiologists (ASA) score, model for end-stage liver disease (MELD) ± 3 points, and age ±3 years. Forty-five patients from the no-TIPS group were propensity score matched with 45 patients from the TIPS group. This final cohort of 90 patients was enrolled in the analyses (Fig. 1). Twenty-five patients of the TIPS cohort remained unmatched; the cohort characteristics of these patients are shown in Table S1. For internal validation with less excluded patients and increased statistical power, an additional 1:2 (TIPS *vs.* no-TIPS) propensity score matching with more permissive matching criteria was performed including 176 patients (n = 62 in the TIPS group and n = 114 in the no-TIPS group).

Data collection

Patient medical records were used to obtain clinical and laboratory data before and after surgery. ACLF was diagnosed retrospectively according to the EASL-Chronic Liver Failure (CLIF) ACLF criteria.[7] To define organ failures of ACLF within the 90-day follow-up period, the Chronic Liver Failure Consortium–Sequential Organ Failure Assessment (CLIF-C-SOFA) score was retrospectively applied as suggested in current EASL guidelines.[1] Respiratory failure was diagnosed when mechanical ventilation was required for reintubation or reasons other than airway protection exceeding the standard postoperative care in the absence of hepatic encephalopathy (HE) grade III or IV. Arterial hypotension (mean arterial pressure below 70 mmHg) or the use of vasopressors with an indication other than hepatorenal syndrome therapy was classified as circulatory failure. Postoperative ascites development was defined as the need for paracentesis, as the observation of ascites in postoperative abdominal drainage, or based on imaging findings within 90 days after surgery. Overt HE was defined clinically using West Haven criteria within 90 days after the surgical procedure.[1]

Statistical analysis

For all variables, descriptive statistics were performed. Non-parametric testing was used to compare the groups. Propensity score matching of the no-TIPS and TIPS groups was performed by using the MatchIt (version 3.0.2) package in R (R Foundation for Statistical Computing, Vienna, Austria). Survival rates were analysed using Kaplan–Meier curves with the log-rank test. Univariate and multivariate Cox regression analysis with stepwise forward selection was used to identify predictors of ACLF development within 28 and 90 days after surgery. Significant parameters in univariate regression analysis and known risk factors were entered in multivariate regression analyses. Scores (*e.g.* Chronic Liver Failure Consortium–Acute Decompensation [CLIF-C AD] score or MELD) were not simultaneously entered with their respective components to avoid collinearity. Sensitivity analysis as published by Ding and Van der Weele[16,17] was performed for the multivariate models. The prognostic value and selection of optimal cut-off values according to the Youden index for CLIF-C AD and MELD were analysed using receiver operating characteristics (ROC) with 90-day ACLF development as the endpoint.

Values of $p < 0.05$ were considered to be statistically significant. Continuous variables are presented as median and range. Categorical variables are presented as absolute cases or percentage. All data were analysed using SPSS (version 24, IBM, Armonk, NY, USA) and R (version 4.0.2), augmented by R Studio (version 1.3.1073, RStudio, Inc., Boston, MA, USA).

Table 2. Univariate and multivariate Cox regression analysis for ACLF development within 90 days after surgery.

	Univariate regression				Multivariate regression			
			95% CI				95% CI	
	p value	HR	Lower	Upper	*p* value	HR	Lower	Upper
Age	0.426	1.018	0.974	1.064	–	–	–	–
Aetiology	0.236	1.933	0.650	5.747	–	–	–	–
BMI	0.313	1.077	0.932	1.244	–	–	–	–
ASA score	0.755	0.881	0.397	1.956	–	–	–	–
CLIF-C AD	*0.020*	*1.077*	*1.012*	*1.146*	**0.016**	**1.085**	**1.015**	**1.159**
CRP	0.593	1.007	0.980	1.035	–	–	–	–
Albumin	*0.144*	*0.944*	*0.873*	*1.020*	–	–	–	–
Visceral/non-visceral	*0.124*	*2.038*	*0.822*	*5.051*	**0.034**	**2.763**	**1.083**	**7.051**
Liver involvement*	0.28	1.62	0.67	3.92	–	–	–	–
Extensive/small†	0.14	0.49	0.19	1.25	–	–	–	–
Emergency/elective	0.46	1.51	0.51	4.49	–	–	–	–
Ascites	0.031	1.840	1.059	3.198	–	–	–	–
HE	0.730	0.049	‡	‡	–	–	–	–
MELD	0.027	1.190	1.020	1.388	–	–	–	–
Child-Pugh score	0.193	1.281	0.882	1.859	–	–	–	–
Surgery without TIPS	*0.029*	*2.869*	*1.113*	*7.398*	**0.016**	**3.256**	**1.248**	**8.499**

Italic—entered in multivariate regression model; **bold**—significant in multivariate regression analysis.
ACLF, acute-on-chronic liver failure; ASA, American Society of Anesthesiologists; BMI, body-mass index; CLIF-C-AD, Chronic Liver Failure Consortium–Acute decompensation; CRP, C-reactive protein; HE, hepatic encephalopathy; HR, hazard ratio; MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt.
* All abdominal surgeries, where the liver was touched or mobilised by the operating surgeons or surgical instruments, were classified as visceral surgery with liver involvement.
† Surgeries with a duration over 90 min were defined as extensive.
‡ No clinical events.

Results

General patient characteristics

Ninety patients (45 from the no-TIPS group 1:1 matched with 45 from the TIPS group) were included in the analyses. Because of strict matching for confounders, there were no differences in sex, aetiology, and Child-Pugh class between the groups. In both groups, patients were predominantly male (n = 32 [71%] in each group) and were mostly categorised into Child-Pugh class B (n = 35 [78%] in each group) at baseline. The most frequent cause of cirrhosis was alcohol-related liver disease (n = 32 [71%] in each group) (Table 1). More than half of the surgical procedures in both groups were visceral (n = 24 [53%] in each group) (Table 1 and Table S2A). Surgery types between the 2 groups did not differ significantly, especially the number of liver resections (5 [11%] in the TIPS group *vs.* 6 [13%] in the no-TIPS group, $p = 0.749$) (Table S2B). Patients were mostly classified with an ASA score of 3 (n = 35 [78%] in each group). The median age was similar between the TIPS and no-TIPS groups (63 [43–80] and 64 [40–77]

Table 3. Univariate and multivariate Cox regression analysis for ACLF development within 90 days after surgery with MELD instead of CLIF-C AD score.

	Univariate regression				Multivariate regression			
			95% CI				95% CI	
	p value	HR	Lower	Upper	*p* value	HR	Lower	Upper
Age	0.426	1.018	0.974	1.064	–	–	–	–
Aetiology	0.236	1.933	0.650	5.747	–	–	–	–
BMI	0.313	1.077	0.932	1.244	–	–	–	–
ASA score	0.755	0.881	0.397	1.956	–	–	–	–
CLIF-C AD	0.020	1.077	1.012	1.146	–	–	–	–
CRP	0.593	1.007	0.980	1.035	–	–	–	–
Albumin	*0.144*	*0.944*	*0.873*	*1.020*	**0.050**	**0.915**	**0.837**	**1.000**
Visceral/non-visceral	*0.124*	*2.038*	*0.822*	*5.051*	**0.015**	**3.211**	**1.257**	**8.202**
Liver involvement*	0.28	1.62	0.67	3.92	–	–	–	–
Extensive/small†	0.14	0.49	0.19	1.25	–	–	–	–
Emergency/elective	0.46	1.51	0.51	4.49	–	–	–	–
Ascites	0.031	1.840	1.059	3.198	–	–	–	–
HE	0.730	0.049	‡	‡	–	–	–	–
MELD	*0.027*	*1.190*	*1.020*	*1.388*	**0.003**	**1.353**	**1.107**	**1.652**
Child-Pugh score	0.193	1.281	0.882	1.859	–	–	–	–
Surgery without TIPS	*0.029*	*2.869*	*1.113*	*7.398*	**0.008**	**3.651**	**1.393**	**9.567**

Italic—entered in multivariate regression model; **bold**—significant in multivariate regression analysis.
ACLF, acute-on-chronic liver failure; ASA, American Society of Anesthesiologists; CLIF-C AD, Chronic Liver Failure Consortium–Acute Decompensation; CRP, C-reactive protein; HE, hepatic encephalopathy; HR, hazard ratio; MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt.
* All abdominal surgeries, where liver was touched or mobilised by the operating surgeons or surgical instruments, were classified as visceral surgery with liver involvement.
† Surgeries with a duration over 90 min were defined as extensive.
‡ No clinical events.

Table 4. Postoperative complications within 90 days after surgery.

	TIPS (n = 45)	No TIPS (n = 45)	*p* value
Duration of postoperative hospital stay (days)	11(1–64)	11 (1–44)	0.94
Postoperative stay at ICU	11 (24%)	21 (47%)	0.03
Postoperative ascites	15 (33%)	25 (56%)	0.04
Overt HE	5 (11%)	4 (9%)	0.73
Postoperative infection	13 (29%)	19 (42%)	0.19
Intraoperative and/or postoperative blood transfusion	11 (24%)	20 (44%)	0.05

Non-parametric testing was used to compare the groups, Mann-Whitney U test for comparison between continous variables and Chi-squared test for comparison between categorical variables. HE, hepatic encephalopathy; ICU, intensive care unit; TIPS, transjugular intrahepatic portosystemic shunt.

years, respectively, $p = 0.54$). The median of CLIF-C AD score was not statistically different between the TIPS and no-TIPS groups at baseline (46 [29–64] *vs*. 49 [28–61], respectively, $p = 0.74$), and MELD and liver-related laboratory parameters did not show any significant differences (Table 1). The distribution of the presence of varices and grades of varices before surgery (for the TIPS group before TIPS placement) was not significantly different between the 2 groups. After TIPS placement, the presence of varices was lower in the TIPS group. Sodium, platelet count, and spleen size as surrogate parameters for portal hypertension were comparable between the 2 groups. None of the patients presented with overt HE at the time of surgery (Table 1). The indication for TIPS placement was refractory ascites in 30 (67%) patients and acute variceal bleeding in 15 (33%) patients. None of the patients showed signs of TIPS dysfunction at the time of surgery. Two patients presented with controlled ascites at surgery, both with TIPS placement only within 1 month before surgery. The median time between TIPS placement and surgery was 6 (0–101) months.

The more permissively 1:2 matched validation cohort included 176 patients (62 with TIPS and 114 without TIPS). The clinical characteristics of the validation cohort are shown in Table S3.

Characteristics of postoperative ACLF

Kaplan–Meier analysis shows significantly lower rates of postoperative ACLF for the TIPS group within 28 days after surgery than those for the no-TIPS group (n = 4 [8.9%] *vs*. n = 13 [28.9%], $p = 0.013$) (Fig. S1). Similarly, within 90 days after surgery, patients in the TIPS group developed significantly less ACLF than those in the no-TIPS group (n = 6 [13%] *vs*. n = 15 [33%], $p = 0.020$) (Fig. 2A). The same results could be shown in the more permissively matched validation cohort (62 with TIPS *vs*. 114 without TIPS). Patients in the no-TIPS group developed postoperative ACLF significantly more often than patients in the TIPS group (28 days: n = 33 [29%] *vs*. n = 6 [10%], $p = 0.004$; and 90 days: n = 36 [31%] *vs*. n = 9 [15%], $p = 0.016$) (Fig. S2). A competing risk analysis was not performed because of the small number of liver transplantations (only 1 and 2 events within 90 days and 12 months, respectively).

The distribution of ACLF grades and organ failures is presented in Table S4. There was a trend of higher ACLF grades in the no-TIPS group than in the TIPS group, although it was not statistically significant. Acute kidney injury was present in almost all patients. Precipitating events in the TIPS group were mostly associated with infections (83%). The no-TIPS group had a significantly higher proportion of unknown precipitating events compared with the TIPS group (60 *vs*. 0%, $p = 0.014$) (Table S4).

Predictors of postoperative ACLF development

Cox regression analysis showed that in the no-TIPS group, the risk of 28- and 90-day ACLF development is increased more than 3-fold. Moreover, CLIF-C AD was an independent predictor of ACLF development 28 and 90 days after surgery (Table 2 and

Table 5. Univariate and multivariate Cox regression analysis for 1-year mortality after surgery.

	Univariate regression				Multivariate regression			
			95% CI				95% CI	
	p value	HR	Lower	Upper	*p* value	HR	Lower	Upper
Age	0.146	1.032	0.989	1.078	–	–	–	–
Aetiology	0.212	1.868	0.701	4.981	–	–	–	–
BMI	0.710	0.973	0.844	1.123	–	–	–	–
ASA score	0.107	1.863	0.874	3.973	–	–	–	–
CLIF-C AD	*0.002*	*1.097*	*1.035*	*1.163*	**0.006**	**1.098**	**1.028**	**1.173**
CRP	*0.040*	*1.023*	*1.001*	*1.046*	–	–	–	–
Albumin	*0.006*	*0.897*	*0.830*	*0.970*	–	–	–	–
Visceral/non-visceral	0.38	1.43	0.64	3.18	–	–	–	–
Liver involvement*	0.81	1.11	0.48	2.58	–	–	–	–
Extensive/small†	0.75	0.88	0.39	1.95	–	–	–	–
Emergency/elective	0.89	1.08	0.37	3.15	–	–	–	–
MELD	0.003	1.266	1.082	1.482	–	–	–	–
Child-Pugh score	0.046	1.428	1.007	2.024	–	–	–	–
Surgery without TIPS	*0.029*	*2.554*	*1.102*	*5.922*	**0.009**	**3.320**	**1.356**	**8.128**

Italic—entered in multivariate regression model; **bold**—significant in multivariate regression analysis.
ASA, American Society of Anesthesiologists; CLIF-C AD, Chronic Liver Failure Consortium–Acute Decompensation; CRP, C-reactive protein; HR, hazard ratio; MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt.
* All abdominal surgeries, where the liver was touched or mobilised by the operating surgeons or surgical instruments, were classified as visceral surgery with liver involvement.
† Surgeries with a duration over 90 min were defined as extensive.

Table S5A). With MELD instead of CLIF-C AD included into the multivariate analysis, MELD and surgery without preoperative TIPS remained as predictors for 28- and 90-day ACLF development with hazard ratios (HRs) of 4.6 and 3.7, respectively (Table 3 and Table S5B). Univariate analysis of surgery with liver involvement and the extensiveness of surgery were not statistically significant. However, visceral surgery was significantly associated with ACLF development for both 28 and 90 days in the multivariate model (Tables S2A and S2B and Tables S5A and S5B). Stratified by the sub-cohorts of visceral and non-visceral surgery, multivariate analysis showed that surgery without preoperative TIPS is a predictor for 90-day ACLF development in patients undergoing visceral surgery but not non-visceral surgery (Tables S6A and S6B).

Sensitivity analysis shows an E-value of 3.902, which indicates that the observed HR of 3.256 for ACLF development in the absence of TIPS at surgery could be explained away by an unmeasured confounder that is associated with both the presence of TIPS and ACLF development by a risk ratio of 3.9-fold each, above and beyond the measured confounders, but weaker confounding could not do so.

Identification of high-risk patients

ROC analysis was performed for CLIF-C AD with 90-day ACLF development as the endpoint for the TIPS and no-TIPS groups. The results show a significant AUC (Harrell's c 0.69; 95% CI 0.534–0.876) for the no-TIPS group (p = 0.041), whereas it does not for the TIPS group (Harrell's c 0.537; 95% CI 0.256–0.817; p = 0.143). A CLIF-C AD cut-off of 45 in the no-TIPS group was chosen according to the Youden index. In patients with CLIF-C AD ≤45, no significant difference in the development rate of ACLF between the TIPS and no-TIPS groups could be detected (p = 0.610) (Fig. S3). However, in patients with CLIF-C AD >45, patients with TIPS showed a significantly lower rate of ACLF development after surgery (p = 0.015) (Fig. 2C). Adjusted for MELD, a MELD cut-off of ≥10 was identified by the Youden index for the identification of high-risk patients (Harrell's c 0.660 for all patients; 95% CI 0.534–0.785; p = 0.027) (Fig. S4A and S4B).

Postoperative outcome

The median duration of postoperative hospital stay was 11 days in both groups (11 [1–64] days in the TIPS *vs.* 11 [1–44] days in the no-TIPS group, p = 0.94). Patients in the no-TIPS group had significantly higher rates of unplanned readmissions to the intensive care unit owing to postoperative complications compared with the TIPS group (n = 21 [47%] *vs.* n = 11 [24%], p = 0.03). Within 90 days after surgery, patients in the TIPS group showed significantly lower rates of ascites development compared with those in the no-TIPS group (n = 15 [33%] *vs.* n = 25 [56%], p = 0.04). Postoperative blood transfusions were significantly more needed in patients of the no-TIPS group than in those of the TIPS group (n = 20 [44%] *vs.* n = 11 [24%], p = 0.05) (Table 4). Of note, there was no significant difference in the development of postoperative episodes of HE (TIPS: n = 5 [11%] *vs.* no-TIPS: n = 4 [9%], p = 0.73) and postoperative infections (TIPS: n = 13 [29%] *vs.* no-TIPS: n = 19 [42%], p = 0.19) between the groups (Table 4).

Postoperative 1-year mortality

In total, 25 (28%) patients died within 1 year after surgery. Patients in the no-TIPS group had significantly higher 1-year mortality than those in the TIPS group (n = 17 [38%] *vs.* n = 8 [18%], p = 0.023) as shown in the survival curve (Fig. 2B). The most common cause of death was ACLF (n = 21), accounting for 84% of all deaths. The causes of death (ACLF *vs.* non-ACLF related) were not significantly different (Table S7).

Cox regression analysis revealed CLIF-C AD and surgery without preoperative TIPS as independent predictors of 1-year mortality. The type of surgery had no significant impact on the survival rate within 1 year (Table 5).

Discussion

This study is the first to evaluate the postoperative development of ACLF between patients with cirrhosis with and without preoperative TIPS. It shows that the rate of ACLF development is significantly lower in patients with TIPS than in those without. This suggested effect seems to be more pronounced in high-risk patients with CLIF-C-AD scores above 45.

Surgical procedures in patients with cirrhosis are associated with a high complication rate despite advancements in surgical techniques and medical management and carry a mortality rate ranging from 10 to 57%.[18–20] Preoperative risk stratification in clinical practice is done according to traditional established scores such as Child-Pugh or MELD. Recently, the Veterans Outcomes and Costs Associated with Liver Disease (VOCAL)-Penn score was established with excellent prediction for postoperative mortality risk of different surgery types.[21] Among the risk factors for all patients such as the ASA score, portal hypertension has been shown as 1 of the main predictors of fatal postoperative outcome.[22] Owing to splanchnic vasodilation and portosystemic shunting, patients with portal hypertension have reduced hepatic blood flow, predisposing them to hypoperfusion of the liver during surgery, which can subsequently result in liver failure.[19,23,24] Moreover, in a recent study, it was shown that HVPGs of >16 and ≥20 before surgery independently identify high-risk patients.[15]

The high perioperative risk in patients with cirrhosis and portal hypertension may preclude them from undergoing surgical procedures, which may be curative or improve quality of life. Thus, some smaller studies evaluated the feasibility of surgery in those patients, suggesting a benefit of decompression of portal pressure for postoperative complications associated with AD and outcome. Current data indicate that lowering of HVPG by TIPS before surgery may indeed increase the feasibility of planned surgeries in 52–85% of the patients.[25–28] However, only 2 studies addressed postoperative outcome in patients with TIPS compared with those without.[26,29] Unfortunately, the cohorts were matched neither for ASA score nor for liver function, resulting in significantly different Child-Pugh scores between the compared groups and not showing a significant difference in postoperative survival. Our study's approach is unique in 2 ways: Firstly, it is the first to assess ACLF as the primary outcome. Secondly, the study results are based on a 1:1 matched cohort, which is controlled for all of the known confounders such as liver function (MELD and Child-Pugh), ASA score, type of surgery, age, sex, and aetiology of liver cirrhosis. Thus, our study is well controlled for confounders that could influence the results.

However, some unknown confounders may not be ruled out. Recently, TIPS has been shown to improve sarcopaenia and body composition,[30–33] which is not only a risk factor for patients with liver cirrhosis in general but also for surgical procedures.[34–36] Even though our study did not specifically control for sarcopaenia, the BMI, as a surrogate of body composition, was not

significantly different in our study. However, we acknowledge that BMI does not represent sarcopaenia or body composition in patients with ascites. Patients with TIPS showed less ascites than those without and thus may have better body composition and nutritional reserve and have lower rates of sarcopenia with similar BMI as compared with patients without TIPS. This would be in line with the known obesity paradox, which has been also noted in patients undergoing surgery.[37–42] Thus, a potential influence on the observed difference in outcome cannot be ruled out. Although this should be further investigated, it is beyond the scope of this study. Moreover, the optimal rate of reduction of portosystemic pressure gradient should be explored in future prospective studies. Recent studies suggest beneficial effects of the use of smaller stent diameter.[43–45]

When looking at sub-cohorts, analyses reveal that surgery without preoperative TIPS is a predictor for ACLF development in visceral but not non-visceral surgeries. Many studies have shown that abdominal hepatic and non-hepatic surgeries are at an increased risk of poor outcome and that the type of surgery constitutes a major predictor in patients with cirrhosis.[46–48] Elevated HVPG levels before surgery seem to predict outcomes especially in patients undergoing extrahepatic abdominal or open chest surgery. Moreover, animal models showed elevated portal pressure after extrahepatic visceral surgery.[49] These data suggest that increased postoperative mortality might be associated with aggravated portal hypertension in visceral surgery. Recent studies have been focussing on the heterogeneous postoperative risk in patients with cirrhosis and discuss an overprediction of mortality for certain subgroups. The recently established VOCAL-Penn score, differentiating between different types of abdominal, major orthopaedic, or open chest surgery may substantially improve postoperative mortality predictions in patients with cirrhosis.[21,47] In this prediction model, major orthopaedic surgery and vascular surgery were not significantly associated with outcome. In our study, major orthopaedic and vascular surgeries represent the majority of surgeries categorised into non-visceral surgery. However, data on the influence of surgery types regarding ACLF as an endpoint are scarce. Moreover, the patient number in our study is small; thus, conclusions concerning the effect of preoperative TIPS on ACLF in different surgery categories should be considered with caution and be addressed in larger multicentric studies.

In our study, most of the deaths were related to ACLF. This is well in line with the high mortality rate of ACLF reported in the current literature.[7,9] Moreover, TIPS was suggested to be beneficial to very sick patients with cirrhosis with acute variceal bleeding and presence of ACLF regarding mortality and rebleeding rates.[13] Thus, our results, showing the highest effect of TIPS on ACLF development in patients with high CLIF-C-AD scores above 45, are further underlining the robustness of our data in the context of the current literature.

Despite the well-characterised cohort, our study has several limitations. This is a monocentric, retrospective study, which limits the generalisability of the results. Moreover, the study describes a relatively small cohort. Nevertheless, it represents the largest reported cohort of its kind in the current literature and is well controlled (by strict matching criteria) for known confounders of ACLF development and mortality. Moreover, our results are confirmed and strengthened by an internal validation cohort with more permissive 1:2 matching criteria, which allowed us to include almost all patients with preoperative TIPS. Therefore, the number of excluded patients of eligible study patients in the TIPS group was low (11 *vs.* 36%), which reduces the risk of selection bias. ACLF was diagnosed retrospectively; thus, punctual mis-grading of organ failure cannot be ruled out. However, information on the components of ACLF was retrieved from detailed digitalised patient data. Data of HVPG measurements before surgery were not routinely acquired but should be evaluated further in larger studies. However, surrogate parameters of portal hypertension such as varices status, platelet count, and spleen size were comparable. Another important factor for outcome is active alcohol misuse. Comprehensive anamnesis about ongoing alcohol misuse was not available in this retrospective dataset. However, we did not detect persistent harmful alcohol abuse at the time of surgery according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria. Finally, the TIPS group did not specifically receive TIPS for the surgical procedure; thus, an allocation bias of the patients with TIPS cannot be ruled out. However, in a real-life clinical setting, many patients eligible for TIPS do not receive TIPS in the context of acute variceal bleeding, because of TIPS insertion not being possible in every hospital and patients missing the window of opportunity. This underlines that the data we are presenting are representative.[6]

In conclusion, this study suggests for the first time that patients with preoperative TIPS have lower rates of postoperative ACLF development compared with those without. The strongest effect is observed in patients undergoing visceral surgery and those with a CLIF-C AD score above 45.

Abbreviations

ACLF, acute-on-chronic liver failure; AD, acute decompensation; ASA, American Society of Anesthesiologists; CLIF-C AD, Chronic Liver Failure Consortium–Acute Decompensation; HE, hepatic encephalopathy; HR, hazard ratio; HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease; ROC, receiver-operation characteristics; TIPS, transjugular intrahepatic portosystemic shunt; VOCAL, Veterans Outcomes and Costs Associated With Liver Disease.

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Conflicts of interest

The authors have no conflicts of interest. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: JT, MP. Study supervision: JT, MP. Acquisition of data: JC, PH, NB, PL. Analysis of data: JC, PH, NB, PL, JT, MP. Interpretation of data: JC, PH, NB, PL, JT, MP, SM, JD, DK, CJ, CM. Statistical analysis: JC, PH. Administrative, technical, and material support: JCK, CPS, JT, MP. Drafting of the manuscript: JC, PH, JT, MP. Critical revision of the manuscript regarding important intellectual content: NB, PL, SM, JD, DK, CJ, CM, JCK, CPS, JT, MP. Final approval of the version of the manuscript to be published: JT, MP

Data availability statement

Source data are not openly available because of GDPR restrictions but can be requested via the corresponding author.

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Supplementary data

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3.4 Etablierung eines Tiermodells der extrahepatischen Operation bei Zirrhose

“Extrahepatic Surgery in Cirrhosis Significantly Increases Portal Pressure in Preclinical Animal Models.”
Chang J, Meinke J, Geck M, Hebest M, Böhling N, Dolscheid-Pommerich R, Stoffel-Wagner B, Kristiansen G, Overhaus M, Peyman LO, Klein S, Uschner FE, Brol MJ, Vilz TO, Lingohr P, Kalff JC, Jansen C, Strassburg CP, Wehner S, Trebicka J, Praktiknjo M.
Frontiers in Physiology. *2021 Aug; 12:720898.*

Zielsetzung und Methoden

Wie in dieser Habilitationsschrift erörtert, ist die postoperative Dekompensation / ACLF-Entwicklung ein klinisch relevantes Problem bei Patienten mit Leberzirrhose. Der operative Insult ist als auslösendes Ereignis für die Entwicklung von postoperativem ACLF in den vorangegangenen Arbeiten aufgezeigt worden (Chang et al., 2021a, 2022; Klein et al., 2020). Jedoch ist über die zugrundeliegenden Pathomechanismen wenig bekannt. Obwohl die Rolle des präoperativen Portaldrucks auf das postoperative Outcome untersucht wurde, existieren über die postoperative Entwicklung des Portaldrucks keine Daten. Auch geeignete Tiermodelle für die Untersuchung dieser Fragestellung sind bisher nicht bekannt. Um die postoperative Entwicklung von ACLF im Tiermodell untersuchen zu können, wurde in dieser Arbeit ein Tiermodell etabliert, um einen standardisierten extrahepatischen Eingriff in bekannten Tiermodellen der Zirrhose zu simulieren. Dies führte zwei standardisierte Modelle zusammen, nämlich die Methoden der Zirrhoseinduktion durch die Gallengangsligatur (*bile-duct-ligation*, BDL) bzw. der Tetrachlormethan (CCL_4)-Intoxikation mit der intestinalen Manipulation (IM). Nach Erreichen eines kompensierten Stadiums der Zirrhose wurde eine IM durchgeführt. Zwei (2) und sieben (7) Tage später wurden als primärer Endpunkt Messungen der portalen Hämodynamik durchgeführt. Weiterhin erfolgten Untersuchungen zur Erfassung der Fibrose und hepatischen Inflammation.

Ergebnisse

Die postoperative Entwicklung des Portaldrucks nach intestinaler Manipulation

Die Haupterkenntnis der Arbeit war, dass in beiden Zirrhosemodellen und zu beiden Analysezeitpunkten (2 und 7 Tage nach IM) der in-vivo Portaldruck nach IM signifikant

erhöht war vs. Sham-Operation (Medianlaparotomie, LAP) (BDL 2 d: IM 13,9 ± 0,8 mmHg vs. LAP 10,8 ± 0,5 mmHg, p = 0,01; BDL 7 d: IM 12,4 ± 0,6 mmHg vs. LAP 10,0 ± 0,7 mmHg, p = 0,02; CCL4 2 d: IM 13,3 ± 0,8 mmHg vs. LAP 10,7 ± 0,3 mmHg, p = 0,03; CCL4 7 d: IM 13,7 ± 1,1 mmHg vs. LAP 10,2 ± 0,6 mmHg, p = 0,02).

Klinische Parameter, Fibroseprogression und hepatische Inflammation nach intestinaler Manipulation

Postoperativ war in den Zirrhosemodellen im Gegensatz zu den Nicht-Zirrhosemodellen ein signifikanter Gewichtsverlust zu verzeichnen. Laborchemisch waren in den Zirrhosegruppen, so wie man es auch klinisch beim Menschen sieht, nach IM vs. LAP die Transaminasen-Serumlevel signifikant erhöht und das Serumalbuminlevel erniedrigt. In der BDL-Gruppe zeigte sich 7 Tage nach IM eine Progression der Fibrose in Analysen der Sirius-Rot-Färbung, des Hydroxyprolingehalts und in der mRNA-Genexpression von alpha-SMA und Kollagen 1. Bei der mRNA-Genexpression waren 7 Tage nach IM Parameter der (hepatischen) Inflammation signifikant aufreguliert, darunter Transforming growth factor beta 1 (TGF-beta), Interleukin 6 (IL-6), Interleukin 1 beta (IL-1b), Tumornekrosefaktor alpha (TNF-alpha), Chemokine (C-C motif) ligand 2 (CCL2), EGF like module containing mucin-like hormone receptor-like 1 (EMR-1), Toll-like receptor 4 (TLR-4). Zirkulierende Endotoxine waren zwar bei Tieren mit Zirrhose im Gegensatz zu den Kontrolltieren ohne Zirrhose signifikant erhöht, jedoch zeigten sich keine Unterschiede in verschiedenen Gefäßkompartimenten (*Vena cava inferior* vs. Pfortader).

<u>Schlussfolgerungen</u>

Ein Modell zur weiteren Erforschung der postoperativen Dekompensation und ggf. Entwicklung von ACLF konnte etabliert werden. Die klinischen Merkmale nach IM ähneln der dekompensierten Zirrhose beim Menschen. Nach intestinaler Manipulation ist der Portaldruck im Zirrhosemodell signifikant erhöht im Vergleich zur Medianlaparotomie. In der Leber ist dies mit einer Inflammationsreaktion assoziiert. Im Modell der kontinuerlichen Leberschädigung (BDL) zeigt sich zusätzlich eine Progression der Fibrose. Der Effekt der Inflammation insbesondere in Bezug auf die Leber-Darm Achse ist weiter zu erforschen.

ORIGINAL RESEARCH
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Extrahepatic Surgery in Cirrhosis Significantly Increases Portal Pressure in Preclinical Animal Models

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Background: Liver cirrhosis is a relevant comorbidity with increasing prevalence. Postoperative decompensation and development of complications in patients with cirrhosis remains a frequent clinical problem. Surgery has been discussed as a precipitating event for decompensation and complications of cirrhosis, but the underlying pathomechanisms are still obscure. The aim of this study was to analyze the role of abdominal extrahepatic surgery in cirrhosis on portal pressure and fibrosis in a preclinical model.

Methods: Compensated liver cirrhosis was induced using tetrachlormethane (CCL4) inhalation and bile duct ligation (BDL) models in rats, non-cirrhotic portal hypertension by partial portal vein ligation (PPVL). Intestinal manipulation (IM) as a model of extrahepatic abdominal surgery was performed. 2 and 7 days after IM, portal pressure was measured *in-vivo*. Hydroxyproline measurements, Sirius Red staining and qPCR measurements of the liver were performed for evaluation of fibrosis development and hepatic inflammation. Laboratory parameters of liver function in serum were analyzed.

Results: Portal pressure was significantly elevated 2 and 7 days after IM in both models of cirrhosis. In the non-cirrhotic model the trend was the same, while not statistically significant. In both cirrhotic models, IM shows strong effects of decompensation, with significant weight loss, elevation of liver enzymes and hypoalbuminemia. 7 days after IM in the BDL group, Sirius red staining and hydroxyproline levels showed significant progression of fibrosis and significantly elevated mRNA levels of hepatic inflammation compared to the respective control group. A progression of fibrosis was not observed in the CCL4 model.

Conclusion: In animal models of cirrhosis with continuous liver injury (BDL), IM increases portal pressure, and development of fibrosis. Perioperative portal pressure and hence inflammation processes may be therapeutic targets to prevent post-operative decompensation in cirrhosis.

Keywords: surgery, acute decompensation, cirrhosis, ACLF, portal pressure, HVPG, intestinal manipulation

INTRODUCTION

Liver cirrhosis is the common end-stage of chronic liver diseases. Acute decompensation (AD) such as variceal bleeding, refractory ascites, hepatorenal syndrome, or hepatic encephalopathy can develop and define advanced stages (Angeli et al., 2018). AD may also precipitate acute-on-chronic liver failure (ACLF), a distinct syndrome recently characterized in the CANONIC- and PREDICT-study (Moreau et al., 2013; Gustot et al., 2015; Trebicka et al., 2019, 2020a,b). ACLF is defined by the development of multiorgan failure resulting in high short-term mortality.

Postoperative decompensation of cirrhosis is a well-known but still unsolved problem in surgery. Even though there has been substantial progress in the fields of hepatology and surgery in managing patients with cirrhosis, surgery-associated AD and mortality remains high and correlates with severity of liver disease (Friedman, 2010; de Goede et al., 2012). Recently, the role of surgery as a precipitating event for ACLF development has been characterized, resulting in high rates of ACLF development even after electively performed surgical procedures (Klein et al., 2020; Chang et al., 2021). Therefore, in many hospitals, with the presence of cirrhosis especially in advanced stages is considered a contraindication for all kinds of surgery.

Clinically significant portal hypertension has been associated with increased numbers of episodes of acute decompensation after hepatic surgery (Bruix et al., 1996). In a recent prospective study, hepatic venous pressure gradient (HVPG) has also been described as a predictor for mortality after extrahepatic surgery, indicating that optimization of portal hypertension might be the key to improve postoperative outcome (Reverter et al., 2019). However, data about underlying mechanisms of post-operative decompensation and characterization of portal pressure in the pre- and post-operative period are at best scarce and thus need to be studied more to shed light on the pathophysiology involved in the post-operative development of AD and ACLF.

In this context, preclinical models to characterize proinflammatory downstream signaling and portal hemodynamics that help to understand the pathophysiology of post-operative decompensation of cirrhosis are needed. This study aimed to establish a preclinical model of extrahepatic abdominal surgery in animal models of portal hypertension and to study consecutive changes of portal pressure and liver fibrosis.

Abbreviations: 18s rRNA, Eukaryotic 18S ribosomal ribonucleic acid; ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BDL, bile-duct ligation; CCL2, chemokine (C-C motif) ligand 2; CCL4, tetrachlormethane; cDNA, complementary desoxyribonucleic acid; CTP, Child-Turcotte-Pugh; EMR-1, EGF-like module containing mucin-like hormone receptor-like 1; HE, hematoxylin and eosin; HVPG, hepatic venous pressure gradient; i.p., intraperitoneal; ICU, intensive care unit; IL-6, interleukin 6; IL1b, interleukin 1 beta; IM, intestinal manipulation; LAP, median laparotomy; mRNA, messenger ribonucleic acid; PE, Polyethylen; qPCR, real-time polymerase chain reaction; TGF-beta, transforming growth factor beta 1; TIPS, transjugular portosystemic shunt; TLR-4, toll-like receptor 4; TNF-alpha, tumor necrosis factor alpha; TP, total protein.

MATERIALS AND METHODS

Animal Experiments

Specific pathogen-free male Sprague Dawley rats were used for this study. Animals were acquired from Charles-River (Sulzfeld, Germany) and maintained in the animal facility at the University Clinic of Bonn, Department for Experimental Therapy in individually ventilated cages with a 12:12-h day-night cycle at 22 °C. Water and chow were provided *ad libitum*. Animal studies were performed in accordance with the German Animal Welfare Act and standard operation procedures of the Laboratory of Liver Fibrosis and Portal Hypertension and the animal care facility. Studies were approved by the Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen (LANUV, Reference: 81-02-04.2018.A348). Animals were sufficiently handled before all operations and received sufficient pain medication after all operations. When reaching human endpoint the experiment was stopped and animals were euthanized.

Establishing a Preclinical Model of Extrahepatic Abdominal Surgery in Cirrhosis and Non-cirrhotic Portal Hypertension

A two-step animal model of extrahepatic abdominal surgery was established. Cirrhosis was induced via bile duct ligation (BDL) and CCL4-intoxication via inhalation, non-cirrhotic portal hypertension via partial portal vein ligation (PPVL) as previously described (Uschner et al., 2015; Klein et al., 2017). 3 weeks after BDL or PPVL and 14 weeks after CCL4-intoxication (stage of compensated cirrhosis) intestinal manipulation (IM) was performed as previously described (Bortscher et al., 2012; Chang et al., 2012). 2 and 7 days after IM *in-vivo* portal pressure measurement was performed according to established protocol. Animals were then sacrificed and harvested. The experimental design is shown in **Figure 1**.

Bile Duct Ligation (BDL)

BDL was performed as previously described in a sterile environment (Uschner et al., 2015; Klein et al., 2017). In short, the common bile duct was ligated twice and dissected between the two ligatures to induce cholestatic cirrhosis. Sham animals received a median laparotomy (group name: Sham). All BDL procedures were performed by the same individual.

CCL4-Inhalation

Inhalation with CCL4 (abcr, Karlsruhe, Germany) was started at the age of 4 weeks (80–100 g body weight) and performed as previously described (Klein et al., 2017; Brol et al., 2019). Inhalation was done twice a week in growing intervals of 30 s. Reaching 5 min, animals inhaled CCL4 until week 14 (stage of compensated cirrhosis). All animals received phenobarbital (0.33 g/l) via drinking water for induction of cytochrome P-450 metabolic activity starting from 1 week before CCL4 inhalation until animal sacrifice. Inhalation was stopped 3 days before IM as a model of toxic cirrhosis with removal of the injuring agent. Age-matched animals without CCL4 inhalation served as controls (group name: AIR).

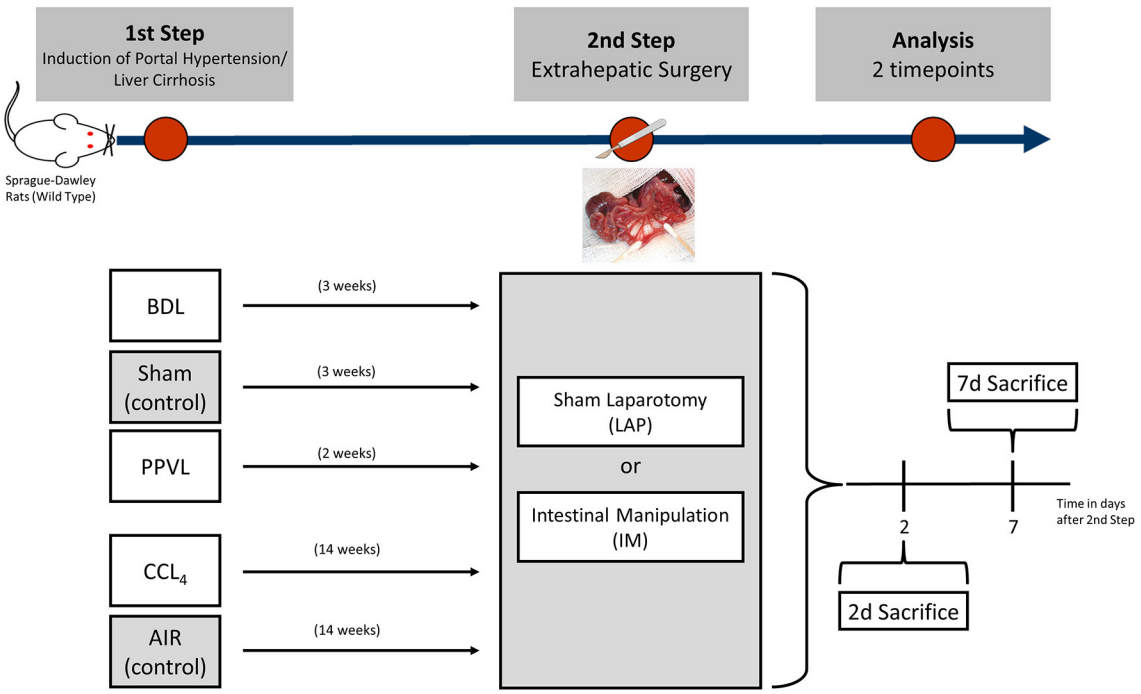

FIGURE 1 | Diagram showing how a two-step pre-clinical model of extrahepatic abdominal surgery (intestinal manipulation) in Sprague-Dawley rats with cirrhosis induced through bile duct ligation (BDL) or inhalation of tetrachlormethan (CCL4) and non-cirrhotic portal hypertension via partial portal vein ligation (PPVL) was established with two timepoints of final analysis.

Partial Portal Vein Ligation (PPVL)

To induce non-cirrhotic portal hypertension via PPVL, the portal vein was ligated around a 22 G needle. After ligation, the 22 G needle was removed immediately, resulting in a smaller diameter of the portal vein with consecutive development of non-cirrhotic portal hypertension. The same sham group used for the BDL group served as controls (group name: Sham). All PPVL procedures were performed by the same individual.

Intestinal Manipulation (Model of Extrahepatic Abdominal Surgery)

Intestinal manipulation (IM) was performed as previously described (Chang et al., 2012). IM was chosen as an established standardized model associated with postsurgical local inflammation and breakup of extracellular matrix in the gut wall (Chang et al., 2012). After median laparotomy, cecum and small bowel were placed on moist gauze outside the abdominal cavity. Then the entire small bowel and colon were manipulated between two sterile cotton swabs twice in a standardized fashion. The intestine was kept moist with saline at all times. After IM the intestine was placed back into the abdominal cavity, the abdomen was then closed with two layers of sutures. Age-matched animals only receiving a median laparotomy without IM served as sham controls (group name: LAP). All IM procedures were performed by the same individual.

Portal Pressure Measurement and Animal Sacrifice

Before sacrifice animals were put into anaethesia with an intraperitoneal injection of ketamine/xylazin (dose: ketamin 100 mg/kg/body weight (bw)/xylazin: 20 mg/kg/bw). After median laparotomy, for *in-vivo* portal pressure measurements the portal vein was dissected and punctured with a polyethylen catheter (B. Braun, Melsungen, Germany). The catheter was fixated with a vascular clamp. Portal pressure was then recorded over a time of 5 min under echocardiogram monitoring using PowerLab 8/35 and LabChart Software (ADInstruments, Dunedin, New Zealand). The used value of portal pressure and heart frequency of one biological replicate for further analysis, was determined as mean of three randomly chosen values in the recorded phase after calibrated recording. After portal pressure measurement and aquiring blood samples from the caval vein, the animal was sacrificed by dissecting the inferior caval vein. Liver samples were snap frozen in liquid nitrogen at −80 °C, fixated in 4% paraformaldehyde and embedded in paraffin or in Tissue Tek OCT (Sakura Finetek, Staufen, Germany).

Measurement of Hydroxproline Content in Liver Samples

Hydroxyproline content measurement was performed as described previously (Brol et al., 2019). Snap-frozen liver samples were weighed and dissolved in 12 N hydrochloric acid at 110 °C, then homogenized and incubated for another 16 h

at 110 °C. After filtering, samples were dissolved in methanol and oxidized in a chloramine T buffer. Finally, Ehrlich's reagent was added, the photometric product was measured at 558 nm wave length.

Parameters of Hepatic Inflammation and Circulating Endotoxin Levels

Hepatic inflammation was assessed by mRNA gene expression. RNA isolation was done using the ReliaPrep RNA Miniprep Systems (Promega, Madison, WI). For cDNA synthesis ImProm-II Reverse Transcription System (Promega, Madison, WI) was used. For every sample, two DNase digestion steps were done for genomic DNA to be disposed. Quantitative PCR (qPCR) was carried out using TaqMan gene expression assays (Thermo Fisher Scientific, Waltham, MA) according to the manufacturer's protocol. qPCR amplification was performed on the 7300 Real-Time PCR Cycler (Applied Biosystems, Foster City, CA). qPCR analyses were done using duplicates. Gene expression was calculated with the Delta-Delta CT method. 18s rRNA was used as housekeeping gene. Levels of gene expression are shown as x-fold compared to the respective control group. A list of gene expression assays is shown in **Supplementary Table 1**.

Circulating endotoxin levels were measured using the Pierce Limulus Amebocyte Lysate (LAL) Chromogenic Endotoxin Quantitation Kit (Thermo Fisher Scientific, Oberhausen, Germany) according to the manufacturer's protocol. In short, all samples were diluted and adjusted to a pH between 6 and 8. After pipetting standards and samples on a 96-well plate and incubating at 37 °C for 4 h, activation in the modified LAL was stopped. Endotoxin concentration was then photometrically measured at 405 nm wavelength. Levels of endotoxin are expressed as EU/ml. Only endotoxin-free plastic ware or sterile glass ware was used for the experiment.

Histological Staining and Quantification

Sirius red and Hematoxylin and eosin (HE) stainings were performed on paraffin slides (2–3 μm) of the liver as previously described (Trebicka et al., 2011; Schierwagen et al., 2015; Brol et al., 2019). Stainings were captured with a Nikon Digital Sight DS-Vi1 microscope (Chiyoda, Tokyo, Japan) and quantified via ImageJ software (V.1.51q; National Institutes of Health, Bethesda, USA) using macros for automatized quantification and color detection. Individual samples were controlled for correct analysis, if color analysis was not executed properly, threshold was adjusted manually. Images were taken in 10-fold magnification and a minimum of 10 representative fields per biological replicate were taken into analysis.

Analysis of Laboratory Parameters of Liver Function

Electrolytes (sodium, potassium) and parameters of liver function (alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), total protein, and ammonia were analyzed in serum using the Cobas 8000 (Roche Diagnostics, Rotkreuz, Switzerland), modules 8000 ISE, c502, and c702 according to the manufacturer's protocol.

Statistical Analyses

Statistical analyses were performed using Prism V.5.0 (GraphPad, San Diego, CA). Data are expressed as means ± SEM. For comparisons between two groups, student's *t*-test was used. *P*-values ≤ 0.05 were considered significant.

RESULTS

Establishing a Preclinical Model of Extrahepatic Intestinal Surgery in Different Animal Models of Cirrhotic or Non-cirrhotic Portal Hypertension

Only animals that recovered completely from the first operation (BDL, PPVL, Sham) were included in the final analysis. Animals were then randomized into a group that underwent intestinal manipulation (IM) or median laparotomy (LAP). Animals presenting with ascites as a clinical sign of AD prior to IM or LAP were excluded from the experiment.

Due to the more aggressive nature of cirrhosis and expected higher postoperative mortality rate in BDL, a preliminary study had to be performed to determine the optimal time for IM after induction of cirrhosis. This preliminary study was approved within the applied project. When IM was performed 28 days after BDL, postoperative mortality was high, as expected (30%, data not shown). Therefore, the time point of 21 days (3 weeks) after BDL with a mortality of 10% after IM was established for the experiment.

Postoperative Mortality and Development of Ascites After Intestinal Manipulation

Combined postoperative mortality for BDL, PPVL, and CCL4 groups after IM for both timepoints (2 and 7 days after IM) was 10, 0, and 6%, respectively. Due to a low number of animal deaths without significant distribution concerning time after IM or operation type (IM/LAP), survival analysis was not performed. No deaths were recorded in all control groups (Sham (controls for BDL and PPVL), AIR (controls for CCL4) (**Figure 1**) after IM or LAP. In the BDL group that underwent IM and were sacrificed 7 days after IM, 3 (43%) developed ascites, vs. 1 (13%) animal in the control group ($p = 0.3$). The rate of development of ascites in the CCL4 group was similar 7 days after IM (IM 3 (38%) vs. LAP 1 (14%), $p = 0.5$). No animals in in BDL and CCL4 groups developed ascites 2 days after IM, also none of the animals belonging to the PPVL groups developed ascites.

Weight Development

Significant weight differences were observed in all models of cirrhosis or non-cirrhotic portal hypertension at time of IM, compared to the respective control groups (Sham, Air), with a significantly lower body weight in the PPVL, BDL, and CCL4 groups at the time of IM vs. LAP (**Supplementary Figure 1**).

Moreover, significant weight loss was observed in some groups after IM vs. LAP. In the BDL model, 7 days after IM animals lost significantly more weight compared to LAP, but not at 2 days (**Table 1B**). The same effect was observed in the CCL4 groups

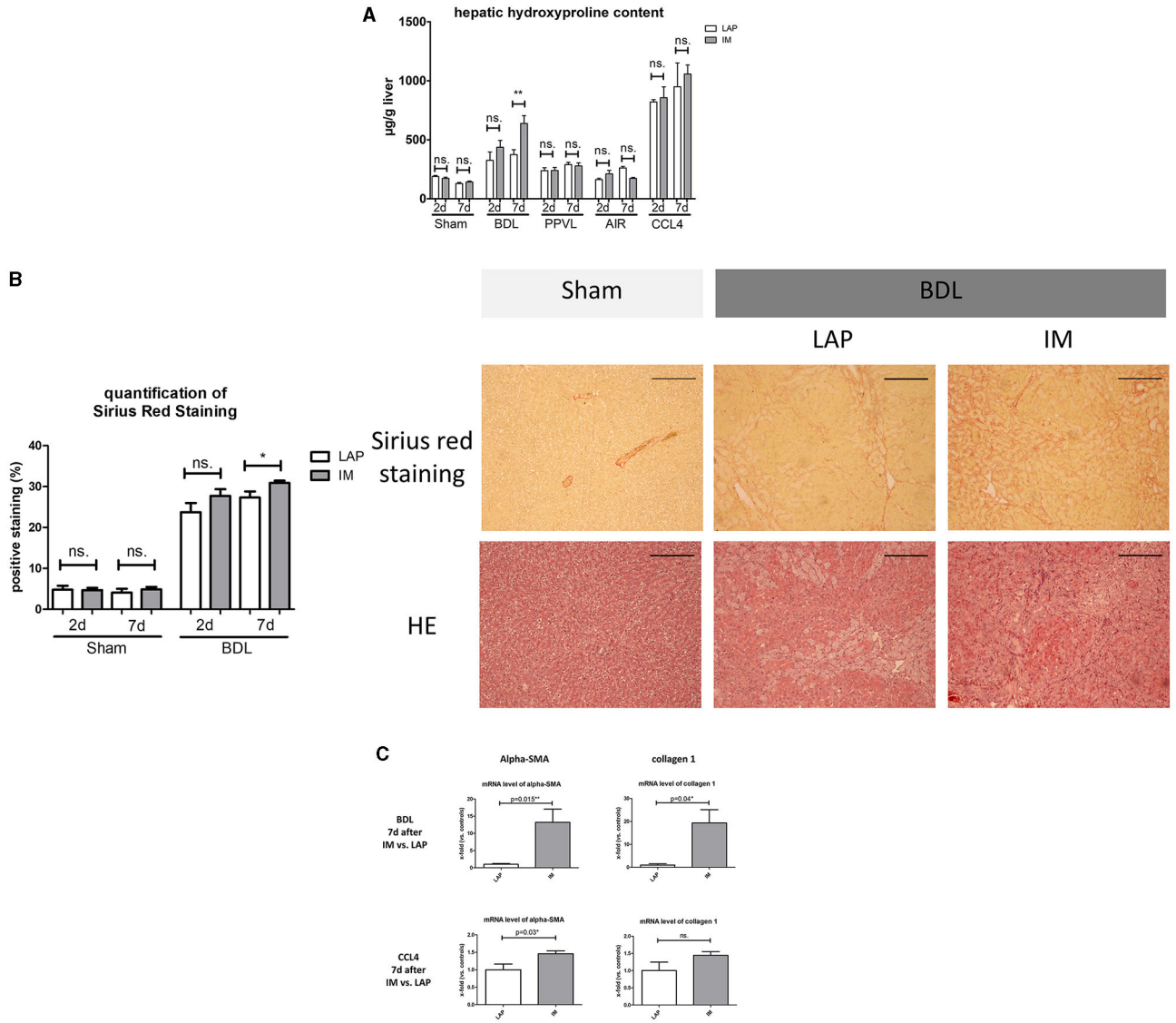

FIGURE 2 | (A) Hepatic hydroxyproline content measurements 2 or 7 days after IM vs. LAP, showing progression of fibrosis through a highly significant elevation of hydroxyproline concentration (expressed in µg/g liver) of the liver in the BDL group 7 days after IM vs. LAP. No differences are seen within the Sham, PPVL, and CCL4 groups. **(B)** Representative images of liver samples with Sirius-red staining for assessment of fibrosis with observed significant differences of fibrosis (expressed as percentage of positive stained area) 7 days after intestinal manipulation vs. the respective control group (LAP). Images of Hematoxylin Eosin staining are shown for morphologic comparison. The scale bar is 200 µm. **(C)** mRNA gene expression for alpha-SMA and collagen 1, showing a significant increase of both parameters of fibrosis progression in the BDL group 7 days after IM and for alpha-SMA in the CCL4 group 7 days after IM. Levels of gene expression are shown as x-fold compared to the respective control group. *$p \leq 0.05$; **$p \leq 0.01$; ns. ($p > 0.05$).

(**Table 1D**). In the control and PPVL groups, weight loss before and after IM, was not statistically significant (**Tables 1B**,**D**,**F**).

Laboratory Parameters of Liver Function at the Time of Sacrifice

Among laboratory parameters representing liver function in the Sham and AIR groups, no significant changes could be observed between IM and LAP groups (**Table 1A**).

In the BDL groups, Alkaline phosphatase (ALP) and Aspartate aminotransferase (AST) were significantly elevated 7 days after IM vs. LAP (**Table 1A**). Albumin levels were significantly lower, 2 and 7 days after IM vs. LAP (**Table 1A**). Interestingly, ammonia serum levels were elevated 2 days after IM vs. LAP (**Table 1B**).

In the CCL4 group, AST and ALT were significantly elevated 7 days after IM vs. LAP (**Table 1D**), while albumin levels were significantly lower (**Table 1D**). No significant differences in laboratory parameters were observed 2 days after IM vs. LAP.

In the PPVL group 2 days after IM, AST was significantly elevated vs. LAP (**Table 1E**). No other significant differences were observed 2 and 7 days after IM vs. LAP.

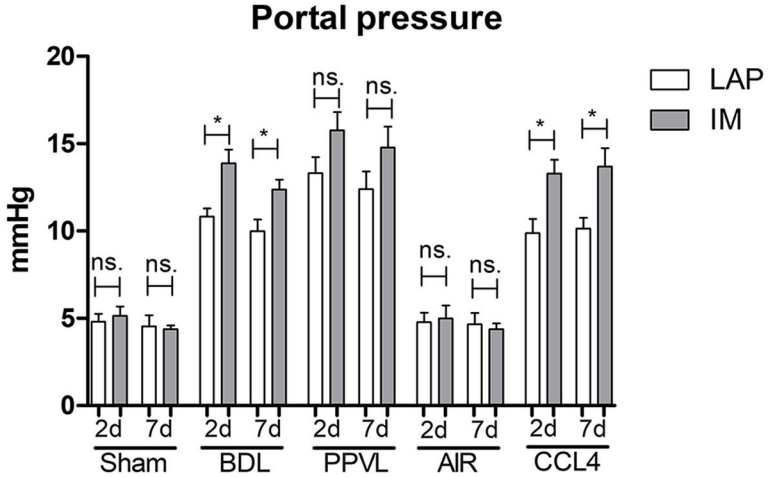

FIGURE 3 | *In-vivo* portal pressure development 2 or 7 days after IM vs. LAP in the different animal models (BDL and PPVL vs. Sham and CCL4 vs. AIR), showing significantly elevated portal pressure after IM in all BDL and CCL4 groups. *$p \leq 0.05$; ns. ($p > 0.05$).

Development of Hepatic Fibrosis After Intestinal Manipulation

Hydroxyproline measurement showed significant increase of hydroxyproline levels and significantly larger Sirius-Red stained areas in the BDL group 7 days after IM vs. LAP (**Figures 2A,B**). In the BDL group 7 days after IM, mRNA expression of alpha-SMA (a marker of profibrogenic hepatic stellate cells) and collagen 1 were significantly upregulated compared to LAP (13- and 19-fold, $p = 0.02$ and $p = 0.04$, respectively) (**Figure 2C**). In the other cirrhotic and non-cirrhotic groups (PPVL, Sham, Air, CCL4), no significant differences in fibrosis development between animals receiving IM vs. LAP could be observed, except a slight, but significant upregulation of alpha-SMA gene expression in the CCL4 group 7 days after IM compared to LAP (**Figures 2A,C**; **Supplementary Figure 2**).

Portal Pressure After Intestinal Manipulation

In the cirrhotic groups (BDL and CCL4) portal pressure was significantly elevated 2 and 7 days after IM compared to LAP (BDL 2 d: IM 13.9 ± 0.8 mmHg vs. LAP 10.8 ± 0.5 mmHg, $p = 0.01$*; BDL 7 d: IM 12.4 ± 0.6 mmHg vs. LAP 10.0 ± 0.7 mmHg, $p = 0.02$; CCL4 2 d: IM 13.3 ± 0.8 mmHg vs. LAP 10.7 ± 0.3 mmHg, $p = 0.03$; CCL4 7 d: IM 13.7 ± 1.1 mmHg vs. LAP 10.2 ± 0.6 mmHg, $p = 0.02$) (**Figure 3**; **Tables 1A–D**). The control groups (Sham, AIR) did not show any significant increase of portal pressure after IM or LAP (**Figure 3**; **Tables 1A–D**). While there was a trend of higher portal pressure after IM in the PPVL group, results were not significantly different compared to LAP (**Figure 3**; **Tables 1E,F**).

Parameters of Hepatic Inflammation and Circulatory Level of Endotoxins

Transforming growth factor beta 1 (TGF-beta), interleukin 6 (IL-6), interleukin 1 beta (IL-1b), tumor necrosis factor alpha (TNF-alpha), chemokine (C-C motif) ligand 2 (CCL2), EGF-like module containing mucin-like hormone receptor-like 1 (EMR-1), toll-like receptor 4 (TLR-4) were measured in liver samples via mRNA gene expression as parameters of hepatic inflammation. These inflammatory parameters were elevated in the BDL group 7 days after IM but not 2 days after IM vs. LAP, especially IL-6 (25-fold), TNF-alpha (14-fold) and CCL2 (8-fold) ($p = 0.05$, $p = 0.006$, $p = 0.02$, respectively) (**Figure 4**). In the CCL4 model IL-6 gene expression was significantly upregulated after IM vs. LAP among the measured inflammatory parameters (**Supplementary Figure 3**).

Endotoxin levels were measured in the different models 2 and 7 days after IM/LAP as a marker of bacterial translocation as possible trigger for upregulation of hepatic inflammation. No significant differences could be detected 2 and 7 days after IM/LAP between operation type (IM vs. LAP) or blood compartment (portal vein vs. caval vein). However, in both cirrhosis models circulatory level of endotoxins was significantly higher than in the non-cirrhotic groups (**Supplementary Figure 4**).

DISCUSSION

This study is the first to characterize portal pressure after abdominal extrahepatic surgery in preclinical models of cirrhosis with ongoing hepatic injury (BDL) and discontinued hepatic injury (CCL4) prior to surgery. It shows that an abdominal extrahepatic surgical procedure significantly increases portal pressure, rendering our model suitable for studying pathomechanisms of post-operative acute decompensation (AD).

Postoperative AD in patients with cirrhosis is a long existing clinical problem which to date limits surgical procedures in cirrhosis. Moreover, AD can precipitate ACLF, resulting in multiorgan-failure and high short-term mortality (Moreau et al., 2013; Trebicka et al., 2020a). In previous studies, our group

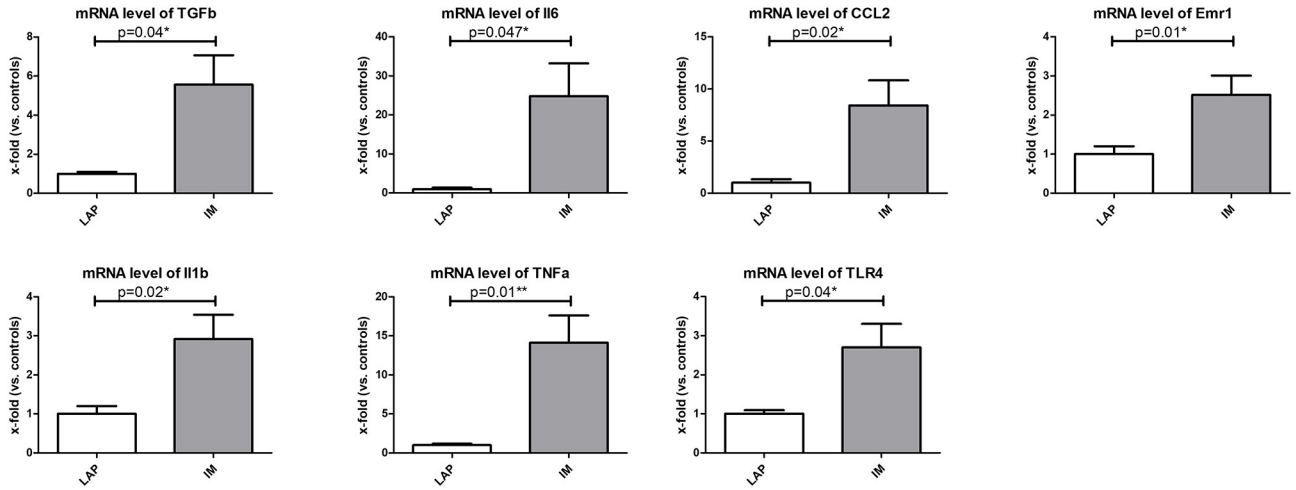

FIGURE 4 | Analysis of parameters of hepatic inflammation (TGFb, IL-6, IL-1b, TNF-alpha, Emr1, TLR-4) in the BDL group 7 days after IM vs. LAP, all significantly elevated. Levels of gene expression are shown as x-fold compared to the respective control group. $^{*}p \leq 0.05$; $^{**}p \leq 0.01$; ns. ($p > 0.05$).

TABLE 1A | General characteristics and clinical data of rats undergoing Sham/BDL at sacrifice 2 days after IM/LAP.

Parameter		Sham + LAP $n = 8$	Sham + IM $n = 8$	*p*	BDL + LAP $n = 7$	BDL + IM $n = 7$	*p*
Weight data	Liver weight [g]	15 ± 0.6	14.4 ± 0.8	0.41	13.7 ± 0.8	13.3 ± 0.8	0.7
	Body weight at sacrifice [g]	394.6 ± 8.5	393.2 ± 17.9	0.94	330.9 ± 18.2$^{\#}$	329 ± 15.3$^{\#}$	0.94
	Weight development surgery - sacrifice [%]	−0.25 ± 1.3	−2.7 ± 3.2	0.52	−5.3 ± 2.2$^{\$}$	−5.4 ± 0.9$^{\$}$	0.94
Baseline laboratory	Sodium [mmol/l]	134.8 ± 2.6	137.0 ± 1.2	0.41	137.4 ± 1.2	139 ± 1.1	0.39
	ALP [U/L]	148.2 ± 21.3	141.3 ± 10.4	0.76	131.3 ± 8.3$^{\$}$	151.8 ± 29.3$^{\$}$	0.48
	AST [U/L]	88.8 ± 15.7	81.3 ± 6.3	0.63	96 ± 4.7$^{\$}$	110.8 ± 17.3$^{\$}$	0.39
	ALT [U/L]	47.3 ± 4	38.7 ± 3.4	0.15	47.3 ± 3.5$^{\$}$	47.3 ± 3.5$^{\$}$	0.47
	ALB [g/L]	30.4 ± 0.5	31.7 ± 1.3	0.41	30.6 ± 0.5$^{\$}$	27.3 ± 0.9$^{\#}$	0.009**
	TP [g/L]	50.3 ± 0.6	51.9 ± 1.8	0.49	50 ± 0.6$^{\$}$	47.3 ± 1.3$^{\$}$	0.07
	Urea [mg/dl]	38.0 ± 2.4	44.3 ± 6.0	0.41	37.8 ± 2.5$^{\$}$	42.0 ± 4.9$^{\$}$	0.44
	Ammonia [μmol/L]	121.3 ± 6.4	106.7 ± 8.1	0.2	101.6 ± 18.5$^{\$}$	191.5 ± 17.6$^{\#}$	0.007**
Hemodynamics	Portal Pressure [mmHg]	4.8 ± 0.5	5.1 ± 0.5	0.64	10.8 ± 0.5$^{\#\#}$	13.9 ± 0.8$^{\#\#\#}$	0.011*
	Heart frequency [bpm]	195 ± 12.8	200 ± 12.8	0.77	202.2 ± 22.0	208.9 ± 13.9	0.82

Sham vs. BDL: $^{\#}p \leq 0.05$; $^{\#\#}p \leq 0.01$; $^{\#\#\#}p \leq 0.001$; $^{\$}$ns. ($p > 0.05$). BDL + LAP vs. BDL + IM: $^{*}p \leq 0.05$.

showed that about 25% of patients with cirrhosis develop post-operative ACLF, including emergency surgery (Klein et al., 2020). Similar rates of post-operative ACLF are demonstrated even in elective surgical procedures, thus establishing surgical procedures as a precipitant of ACLF (Chang et al., 2021). In clinical practice, Child-Turcotte-Pugh-Score is commonly used for pre-operative risk stratification. Higher Child-Turcotte-Pugh-Score at the time of surgery is associated with higher mortality (Friedman, 2010). However, more biomarkers and clinical parameters are needed for better risk stratification for patients with liver cirrhosis in need of a surgical procedure.

Portal pressure seems to play an important role in post-operative outcome of patients with cirrhosis. In a recent prospective study, it was shown that preoperative HVPG below 16 mmHg before a surgical procedure is associated with a better postoperative outcome (Reverter et al., 2019). In a series of smaller studies it was shown that preoperative decompression of portal pressure via transjugular portosystemic shunt (TIPS) improves post-operative outcome, thus the concept of preoperative TIPS has been discussed as well (García-Pagán et al., 2020). However, no studies investigated the evolution of portal pressure after surgery, limiting the investigation

TABLE 1B | General characteristics and clinical data of rats undergoing Sham/BDL at sacrifice 7 days after IM/LAP.

Parameter		Sham + LAP $n = 8$	Sham + IM $n = 8$	p	BDL + LAP $n = 8$	BDL + IM $n = 7$	p
Weight data	Liver weight [g]	17.2 ± 0.4	15.9 ± 0.8	0.17	12.8 ± 1.3	15.3 ± 1.4	0.24
	Body weight at sacrifice [g]	408.5 ± 7.3	396.3 ± 12.6	0.42	345.0 ± 34.4$^{\$}$	312.6 ± 16.6$^{\#\#}$	0.42
	Weight development surgery - sacrifice [%]	−1.1 ± 1	−1.4 ± 1.8	0.9	4.5 ± 4$^{\$}$	−8.4 ± 3$^{\$}$	0.03*
Baseline laboratory	Sodium [mmol/l]	135.9 ± 1.1	137.4 ± 0.6	0.31	141.4 ± 1.4	141.8 ± 0.5	0.83
	ALP [U/L]	160.0 ± 7.1	147.8 ± 11.6	0.36	154 ± 19.7$^{\$}$	340.8 ± 57.4$^{\#}$	0.01*
	AST [U/L]	76.3 ± 6.4	81.5 ± 4	0.48	116.2 ± 22.7$^{\$}$	288.3 ± 80.4$^{\#}$	0.05*
	ALT [U/L]	49.4 ± 3.5	45.2 ± 1.6	0.36	50.2 ± 11.7$^{\$}$	69.8 ± 13.7$^{\$}$	0.31
	ALB [g/L]	32.6 ± 0.6	32.7 ± 0.9	0.92	32.7 ± 1.6$^{\$}$	22.3 ± 2.1$^{\#\#}$	0.002**
	TP [g/L]	52.1 ± 0.6	50.3 ± 1.4	0.22	50.5 ± 1.7$^{\$}$	42.5 ± 2.7$^{\#\#}$	0.01*
	Urea [mg/dl]	36.7 ± 3.6	31.3 ± 1.8	0.25	29.5 ± 2.4$^{\$}$	44.1 ± 5.7$^{\$}$	0.07
	Ammonia [μmol/L]	92.2 ± 14.4	80.3 ± 19.11	0.63	100 ± 12.9$^{\$}$	223.6 ± 65$^{\$}$	0.07
Hemodynamics	Portal Pressure [mmHg]	4.5 ± 0.6	4.4 ± 0.2	0.82	10.0 ± 0.7$^{\#\#\#}$	12.4 ± 0.6$^{\#\#\#}$	0.02*
	Heart frequency [bpm]	205.8 ± 16.7	196.6 ± 14.2	0.73	199.1 ± 20.34	197.2 ± 15.37	0.94

Sham vs. BDL: $^{\#}p \leq 0.05$; $^{\#\#}p \leq 0.01$; $^{\#\#\#}p \leq 0.001$; $^{\$}$ns. ($p > 0.05$). BDL + LAP vs. BDL + IM: $^{*}p \leq 0.05$.

TABLE 1C | General characteristics and clinical data of rats receiving AIR/CCL4 at sacrifice 2 days after IM/LAP.

Parameter		Air + LAP $n = 8$	Air + IM $n = 8$	p	CCL4 + LAP $n = 7$	CCL4 + IM $n = 8$	p
Weight data	Liver weight [g]	19.6 ± 0.6	18.9 ± 0.7	0.45	19.2 ± 0.7	17.6 ± 0.6	0.1
	Body weight at sacrifice [g]	546.5 ± 11.7	546.8 ± 11.4	0.99	438.4 ± 15.12$^{\#\#\#}$	422.8 ± 22.58$^{\#\#}$	0.57
	Weight development surgery - sacrifice [%]	−3.8 ± 0.6	−6.1 ± 1.0	0.1	−1.6 ± 2.0$^{\$}$	−7.1 ± 1.3$^{\$}$	0.07
Baseline laboratory	Sodium [mmol/l]	139.4 ± 0.2	138.2 ± 1.9	0.6	142.2 ± 0.3	142.5 ± 1.0	0.8
	ALP [U/L]	95.7 ± 10.7	79.6 ± 7.2	0.3	177.4 ± 20$^{\#}$	150 ± 27.4$^{\#}$	0.4
	AST [U/L]	94.8 ± 10.9	102.4 ± 7.0	0.6	338.3 ± 29.2$^{\#\#\#}$	405 ± 77.7$^{\#}$	0.5
	ALT [U/L]	42.8 ± 1.2	36.6 ± 3.5	0.13	132.4 ± 16.7$^{\#\#\#}$	131.2 ± 22.7$^{\#\#}$	0.96
	ALB [g/L]	33.5 ± 0.9	35.0 ± 1.2	0.4	33.3 ± 0.9$^{\$}$	32.5 ± 0.8$^{\$}$	0.6
	TP [g/L]	51.4 ± 1.8	53.4 ± 2.0	0.5	49.5 ± 1.3$^{\$}$	50.2 ± 1.4$^{\$}$	0.7
	Urea [mg/dl]	36.4 ± 1.2	39.9 ± 2.0	0.2	25.2 ± 2.6$^{\#\#}$	29.6 ± 3.3$^{\#}$	0.3
	Ammonia [μmol/L]	73.8 ± 5.3	106.8 ± 26	0.24	107.6 ± 17.9$^{\#\#}$	85.8 ± 6.0$^{\#\#\#}$	0.3
Hemodynamics	Portal Pressure [mmHg]	4.8 ± 0.6	5.0 ± 0.7	0.81	10.7 ± 0.3$^{\#\#\#}$	13.3 ± 0.8$^{\#\#\#}$	0.03*
	Heart frequency [bpm]	205.9 ± 11.03	201.0 ± 14.6	0.8	203.7 ± 15.0	197.5 ± 34.8	0.86

AIR vs. CCL4: $^{\#}p \leq 0.05$; $^{\#\#}p \leq 0.01$; $^{\#\#\#}p \leq 0.001$; $^{\$}$ns. ($p > 0.05$). BDL + LAP vs. BDL + IM: $^{*}p \leq 0.05$.

of pathophysiological pathways driving post-operative hepatic decompensation. Prospective clinical studies to characterize post-operative measurements of portal pressure in patients with cirrhosis are ethically difficult to perform, given that patients are mostly under postoperative care in the intensive care unit and in danger of AD or ACLF development. Therefore, animal models are needed to explore the mechanisms of postoperative AD or ACLF, and to study the evolution of portal pressure after surgery and its association with potential underlying inflammatory processes.

In our study, we show in two different animal models of cirrhosis (BDL and CCL4), that portal pressure is significantly elevated 2 and 7 days after IM vs. LAP (median laparotomy). Accordingly, in both models, 7 days after IM, there were more clinical events of decompensation such as the development of ascites or significant weight loss. The BDL model seems to mimic the clinical situation after surgery in patients more accurately, showing progression of fibrosis and significant elevation of parameters of hepatic inflammation 7 days after IM and elevation of liver enzymes and ammonia acutely within 2 days after IM. In the BDL model, IM was performed in an earlier stage of fibrosis (3 weeks after BDL), leading to progression of fibrosis and earlier decompensation events after IM vs. LAP. In the CCL4 group however, no significant changes of the fibrosis parameters could be observed after IM compared to LAP. A possible reason might be that IM was performed at more advanced stages of cirrhosis. However, a regression of fibrosis after withdrawal of the injuring agent has been described in the CCL4 model (Nevzorova

TABLE 1D | General characteristics and clinical data of rats receiving AIR/CCL4 at sacrifice 7 days after IM/LAP.

Parameter		Air + LAP $n = 8$	Air + IM $n = 8$	p	CCL4 + LAP $n = 8$	CCL4 + IM $n = 7$	p
Weight data	Liver weight [g]	18.1 ± 0.9	18.8 ± 0.6	0.7	17.7 ± 1.1	16.2 ± 0.9	0.3
	Body weight at sacrifice [g]	540.7 ± 14.8	553.0 ± 14.1	0.6	465.6 ± 4.1$^{\#\#}$	404.6 ± 9.7$^{\#\#\#}$	<0.001***
	Weight development surgery - sacrifice [%]	−4.0 ± 0.5	−3.9 ± 0.7	0.9	−1.2 ± 0.3$^{\$}$	−10.7 ± 2.2$^{\$}$	0.005**
Baseline laboratory	Sodium [mmol/l]	138.8 ± 0.3	139.8 ± 0.6	0.2	141.6 ± 0.8	141.5 ± 1.3	1
	ALP [U/L]	79.2± 11.6	77.4 ± 2.8	0.9	146 ± 23$^{\#}$	194.1 ± 22.6$^{\#\#}$	0.17
	AST [U/L]	75.8 ± 5.7	103. ± 12.1	0.08	171.0 ± 29.0$^{\#}$	306.7 ± 30.7$^{\#\#\#}$	0.02*
	ALT [U/L]	38.0 ± 2.1	43.8 ± 3.7	0.21	77.4 ± 5.4$^{\#\#\#}$	118.7 ± 6.0$^{\#\#\#}$	<0.001***
	ALB [g/L]	34.2 ± 1.0	33.2 ± 0.6	0.4	34.6 ± 1.2$^{\$}$	28.0 ± 1.0$^{\#\#}$	0.0017**
	TP [g/L]	47.7 ± 1.4	48.0 ± 1.5	0.9	49.1 ± 1.1$^{\$}$	45.4 ± 1.3$^{\$}$	0.1
	Urea [mg/dl]	31.9 ± 0.9	40.3 ± 3.3	0.02*	25.8 ± 2.1$^{\#}$	30.7 ± 1.9$^{\#}$	0.1
	Ammonia [μmol/L]	100.2 ± 18.7	109.4 ± 38.4	0.8	86.8 ± 18.3$^{\#}$	111.75 ± 27$^{\$}$	0.5
Hemodynamics	Portal Pressure [mmHg]	4.7 ± 0.7	4.4 ± 0.3	0.71	10.2 ± 0.6$^{\#\#\#}$	13.7 ± 1.1$^{\#\#\#}$	0.02*
	Heart frequency [bpm]	210.2 ± 27.94	194.0 ± 0.5	0.59	190.8 ± 8.3	191.2 ± 8.6	0.43

AIR vs. CCL4: $^{\#}p \leq 0.05$; $^{\#\#}p \leq 0.01$; $^{\#\#\#}p \leq 0.001$; $^{\$}$ns. ($p > 0.05$). CCL4 + LAP vs. CCL4 + IM: $^{*}p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$.

TABLE 1E | General characteristics and clinical data of rats undergoing Sham/PPVL at sacrifice 2 days after IM/LAP.

Parameter		Sham + LAP n =8	Sham + IM $n = 8$	p	PPVL + LAP $n = 8$	PPVL + IM $n = 8$	p
Weight data	Liver weight [g]	15 ± 0.6	14.4 ± 0.8	0.41	14.1 ± 0.7	15.4 ± 1.0	0.34
	Body weight at sacrifice [g]	394.6 ± 8.5	393.2 ± 17.9	0.94	388.1 ± 11.1$^{\$}$	385.7 ± 9.1$^{\$}$	0.87
	Weight development surgery - sacrifice [%]	−0.25 ± 1.3	−2.7 ± 3.2	0.52	0.8 ± 1.0$^{\$}$	−1.8 ± 0.5$^{\$}$	0.16
Baseline laboratory	Sodium [mmol/l]	134.8 ± 2.6	137.0 ± 1.2	0.41	140.1 ± 1.0	139.9 ± 0.6	0.85
	ALP [U/L]	148.2 ± 21.3	141.3 ± 10.4	0.76	132.1 ± 8.3$^{\$}$	135.5 ± 5.6$^{\$}$	0.73
	AST [U/L]	88.8 ± 15.7	81.3 ± 6.3	0.63	82.0 ± 6.0$^{\$}$	123 ± 16.6$^{\$}$	0.04*
	ALT [U/L]	47.3 ± 4	38.7 ± 3.4	0.15	57.4 ± 3.1$^{\$}$	60.2 ± 4.0$^{\$}$	0.6
	ALB [g/L]	30.4 ± 0.5	31.7 ± 1.3	0.41	31.7 ± 0.8$^{\$}$	31.6 ± 0.6$^{\$}$	0.96
	TP [g/L]	50.3 ± 0.6	51.9 ± 1.8	0.49	48.6 ± 0.9$^{\$}$	48.8 ± 1.0$^{\$}$	0.85
	Urea [mg/dl]	38.0 ± 2.4	44.3 ± 6.0	0.41	41 ± 2.4$^{\$}$	36.3 ± 1.4$^{\$}$	0.1
	Ammonia [μmol/L]	121.3 ± 6.4	106.7 ± 8.1	0.2	138.8 ± 15.1$^{\$}$	136.2 ± 13.8$^{\$}$	0.91
Hemodynamics	Portal Pressure [mmHg]	4.8 ± 0.5	5.1 ± 0.5	0.64	13.3 ± 0.9$^{\#\#\#}$	15.8 ± 1.0$^{\#\#\#}$	0.11
	Heart frequency [bpm]	195 ± 12.8	200 ± 12.8	0.77	211.1 ± 12.2	207.3 ± 14.6	0.84

Sham vs. PPVL: $^{\#}p \leq 0.05$; $^{\#\#}p \leq 0.01$; $^{\#\#\#}p \leq 0.001$; $^{\$}$ns. ($p > 0.05$). CCL4 + LAP vs. CCL4 + IM: $^{*}p \leq 0.05$.

et al., 2020). In our model CCL4 inhalation was stopped 3 days before IM, which might be masking progression of fibrosis in this model by IM. However, the perioperative discontinuation of the hepatotoxic agents such as alcohol reflects clinical reality. Still, in our CCL4 model IM leads to significantly elevated portal pressure, elevated levels of liver enzymes and alpha-SMA and IL-6 gene expression after IM compared to LAP as relevant surrogate parameters for hepatic inflammation and decompensation.

An elevated portal pressure after surgery may be the expression of increased systemic inflammation. Our data shows significantly upregulated parameters of inflammation after IM, suggesting an association between inflammation and the development of elevated portal pressure after surgery. A close association of HVPG and systemic inflammation has been shown recently (Praktiknjo et al., 2020). A hyperinflammatory state is also a key element of ACLF (Trebicka et al., 2019).

Inflammatory pathways driven by bacterial translocation and mechanisms of sterile inflammation may play a role in post-operative portal pressure elevation. In a recent retrospective study, bowel-related surgery was associated with a poor outcome in patients with cirrhosis, especially in those presenting with ascites and thrombocytopenia (Wetterkamp et al., 2020). Our study supports the role of bacterial translocation, indicated by the significant increase of hepatic TLR-4 expression in the BDL model 7 d after IM and significantly higher levels of endotoxin in the cirrhosis models. However, our data do not show differences of endotoxin levels between IM and LAP groups at 2 and 7 days. It has been shown that major abdominal surgery is associated

TABLE 1F | General characteristics and clinical data of rats undergoing Sham/PPVL at sacrifice 7 days after IM/LAP.

Parameter		Sham + LAP $n = 8$	Sham + IM $n = 8$	p	PPVL + LAP $n = 8$	PPVL + IM $n = 8$	p
Weight data	Liver weight [g]	17.2 ± 0.4	15.9 ± 0.8	0.17	14.2 ± 0.3	13.9 ± 0.4	0.58
	Body weight at sacrifice [g]	408.5 ± 7.3	396.3 ± 12.6	0.42	378.6 ± 8.5$^{\$}$	369.3 ± 7.7$^{\$}$	0.42
	Weight development surgery - sacrifice [%]	−1.1 ± 1	−1.4 ± 1.8	0.9	−0.3 ± 1.71$^{\$}$	−2.2 ± 1.5$^{\$}$	0.41
Baseline laboratory	Sodium [mmol/l]	135.9 ± 1.1	137.4 ± 0.6	0.31	139.0 ± 1.1$^{\$}$	140.7 ± 0.5$^{\$}$	0.2
	ALP [U/L]	160.0 ± 7.1	147.8 ± 11.6	0.36	127.3 ± 7.8$^{\#}$	139.7 ± 11.4$^{\$}$	0.42
	AST [U/L]	76.3 ± 6.4	81.5 ± 4	0.48	71.9 ± 4.8$^{\$}$	79.5 ± 7.3$^{\$}$	0.42
	ALT [U/L]	49.4 ± 3.5	45.2 ± 1.6	0.36	48.7 ± 1.4$^{\$}$	40.7 ± 2.7$^{\#}$	0.11
	ALB [g/L]	32.6 ± 0.6	32.7 ± 0.9	0.92	31.7 ± 0.6$^{\$}$	30.0 ± 1.0$^{\$}$	0.17
	TP [g/L]	52.1 ± 0.6	50.3 ± 1.4	0.22	50.2 ± 0.7$^{\#}$	46.6 ± 2.2$^{\$}$	0.15
	Urea [mg/dl]	36.7 ± 3.6	31.3 ± 1.8	0.25	37.8 ± 2.1$^{\$}$	34.2 ± 2.1$^{\$}$	0.23
	Ammonia [μmol/L]	92.2 ± 14.4	80.3 ± 19.11	0.63	89.5 ± 16$^{\$}$	151.7 ± 46.3$^{\#}$	0.18
Hemodynamics	Portal Pressure [mmHg]	4.5 ± 0.6	4.4 ± 0.2	0.82	12.4 ± 1.0$^{\#\#\#}$	14.8 ± 1.2$^{\#\#\#}$	0.16
	Heart frequency [bpm]	205.8 ± 16.7	196.6 ± 14.2	0.73	222.2 ± 16.9	200.9 ± 2.9	0.1

Sham vs. PPVL: $^{\#}p \leq 0.05$; $^{\#\#\#}p \leq 0.001$; $^{\$}$ns. ($p > 0.05$).

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BDL, bile-duct ligation; bpm, beats per minutes; CCL4, tetrachlormethane; IM, intestinal manipulation; LAP, median laparotomy; ns, no significance; PPVL, partial portal vein ligation; TP, total protein.

with transient endotoxemia that peak between 1 and 24 h after surgery (Buttenschoen et al., 2001, 2009). Endotoxin levels might be significantly higher immediately after IM and then quickly decrease after increase of systemic and inflammation markers and upregulation of hepatic inflammation. This hypothesis needs to be further investigated in the future.

It has also been shown that IM leads to a disruption of the gut wall with the release of sterile proinflammatory agents, e.g., extracellular matrix components that lead to local and systemic inflammation (Bortscher et al., 2012; Chang et al., 2012; Nielsen et al., 2015; Lehmann et al., 2019). Our data show significant upregulation of collagen type 1 and elevated hepatic hydroxyproline levels in the BDL model 7 days after IM as expression of fibrosis progression and clinical events of decompensation. A boost of collagens and fragments or neoepitopes of extracellular matrix systemically and in the portal vein have been shown to be significantly associated with outcome in patients with advanced stages of cirrhosis (Leeming et al., 2013, 2015; Nielsen et al., 2015; Praktiknjo et al., 2018a; Lehmann et al., 2019). Our data indicate that extrahepatic bowel surgery, especially in the model of continuous liver injury, may have the same effect, but needs to be confirmed in further studies using this model. We believe that our model is well-suited to study different pathways of inflammation and thus to investigate pathomechanisms of postoperative hepatic decompensation.

Interestingly in the PPVL groups, portal pressure was not significantly elevated after IM but showed the same trend as the cirrhotic groups. No deaths or signs of decompensation after IM in this model were recorded, at best, only transient changes were seen in the expression of liver enzymes. IM in this important non-cirrhotic control group was performed relatively early after PPVL. Patients with portal hypertension without cirrhosis, e.g., with vascular disorders of the liver have better postsurgical prognosis, if they are treated early before the presence of liver decompensation (Elkrief et al., 2019). Our data show distinct post-surgical differences of inflammatory pathways between cirrhosis and non-cirrhotic portal hypertension, which can be further evaluated using this model.

Sarcopenia seems to play a role in these animal models of cirrhotic and non-cirrhotic portal hypertension. Our data show significant weight differences during the time of development of cirrhosis or non-cirrhotic portal hypertension. Weight loss seems to be more significant after IM in models of cirrhosis than in sham and PPVL animals. While weight loss in cirrhosis is a well-known fact, molecular mechanisms are still not fully understood, since obtaining muscle biopsies in patients might be ethically difficult. In recent studies it has been shown that muscle mass in patients with cirrhosis is associated with outcome and ACLF (Praktiknjo et al., 2018b, 2019). Pathophysiological investigation of the role of sarcopenia in the development of AD and ACLF especially after surgery in this model should be performed in the future, but is beyond the scope of this study.

There are several limitations to the study. Different surgical models, especially IM, might be dependent on the animal surgeon. However, to remove bias, all surgical procedures were performed by the same and trained individual for each surgery type (BDL, Sham, IM, LAP). Surgical procedures were performed in a block design, and animals were randomized into the different groups. Clear-cut criteria of AD in animals are missing, but our data includes relevant surrogate parameters of systemic inflammation and important laboratory parameters as well as clinical features of decompensation. Whether progression of fibrosis and inflammation can be seen more clearly in the CCL4 model without the removal of the hepatotoxic agent CCL4 remains to be investigated. Finally, the role and relevance of bacterial translocation and integrity of intestinal barrier need

to be assessed in more detail in further experiments including groups treated with antibiotics.

In conclusion, this study showed significantly elevated portal pressure and systemic inflammation in preclinical models of cirrhosis after IM. It also shows progression of fibrosis especially in models of continuous liver injury. These models may be useful to investigate pathophysiological mechanisms of post-operative decompensation. Lowering the risk of postoperative portal pressure elevation may be a therapeutic target.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because restrictions according to GDPR and LANUV (local animal authority) apply. Requests to access the datasets should be directed to Dr. Michael Praktiknjo, michael.praktiknjo@ukbonn.de.

ETHICS STATEMENT

The animal study was reviewed and approved by Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen (81-02-04.2018.A348).

AUTHOR CONTRIBUTIONS

JC, JM, MG, and MH: acquisition of data, analysis, interpretation of data, drafting of the manuscript, and statistical analysis. NB, RD-P, BS-W, and GK: acquisition of data, analysis, and interpretation of data and critical revision of the manuscript regarding important intellectual content. MO, LP, SK, FU, MB, TV, PL, and JK: interpretation of data and critical revision of the manuscript regarding important intellectual content. CJ and CS: administrative, technical and material support, and critical revision of the manuscript regarding important intellectual content. SW, JT, and MP: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript regarding important intellectual content, final approval of the version to be published, administrative, technical and material support, and study supervision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2021.720898/full#supplementary-material

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4. Diskussion

Die oben aufgeführten Arbeiten beschäftigen sich inhaltlich mit der Rolle des operativen Insultes bei der postoperativen Dekompensation, Mortalität und insbesondere der Entwicklung von ACLF. Die einzelnen Arbeiten tragen zudem dazu bei, Hochrisikopatienten für eine postoperative Entwicklung von ACLF besser zu identifizieren, um präventive Maßnahmen ergreifen zu können. Vor dem Hintergrund der aktuell noch stark limitierten Behandlungsoptionen des ACLF und der weiter steigenden notwendigen Operationszahlen bei Patienten mit Zirrhose erscheint dies bedeutend für das Outcome dieses Patientenklientels.

Dass der operative Insult eine klinische Herausforderung für Patienten mit Leberzirrhose darstellt, ist lange bekannt und beschrieben. Die Risikostratifizierung bezüglich des postoperativen Outcomes dieser Patienten erfolgt jedoch immer noch zumeist durch traditionelle Scores wie den CTP- oder MELD-Score (Garrison et al., 1984; Mahmud et al., 2019; Mansour et al., 1997). In den meisten klinischen Zentren ist eine dekompensierte Leberzirrhose eine Kontraindikation für einen operativen Eingriff, sodass vielen Patienten notwendige Operationen im elektiven Rahmen verwehrt bleiben. Kommt es dann zu einer Notfalloperation, ist die postoperative Mortalitätsrate sehr hoch. Sowohl auf den Gebieten der Chirurgie als auch der Hepatologie hat sich jedoch in den letzten Dekaden viel getan. Die Etablierung von neuartigen Scores, die vor allem operationsspezifische Parameter enthalten, ist daher von großer Wichtigkeit. Der letzte an Patienten mit Leberzirrhose validierte Score wurde 2007 etabliert (Teh et al., 2007), dieser findet jedoch im europäischen Kontext keine standardisierte Anwendung. Ganz aktuell wurde ein neuer Score mit operationsspezifischen Parametern, der sogenannte VOCAL-Penn-Score, an einer multizentrischen retrospektiven Veteranenkohorte etabliert und validiert (Mahmud et al., 2021).

Kürzlich wurde eine neue Krankheitsentität bei Patienten mit Leberzirrhose, das akut-auf-chronische Leberversagen (ACLF), an der CANONIC-Kohorte beschrieben (Arroyo et al., 2015b; Moreau et al., 2013b; Trebicka et al., 2020b). Das Syndrom ist durch eine erhöhte systemische Inflammation gekennzeichnet, assoziiert mit extrahepatischem Organversagen, was eine hohe Kurzzeitmortalität zur Folge hat. Obgleich

Überschneidungen bestehen, grenzt sich das ACLF dadurch eindeutig von der „einfachen“ akuten Dekompensation ab. Der Zusammenhang zwischen ACLF und operativen Eingriffen wurde bisher nicht beschrieben, obgleich operative Eingriffe und Interventionen an der Leber, neben den drei Hauptauslösern bakterielle Infekte, gastrointestinale Blutungen und Alkoholabusus, als Auslöser diskutiert werden (Chang et al., 2021a; Clària et al., 2016; Leal et al., 2019; Trebicka et al., 2020c). In die Etablierung der oben genannten Scores wurde das ACLF nicht miteinbezogen. Daher ist eine Charakterisierung und genaue Evaluation des Zusammenhangs von operativem Eingriff und ACLF von großer Wichtigkeit. Zusätzlich ist für dieses spezielle und wichtige Patientenklientel die Validierung von bestehenden Scores und Optimierung neu etablierter Scores für die Risikostratifizierung von immenser Bedeutung.

Den Zusammenhang zwischen ACLF und operativen Eingriffen konnten wir erstmalig in einer unserer Studien herausarbeiten (Klein et al., 2020). Wir konnten hier vor allem zeigen, dass etwa ein Viertel der Patienten postoperativ ein ACLF entwickelt. Wiesen die Patienten bereits zum Zeitpunkt der Operation eine akute Dekompensation auf, entwickelten sie sogar signifikant häufiger ein ACLF. Der prozentuale Anteil von 25% der Patienten, die postoperativ ein ACLF entwickeln, ist sehr hoch in Anbetracht dessen, dass in der CANONIC-Kohorte ca. 13% Patienten, die mit einer akuten Dekompensation hospitalisiert wurden, ein ACLF entwickeln (Moreau et al., 2013a). Die postoperative Entwicklungsrate von ACLF durch den operativen Insult scheint also noch höher zu sein. Hierdurch wird die Wichtigkeit einer optimierten präoperativen Risikostratifizierung für Patienten, die einen operativen Eingriff benötigen, hervorgehoben. Es konnte auch gezeigt werden, dass präoperative Infekte mit der Entwicklung eines ACLF innerhalb von 28 Tagen nach Operation assoziiert waren. Wenn eine Operation während einer ACLF-Episode durchgeführt wurde, war die Prognose besonders schlecht. Diese Daten deuten darauf hin, dass Operationen, wenn Infekte, akute Dekompensationen oder ein ACLF vorhanden sind, soweit möglich vorerst verschoben werden sollten, um einen optimierten Ausgangspunkt für die Operation zu erreichen.

Die vorwiegenden ACLF-Grade waren in den ersten postoperativen Tagen Grad I und Grad II, a.e. als Ausdruck von transienten Organversagen aufgrund des chirurgischen Insultes. Während sich ein Teil der ACLF zurückbildete, entwickelten sich in einem nicht

unbedeutenden Anteil der Patienten eine Woche nach der Operation höhergradige ACLF Ausprägungen (II und III). ACLF Grad III endet zu 90% tödlich; daher bestätigen diese Daten noch einmal, dass die postoperative Transformation von einer akuten Dekompensation in ein ACLF mit allen Mitteln aufgehalten werden sollte. Die postoperativen ACLF-Episoden waren häufig mit Infekten assoziiert. Dies zeigt die Robustheit unser Daten, da viele aktuelle Studien eine Assoziation von ACLF mit Infekten zeigen (Laleman et al., 2018; Monteiro et al., 2020; Praktiknjo et al., 2020a; Trebicka et al., 2019, 2020a, 2020b).

Obwohl in der CANONIC-Kohorte die Entwicklung von ACLF stark mit der Ätiologie der Zirrhose assoziiert ist (Moreau et al., 2013b), hatte sie in unseren Daten bei den operativen Eingriffen keinen Einfluss auf die Entwicklung von ACLF. Auch Surrogatparameter der systemischen Inflammation wie CRP waren nicht mit der Entwicklung von ACLF assoziiert. Dies deutet auf eine charakteristische, inflammatorische Antwort des operativen Insultes hin, die weiter untersucht werden sollte. Sowohl sterile Mechanismen als auch die bakterielle Translokation könnten hier eine Rolle spielen (Albillos et al., 2014; Bernardi et al., 2015; Chang et al., 2012, 2021b; Medzhitov, 2008; Úbeda et al., 2010).

Weitere Ergebnisse zeigen, dass die Entwicklung von ACLF innerhalb von 28 Tagen nach chirurgischem Eingriff eng mit der 3-Monats-Mortalität assoziiert ist. Dieser Effekt wurde bei Analyse der 1-Jahres-Mortalität nicht mehr gesehen. Dies bestätigt die Robustheit unserer Daten, da auch in der bestehenden Literatur der gravierendste Effekt von ACLF bei der Kurzzeitmortalität besteht. Die Operationstypen (viszeral vs. nicht-viszeral, Beteiligung der Bauchhöhle, Ausmaß der Operation) hatten keinen Einfluss auf die Mortalität, was darauf hindeutet, dass der starke Effekt von ACLF auf die Mortalität andere möglichen Einflussparameter wahrscheinlich außer Kraft setzt.

Eine Limitation der Arbeit war, dass nicht zwischen Notfalloperationen und elektiven Eingriffen unterschieden wurde, was ohne Zweifel einen Einfluss auf die Entwicklung von ACLF hat. Andererseits ist jedoch anzunehmen, dass die Patienten, bei denen ein Notfalleingriff durchgeführt wurde, sich in der Gruppe befanden, die ein ACLF bereits zum Operationszeitpunkt aufwiesen und daher weitgehend nicht in die Hauptanalysen mit eingeflossen sind.

Diesen Aspekt wollten wir weiter untersuchen. Außerdem wollten wir weitere Hinweise zu pathophysiologischen Mechanismen und Biomarker des postoperativen ACLF evaluieren. Zusätzlich fragten wir uns, welche Rolle die Implantation eines TIPS als Intervention bei der Entwicklung eines postinterventionellen ACLF spielt. Der TIPS ist eine Therapiemöglichkeit der portalen Hypertension. Daher ist erwartbar, dass Patienten nach der Implantation eine Besserung der Symptome zeigen. Jedoch wurde bis vor kurzem auch die Implanation des TIPS selbst als eine Möglichkeit der Auslösung von ACLF diskutiert (Arroyo et al., 2016; Clària et al., 2016). Patienten können beispielsweise nach Implantation eines TIPS ein Leberversagen entwickeln, so wie man es z.B. bei der endoskopischen retrograden Cholangiopankreatikographie (ERCP)-Intervention kennt. Nach TIPS-Implantation kommt es zu einem Insult des Lebergewebes und Änderung der Strömungs- und Perfusionsverhältnisse in der Leber (Leal et al., 2019; Praktiknjo et al., 2020b). Auch über kardiale Dekompensationsmechanismen kann sich durch den erhöhten Blutstrom zum Herzen postprozedural ein ACLF entwickeln.

Die o.g. Kohorte wurde extensiv überarbeitet; insbesondere wurden klare Unterteilungen in elektive Eingriffe und Notfalleingriffe herausgearbeitet. Anschließend wurde ein Propensity Score Matching (PSM) von Patienten mit elektiven chirurgischen Eingriffen (OP-Gruppe) zu Patienten mit TIPS-Implantation (TIPS-Gruppe) durchgeführt. In dieser Studie konnten wir bei den Patienten der OP-Gruppe zeigen, dass auch bei alleiniger Betrachtung der elektiven chirurgischen Eingriffe ein Viertel der Patienten postoperativ ein ACLF entwickelt (Chang et al., 2021a). Dies untermauert die Datenqualität der vorangegangenen Studie. Die Studie bestätigte also erneut, dass chirurgische Eingriffe ein auslösendes Ereignis für eine postoperative Entwicklung von ACLF darstellen. Vor allem konnte neu herausgearbeitet werden, dass Patienten mit einem CLIF-C AD-Score < 50 zum Operationszeitpunkt nur transiente ACLF-Grade postoperativ entwickelten, während ein CLIF-C AD-Score ≥ 50 mit hoher ACLF bedingter Mortalität assoziiert war. Für den Kliniker als einfaches und gut zugängliches Modell ergäbe sich die Empfehlung, dass bei Patienten mit CLIF-C AD ≥ 50 elektive Eingriffe möglicherweise vermieden oder verschoben werden sollten. Da auch die Leukozytenzahlen in den CLIF-C AD-Score mit einfließen, könnte das z.B. über Behandlung eines Infektes geschehen. Gegebenenfalls

sollte bei diesen Patienten sogar, falls die Operation unumgänglich ist, eine präoperative Listung zur Lebertransplantation erfolgen.

Eine andere wichtige Erkenntnis der Studie war, dass das Risiko von Patienten, nach der TIPS-Implantation ein ACLF zu entwickeln, vernachlässigbar gering ist. Diese Daten werden auch durch Ergebnisse einer großen multizentrischen Studie gestützt, die zeigen konnte, dass Patienten mit akuter Varizenblutung und ACLF von einer TIPS-Anlage profitieren (Trebicka et al., 2020d). Der hepatische Insult durch eine TIPS-Implantation scheint also bei der postprozeduralen ACLF-Entstehung keine bedeutende Rolle zu spielen. Ein Grund der Verbesserung von ACLF nach TIPS wird vor allem die Verbesserung der renalen Perfusion sein, da die renale Dysfunktion einer der Hauptpfeiler von ACLF darstellt, was wir in unseren Ergebnissen bestätigen können.

Bezüglich pathophysiologischer Mechanismen von postoperativem ACLF zeigte sich in der OP-Gruppe ein großer Anteil an ACLF der renalen Dysfunktion geschuldet. Transiente ACLF-Grade scheinen also eine Rolle bei der Entstehung von postoperativem ACLF zu spielen und stellen daher einen möglichen Therapieansatz dar. Es zeigte sich auch, dass die CRP- und Leukozytenwerte postoperativ im Gegensatz zum präoperativen Zustand signifikant erhöht/ansteigend waren, im Gegensatz zu TIPS-Patienten, wo sich kein relevanter Unterschied prä- und postprozedural zeigte. Genaue pathophysiologische Inflammationsmechanismen des operativen Insultes, sowohl der sterilen als auch der bakteriellen Inflammation, sollten in prospektiven Studien evaluiert werden.

Im Rahmen dieser Arbeit zeigte sich also, dass die TIPS-Implantation keine bedeutende Rolle bei der ACLF-Entstehung spielt, und sogar ggf. invers mit der Entwicklung von ACLF assoziiert ist. Daher untersuchten wir in der nächsten Arbeit den Einfluss einer präoperativen Dekompression der portalen Hypertension mittels TIPS auf die Entwicklung von postoperativem ACLF (Chang et al., 2022). Hierfür wurden Patienten, die präoperativ einen TIPS in der Vorgeschichte aufwiesen (TIPS-Gruppe) in einem PSM-Ansatz mit Patienten zum Operationszeitpunkt verglichen, die keinen präoperativen TIPS erhalten hatten (no-TIPS-Gruppe).

Hier konnten wir zeigen, dass das Risiko innerhalb von 90 Tagen nach dem operativen Eingriff ein ACLF zu entwickeln in der TIPS-Gruppe signifikant geringer ist. Dieser

vorteilhafte Effekt zeigte sich insbesondere bei Patienten mit einem CLIF-C AD-Score über 45 zum Operationszeitpunkt. Es war bereits in einer großen multizentrischen, prospektiven Studie gezeigt worden, dass der Portaldruck vor dem operativen Eingriff ein prognostischer Marker für das Überleben ist. Patienten mit höherem Portaldruck hatten auch ein signifikant erhöhtes Risiko zu versterben (Reverter et al., 2019). Unsere Ergebnisse bestätigen diese Daten und ergänzen diese im Hinblick auf die postoperative Entwicklung von ACLF. Klinisch ergibt sich eine klare Empfehlung, dass ausgewählte Patienten mit einem CLIF-C AD Score > 45 vor einem viszeralen Eingriff möglicherweise von einer präemptiven TIPS-Anlage profitieren.

Das höhere Risiko bei Patienten ohne präoperativen TIPS ein ACLF innerhalb von 90 Tagen zu entwickeln, konnte für viszerale Eingriffe gezeigt werden, jedoch nicht für nicht-viszerale Eingriffe. Diese Daten sind im Einklang mit der aktuellen Literatur, wo insgesamt ein niedrigeres postoperatives Mortalitätsrisiko für nicht-viszerale Eingriff vs. viszerale Eingriffe vorbeschrieben ist (Mahmud et al., 2019). Jedoch waren die Operationszahlen der nicht-viszeralen Eingriffe in unserer Kohorte zu niedrig, um eine Aussage zu treffen, die auf größeren Kontext anwendbar ist. Dies sollte daher weiter in prospektiven Studien validiert werden. Eine weitere Limitation dieser Studie war, dass keine HVPG-Messungen vor der Operation durchgeführt wurden. Jedoch sind Surrogatparameter der portalen Hypertension wie die Milzgröße, der Varizenstatus etc. zwischen den beiden Gruppen vergleichbar gewesen, so dass die Patienten zum Operationszeitpunkt bezüglich der Selektion keinem statistischen Bias unterlagen.

Als Limitation dieser retrospektiven Arbeiten ist insbesondere das monozentrische und retrospektive Studiendesign zu nennen. Jedoch sind die Kohorten sehr gut charakterisiert, und die Ergebnisse stehen in Einklang mit der aktuellen Datenlage. Ein weiterer Aspekt ist die zentrumsspezifische Kategorisierung der einzelnen Operationen. Die Daten wurden jedoch von zwei ausgebildeten und geblindeten Experten kategorisiert und flossen in die Regressionsanalysen mit ein.

Um die postoperative Dekompensation in der Leberzirrhose mit den dazugehörigen Pathomechanismen weiter untersuchen zu können, wurde schließlich ein Tiermodell etabliert (Chang et al., 2021c). Hierbei wurde in etablierten Modellen der kompensierten

Zirrhose bzw. der nicht-zirrhotischen portalen Hypertension eine intestinale Manipulation (IM) durchgeführt um das Modell einer extrahepatischen Operation zu simulieren.

Das Tiermodell konnte erfolgreich etabliert werden. Die Haupterkenntnis dieser Arbeit war, dass der in-vivo Portaldruck zwei und sieben Tage nach IM signifikant erhöht war im Gegensatz zu der Kontrolloperation (Medianlaparotomie, LAP). Klinische Studien haben den Einfluss des Portaldrucks vor dem operativen Eingriff beschrieben, aber es existieren keine Daten über die Charakterisierung des Portaldrucks nach einer extrahepatischen Operation. Im klinischen Alltag oder Studiensetting wäre eine HVPG-Messung bei Patienten postoperativ nur schwierig umzusetzen, da diese sich zumeist auf Intensivstation befinden. Auch ist die Erhebung von nicht invasiven Fibrosemessungen, wie dem Fibroscan, bei häufigem postoperativen Auftreten von Aszites oder Wundflüssigkeit nicht einfach zu standardisieren. Der postoperativ erhöhte Portaldruck in diesem Modell gibt daher eine wichtige Information über Pathomechanismen der postoperativen Dekompensation und ggfs. einen möglichen Therapieansatz. Zusammen mit dem erhöhten Portaldruck waren in Genexpressionsmessungen der Leber die Parameter der hepatischen Inflammation hochreguliert. Hierzu zählte unter anderen TLR-4, was eine Assoziation von erhöhtem Portaldruck und Inflammation nahelegt. Es ist anhand dieses Modells noch weiter zu erforschen, ob die Portaldruckerhöhung durch Inflammation durch Mediatoren aus der Leber oder aus dem Darm stimuliert bzw. unterhalten wird. In jedem Fall scheint systemische Inflammation hierbei eine Rolle zu spielen, was auch einer der definierenden Säulen des ACLF ist. Ein Unterschied im zirkulierenden Endotoxin-Serumlevel zeigte sich nicht zwischen IM vs. LAP, jedoch ist anzunehmen, dass ein Unterschied sich vor allem innerhalb der ersten 24 Stunden nach IM zeigen wird.

Das etablierte Modell eröffnet die Möglichkeit die Forschung zur postoperativen Dekompensation zu standardisieren, da wir zeigen konnten, dass es postoperativ klinisch zu ähnlichen Eigenschaften wie bei einer dekompensierten Leberzirrhose kommt, z.B. zur Bildung von Aszites oder signifikantem Gewichtsverlust, Erhöhung der Transaminasen und erniedrigtem Serumalbumin. Wir sehen im BDL-Modell sogar eine Progression der Fibrose innerhalb von 7 Tagen nach IM vs. LAP, was darauf hindeutet, dass der operative Insult und die damit assoziierte Inflammation auch beim Menschen mit einer Aggravierung

der Fibrose einhergehen könnte. In anderen Arbeiten unserer Arbeitsgruppe konnten wir bereits zeigen, dass in fortgeschrittenen Stadien der Leberzirrhose aus der Leber stammende Neoepitope der Extrazellularmatrix zirkulatorisch freigesetzt werden, die wiederum mit schlechterem Outcome assoziiert sind (Blaya et al., 2021; Lehmann et al., 2019; Nielsen et al., 2015; Praktiknjo et al., 2018b). Der operative Insult könnte eine ähnliche Rolle spielen. Dies wäre eine weiter zu untersuchende, klinisch relevante, translationale Fragestellung.

Limitationen dieser tierexperimentellen Studie waren, dass die IM vom Operateur abhängig sein kann. Die Operationen wurden jedoch alle durch dieselbe trainierte Person, verblindet und im Blockdesign durchgeführt, und die Tiere wurden in die einzelnen Gruppen randomisiert. Ob das etablierte Modell als ACLF-Modell genutzt werden kann, ist noch zu überprüfen. Harte Kriterien eines ACLF in den Laborwerten zeigten sich in den aktuell vorliegenden Parametern nicht, jedoch zeigen die Ergebnisse Surrogatparameter der systemischen Inflammation und klinische Merkmale einer Dekompensation. Zusammenfassend kann dieses Modell nützlich sein, postoperative Dekompensation besser zu verstehen und damit zusammenhängende pathophysiologische Mechanismen aufzudecken. Postoperativ den Portaldruck zu senken kann ggf. sogar im klinischen Alltag ein therapeutisches Target darstellen, um das postoperative Outcome zu verbessern.

5. Zusammenfassung

Zusammenfassend beschäftigte ich mich in dieser Arbeit mit der Rolle des operativen Insultes auf die postoperativen Komplikationen bei Patienten mit Leberzirrhose, insbesondere mit der Entwicklung eines akut-auf-chronischen Leberversagens (ACLF). Ein erhöhtes postoperatives Mortalitätsrisiko und Auftreten von Komplikationen bei Patienten mit Zirrhose ist bekannt, aber im Hinblick auf den medizinischen Fortschritt und neuen Krankheitsentitäten wie das akut-auf-chronische Leberversagen (ACLF) ist eine genaue Charakterisierung dieses Patientenklientels und die Weiterentwicklung von Scores zur Risikostratifizierung notwendig. Zudem ist die Entwicklung und das Auftreten von ACLF nach operativen Eingriffen noch nicht beschrieben oder charakterisiert.

Hierzu wurde in einer großen Kohorte von Patienten mit Leberzirrhose, bei denen ein operativer Eingriff durchgeführt wurde, erstmalig die Entwicklung von postoperativem ACLF beschrieben. Es konnte gezeigt werden, dass 25% der Patienten postoperativ ein ACLF entwickeln und dass bei einem nicht unwesentlichen Teil dieser Patienten der letale Ausgang signifikant wahrscheinlicher ist als bei den Patienten, die kein ACLF entwickeln. Bestand zum Zeitpunkt der Operation ein ACLF, so war die Prognose dieser Patienten ähnlich schlecht. Hochrisikopatienten für die Entwicklung von postoperativem ACLF sind ältere Patienten mit kompromittierter Leberfunktion und Infekten zum Zeitpunkt der Operation.

Ferner konnte in einer weiteren Studie, in der Patienten mit elektiven chirurgischen Eingriffen zu Patienten mit einer TIPS-Implantation verglichen wurden, gezeigt werden, dass auch bei elektiven chirurgischen Eingriffen das Risiko ein ACLF nach dem Eingriff zu entwickeln bei 25% liegt, während das Potential, ein ACLF durch eine TIPS-Implantation auszulösen, vernachlässigbar gering ist. Die Operation selber ist also als ein auslösendes Ereignis für ein ACLF zu sehen und stellt zusätzlich einen starken Prädiktor für die postoperative Sterblichkeit dar. Patienten mit einem CLIF-C-AD-Score ≥ 50 und hohem CRP wurden als Hochrisikogruppe identifiziert. Vor allem die renale Dysfunktion und Parameter der systemischen Inflammation scheinen Teil der treibenden Kraft des postoperativen ACLF zu sein.

Weitere Daten zur Analyse des Einflusses eines präoperativ implantierten TIPS zur Dekompression der portalen Hypertension zeigten, dass Patienten mit einem präoperativen TIPS ein signifikant geringeres Risiko aufwiesen, innerhalb von 90 Tage nach dem chirurgischen Eingriff ein ACLF zu entwickeln. Auch das Überleben in der Patientengruppe mit präoperativem TIPS war signifkant besser. Subkohortenanalysen suggerieren diesen vorteilhaften Effekt vor allem bei Patienten mit viszeralchirurgischen Eingriffen und mit einem CLIF-C AD Score > 45 zum Operationszeitpunkt. Patienten, die diese Kriterien erfüllen, stellen somit die Patientengruppe dar, unter denen ausgewählte Patienten präoperativ von einer präemptiven TIPS-Implantation profitieren könnten.

Zuletzt beschäftigte ich mich im Sinne des translationalen Forschungsansatzes damit, ein Tiermodell zu etablieren, um postoperative Dekompensation bzw. Entwicklung von ACLF auch im Tiermodell studieren zu können. Hierzu wurde ein Tiermodell etabliert, bei der eine standardisierte intestinale Manipulation (IM) in verschiedenen Modellen der Zirrhose bzw. nicht-zirrhotischen portalen Hypertension durchgeführt wurde. Es konnte vor allem gezeigt werden, dass in den Zirrhosemodellen der Portaldruck nach IM im Gegensatz zur Kontrolloperation signifikant erhöht ist. Obgleich es Daten zu der präoperativen Rolle des Portaldrucks gibt, existieren keine Studien zum postoperativen Portaldruck. Diese Studie gibt erste Hinweise dafür, dass der operative Insult zu einer inflammatorischen Reaktion führt, die in einer Aggravierung der portalen Hypertension resultiert. Welche Mediatoren welchen Ursprungs hierbei eine Rolle spielen, ist weiter zu erforschen. Zudem konnten in dem Modell auch eine relevante Progression der Fibrose und klinische Merkmale einer dekompensierten Zirrhose nach IM gezeigt werden, so dass die Möglichkeiten weitere Untersuchungen an dem Modell durchzuführen, weitreichend sind.

Zusammenfassend erweitern diese Arbeiten das Verständnis für die postoperative Entwicklung von ACLF in Patienten mit Zirrhose. Sie geben dem Kliniker potentiell einfachere Werkzeuge an die Hand, um Hochrisikopatienten zu identfizieren und diese zielgerichteter zu behandeln. Zudem wurden translationale Forschungsansätze zur weiteren Erforschung von postoperativem ACLF geschaffen. Vor dem Hintergrund der aktuell noch stark limitierten Behandlungsoptionen des ACLF scheint dies für das Outcome dieser Patienten sehr bedeutsam.

6. Inhaltliche Überlappung mit anderen Habilitationsschriften

Inhaltliche Überlappungen mit anderen Habilitationsschriften sind ausgeschlossen, da jede der hier kumulierten Originalarbeiten ausschließlich in dieser und keiner anderen Habilitationsschrift eingereicht wurden.

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