Aus der

Medizinischen Klinik und Poliklinik I – Allgemeine Innere Medizin mit den Schwerpunkten Gastroenterologie und Hepatologie, Nephrologie, Infektiologie, Endokrinologie und Diabetologie

des Universitätsklinikums Bonn

Direktor: Herr Univ.-Prof. Dr. med. Christian P. Strassburg

Evaluation von Risikofaktoren für die Entwicklung des akut-auf-chronischen Leberversagens bei dekompensierter Leberzirrhose

Habilitationsschrift

zur Erlangung der Venia Legendi

der Hohen Medizinischen Fakultät

der Rheinischen-Friedrich-Wilhelms-Universität Bonn

Für das Lehrgebiet

„Innere Medizin“

Vorgelegt von

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an der Universität Bonn

Bonn 2021

Datum des Habilitationskolloquiums: 28.Oktober 2021

Übersicht

Der vorliegenden Habilitationsschrift mit dem Titel „Evaluation von Risikofaktoren für die Entwicklung des akut-auf-chronischen Leberversagens bei dekompensierter Leberzirrhose“ liegen folgende publizierte Arbeiten zu Grunde:

1. Praktiknjo M, Simón-Talero M, Römer J, Roccarina D, Martínez J, Lampichler K, Baiges A, Low G, Llop E, Maurer MH, Zipprich A, Triolo M, Maleux G, Fialla AD, Dam C, Vidal-González J, Majumdar A, Picón C, Toth D, Darnell A, Abraldes JG, López M, Jansen C, Chang J, Schierwagen R, Uschner F, Kukuk G, Meyer C, Thomas D, Wolter K, Strassburg CP, Laleman W, La Mura V, Ripoll C, Berzigotti A, Calleja JL, Tandon P, Hernandez-Gea V, Reiberger T, Albillos A, Tsochatzis EA, Krag A, Genescà J, Trebicka J; Baveno VI-SPSS group of the Baveno Cooperation. *Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis.*
Erschienen in ***Journal of Hepatology*** *2020 Jun;72(6):1140-1150*.

2. Praktiknjo M*, Torner J*, Simón-Talero M, Gu W, Perez-Poch A, Torre C, Val ID, Alpiste F, Genescà J, Trebicka J. *Reply to: “Definition of SPSS: we need to speak the same language”: Computer-assisted image processing for better quantification.*
Erschienen in ***Journal of Hepatology*** *2020 Aug;73(2):464-465.*

3. Praktiknjo M, Clees C, Pigliacelli A, Fischer S, Jansen C, Lehmann J, Pohlmann A, Lattanzi B, Krabbe VK, Strassburg CP, Arroyo V, Merli M, Meyer C, Trebicka J. *Sarcopenia Is Associated With Development of Acute-on-Chronic Liver Failure in Decompensated Liver Cirrhosis Receiving Transjugular Intrahepatic Portosystemic Shunt*.
Erschienen in ***Clinical and Translational Gastroenterology.*** *2019 Apr;10(4):e00025.*

4. Praktiknjo M*, Book M*, Luetkens J, Pohlmann A, Meyer C, Thomas D, Jansen C, Feist A, Chang J, Grimm J, Lehmann J, Strassburg CP, Abraldes JG, Kukuk G, Trebicka J. *Fat-free muscle mass in magnetic resonance imaging predicts acute-on-chronic liver failure and survival in decompensated cirrhosis*.
Erschienen in ***Hepatology****. 2018 Mar;67(3):1014-1026.*

5. Praktiknjo M*, Monteiro S*, Grandt J, Kimer N, Madsen JL, Werge MP, William P, Brol MJ, Turco L, Schierwagen R, Chang J, Klein S, Uschner FE, Welsch C, Moreau R, Schepis F, Bendtsen F, Gluud LL, Møller S, Trebicka J. *Cardiodynamic state is associated with systemic inflammation and fatal acute-on-chronic liver failure*.
Erschienen in ***Liver International*** *2020 Jun;40(6):1457-1466*.

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Inhaltsverzeichnis

1. Einleitung

1.1 Die Leberzirrhose und ihre Komplikationen

In den weltweiten Gesundheitssystemen spielen chronische Lebererkrankungen eine wachsende Rolle. Durch kontinuierliche Schädigung der Leber kommt es zu einer fortschreitenden Vernarbung (Fibrogenese) des Lebergewebes. Unter Fibrogenese versteht man den Prozess der reaktiven Bindegewebsvermehrung bzw. der Ansammlung von extrazellulärer Matrix, was zu Fibrose und Zirrhose führt (Friedman, 2008). Die Leberzirrhose ist das gemeinsame Endstadium der meisten chronischen Lebererkrankungen und wird definiert als Zerstörung der physiologischen Läppchen- und Gefäßstruktur der Leber, begleitet von einer Bindegewebsvermehrung.

Die Leberzirrhose stellt ein wachsendes klinisches und volkswirtschaftliches Problem dar (Pimpin et al., 2018). Im Allgemeinen hat Europa die weltweit größte Anzahl an chronischen Lebererkrankungen (Global Health Data Exchange., 2020). In Deutschland im Speziellen leiden etwa 2 % der Bevölkerung an einer Leberzirrhose und deren Komplikationen. Bei den Betroffenen führt die Leberzirrhose zu einer entsprechend hohen Morbidität und Mortalität (Chirapongsathorn et al., 2016). Die Zahl an vollstationären Behandlungen der Leberzirrhose in Deutschland ist in den Jahren 2000 bis 2017 von 79.647 auf 89.613 angestiegen (Gesundheitsberichterstattung des Bundes, 2019). Die mittlere Überlebenszeit von Patienten mit einer klinisch kompensierten Leberzirrhose beträgt nur etwa sieben Jahre. Die Wahrscheinlichkeit einer Dekompensation beträgt bis zu 10% pro Jahr bei diesen Patienten. Ist sie eingetreten, sinkt das Zwei-Jahres-Überleben auf unter 50% (Talwalkar and Kamath, 2005).

Komplikationen der Leberzirrhose

Durch den Anstieg des vaskulären Widerstandes in der Leber kommt es zu einem Druckanstieg in den Gefäßen des portalvenösen Systems und zur Ausbildung der sogenannten Portalen Hypertension. Während des Progresses der Zirrhose kann es zu akuten Dekompensationen wie Varizenblutungen, Aszitesentwicklung oder hepatischer Enzephalopathie kommen (Angeli et al., 2018). Eine fortschreitende Vernarbung, Entzündungen und permanente Leberschädigungen sind als treibende Kräfte dieser

akuten Dekompensationen, Morbidität und Mortalität beschrieben (Bataller and Brenner, 2005; Friedman, 2008).

Interessanterweise neigen Patienten mit dekompensierter Leberzirrhose dazu weitere Dekompensationen zu entwickeln, ohne dass hierfür ein genauer Pathomechanismus bekannt ist (Gustot et al., 2015). Neben der Behandlung der Grunderkrankung werden die Komplikationen der Leberzirrhose und portalen Hypertension zunächst konservativ-medikamentös bzw. endoskopisch und in fortgeschrittenen Stadien auch interventionell behandelt (Angeli et al., 2018; Gerbes et al., 2019).

Ösophagusvarizen / Varizenblutung

Mit Ausbildung von Ösophagusvarizen besteht auch das Risiko der Varizenblutung, die eine hohe Mortalität hat (de Franchis and Baveno VI Faculty, 2015; Götz et al., 2017). Primär ist zur Prophylaxe einer Varizenblutung eine medikamentöse Behandlung mit nicht-selektiven Betablockern empfohlen, die eine Reduktion des Blutungsrisikos von 11% und der Mortalität von 9% erreicht (Cheng et al., 2003). Alternativ zur medikamentösen Therapie kann eine endoskopische Varizenligatur erfolgen, die in einer Cochrane-Analyse vergleichbare Ergebnisse zu nicht-selektiven Betablockern zeigt (Gluud and Krag, 2012). Bei Patienten, die bereits eine Varizenblutung überlebten, besteht ein hohes Risiko (60%) für eine Rezidivblutung mit hoher (33%) Mortalität (Bari and Garcia-Tsao, 2012), sodass eine Sekundärprophylaxe unerlässlich für das Outcome dieser Patienten ist. In dieser Situation ist nach aktueller Datenlage eine Kombinationstherapie aus nicht-selektiver Betablockade und endoskopischer Ligaturtherapie angezeigt (Puente et al., 2014; Thiele et al., 2012). In ausgewählten Fällen (Child-Pugh Stadium C < 14 Punkte oder Child-Pugh Stadium B mit aktiver Blutung) kann ein sogenannter transjugulärer intrahepatischer portosystemischer Shunt (TIPS) innerhalb von 72 Stunden implantiert werden. Der TIPS ist ein interventionell implantierter Shunt, der endovaskulär den hepatischen Ausflusstrakt mit dem Pfortadersystem verbindet (Rössle, 2013). Der Hochdruck des portalvenösen Systems wird durch die teilweise Umgehung des physiologischen hepatischen Pfortaderflusses gesenkt und somit die Varizen entlastet. Hierdurch werden bei ausgewählten Patienten Rezidivblutungen nahezu eliminiert und das Überleben verbessert (García-Pagán et al., 2010; Hernández-Gea et al., 2019; Lv et al., 2019).

Aszites

Der klinische Nachweis von Aszites zeigt eine schwere fortgeschrittene Erkrankung bzw. portalen Hypertension an und definiert ein Voranschreiten der Leberzirrhose mit einer Verschlechterung der Prognose (D'Amico et al., 2006; Guardiola et al., 2002; Planas et al., 2006), vor allem durch die sekundäre Entwicklung von spontan bakteriellen Peritonitiden oder eines hepatorenalen Syndroms (Ginès et al., 2004).
In der ersten Linie ist eine medikamentöse (diuretische) Therapie mit Aldosteronantagonisten und bei unzureichender Aszitesmobilisation die Kombination mit einem Schleifendiuretikum angezeigt (Gerbes et al., 2019).
Im Falle einer weiter fortschreitenden Leberzirrhose kann therapierefraktärer oder intraktabler Aszites entstehen. Hier können wiederholte großvolumige Parazentesen und der transjuguläre intrahepatische portosystemische Shunt (TIPS) therapeutisch eingesetzt werden (Bureau et al., 2017a; Solà et al., 2017; Thomas et al., 2015).
Großvolumige Parazentesen können zu hämodynamischen Veränderungen führen; die sogenannte zirkulatorische Dysfunktion nach Parazentese (Ginès et al., 1996, 1988; Pozzi et al., 1994). Interessanterweise besteht bei Patienten mit Leberzirrhose oft bereits eine gewisse zirkulatorische Dysfunktion, die möglicherweise bereits einen Einfluss auf das Outcome hat (Turco et al., 2018a).
Die TIPS-Anlage reduziert den portalen Druck als zugrundeliegende Pathologie und verbessert durch Verbesserung der renalen Perfusion die Nierenfunktion (Allegretti et al., 2016; Brensing et al., 2000; Lebrec et al., 1996; Wong et al., 1995). Im Vergleich zur wiederholten großvolumigen Parazentese ist die TIPS-Anlage effektiver, verbessert die Lebensqualität und ist auch bezüglich der Mortalität überlegen (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) ist ein Syndrom, welches die Summe aller Störungen des Zentralnervensystems, die als Komplikation akuter oder chronischer Lebererkrankungen und/oder portosystemischer Kollateralkreisläufe auftreten können, umfasst (Ferenci et al., 2002; Vilstrup et al., 2014). Pathophysiologisch liegt der HE eine reduzierte Kapazität der erkrankten 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).
Klinisch zeigt sich eine charakteristische zunehmende psychomotorische Verlangsamung bis hin zum Koma sowie ein breites Spektrum variabel auftretender intellektueller, emotionaler, kognitiver, psychischer und motorischer Störungen (Ferenci et al., 2002). Selbst bei klinisch unauffälligen Patienten lassen sich bei 20 – 85 % kognitive Einschränkungen feststellen (Ferenci et al., 2002; Labenz et al., 2017; Poordad, 2007; Romero-Gómez et al., 2001; Saunders et al., 1981; Vilstrup et al., 2014).
Das Auftreten einer HE bei Patienten mit Leberzirrhose ist ein Prädiktor für die Mortalität mit einer Ein-Jahres-Sterblichkeit von 64 % (Bustamante et al., 1999; Hartmann et al., 2000; Jepsen et al., 2010).

1.2 Das akut-auf-chronische Leberversagen (ACLF)

Die akut dekompensierte Leberzirrhose und das akut-auf-chronische Leberversagen (ACLF) sind zwei wichtige Zustände, die bei Patienten mit dekompensierter Leberzirrhose beobachtet werden können. Die akut dekompensierte Leberzirrhose umfasst die Entwicklung von Aszites, HE, gastrointestinaler Blutung und jedwede Kombination dieser Komplikationen bei Patienten mit Zirrhose (Moreau et al., 2013a; Sarin et al., 2019). Das Konzept des ACLF entstand aus Studien, die die Entwicklung eines Syndroms mit hoher Kurzzeit-Sterblichkeit (Tod innerhalb von 28 Tagen nach Hospitalisation) in Patienten mit akut dekompensierter Zirrhose zeigten. Drei Hauptmerkmale charakterisieren dieses Syndrom: Es tritt im Kontext einer ausgeprägten systemischen Inflammation auf, entwickelt sich in engem zeitlichen Zusammenhang mit proinflammatorischen auslösenden Ereignissen (z.B. Infektionen, Alkoholhepatitis, gastrointestinale Blutung) und ist mit dem Versagen mindestens eines Organsystems verbunden (Arroyo et al., 2020; Trebicka et al., 2020).
Aufgrund der äußerst hohen Mortalität des ACLF von bis über 90% in 90 Tagen und den, mit Ausnahme der Lebertransplantation, noch fehlenden therapeutischen Optionen, ist ein frühes Erkennen von Risikopatienten entscheidend (Moreau et al., 2013b).

Die Evaluation von Biomarkern zur Risikostratifizierung von Patienten mit Leberzirrhose für die Entwicklung eines ACLF ist eine zentrale Fragestellung dieser Habilitation. Die einzelnen untersuchten Aspekte werden im Folgenden eingeführt.

1.3 Die systemische Inflammation in der Leberzirrhose

In der Erarbeitung der pathophysiologischen Mechanismen des ACLF kommt der systemischen Inflammation eine besondere Rolle zu (Clària et al., 2016). Diese systemische Inflammation kann chronisch, durch Translokation von proinflammatorischen Signalen aus dem Intestinum in die systemische Zirkulation, auftreten (Albillos et al., 2014; Bernardi et al., 2015; Medzhitov, 2008; Úbeda et al., 2010). Es konnte bereits gezeigt werden, dass Infektionen besonders häufige Auslöser von ACLF sind (Piano et al., 2019; Trebicka et al., 2020). Bei Patienten mit ACLF findet sich im Besonderen jedoch ein Sturm proinflammatorischer Mediatoren (Laleman et al., 2018; Monteiro et al., 2020; Trebicka et al., 2019a). Bei Patienten mit portaler Hypertension wurde vor Kurzem gezeigt, dass Serum C-reaktives Protein (CRP, als Surrogat für systemische Inflammation) und eine hypo- oder hyperdyname Kreislaufsituation (jeweils definiert als cardiac index (CI) <3.2L/min/m^2 bzw. CI >4.2 L/min/m^2) mit der Entwicklung von Aszites und erhöhter Mortalität assoziiert sind (Turco et al., 2018b). Zudem wurde in einer Kohorte von ambulanten Zirrhosepatienten gezeigt, dass ein niedriger Blutdruck, als Ausdruck der kardiozirkulatorischen Dysfunktion, unabhängig mit der Entwicklung von ACLF assoziiert ist (Piano et al., 2017). Das Zusammenspiel von Markern der systemischen Inflammation (außer CRP) und systemischer Hämodynamik mit der Entwicklung von ACLF bei Patienten mit Leberzirrhose ist nicht untersucht und daher eine Fragestellung dieser Habilitationsarbeit.

1.4 Die Sarkopenie in der Leberzirrhose

Patienten mit Leberzirrhose sind häufig mangelernährt und zeigen dabei einerseits Eiweißmangel und Muskelschwund (Sarkopenie) sowie andererseits einen Überschuss an extrazellulärem Wasser (Peng et al., 2007). Eine Sarkopenie kann bei 40 – 60 % der Patienten mit Leberzirrhose nachgewiesen werden.

Ein normaler oder erhöhter Body Mass Index (BMI) schließt eine Mangelernährung nicht aus und ist bei Zirrhosepatienten durch die Wassereinlagerung oft irreführend (Peng et al., 2007). Die Sarkopeniediagnostik aus einem Schnittbild (Computertomographie oder Magentresonanztomographie) zur Quantifizierung der Muskelmasse ist in Leitlinien aufgrund mangelnder Datenlage noch nicht konsentiert (Durand et al., 2014; European Association for the Study of the Liver., 2019; Montano-Loza et al., 2012, 2016).
Schnittbildgebungen werden jedoch bei diesen Patienten häufig aufgrund anderer Indikationen durchgeführt, z.B. im Rahmen einer Evaluation zur Lebertransplantation, zur TIPS-Implantation oder beim Screening auf ein hepatozelluläres Karzinom (HCC), sodass aus diesen Daten gleichzeitig auch Daten zur Sarkopenie erhoben werden können.
Einige Methoden und Grenzwerte zur Quantifizierung der Sarkopenie aus Schnittbildgebungen wurden vorgeschlagen (Carey et al., 2017; Cruz-Jentoft et al., 2010; Durand et al., 2014; Giusto et al., 2015; Golse et al., 2017; Praktiknjo et al., 2018a). Die meisten Methoden beschreiben spezifisch Muskelparameter aus CT-Untersuchungen, wobei zumeist spezielle Software benötigt wird, welche die Messungen im klinischen Alltag zu zeitaufwendig machen könnten (Golse et al., 2017; Montano-Loza, 2014).

Eine einfache und schnell erfassbare Methode ist die Messung der transversalen Psoasmuskeldicke (TPMT) normalisiert auf die Körpergröße, welche bereits als Prädiktor der Sterblichkeit von Patienten auf der Warteliste für eine Lebertransplantation beschrieben wurde (Durand et al., 2014; Huguet et al., 2018). Die Muskulatur ist abhängig von einer Vielzahl an Faktoren. Insbesondere das Geschlecht beeinflusst die Muskelstruktur und -masse (Moctezuma-Velázquez et al., 2018). Die verfügbare Literatur deutet zunehmend darauf hin, dass unterschiedliche Grenzwerte für die Definition der Sarkopenie für Männer und Frauen herangezogen werden sollten. Klare geschlechtsspezifische Grenzwerte existieren jedoch noch nicht für Patienten mit dekompensierter Zirrhose (Giusto et al., 2015; Praktiknjo et al., 2018a).

Ein Zusammenhang der altersbedingten Sarkopenie mit einer erhöhten systemischen Inflammation ist bereits beschrieben, ebenso wie ein Zusammenhang von systemischer Inflammation mit der Entwicklung von ACLF (Dalle et al., 2017; Laleman et al., 2018). Während bereits eine Reihe von Risikofaktoren für die Entwicklung von ACLF diskutiert

wurden, ist die Beziehung von Sarkopenie mit der Entwicklung von ACLF noch unbekannt (Gustot et al., 2015; Moreau et al., 2013b; Praktiknjo et al., 2018b).

Die Evaluation der Rolle der CT-definierten Sarkopenie, via geschlechts-spezifischer TPMT, auf die Entwicklung von ACLF von Patienten mit dekompensierter Leberzirrhose ist daher ein weiterer Fokus dieser Habilitationsarbeit.

Die CT hat einige Nachteile wie die methodenbedingte Strahlenexposition der Patienten oder das Risiko der Auslösung oder Aggravation einer Niereninsuffizienz durch das entsprechende iodhaltige Kontrastmittel (Kontrastmittel-induzierte Nephropathie) (Rudnick et al., 1995). Bei Patienten mit Kontraindikationen gegen CT-Kontrastmittel und auch für spezifische medizinische Fragestellungen (z.B. genauere Detektion von HCC) findet die MRT heutzutage immer häufiger Anwendung (Lee et al., 2015). Neben der Gesamtmuskelmasse scheint auch die Qualität und Funktion der Muskulatur von Bedeutung für das Outcome der Patienten zu sein, was in bestimmten Myokinen, wie dem Follistatin, als Surrogatparameter reflektiert wird (Dasarathy et al., 2011; Tsuchida, 2008; Wagner, 2005). Mittels MRT kann nicht nur die Gesamtmuskelfläche, sondern auch der Fettanteil der Muskulatur identifiziert und quantifiziert werden.

MRT-definierte Muskelparameter zur Prognoseeinschätzung bei Patienten mit dekompensierter Leberzirrhose wurden im Gegensatz zu CT-definierten Muskelparametern bislang noch überhaupt nicht untersucht.

Die Evaluation neuartiger Muskelparameter aus MRT-Untersuchungen und ihre prognostische Bedeutung für die Entwicklung von ACLF bei Patienten mit dekompensierter Leberzirrhose ist daher eine Fragestellung dieser Habilitationsschrift.

1.5 Spontane portosystemische Shunts (SPSS)

Im Verlauf der Leberzirrhose kann die portale Hypertension zur Ausbildung von spontanen portosystemischen Shunts (SPSS) als Umgehungskreisläufe zur Reduktion des portalvenösen Druckes führen. Eine Assoziation von SPSS oder chirurgisch/interventionell angelegter Shunts mit der Entwicklung von HE ist lange

bekannt und die ersten Embolisationen von SPSS als Therapieoptionen wurden bereits in den 1980er Jahren beschrieben (Henderson, 1989; Ohnishi et al., 1986; Uflacker et al., 1987). Seitdem wurden wenige Studien zu SPSS als Therapieziel bei Patienten mit Leberzirrhose veröffentlicht (Aseni et al., 1986; Miyamoto et al., 2003; Shioyama et al., 1996; Tarantino et al., 2009; Zidi et al., 2007). Eine große multizentrische Studie bestätigte eine Assoziation von großen SPSS (> 8mm Durchmesser) mit dem Auftreten von HE (Simón-Talero et al., 2018).

Eine große multizentrische Studie bestätigte eine Assoziation von großen SPSS (> 8mm Durchmesser) mit dem Auftreten von HE (Simón-Talero et al., 2018). In dieser Studie wurde der Nachweis von SPSS, ähnlich wie die oben beschriebenen Muskelparameter, aus CT-Untersuchungen erhoben, die aus medizinischer Indikation erfolgten.

Aufgrund der mangelnden Datenlage fehlt es in aktuellen Leitlinien an Empfehlungen zum Management von SPSS (American Association for the Study of Liver Diseases and European Association for the Study of the Liver, 2014; Angeli et al., 2018; de Franchis and Baveno VI Faculty, 2015; Sarin et al., 2014). Der Einfluss von SPSS im Allgemeinen und ihrer kumulativen Durchmesser im Speziellen auf das Überleben von Patienten wurde noch nicht untersucht. Aus pathophysiologischer Sicht nahmen wir an, dass die Summe der Querschnittsflächen aller SPSS (Total SPSS Area, TSA) das portosystemisch „geshuntete“ Blutvolumen besser abbildet als die einfachen Durchmesser (Gao and Drew, 2014).

Der Einfluss der TSA auf die Mortalität und insbesondere ACLF-Entwicklung von Patienten mit Leberzirrhose war daher ein Aspekt der Fragestellung dieser Habilitationsarbeit.

1.6 Fragestellung

In den vorangegangenen Abschnitten wurde die besondere klinische Schwere des ACLF für Patienten mit Leberzirrhose dargelegt. Außer der Lebertransplantation als ultima ratio stehen aktuell noch kaum therapeutische Optionen zur Verfügung.
Verlässliche Biomarker zur Identifizierung von Zirrhosepatienten mit hohem Risiko für die Entwicklung von ACLF sind hierfür notwendig, aber noch wenig untersucht. In dieser Habilitationsschrift werden vor allem nicht-invasive Biomarker evaluiert.
Zum einen wird TSA, ein neuartiger Parameter des portosystemischen Shuntings, der zusätzlich aus bereits vorhandenen CT-Untersuchungen ermittelt werden kann, bezüglich der prognostischen Wertigkeit auf das Outcome von Patienten mit Leberzirrhose untersucht. Zum anderen wird die Möglichkeit der Quantifizierung der Muskelmasse aus CT- und MRT-Untersuchungen bei Patienten mit Leberzirrhose und deren Bedeutung als Prädiktor für die Entwicklung von ACLF evaluiert.
Abschließend werden zirkulierende Marker der systemischen Inflammation im Kontext der Kreislaufsituation für die Prädiktion von ACLF evaluiert.

2. Ergebnisse

2.1 Spontane portosystemische Shunts als Risikofaktor der Leberzirrhose

"Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis."
Praktiknjo M, Simón-Talero M, Römer J, Roccarina D, Martínez J, Lampichler K, Baiges A, Low G, Llop E, Maurer MH, Zipprich A, Triolo M, Maleux G, Fialla AD, Dam C, Vidal-González J, Majumdar A, Picón C, Toth D, Darnell A, Abraldes JG, López M, Jansen C, Chang J, Schierwagen R, Uschner F, Kukuk G, Meyer C, Thomas D, Wolter K, Strassburg CP, Laleman W, La Mura V, Ripoll C, Berzigotti A, Calleja JL, Tandon P, Hernandez-Gea V, Reiberger T, Albillos A, Tsochatzis EA, Krag A, Genescà J, Trebicka J; on behalf of the Baveno VI-SPSS group of the Baveno Cooperation.
Erschienen in ***Journal of Hepatology*** *2020 Jun;72(6):1140-1150*.

"Reply to: "Definition of SPSS: we need to speak the same language": Computer-assisted image processing for better quantification."
Praktiknjo M, Torner J, Simón-Talero M, Gu W, Perez-Poch A, Torre C, Val ID, Alpiste F, Genescà J, Trebicka J.
Erschienen in ***Journal of Hepatology*** *2020 Aug;73(2):464-465.*

Zur Messung der Gesamtfläche aller SPSS (total SPSS area, TSA) wurden retrospektiv in CT-Untersuchungen sämtliche SPSS manuell identifiziert und vermessen. Hieraus wurde dann die TSA berechnet und anschließend mit Daten des klinischen Verlaufes der Patienten korreliert. Wir untersuchten zunächst 301 Patienten mit Leberzirrhose aus der eigenen Kohorte am Universitätsklinikum Bonn und bestätigten die Ergebnisse in einer internationalen, multizentrischen (12 Zentren aus 9 Ländern) Kohorte von 607 Patienten der internationalen Baveno-Studiengruppe (Abb. 2.1.1). Primärer Endpunkt war das Ein-Jahres-Überleben.

Überleben stratifiziert nach TSA

Zunächst wurde in der Trainingskohorte mittels Receiver Operating Characteristics (ROC) Analyse ein optimaler Grenzwert der TSA von 83 mm^2 berechnet und die Patienten entsprechend in L-TSA (große TSA, > 83 mm^2) und S-TSA (kleine TSA, ≤ 83 mm^2) eingeteilt. Die Kaplan-Meier Kurve für das Ein-Jahresüberleben zeigt eine signifikant höhere Sterblichkeit in der L-TSA im Vergleich zu der S-TSA Gruppe (Abb. 2.1.2 A). Dieses Ergebnis konnte in der Validierungskohorte bestätigt werden (Abb. 2.1.2 B). Die häufigste Ursache in beiden Kohorten war ACLF in jeweils 63% und 55% der Todesfälle.

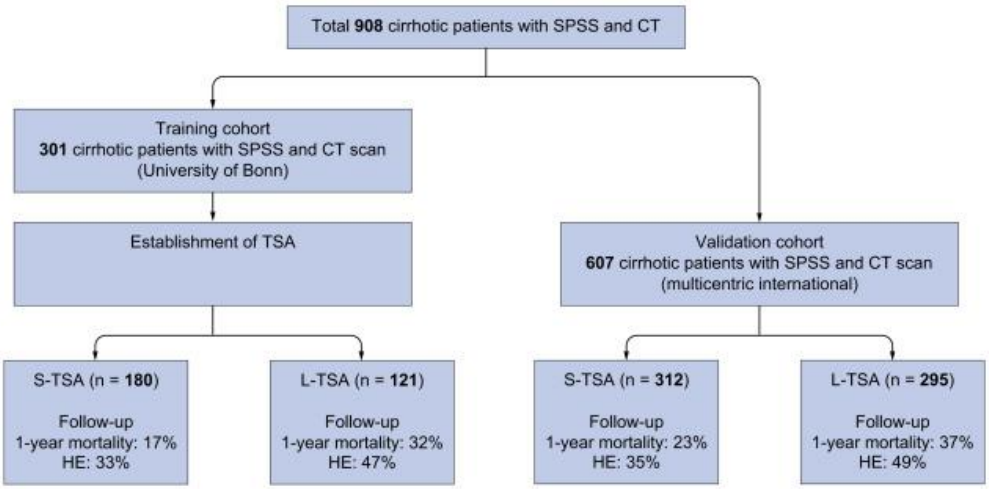

Abbildung. 2.1.1: Flowchart der eingeschlossenen Patienten. Es wurde 301 Patienten aus der eigenen Kohorte in Bonn als Trainingskohorte untersucht und die gewonnenen Ergebnisse in einer internationalen, multizentrischen Validierungskohorte bestätigt. SPSS (spontane portosystemische Shunts), CT (Computertomographie), TSA (Gesamtfläche aller SPSS), S-TSA (Kleines TSA), L-TSA (große TSA), HE (Hepatische Enzephalopathie).

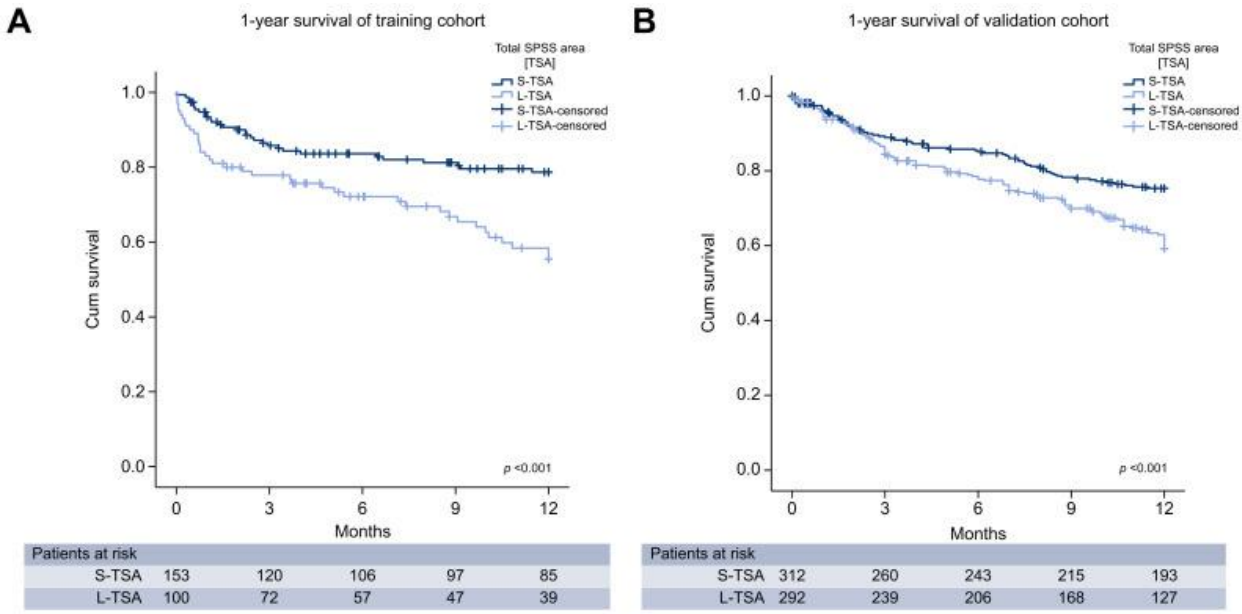

Abbildung. 2.1.2: Kaplan-Meier Kurve für das Ein-Jahresüberleben. (A) In der Trainingskohorte zeigte die L-TSA Gruppe (hellblau) eine signifikant höhere Sterblichkeit im Vergleich zu der S-TSA Gruppe (dunkelbau). (B) Dieses Ergebnis zeigt sich auch in der Validierungskohorte. P durch log-rank Test. TSA (Gesamtfläche aller SPSS), S-TSA (Kleines TSA), L-TSA (große TSA).

Die Patienten wurden ebenfalls mittels einfachem Durchmesser der SPSS eingeteilt, da diese klinisch einfacher zu bestimmen ist. Allerdings konnten die Patienten hierdurch nicht signifikant stratifiziert werden.

Uni- und multivariate Cox Regressionsanalysen bestätigten das Vorhandensein von L-TSA als unabhängigen Prädiktor für das Ein-Jahresüberleben in beiden Kohorten mit ACLF als häufigster Todesursache (Tabelle 2.1.1)

Tabelle. 2.1.1: Univariate und multivariate Cox Regressionsanalyse der Trainingskohorte für 1-Jahressterblichkeit.

1-year mortality	**univariate Cox regression**				**multivariate Cox regression**			
Parameter	**p**	**HR**	**CI**		**p**	**HR**	**CI**	
age[1]	0.025	1.027	1.003	1.051	<0.001	1.060	1.031	1.089
sex	0.332							
L-TSA	0.001	2.266	1.407	3.650	0.040	1.660	1.023	2.695
hepatic encephalopathy at baseline	<0.001	3.519	2.190	5.657	0.002	2.204	1.342	3.619
hepatorenal syndrome at baseline	<0.001	5.781	3.561	9.386	0.024	1.890	1.088	3.283
ascites at baseline	0.002	2.566	1.427	4.615	0.507			
SBP at baseline	0.001	2.736	1.541	4.857	0.693			
MELD at baseline	<0.001	1.180	1.144	1.217	<0.001	1.175	1.129	1.222
sodium at baseline[2]	0.022	0.950	0.909	0.993				
creatinine at baseline[3]	<0.001	2.171	1.783	2.643				
bilirubin at baseline[3]	<0.001	1.122	1.092	1.153				
INR at baseline	<0.001	4.469	3.221	6.202				

kursiv – in multivariate Analyse eingeschlossen, fett – signifikant in multivariater Analyse. MELD – model of end-stage liver disease, INR – international normalized ratio, L-TSA (große TSA), SBP – spontan-bakterielle Peritonitis, 1-[Jahre], 2- [mmol/l], 3-[mg/dl]

Computer-assistierte, automatisierte Messung von TSA

Insgesamt wurden in beiden Kohorten 990 SPSS identifiziert und manuell die TSA gemessen und berechnet. Zur Vereinfachung dieses Prozesses für den klinischen Alltag entwickelten unsere Kooperationspartner des Department of Engineering Design, Universitat Politècnica de Catalunya BarcelonaTech (Barcelona, Spanien) eine MATLAB-basierte Applikation zur automatisierten Messung und Berechnung der TSA auf Grundlage der oben beschriebenen CT-Daten.

Research Article
Cirrhosis and Liver Failure

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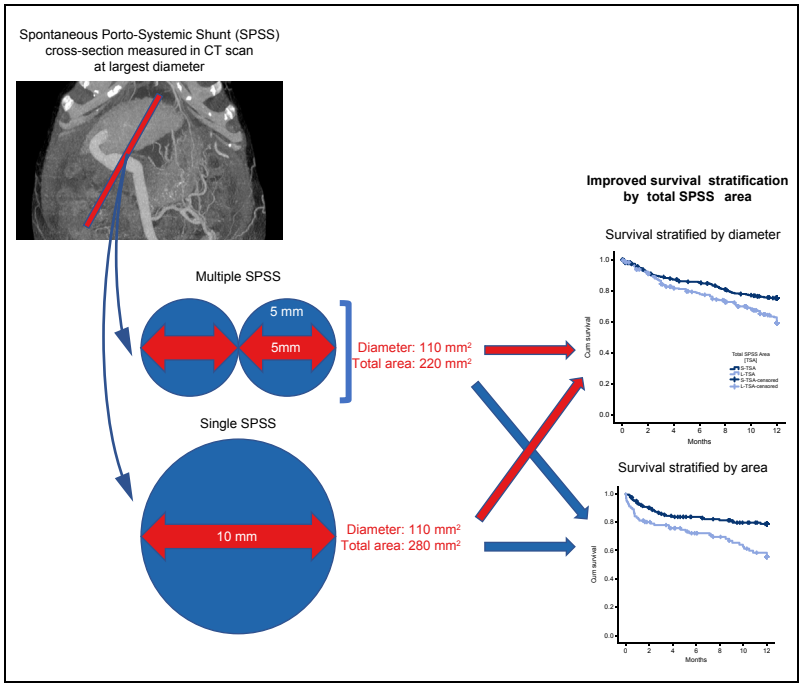
Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis

Graphical abstract



Highlights

- Total cross-sectional SPSS area (TSA) predicts survival in patients with advanced chronic liver disease.
- The cut-off for TSA that is associated with worse survival corresponds to a single shunt of >10 mm diameter.
- This study may impact on the clinical use of TSA/SPSS for risk stratification and decision-making in the management of patients with cirrhosis.

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Lay summary

The prevalence of spontaneous portosystemic shunts (SPSS) is higher in patients with more advanced chronic liver disease. The presence of more than 1 SPSS is common in advanced chronic liver disease and is associated with the development of hepatic encephalopathy. This study shows that total cross-sectional SPSS area (rather than diameter of the single largest SPSS) predicts survival in patients with advanced chronic liver disease. Our results support the clinical use of total cross-sectional SPSS area for risk stratification and decision-making in the management of SPSS.

https://doi.org/10.1016/j.jhep.2019.12.021

Research Article
Cirrhosis and Liver Failure

JOURNAL OF HEPATOLOGY

Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis ☆

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Background & Aims: Spontaneous portosystemic shunts (SPSS) frequently develop in liver cirrhosis. Recent data suggested that the presence of a single large SPSS is associated with complications, especially overt hepatic encephalopathy (oHE). However, the presence of >1 SPSS is common. This study evaluates the impact of total cross-sectional SPSS area (TSA) on outcomes in patients with liver cirrhosis.

Methods: In this retrospective international multicentric study, CT scans of 908 cirrhotic patients with SPSS were evaluated for TSA. Clinical and laboratory data were recorded. Each detected SPSS radius was measured and TSA calculated. One-year survival was the primary endpoint and acute decompensation (oHE, variceal bleeding, ascites) was the secondary endpoint.

Results: A total of 301 patients (169 male) were included in the training cohort. Thirty percent of all patients presented with >1 SPSS. A TSA cut-off of 83 mm^2 was used to classify patients with small or large TSA (S-/L-TSA). Patients with L-TSA presented with higher model for end-stage liver disease score (11 *vs.* 14) and more commonly had a history of oHE (12% *vs.* 21%, p <0.05). During follow-up, patients with L-TSA experienced more oHE episodes (33% *vs.* 47%, p <0.05) and had lower 1-year survival than those with S-TSA (84% *vs.* 69%, p <0.001). Multivariate analysis identified L-TSA (hazard ratio 1.66; 95% CI 1.02–2.70, p <0.05) as an independent predictor of mortality. An independent multicentric validation cohort of 607 patients confirmed that patients with L-TSA had lower 1-year survival (77% *vs.* 64%,

Keywords: Spontaneous portosystemic shunt; Ascites; TIPS; SPSS; Computed tomography; Cirrhosis; Liver; Acute decompensation; Portal hypertension; Hepatic encephalopathy; Acute-on-chronic liver failure; ACLF.
Received 19 July 2019; received in revised form 12 December 2019; accepted 21 December 2019; available online 15 January 2020

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☆ Guest Editor: Didier Samuel.

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https://doi.org/10.1016/j.jhep.2019.12.021

p <0.001) and more oHE development (35% *vs.* 49%, p <0.001) than those with S-TSA.

Conclusion: This study suggests that TSA >83 mm^2 increases the risk for oHE and mortality in patients with cirrhosis. Our results support the clinical use of TSA/SPSS for risk stratification and decision-making in the management of patients with cirrhosis.

Lay summary: The prevalence of spontaneous portosystemic shunts (SPSS) is higher in patients with more advanced chronic liver disease. The presence of more than 1 SPSS is common in advanced chronic liver disease and is associated with the development of hepatic encephalopathy. This study shows that total cross-sectional SPSS area (rather than diameter of the single largest SPSS) predicts survival in patients with advanced chronic liver disease. Our results support the clinical use of total cross-sectional SPSS area for risk stratification and decision-making in the management of SPSS.

Introduction

In the course of liver cirrhosis, the development of portal hypertension is a major driver of complications and therefore a frequent cause of acute decompensation (AD).[1,2] AD may lead to a systemic inflammatory response and progress to acute-on-chronic liver failure (ACLF), a syndrome with high short-term mortality.[3–6] Portal hypertension also drives the development of spontaneous portosystemic shunts (SPSS) in patients with cirrhosis.

The association of SPSS or surgical/interventional shunting with hepatic encephalopathy is well-known and the first embolizations of SPSS, aimed at limiting the complications of portal hypertension, were reported more than 30 years ago.[7–9] However, since then, few reports on the role of SPSS in cirrhosis and their possible treatment have been published.[10–14] A large multicentric study confirmed the association of a single large (diameter >8 mm) SPSS with the occurrence of hepatic encephalopathy.[15] Other reports have also demonstrated that interventional embolization of SPSS can improve refractory hepatic encephalopathy and liver failure in selected patients.[16,17] Since the procedure of SPSS-embolization is invasive and in many cases requires direct portal venous access, there is an open discussion as to whether or when the procedure is indicated.[12,18–20] As a result, recommendations for the management of SPSS are still missing from current guidelines.[2,21–23]

The presence of SPSS and especially their cumulative size has not been associated with hard endpoints such as survival. From a pathophysiological point of view the total cross-sectional shunt area of an SPSS (or cumulative area of several SPSS) may reflect the portosystemically shunted blood volume[24] more accurately than SPSS diameter. With the improved quality of imaging, especially with CT, the detection of SPSS in clinical routine is feasible and reliable. This present study aimed to evaluate the role of the combined cross-sectional area of all SPSS, as a surrogate marker of portosystemically shunted blood volume, in the natural course of patients with liver cirrhosis.

Patients and methods

Study population

For this retrospective study, a total of 301 patients from the University Hospital of Bonn were identified for inclusion as a training cohort. Inclusion criteria were age 18 years or older, diagnosis of cirrhosis (clinical, radiologic or histologic) and SPSS of at least 5 mm of diameter in CT scans between October 2006 and April 2016. Since precision was needed to measure SPSS diameter, a minimum diameter of >5 mm was considered by our radiologist to provide accurate SPSS size. The date of CT scan was defined as baseline. Exclusion criteria were presence of hepatocellular carcinoma beyond Milan criteria, previous transjugular intrahepatic portosystemic shunt (TIPS) or surgical shunt, any medical condition with expected survival of less than 6 months, presence of neurologic, or psychiatric disorder preventing a proper hepatic encephalopathy evaluation and absence of critical information in the medical history.[15] The validation cohort was formed of 607 consecutive patients, identified between 2010 and 2015, with the same selection criteria as the training cohort from the rest of the participating centers in the previously published multicenter study.[15] Although excluding small SPSS of less than 5 mm was not an original criterion in the prior multicenter study, it was applied to the validation cohort for consistency. In all patients, cross-sectional area of all detectable SPSS was assessed and calculated in CT scans. Clinical and laboratory blood analysis data was followed up until end of follow-up, death or liver transplantation (LT).

The primary endpoint was 1-year survival and secondary endpoints were acute decompensations (hepatic encephalopathy, variceal bleeding and ascites) during follow-up.

The local ethics committee of the participating centers approved the study. The study was performed in accordance with the Helsinki Declaration.

Assessment of SPSS parameters

All CT scans were reviewed by radiologists with expertise in liver diseases. SPSS were defined as previously described.[15] The radiological study protocol is shown in the supplementary materials and methods. All CT scans were screened for any SPSS by scrolling through the abdominal CT scan in the axial plane. If available, portal venous phase was preferred. The radiologists looked for any additional veins leaving the inferior vena cava, portal vein, splenic vein, right/left renal vein and superior/inferior mesenteric vein. The presence of SPSS was verified in the coronal and sagittal plane.

The position of the SPSS with the largest diameter was then identified. At this position the short-axis diameter was reconstructed and measured between both walls of the vessel.

The 607 CT scans from the validation cohort were reviewed again to measure the total cross-sectional SPSS area (TSA) for the present study by the same radiologists who evaluated them in the prior study.[15] We have chosen to measure the cross-sectional area instead of the diameter because more than 1 SPSS can occur in patients with liver cirrhosis and portal hypertension.[15] Though the sum of diameters of all SPSS can be the same, the sum of cross-sectional areas can be vastly different as shown in Fig. S1. We hypothesized that TSA reflects the shunted blood volume better than diameters. For each SPSS we calculated the area by the formula πr^2. All SPSS areas were then summed up to calculate the TSA for each patient.

The diameters of the SPSS were measured twice (initial data were collected from the previous study by Simón-Talero *et al.*;[15] for the current work, all the CTs were reviewed again by the same expert radiologists). Therefore, the intra-rater variability of the measurement has been calculated, with an intraclass correlation coefficient of 0.95 (95% CI 0.94–0.96).

Esophageal and gastric varices were documented, but not measured. Rectal varices were neither measured nor

documented. This is because, in both cases, the shunts are more of a network than a single vessel that can be determined.

Statistical analysis

We performed descriptive statistics for all variables. Non-parametric testing was used to compare different groups when suitable. Paired non-parametric testing was used to compare data of baseline and follow-up of the same patients. Correlation of metric variables was performed using Spearman's correlation. For the selection of cut-off values of TSA, receiver-operating characteristics analysis with 1-year survival as the endpoint was calculated. To examine the impact of TSA on survival we used a Kaplan-Meier curve with log-rank test. Univariate and multivariate risk factor analyses were performed with Cox regression for 1-year mortality and episodes of hepatic encephalopathy as endpoints. Univariate analysis included general characteristics (age, sex) and clinical conditions (hepatic encephalopathy, hepatorenal syndrome, ascites, spontaneous bacterial peritonitis) as well as prognostic score (model for end-stage liver disease [MELD]) and laboratory parameters (Na, creatinine, bilirubin, international normalized ratio [INR]) at baseline. Multivariate analysis included all values with p <0.05 from univariate Cox regression. To avoid multicollinearity, calculated scores such as MELD were not entered simultaneously with their components, while scores with overlapping components (Child-Pugh) were not entered simultaneously either. Continuous variables are presented as median (range), unless otherwise specified. Categorical variables are presented as absolute cases and/or percentage. The intra-rater reliability was calculated using the interclass correlation coefficient. All data was analyzed using SPSS (version 24, IBM, Armonk, NY, USA) or R statistics (version 3.4.4, The R Foundation).

Results

General patient characteristics

Training cohort

Of all 908 patients, 301 patients from University of Bonn were included in the training cohort (Fig. 1), of whom 169 were male. Median age at baseline was 56 (28-85) years. Alcohol was the most common etiology of cirrhosis (57% of patients), while 20% of patients had chronic viral hepatitis B and/or C infection. Other etiologies were present in 23% of patients. Most of the patients were decompensated (Child-Pugh B or C in 59%) with 64% of the patients exhibiting ascites at time of CT scan; 16% had experienced at least 1 episode of hepatic encephalopathy and 26% had hepatic encephalopathy at baseline. A history of variceal bleeding was present in 28% of the patients. Median MELD score was 13 (6-40). Detailed general characteristics are displayed in Table 1. Of note, high platelet counts >250×10^9/L were found in 26 patients, of whom 9 had infection, 3 recent bleeding and 2 iron deficiency, as likely causes for high platelet counts. Median follow-up time was 15 (0–117) months. Median time from diagnosis of liver cirrhosis to CT scan was 17 months (0–1,322). Indications for CT scans are displayed in Table S1.

Follow-up data on survival status was available in 254 patients (Table 1). During follow-up MELD decreased slightly, while other prognostic scores (MELD-Na, Child-Pugh) did not change significantly. Compared to baseline, the rate of patients developing hepatorenal syndrome (23%) and episodes of hepatic encephalopathy (38%) increased significantly. The rate of patients with ascites and variceal bleeding did not change significantly (Table 1). In total, 23 patients were treated with TIPS (16 for refractory ascites, 7 for variceal hemorrhage) during follow-up. Detailed analysis of number of TIPS and LT in relation to MELD is shown in Table S2.

SPSS characteristics. In the training cohort of 301 patients, a total of 392 SPSS were identified. Most patients had a single SPSS (70%), while almost one-third (30%) were diagnosed with more than 1 SPSS (Table 1).

The most common SPSS types were para-umbilical shunts representing 57% of all shunts, followed by splenorenal shunts (32%), mesocaval shunts in the gastrorenal vein (5%) and in the adrenal vein (2%). Infero-mesenterico-caval, right renal vein and mesorenal shunts were each found in only 1% of SPSS.

Validation cohort

A total of 607 patients from 11 participating centers were included in the validation cohort (Table S3, Fig. 1). Median age

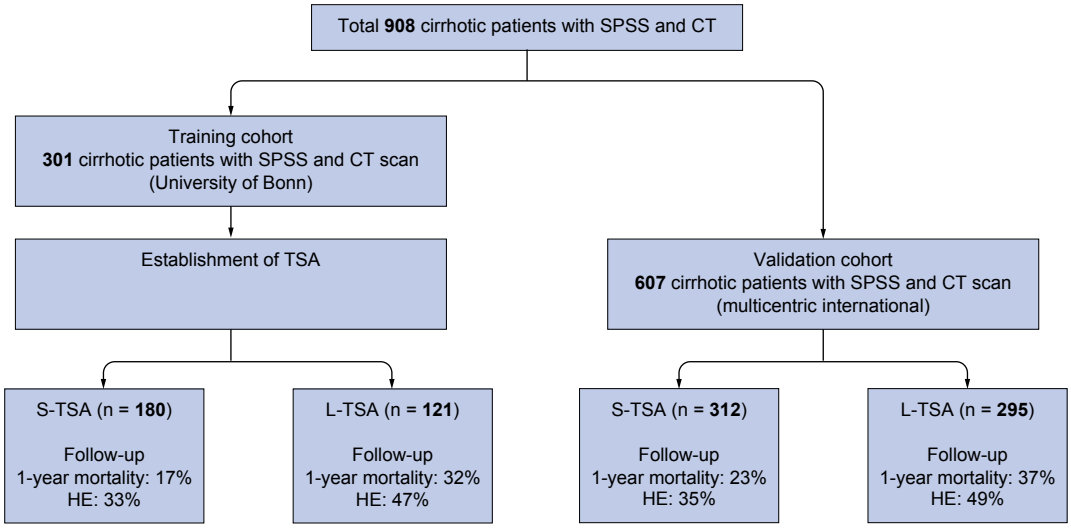

Fig. 1. Flowchart of patient selection.

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Table 1. General characteristics of the training cohort (n = 301).

Parameter	History	Baseline	Follow-up
Median (range) or absolute (percentage)			
General			
Age [years]		58 (28-85)	
Gender [male/female]		169/132 (56/44%)	
Etiology of cirrhosis [alcohol, viral, other]		173/60/68 (57/20/23%)	
Number of shunts [1/2/3]		213/86/2 (71/29/1%)	
Total SPSS area [mm^2]		59 (6-881)	
Clinical events			
Ascites	143 (48%)	194 (64%)	116 (53%)
Variceal Bleeding	85 (28%)	48 (16%)	29 (13%)
Spontaneous Bacterial Peritonitis	20 (7%)	32 (11%)	20 (9%)
Hepatorenal Syndrome	30 (10%)	49 (16%)	50 (23%)***
Hepatic Encephalopathy	47 (16%)	78 (26%)	84 (38%)***
Scores			
MELD		13 (6-40)	12.5 (6-40)*
MELD-Na		15 (6-40)	14 (6-40)
Child-Pugh		7 (5-13)	7 (5-12)
Child-Pugh class A/B/C		103/143/34 (34/48/11%)	90/68/32 (41/31/15%)
CLIF-C AD		20.65 (10-29)	20.58 (9-32)
Laboratory			
Sodium [mmol/L]		138 (119-154)	140 (119-163)***
Creatinine [mg/dl]		0.97 (0.3-6.04)	1 (0.1-9.39)***
Bilirubin [mg/dl]		1.86 (0.21-48.44)	1.75 (0.19-42.49)
AST [U/L]		52 (12-653)	44.5 (9-5,644)
ALT [U/L]		31 (8-349)	33 (6-1,952)
Albumin [g/L]		29.2 (3.2-59.9)	32.8 (3.2-55)***
INR		1.2 (0.9-4.6)	1.2 (0.9-5.3)
WBC [10^3/μl]		5.86 (1.02-37.17)	5.795 (0.04-36.22)
Platelets [×10^9/L]		105.5 (11-653)	107.5 (14-479)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; INR, international normalized ratio; MELD, model of end-stage liver disease; SPSS, spontaneous portosystemic shunts; WBC, white blood cell count.
*p <0.05; **p <0.01; ***p <0.001.

was 58 (18-87) years with 65% male patients. Alcohol was the most common etiology of cirrhosis (43%), while 27% had viral hepatitis. Most patients (66%) had decompensated cirrhosis (Child-Pugh B or C); 53% of the patients had ascites at the time of CT scan, 30% had experienced at least 1 episode of hepatic encephalopathy, and 25% had hepatic encephalopathy at baseline. A history of variceal bleeding was present in 25% of the patients. Median MELD score was 13 (6-37). Detailed general characteristics are displayed in Table 2.

Follow-up data is shown in Table 2. Briefly, like the training cohort, the rate of patients developing hepatorenal syndrome (11%), as well as episodes of hepatic encephalopathy (42%) increased significantly compared to baseline. The rate of ascites and variceal bleeding did not change significantly (Table 2).

SPSS characteristics

In the validation cohort of 607 patients, 754 SPSS were identified. The majority of patients had a single SPSS (79%), while 21% had multiple SPSS (Table 2). Splenorenal shunts were the most common, representing 41% of cases, followed by para-umbilical shunt (35%). Mesocaval shunt was present in 7% of cases, gastrorenal in 6%, infero-mesenterico-caval in 3% and mesorenal in 1% of SPSS.

Patient stratification by total SPSS area

A receiver-operating characteristics analysis of TSA with 1-year survival as an endpoint was performed and an area under the curve of 0.609 (95% CI 0.531–0.687, p = 0.007) was calculated. The optimal cut-off value for the training cohort was found at 83 mm^2 (sensitivity 55.7%, specificity 66.8%, positive predictive value 39.0%, negative predictive value 79.9%; Table S4). Patients with TSA above 83 mm^2 (corresponding to a single shunt of 10 mm diameter) were classified as having large TSA (L-TSA) and patients with TSA below 83 mm^2 were classified as having small TSA (S-TSA). Median TSA was 59 mm^2 (6–881). Patients with S-TSA had a median TSA of 35 mm^2 (6–82) and L-TSA of 141.46 mm^2 (83–881) (Table 3). In total, 180 patients were classified as S-TSA (60%) and 121 as L-TSA (40%). There were no significant differences in type of SPSS between patients with S-TSA and L-TSA. Time between diagnosis of cirrhosis and CT scan was not significantly different between patients with S-TSA and L-TSA (15 (0–1,322) *vs.* 24 (0–369) months, p = 0.503).

Patients with L-TSA had significantly higher rates of multiple SPSS, as well as higher MELD scores (14 *vs.* 11). Moreover, patients with L-TSA had higher rates of hepatic encephalopathy in their medical history (Table 3). During follow-up, MELD (12 *vs.* 15, p <0.01) and MELD-Na (13 *vs.* 16, p <0.05) score remained significantly higher in the L-TSA compared to S-TSA group. CLIF-C AD score was not significantly different. Additionally, Child-Pugh score (6 *vs.* 7, p <0.05) in follow-up showed higher values for L-TSA. This mainly derives from serum albumin levels being significantly lower in L-TSA (35 *vs.* 31 g/L, p <0.001) (Table 3). No significant differences were detectable in terms of hepatorenal syndrome, ascites and infections.

L-TSA is associated with hepatic encephalopathy

Training cohort

Patients with L-TSA had a significantly higher risk of developing hepatic encephalopathy, as shown by the cumulative hazard

Table 2. General characteristics of external validation cohort (n = 607).

Parameter	History	Baseline	Follow-up
Median (range) or absolute (percentage)			
General			
Age [years]		58 (18-87)	
Sex male/female		397/210 (65/35%)	
Etiology of cirrhosis alcohol/viral/others		259/164/184 (43/27/30%)	
Number of shunts 1/2/3/4		480/110/14/3 (79/18/2/1%)	
Total SPSS area [mm^2]		79 (13-2205)	
Clinical events			
Ascites	345 (58%)	321 (53%)	341 (57%)
Variceal bleeding	151 (25%)	65 (11%)	96 (16%)
Spontaneous bacterial peritonitis	65 (11%)	39 (7%)	72 (12%)
Hepatorenal syndrome	18 (3%)	23 (4%)	63 (11%)***
Hepatic encephalopathy	183 (30%)	152 (25%)	247 (42%)***
Scores			
MELD		13 (6-37)	
MELD-Na		15 (6-40)	
Child-Pugh		8 (5-15)	
Child-Pugh class A/B/C		195/238/147 (34/41/25%)	
Laboratory			
Sodium [mmol/L]		138 (95-164)	
Creatinine [mg/dl]		0.8 (0.3-9.2)	
Bilirubin [mg/dl]		1.8 (0.1-45.2)	
Albumin [g/L]		32 (10-50)	
INR		1.4 (0.9-5.2)	
Platelets [×10^9/L]		87 (13-436)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; INR, international normalized ratio; MELD, model of end-stage liver disease; SPSS, spontaneous portosystemic shunts; WBC, white blood cell count.
*p <0.05; **p <0.01; ***p <0.001.

function for hepatic encephalopathy in Fig. 2A. Blood ammonia levels were available in 154 patients. Median blood ammonia level was 65 μmol/L (9–260). Patients were divided into high (>65 μmol/L) and low (≤65 μmol/L) ammonia levels. Patients with L-TSA showed higher rates (57%) of high ammonia levels than patients with S-TSA (42%) (Table S5).

Validation cohort
In the validation cohort clinical but no blood parameters were available at follow-up (Table 4). Importantly, the significantly higher rates of episodes of hepatic encephalopathy were confirmed as shown in Fig. 2B.

Large TSA is an independent risk factor for 1-year mortality

Training cohort
One-year survival data was available in 253 patients. Fig. 3A shows the Kaplan-Meier curve for 1-year mortality. The Kaplan-Meier curve for 1-year survival excluding patients with high platelet counts showed similar results (Fig. S2). Patients with L-TSA had a significantly higher mortality compared to patients with S-TSA (p <0.001). Most deaths are attributed to infection (63%). Hepatocellular carcinoma and liver failure caused 10% and 13% of deaths, respectively. Six percent died of bleeding and cardiovascular events (Table S6).

Univariate Cox regression was performed to identify risk factors for 1-year mortality. This revealed that besides the expected prognostic MELD score, creatinine, bilirubin and INR, as well as hepatorenal syndrome, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites and L-TSA at baseline were dependent predictors of survival. Multivariate Cox regression identified L-TSA alongside MELD, hepatic encephalopathy, hepatorenal syndrome and ascites as independent risk factors for 1-year survival (Table 5).

A different model with TSA as a continuous variable was calculated, which confirmed TSA (as a continuous variable) as an independent predictor of 1-year survival (Table S7).

Validation cohort
In order to validate these results, the validation cohort was stratified for TSA. A total of 312 patients were classified as S-TSA (51%) and 295 as L-TSA (49%). Patients with L-TSA had significantly higher MELD and Child-Pugh score. There were no significant differences in type of SPSS between patients with S-TSA and L-TSA. Moreover, patients with L-TSA had higher rates of hepatic encephalopathy at baseline and in their medical history (Table 4). Survival data was available in 604 patients. Fig. 3B shows the Kaplan-Meier curve for 1-year mortality. Patients with L-TSA had a significantly higher mortality compared to those with S-TSA (p <0.001). Kaplan-Meier curve for 1-year survival excluding patients with high platelet counts showed similar results (Fig. S3).

Most deaths in the validation cohort were attributed to liver failure (36%), infection (19%) and hepatocellular carcinoma (12%). Six percent died of bleeding, 27% died of other or unknown causes (Table S8).

Univariate Cox regression was performed to identify risk factors for 1-year mortality. In this validation cohort prognostic markers such as MELD, creatinine, bilirubin and INR, as well as hepatorenal syndrome, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites and TSA at baseline were dependent predictors of survival. Multivariate Cox regression confirmed TSA and MELD as independent predictors of 1-year mortality. Moreover, age, hepatorenal syndrome and ascites were shown as independent risk factors for 1-year survival (Table 6).

In an alternative model using TSA as a continuous variable, TSA was still an independent predictor of 1-year mortality, suggesting a linear relationship (Table S9).

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Table 3. Clinical and laboratory characteristics of training cohort stratified for total shunt area.

Parameter	S-TSA	L-TSA
Median (range) or absolute (percentage)	n = 180	n = 121
Baseline general		
Age [years]	57 (28-85)	58 (31-78)
Sex male/female	99/81 (55/45%)	70/51 (58/42%)
Etiology of cirrhosis alcohol/viral/others	103/41/36 (57/23/20%)	70/19/32 (58/16/26%)
Number of shunts 1/2/3	162/18/0 (90/10/0%)	51/68/2 (42/56/2%)***
Total SPSS area [mm^2]	34.72 (5.72-82.34)	141.46 (83.29-880.65)***
History of clinical events		
Ascites	89 (49%)	54 (45%)
Variceal bleeding	48 (27%)	37 (31%)
Spontaneous bacterial peritonitis	12 (7%)	8 (7%)
Hepatorenal syndrome	19 (11%)	11 (9%)
Hepatic encephalopathy	22 (12%)	25 (21%)*
Baseline clinical events		
Ascites	126 (70%)	68 (56%)*
Variceal bleeding	34 (19%)	14 (12%)
Spontaneous bacterial peritonitis	18 (10%)	14 (12%)
Hepatorenal syndrome	26 (14%)	23 (19%)
Hepatic encephalopathy	42 (23%)	36 (30%)
Baseline scores		
MELD	11 (6-35)	14 (6-40)***
MELD-Na	14 (6-36)	16 (6-40)**
Child-Pugh	7 (5-11)	7 (5-13)
Child-Pugh class A/B/C	63/91/13 (35/51/7%)	40/52/21 (33/43/17%)
Baseline laboratory		
Sodium [mmol/L]	138 (119-148)	139 (122-154)
Creatinine [mg/dl]	0.96 (0.3-6.04)	0.99 (0.42-5.09)
Bilirubin [mg/dl]	1.56 (0.21-19.9)	2.45 (0.26-48.44)***
Albumin [g/L]	29.4 (3.2-51.6)	28.9 (4.8-59.9)
INR	1.2 (0.9-2.8)	1.3 (1-4.6)***
Parameter	**S-TSA**	**L-TSA**
Median (range) or absolute (percentage)	n = 180	n = 121
FU		
Survival FU 1 year [months]	12 (0-12)	8.5 (0-12)*
FU state 1-year dead/LT	22 / 9 (17%)	29 /10 (32%)**
Lost to FU	36 (20%)	23 (19%)
FU clinical events		
Ascites	76 (55%)	40 (49%)
Variceal bleeding	22 (16%)	7 (9%)
Spontaneous bacterial peritonitis	14 (10%)	6 (7%)
Hepatorenal syndrome	33 (24%)	17 (21%)
Hepatic encephalopathy	46 (33%)	38 (47%)*
FU scores		
MELD	12 (6-40)	15 (6-40) **
MELD-Na	13 (6-40)	16 (6-40)*
Child-Pugh	6 (5-12)	7 (5-12)*
Child-Pugh class A/B/C	63/41/14 (46/30/10%)	27/27/18 (33/33/22%)*

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; FU, follow-up; INR, international normalized ratio; LT, liver transplantation; L-TSA, large total SPSS area; MELD, model of end-stage liver disease; SPSS, spontaneous portosystemic shunts; S-TSA, small total SPSS area; WBC, white blood cell count.
*p <0.05; **p <0.01; ***p <0.001.

To further investigate the impact of TSA on survival in relation to liver function, we divided the whole cohort into tertiles according to MELD (6–9, 10–13, 14–40), as in our previous study.[15] The rates of 1-year mortality were higher in the L-TSA group and significant in MELD groups 6–9 and 14–40 (Table S10).

SPSS and TSA distribution

In our recent multicenter study,[15] a stratification of patients according to SPSS diameter (8 mm cut-off) did not show significant differences in survival between S-SPSS (<8 mm) and L-SPSS (≥8 mm). Therefore, we investigated the distribution of S-/L-SPSS and S-/L-TSA of the whole cohort. The results are shown in Fig. S4. In total, 35% of patients were classified S-SPSS and S-TSA, 0.3% S-SPSS and L-TSA, 19% L-SPSS and S-TSA and 46% L-SPSS and L-TSA. This suggests mostly concordant classification between S-SPSS and S-TSA. However, a substantial fraction (19%) of patients with L-SPSS are classified as S-TSA as well.

The Kaplan-Meier survival curve shows no significant difference in survival between patients with S-SPSS and L-SPSS (Fig. S5), confirming our previous study.[15] Importantly, Kaplan-Meier survival analysis of only patients with L-SPSS showed a highly significant difference between patients classified as S-TSA and L-TSA, demonstrating that TSA classification clearly outperforms classification by SPSS diameter (Fig. S6).

We performed a Cox regression model for 1-year survival with L-SPSS instead of L-TSA to evaluate the predictive value of

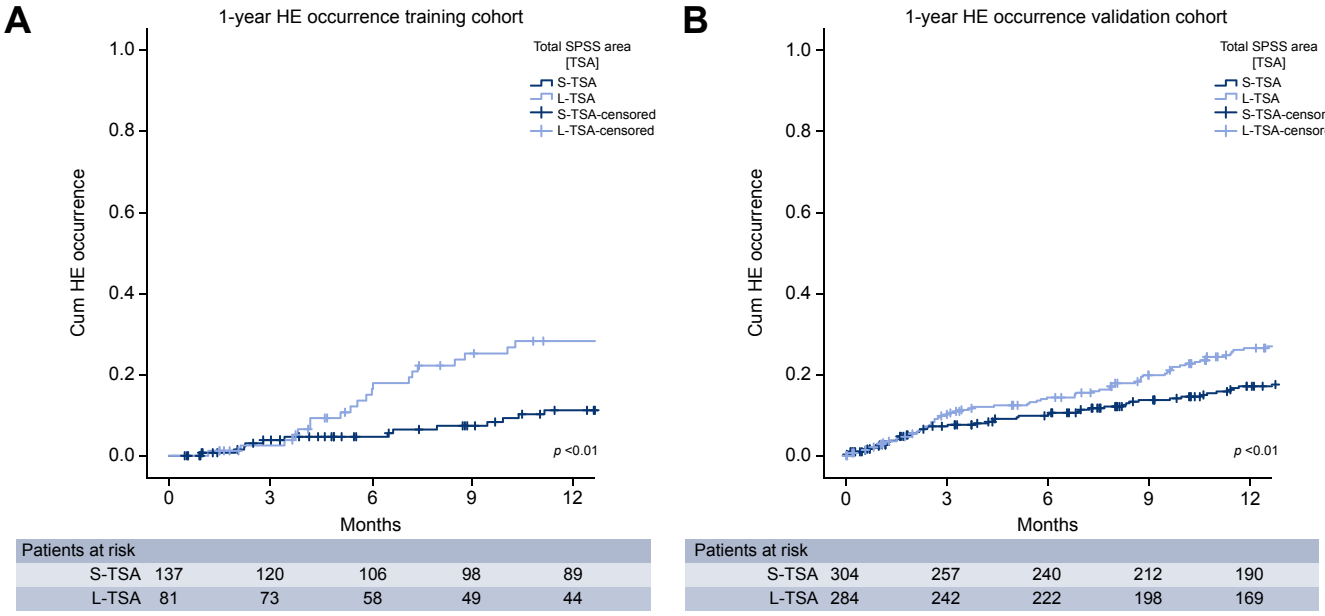

Fig. 2. Cumulative hazard function for the occurrence of overt hepatic encephalopathy in the training and validation cohorts. (A) Cumulative hazard function for the occurrence of overt hepatic encephalopathy during 1-year follow-up in L-TSA (green line) *vs.* S-TSA (blue line) patients in training cohort. (B) Cumulative hazard function for the occurrence of overt hepatic encephalopathy during 1-year follow-up in L-TSA (green line) *vs.* S-TSA (blue line) patients in validation cohort. (S-/L-TSA: small (<83 mm^2) / large (≥83 mm^2) total SPSS area). Statistical analysis: log-rank test. L-TSA, large total SPSS area; SPSS, spontaneous portosystemic shunts; S-TSA, small total SPSS area.

presence of L-SPSS. In both the training and validation cohort SPSS was not significant in multivariate analysis. In the validation cohort, SPSS was not significant in the univariate analysis either (Table S11 and S12).

Discussion

Using a large single center training and a large multicentric international validation cohort, this study demonstrates for the first time that portosystemic shunting is associated with increased mortality in cirrhotic patients independently of severity of liver disease.

These results build up on the previously reported data on the influence of the diameter of largest SPSS, where a clear association with the risk of complications of liver cirrhosis was demonstrated.[15] This study confirms those results, which underlines the robustness of TSA. Another factor supporting the plausibility of our data is the fact that L-TSA was found in more advanced stages of liver cirrhosis, reflected by higher MELD scores, which is in line with previous reports.[15,25] One might argue that retrieving and calculating the cross-sectional area of every SPSS is costly and more time consuming than just measuring the diameter of the largest SPSS. However, having a single SPSS of 10 mm diameter or more qualifies for L-TSA but not multiple SPSS with an added diameter of 10 mm. This situation of multiple SPSS is present in one-third of the presented large cohort. The present study demonstrates that the complete shunting volume, which might be better reflected by TSA, gives independent insight into the progression of liver disease and outcome of cirrhotic patients. This hypothesis is supported by this study because the size of TSA has an independent impact on survival in cirrhotic patients, which could not be demonstrated for diameter of the single largest SPSS (<8 mm *vs.* ≥8 mm).[15] This is especially impactful because, as shown in our and other cohorts, about one-third of the patients have more than 1 SPSS.[15,26,27] Since this study demonstrates TSA as a risk factor for survival independent of MELD, an incorporation of TSA in MELD (TSA-MELD) could improve patient's risk stratification and should be evaluated in future research.

The association of hepatic encephalopathy and SPSS is well established.[7,15,28–31] This association with hepatic encephalopathy is not only apparent for spontaneous shunts but also for therapeutically implanted shunts (*e.g.* TIPS and surgical shunts), where episodes of hepatic encephalopathy occur in up to 50% of patients.[31–33] Although only shown in a few cohorts, the deleterious effect of shunting seems to be additive by the number shunts (spontaneous and intentional) as the presence of SPSS and TIPS has been shown to be associated with more complications than TIPS alone.[34,35] Growing evidence has been published that suggests less complications after TIPS by using smaller diameter stents or dilatation of stents smaller than the nominal diameter, suggesting a beneficial effect of less shunt volume.[36–40]

Regarding other decompensating events, we were unable to find a significant difference in variceal bleeding, hepatorenal syndrome or spontaneous bacterial peritonitis between patients with L-TSA and S-TSA. Considering variceal bleeding, our data are supported by previous reports, in which only the presence of SPSS *vs.* no SPSS was shown to be associated with bleeding, but no differences between small and large SPSS were detected.[7,10,15,29]

Interestingly, the cut-off we found in our patients corresponds to a single shunt of 10 mm diameter. In non-spontaneous SPSS, such as TIPS, it has been previously shown that small diameter TIPS-shunts are associated with less hepatic encephalopathy and better survival than the commonly used 10 mm stents.[37,38,40] However, in case of TIPS, the collaterals and the

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Table 4. Clinical and laboratory characteristics of validation cohort stratified for total shunt area.

Parameter	S-TSA	L-TSA
Median (range) or absolute (percentage)	n = 312	n = 295
Baseline general		
Age [years]	59 (18-87)	57 (20-84)
Sex male/female	209/103 (67/33%)	188/107 (64/36%)
Etiology of cirrhosis alcohol/viral/others	129/86/97 (41/28/31%)	130/78/87 (44/26/30%)
Number of shunts 1/2/3	283/27/2/0 (91/8/1/0%)	67/28/12/3 (67/28/4/1%)***
Total SPSS area [mm^2]	38 (13-79)	201 (89-2205)***
History of clinical events		
Ascites	180 (58%)	165 (57%)
Variceal bleeding	75 (25%)	76 (26%)
Spontaneous bacterial peritonitis	37 (12%)	28 (10%)
Hepatorenal syndrome	9 (3%)	9 (3%)
Hepatic encephalopathy	71 (23%)	112 (38%)***
Baseline clinical events		
Ascites	176 (56%)	145 (49%)
Variceal bleeding	42 (14%)	23 (8%)*
Spontaneous bacterial peritonitis	22 (7%)	17 (6%)
Hepatorenal syndrome	15 (5%)	8 (3%)
Hepatic encephalopathy	64 (21%)	88 (30%)**
Baseline scores		
MELD	12 (6-37)	14 (6-33)**
MELD-Na	15 (6-37)	15 (6-40)
Child-Pugh	8 (5-15)	8 (5-15)*
Child-Pugh class A / B / C	109/120/73 (36/40/24%)	86/118/74 (31/42/27%)
Baseline laboratory		
Sodium [mmol/L]	137 (117-164)	138 (95-148)
Creatinine [mg/dl]	0.8 (0.3-3.8)	0.8 (0.4-9.2)
Bilirubin [mg/dl]	1.5 (0.1-42.9)	2.1 (0.3-45.2)*
Albumin [g/L]	32 (10-50)	32 (15-50)
INR	1.4 (0.9-5.2)	1.4 (1.0-4.1)
Parameter	**S-TSA**	**L-TSA**
Median (range) or absolute (percentage)	n = 312	n = 295
FU		
Survival FU 1 year [months]	12 (0-12)	11 (0-12)*
FU state 1-year dead/LT	45/28 (23%)	78/31 (37%)***
Lost to FU	42 (13%)	56 (19%)
FU clinical events		
Ascites	182 (59%)	159 (56%)
Variceal bleeding	55 (18%)	41 (14%)
Spontaneous bacterial peritonitis	37 (12%)	35 (12%)
Hepatorenal syndrome	34 (11%)	29 (10%)
Hepatic encephalopathy	107 (35%)	140 (49%)***

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; FU, follow-up; INR, international normalized ratio; LT, liver transplantation; L-TSA, large total SPSS area; MELD, model of end-stage liver disease; SPSS, spontaneous portosystemic shunts; S-TSA, small total SPSS area; WBC, white blood cell count.
*p <0.05; **p <0.01; ***p <0.001.

other SPSS have been rigorously embolized in order to limit TSA to 10 mm and other persisting collaterals (in many patients present) may have contributed to non-significant results regarding survival.

This study presents a large, multicentric, international, well characterized cohort of cirrhotic patients with SPSS. However, it has several limitations, which are mainly based on the retrospective nature of the study. Some parameters such as endoscopy and follow-up blood work were not available in all patients. Patients were not specifically screened for non-cirrhotic portal hypertension. Moreover, exploring a pathophysiological mechanism is beyond the scope of this study. Longitudinal data of the impact of SPSS on the natural history are needed. The development of portal venous thrombosis and its relation to medical treatment, such as non-selective betablockers and anticoagulants, should be addressed in future longitudinal studies.[41–45] In this study only cirrhotic patients who underwent CT scan were included. This would lead to a selection bias towards patients without severe kidney dysfunction because those patients would not receive CT scan due to contrast media exposure. Moreover, no data on sarcopenia is available, which has recently been recognized as a risk factor for the development of hepatic encephalopathy after TIPS[46–50] and could be a competing factor to consider against TSA.

In conclusion, this study highlights, for the first time, the prognostic importance of TSA (sum of all cross-sectional SPSS areas) in patients with mostly decompensated liver cirrhosis. The prevalence of more than 1 SPSS among these patients is high and increases with advancing liver disease. L-TSA is an independent predictor of 1-year mortality and is associated with higher rates of hepatic encephalopathy compared to S-TSA. These data suggest that there is a cut-off for portosystemically shunted blood volume where the beneficial effects are outweighed by the deleterious ones. Our results support the clinical use of TSA/SPSS for risk

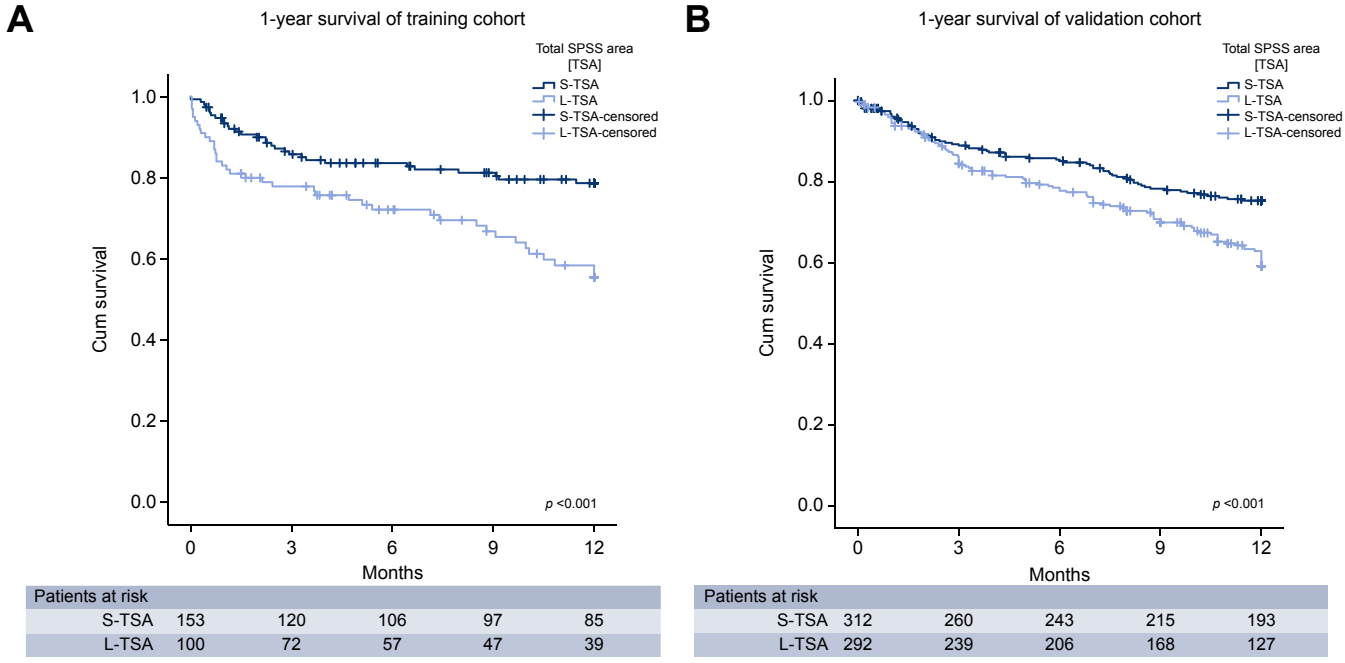

Fig. 3. Kaplan-Meier curve of 1-year survival in training and validation cohorts. (A) Kaplan-Meier curve showing impaired 1-year survival in L-TSA patients (green line) compared to S-TSA patients (blue line) in training cohort. (B) Kaplan-Meier curve showing impaired 1-year survival in L-TSA patients (green line) compared to S-TSA patients (blue line) in validation cohort. (S-/L-TSA: small (<83 mm^2) / large (≥83 mm^2) total SPSS area). Statistical analysis: log-rank test. L-TSA, large total SPSS area; SPSS, spontaneous portosystemic shunts; S-TSA, small total SPSS area.

Table 5. Univariate and multivariate Cox regression analysis of training cohort with 1-year mortality as endpoint.

	Univariate Cox regression				Multivariate Cox regression			
Parameter	**HR**		**95% CI**	***p* value**	**HR**		**95% CI**	***p* value**
***Age*[1]**	1.027	1.003	1.051	0.025	1.060	<0.001	1.089	<0.001
Sex				0.332				
L-TSA	2.266	1.407	3.650	0.001	1.660	0.040	2.695	0.040
Hepatic encephalopathy at baseline	3.519	2.190	5.657	<0.001	2.204	0.002	3.619	0.002
Hepatorenal syndrome at baseline	5.781	3.561	9.386	<0.001	1.890	0.024	3.283	0.024
Ascites at baseline	2.566	1.427	4.615	0.002		0.507		0.507
SBP at baseline	2.736	1.541	4.857	0.001		0.693		0.693
MELD at baseline	1.180	1.144	1.217	<0.001	1.175	<0.001	1.222	<0.001
Sodium at baseline[2]	0.950	0.909	0.993	0.022				
Creatinine at baseline[3]	2.171	1.783	2.643	<0.001				
Bilirubin at baseline[3]	1.122	1.092	1.153	<0.001				
INR at baseline	4.469	3.221	6.202	<0.001				

[1]years; [2]mmol/L; [3]mg/dl
Italic, included in multivariate analysis; Bold, significant in multivariate analysis.
INR, international normalized ratio; L-TSA, large total SPSS area; MELD, model of end-stage liver disease; SBP, spontaneous bacterial peritonitis; SPSS, spontaneous portosystemic shunts.

stratification and decision-making in the management of patients with cirrhosis.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; FU, follow-up; HR, hazard ratio; HRS, hepatorenal syndrome; INR, international normalized ratio; LT, liver transplantation; L-TSA, large total SPSS area; MELD, model of end-stage liver disease; SBP, spontaneous bacterial peritonitis; SPSS, spontaneous portosystemic shunts; S-TSA, small total SPSS area; TIPS, transjugular intrahepatic portosystemic shunt; WBC, white blood cell count.

Financial support

Jonel Trebicka is supported by grants from the Deutsche Forschungsgemeinschaft (SFB TRR57, CRC1382), Cellex Foundation and European Union's Horizon 2020 research and innovation program GALAXY study (No. 668031), LIVERHOPE (No. 731875) and MICROB-PREDICT (No. 825694) and the Cellex Foundation. Joan Genescà is a recipient of a Research Intensification grant from Instituto de Salud Carlos III, Spain. The study was partially funded by grants PI15/00066, and PI18/00947 from Instituto de Salud Carlos III and co-funded by European Union (ERDF/ESF, "Investing in your future"). Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivasis supported by Instituto de Salud Carlos III. Macarena Simón-Talero is a recipient of the grant JR 17/00029 from Instituto de Salud Carlos III.

Table 6. Univariate and multivariate Cox regression analysis of validation cohort with 1-year mortality as endpoint.

	Univariate Cox regression				Multivariate Cox regression			
Parameter	**HR**		**95% CI**	***p* value**	**HR**		**95% CI**	***p* value**
***Age*[1]**			0.148	0.148	1.020	1.006	1.034	0.004
Sex	1.407	1.016	0.040	0.040				
L-TSA	1.724	1.276	<0.001	<0.001	2.220	1.612	3.005	<0.001
Hepatic encephalopathy at baseline	2.109	1.547	<0.001	<0.001				0.268
Hepatorenal syndrome at baseline	4.998	2.885	<0.001	<0.001	2.222	1.172	4.214	0.014
Ascites at baseline	2.928	2.105	<0.001	<0.001	2.054	1.434	2.941	<0.001
SBP at baseline	2.811	1.763	<0.001	<0.001				0.454
MELD at baseline	1.130	1.104	<0.001	<0.001	1.112	1.081	1.143	<0.001
Sodium at baseline[2]	0.943	0.924	<0.001	<0.001				
Creatinine at baseline[3]	1.870	1.560	<0.001	<0.001				
Bilirubin at baseline[3]	1.071	1.046	<0.001	<0.001				
INR at baseline	2.047	1.693	<0.001	<0.001				

[1]years; [2]mmol/L; [3]mg/dl
Italic, included in multivariate analysis; Bold, significant in multivariate analysis.
INR, international normalized ratio; L-TSA, large total SPSS area; MELD, model of end-stage liver disease; SBP, spontaneous bacterial peritonitis; SPSS, spontaneous portosystemic shunts.

The funders had no influence on study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflict of Interest

MP Sponsored lectures: Gore; AZ Sponsored lectures: Gilead, Abbvie, Norgine, Grifols, Bayer, Gore, BMS; AD Sponsored lectures: Bayer; WL Grants: Boston Scientific, Consultant: Boston Scientific, Abbvie, Gilead, Norgine, Gore; VLM Grants: Gilead Sciences research Scholar Program, Consultant: Gore, Sponsored lectures (National or International): Gore, Abbvie, Alfa-sigma; CR Grant: Schweine Stiftung; VHG Sponsored lectures (National or International): GORE; TR Grants: Abbvie, Boehringer Ingelheim, Gilead, MSD, Philips Healthcare, Gore; Consultant: Abbvie, Bayer, Boehringer-Ingelheim, Gilead, Intercept, MSD, Siemens; Sponsored lectures (National or International): Abbvie, Gilead, Gore, Intercept, Roche, MSD; AA Grants: Gilead Sciences, Consultant: AbbVie, Gilead Sciences, Gore, Griffols, Intercept Pharmaceuticals, Pfizer and Merck & Co., Sponsored lectures (National or International): AbbVie, Gilead Sciences, Gore, Griffols, Intercept Pharmaceuticals, Pfizer and Merck & Co.; EAT Consultant: Pfizer, Intercept, Gilead, Promethera, Astra Zeneca; JT Grants: Gore, Consultant: Martins Pharma, Ironwood, Gore, Alexion, BMS, Grifols, Sequana Medicals, Versantis, Sponsored lectures (National or International): Gilead, Gore, Alexion, BMS, Grifols, Sequana Medicals, Norgine, Intercept.

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

Authors' contributions

MP, MST: acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis. JR, DR, JM, KL, AB, GL, EL, MHM, AZ, MT, GM, AD, CD, JVG, AM, CP, DT, AD, JGA, ML, JC, CJ, RS, FU, GK, CM, DT, KW, AK, CS, WL, VLM, CR, AB, JLC, PT, VHG, TR, AA, EAT: acquisition of data, critical revision of the manuscript regarding important intellectual content. JG, JT: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript regarding important intellectual content, funding recipient, administrative, technical and material support, study supervision.

Acknowledgements

Baveno VI-SPSS group: Sergi Quiroga, Dominic Yu, Luis Téllez, Mattias Mandorfer, Juan Carlos Garcia-Pagan, Claudia Berbel, José Ferrusquia, Michel Ble, Mari Angeles Garcia-Criado, Ernest Belmonte, Michael Ney, Cristina Margini, Stefania Casu, Giuseppe Murgia, Christiane Ludwig, Franz Stangl.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.12.021.

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Author names in bold designate shared co-first authorship

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Reply to: "Definition of SPSS: we need to speak the same language"
Computer-assisted image processing for better quantification

To the Editor:

We appreciate the interest of Nicoară-Farcău *et al.* in our recent multicenter study published in *Journal of Hepatology*.[1]

The authors raise issues related to the lack of consensus on the definition of spontaneous portosystemic shunt (SPSS). In fact, the lack of data on SPSS was the reason for members of the international Baveno cooperation to form the Baveno VI-SPSS group and to conduct the largest studies on this topic so far.[1,2]

In response to Nicoară-Farcău and colleagues, we agree that gastrorenal shunts seem important, as they are found in many patients with gastric varices and therefore possibly associate with bleeding. In total, 990 SPSSs in patients with available follow-up data were found. The distribution of SPSSs is shown in Table 1. Moreover, we calculated the fraction of patients developing variceal bleeding according to the presence of a certain SPSS type. The rate of variceal bleeding in patients with gastrorenal shunt was 12.2%, not significantly different from other types of SPSS (Table 1). A possible reason for this finding is the current lack of radiologic predictors of progression of SPSS due to the cross-sectional design of our study.[3] However, splanchnic and systemic hemodynamics in cirrhotic patients can change and longitudinal studies on the dynamics of SPSSs are needed. Another possible reason for this finding relates to difficulties quantifying SPSSs. Currently, those measurements need to be performed manually by a trained professional. This is especially challenging for (para-)esophageal varices, which tend to build collateral networks, which are almost impossible to quantify by hand. Hence, these were not quantified in our recent studies. However, automated, computer-assisted quantification of SPSS could be a solution. Currently, we have developed a computer application based on image processing. This application, based on MATLAB, measures the diameter of each shunt and automatically calculates the cross-sectional area of the SPSS, through image processing, independently of whether it is CT or MRI (see supplementary video). This application may facilitate the calculation of total shunt area and may save significant time for healthcare professionals.

In conclusion, we acknowledge that we need a unified definition of SPSS. Using modern computer-assisted techniques might help us overcome technical obstacles to quantifying all SPSSs, leading us to refer to the same definition in the future.

Table 1. Distribution of different types of SPSS.

Type of SPSS	Total	No Bleeding	Bleeding	Percentage
Splenorenal	384	328	56	14.6
Mesocaval	67	58	9	13.4
Mesorenal	9	8	1	11.1
Inferior mesenteric-caval	22	19	3	13.6
Gastrorenal	49	43	6	12.2
Umbilical	420	347	73	17.4
Others	39	35	4	10.3

SPSS, spontaneous portosystemic shunt.

Received 3 April 2020; accepted 5 April 2020; available online 26 May 2020
https://doi.org/10.1016/j.jhep.2020.04.012

Financial support

Jonel Trebicka is supported by grants from the Deutsche Forschungsgemeinschaft (SFB TRR57), Cellex Foundation and European Union's Horizon 2020 research and innovation program (No 668031). Joan Genescà is a recipient of a Research Intensification grant from Instituto de Salud Carlos III, Spain. The study was partially funded by grants PI15/00066, and PI18/00947 from Instituto de Salud Carlos III and co-funded by European Union (ERDF/ESF, "Investing in your future"). Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivasis supported by Instituto de Salud Carlos III. Macarena Simón-

Talero is a recipient of the grant JR 17/00029 from Instituto de Salud Carlos III. The funders had no influence on study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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

Authors' contributions

MP, JT, acquisition of data, analysis and interpretation of data, drafting of the manuscript. MST, FA, AP, CT, IV: acquisition of data, analysis and interpretation of data. JG, JT: drafting of the manuscript, critical revision of the manuscript regarding important intellectual content.

Legend to supplementary video

First, we select the image (CT/MRI). Once the image is uploaded, we press the detection button in order to select the area of the SPSS. Automatically, the area will appear below the image. If we need to select more SPSS, we can repeat the process. Finally, the total SPSS area is shown.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.04.012.

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Author names in bold designate shared co-first authorship

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Accurate diagnosis of NAFLD-related hepatic fibrosis with non-invasive methods: A comment for moving forward

To the Editor:

I congratulate Boursier *et al.* for their recent study on the non-invasive diagnosis of non-alcoholic fatty liver disease (NAFLD).[1] I would like to raise 2 methodological objections.

The first issue is about the division of the discovery and validation cohorts. Theoretically, randomization can ensure homogenization between different groups, and therefore is mainly used in randomized clinical trial design but not in diagnostic studies. In this diagnostic study, a total of 938 patients with biopsy-proven NAFLD were randomized 2:1 into discovery and validation cohorts (as described in the Methods section). The clinical characteristics of the eligible participants in the discovery and validation cohort did not differ significantly (all p values >0.1, as shown in Table 1), suggesting that the patients between the discovery and validation cohort were homogeneous. Unsurprisingly, the multivariate analysis revealed that the investigating centre was not independently associated with the diagnostic accuracy of Fibrosis-4 (FIB4)-FibroMeter^{VCTE} or vibration-controlled transient elastography (VCTE)-FibroMeter^{VCTE} algorithms. However, as we all know, the patient characteristics of different hospitals in different regions are almost impossible to balance in the real world because of individual differences. The Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement (TRIPOD statement)[2] suggests that splitting the patients randomly into 2 cohorts is not suitable for evaluating the performance of algorithms, because it does not allow for non-random changes between 2 cohorts. Therefore, if the authors are willing to reclassify the study population non-randomly for algorithm development and validation,

Keywords: Nonalcoholic fatty liver disease; Liver cirrhosis; Clinical decision rules.
Received 11 March 2020; received in revised form 12 March 2020; accepted 12 March 2020; available online 13 May 2020
https://doi.org/10.1016/j.jhep.2020.03.020

2.2 Die Rolle der CT-definierten Sarkopenie als Risikofaktor bei Leberzirrhose

"Sarcopenia Is Associated With Development of Acute-on-Chronic Liver Failure in Decompensated Liver Cirrhosis Receiving Transjugular Intrahepatic Portosystemic Shunt."
Praktiknjo M, Clees C, Pigliacelli A, Fischer S, Jansen C, Lehmann J, Pohlmann A, Lattanzi B, Krabbe VK, Strassburg CP, Arroyo V, Merli M, Meyer C, Trebicka J.
Erschienen in ***Clinical and Translational Gastroenterology.*** *2019 Apr;10(4):e00025.*

Zur Evaluation der Rolle der CT-definierten Sarkopenie, via geschlechts-spezifischer TPMT (transversale Psoasmuskeldicke), auf die Entwicklung von ACLF bei Patienten mit dekompensierter Leberzirrhose und TIPS wurden CT-Untersuchungen von 186 Patienten mit dekompensierter Leberzirrhose und TIPS aus der eigenen prospektiven NEPTUN (Non-invasive Evaluation Program for TIPS and Follow Up Network) Kohorte am Universitätsklinikum Bonn analysiert und mit den Daten des klinischen Verlaufes korreliert. Endpunkte der Studie waren das Ein-Jahresüberleben sowie die Entwicklung von ACLF nach TIPS-Anlage (Abb. 2.2.1).

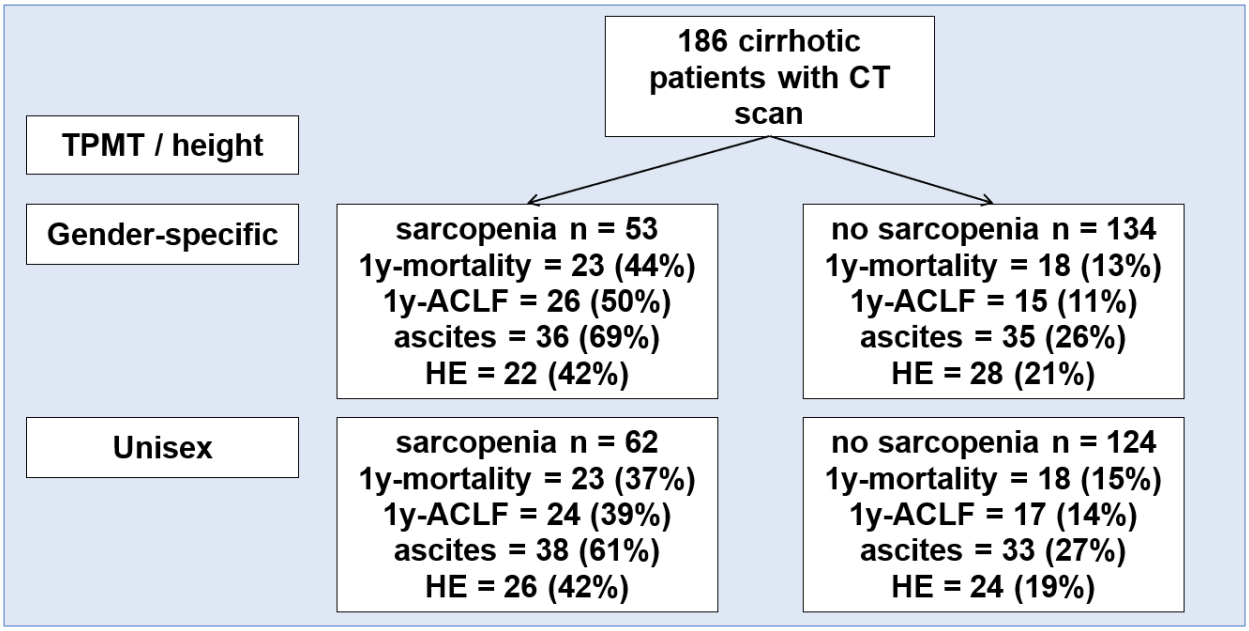

Abbildung. 2.2.1: Flowchart der eingeschlossenen Patienten. Es wurde 186 Patienten aus der eigenen NEPTUN Kohorte in Bonn untersucht und nach TPMT in Sarkopenie und Nicht-Sakopenie Gruppe eingeteilt. Die Grafik zeigt, dass mittels geschlechtsspezifischer (im Vergleich zu unisex) Grenzwerte des TPMT eine bessere Risikostratifizierung der Patienten in Bezug auf Überleben, ACLF-, Aszites- und HE-Entwicklung möglich ist. TPMT (Transversale Psoasmuskeldicke), CT (Computertomographie), ACLF (Akut-auf-Chronisches Leberversagen), HE (Hepatische Enzephalopathie).

Die Bildgebungen aus den CT-Untersuchungen wurden auf Höhe des Umbilicus untersucht. Der rechtsseitige M. psoas wurde hierfür identifiziert und der transversale Durchmesser als TPMT gemessen und auf die Körpergröße normiert (Abb. 2.2.2).

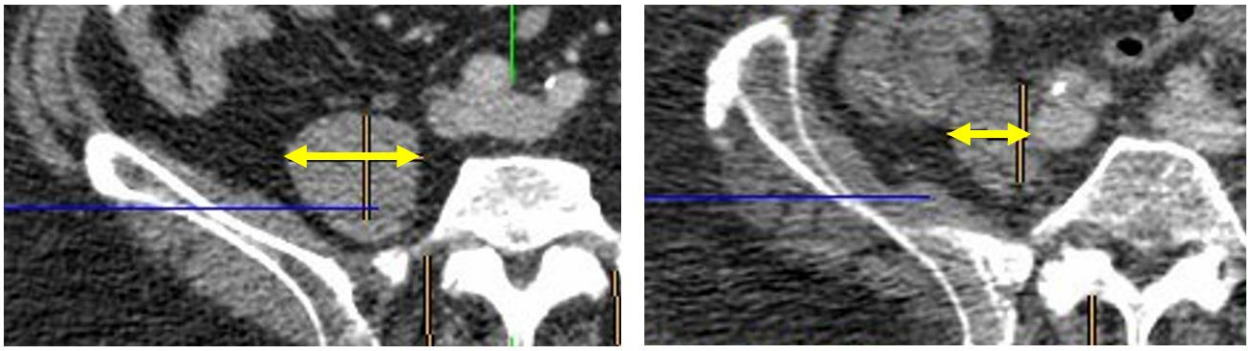

Abbildung. 2.2.2: Exemplarisches CT Schnittbild des rechtsseitigen M. psoas eines Patienten mit großer (links) und geringer (rechts) transversaler Psoasmuskeldicke (TPMT, gelber Doppelpfeil).

Eine Receiver Operating Characteristics (ROC) Analyse von TPMT für das Ein-Jahresüberleben der Patienten zeigte eine gute Diskriminierung mit einer guten Fläche unter der Kurve (AUC) von 0.732. Zunächst wurde die Kohorte anhand des beschriebenen unisex Grenzwertes von 16.8 mm/m in die Sarkopenie bzw. Nicht-Sarkopenie Gruppe klassifiziert (Durand et al., 2014; Golse et al., 2017). Zudem wurden die optimalen geschlechtsspezifische Grenzwerte separat ermittelt, um zu analysieren, ob eine Verbesserung der Risikostratifizierung möglich ist. Für Männer und Frauen zeigte sich jeweils ein optimaler Grenzwert von 17.8 (AUC 0.754) bzw. 14.0 (AUC 0.740) mm/m. Hiermit wurde die Kohorte zusätzlich geschlechtsspezifisch entsprechend in die Sarkopenie bzw. Nicht-Sarkopenie Gruppe klassifiziert.

In der Tat war die Rate an Fehlklassifikationen mit den geschlechtsspezifischen Grenzwerten niedriger als mit dem Unisexwert, was sich am höheren C-Index reflektierte.

Überleben und ACLF stratifiziert nach FFMA

Die Kaplan-Meier Kurve zeigt eine erhöhte Mortalität sowie erhöhte Rate an ACLF-Entwicklung in der Sarkopenie Gruppe. Durch die geschlechtsspezifische Klassifikation kann eine bessere Diskrimination im Vergleich zu der Unisexklassifikation beobachtet werden (Abb. 2.2.3).

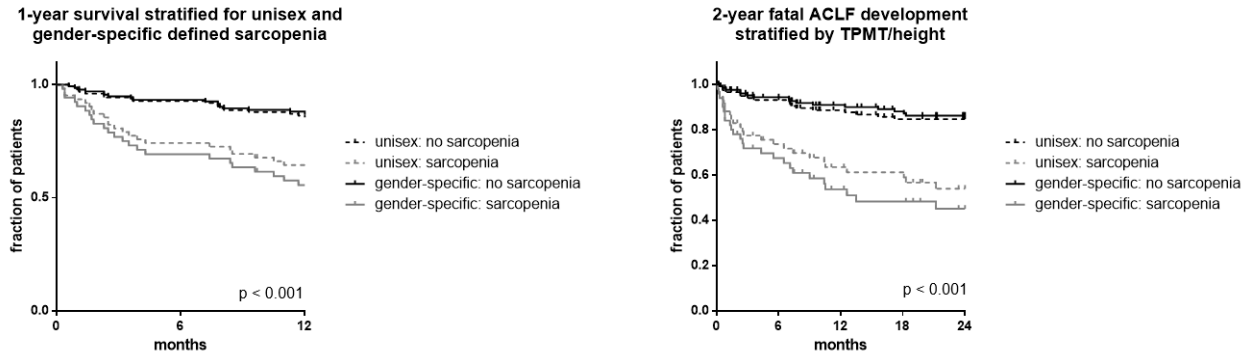

Abbildung. 2.2.3: Kaplan-Meier Kurve für das 1-Jahresüberleben (links) sowie die ACLF-Entwicklung (rechts) stratifiziert nach Sarkopenie (graue Kurven) und Nicht-Sarkopenie (schwarze Kurven) Gruppen. Gestrichelte Kurven zeigen die Stratifizierung mittels Unisexgrenzwerten und die durchgezogenen Kurven mittels geschlechtsspezifischer Grenzwerte. TPMT (transversale Psoasmuskeldicke), ACLF (Akut-auf-Chronisches Leberversagen). P durch log-rank Test.

Uni- und multivariate Cox Regressionsanalysen zeigten, dass die geschlechtsspezifische Sarkopenieklassifikation ein unabhängiger Prädiktor für die Entwicklung von ACLF ist. Interessanterweise war die Unisexklassifikation in der multivariaten Analyse nicht signifikant (Tabelle 2.2.1).

Tabelle 2.2.1: Univariate und multivariate Cox Regressionsanalyse für ACLF-Entwicklung.

1-year ACLF	**univariate Cox regression**				**multivariate Cox regression**			
Parameter	**p**	**HR**	**CI**		**p**	**HR**	**CI**	
age [years]	0.003	1.044	1.015	1.073	0.003	1.056	1.019	1.094
gender	0.286							
TPMT / height [mm/m]	<0.001	0.807	0.745	0.875	<0.001	0.808	0.736	0.886
unisex classification	<0.001	3.492	1.874	6.509				
gender-specific classification	<0.001	5.765	3.047	10.909	<0.001	5.285	2.660	10.499
hepatic encephalopathy at baseline	0.222							
ascites at baseline	0.057							
Child-Pugh at baseline	0.002	1.334	1.114	1.596				
MELD at baseline	<0.001	1.108	1.060	1.157				
MELD-Na at baseline	<0.001	1.101	1.055	1.150				
CLIF-C-AD at baseline	<0.001	1.107	1.068	1.148	<0.001	1.093	1.052	1.136
sodium at baseline [mmol/l]	0.186							
creatinine at baseline [mg/dl]	0.009	1.328	1.074	1.642	<0.001	1.488	1.169	1.894
bilirubin at baseline [mg/dl]	0.006	1.134	1.037	1.240				
INR at baseline	0.007	5.914	1.620	21.596	0.003	10.151	2.257	45.647

fett – signifikant in multivariater Analyse. MELD – model of end-stage liver disease, INR – international normalized ratio, TPMT (transversal Psoasmuskeldicke), CLIF-C AD (Chronic Liver Failure Consortium Acute Decompensation Score).

Sarkopenie und systemische Inflammation

Interessanterweise zeigten sich signifikant erhöhte Leukozytenwerte bei sarkopenen Patienten im Vergleich zu nicht-sarkopenen Patienten. Daneben zeigte die Sarkopenie-Gruppe schlechtere Prognose Scores (MELD, Child-Pugh, CLIF-C AD) in der Nachbeobachtungszeit.

Sarcopenia Is Associated With Development of Acute-on-Chronic Liver Failure in Decompensated Liver Cirrhosis Receiving Transjugular Intrahepatic Portosystemic Shunt

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INTRODUCTION: **Muscle mass has been shown to be a prognostic marker in patients with liver cirrhosis. Transversal psoas muscle thickness normalized by height (TPMT/height) obtained by routine computed tomography is a simple surrogate parameter for sarcopenia. TPMT/height, however, is not sex specific, which might play a role in risk stratification. Its association with acute-on-chronic liver failure (ACLF) has not been established yet. ACLF is associated with systemic inflammatory dysregulation. This study aimed at evaluating the role of sarcopenia in ACLF development of patients with decompensated cirrhosis receiving transjugular intrahepatic portosystemic shunt (TIPS) using sex-specific TPMT/height.**

METHODS: **One hundred eighty-six patients from the prospective Non-invasive Evaluation Program for TIPS and Follow Up Network cohort (observational, real-world TIPS cohort with structured follow-up) were analyzed. TPMT/height was measured from routine computed tomography. The sex-specific cutoff was determined to classify patients as sarcopenic and nonsarcopenic for 1-year mortality after TIPS. Clinical outcome was compared. Primary end points were ACLF and 1-year mortality after TIPS. Secondary end points were development of decompensations (hepatic encephalopathy and ascites) after TIPS.**

RESULTS: **The sex-specific cutoff increases the diagnostic accuracy with regard to primary and secondary end points compared with the unisex cutoff. Sex-specific sarcopenia classification is an independent predictor of 1-year mortality and ACLF development in patients with cirrhosis receiving TIPS. Patients in the sarcopenia group showed significantly higher rates of mortality, ascites, overt hepatic encephalopathy, and ACLF after TIPS compared with the nonsarcopenia group. The Chronic Liver Failure Consortium Acute Decompensation score as a marker of systemic inflammation was significantly higher in sarcopenic patients.**

CONCLUSIONS: **This study demonstrates for the first time that sarcopenia is related to ACLF development and systemic inflammation. The prognostic value of TPMT/height can be improved by using sex-specific cutoffs. ClinicalTrials.gov identifier: NCT03584204.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A22

Clinical and Translational Gastroenterology 2019;10:e-00025. https://doi.org/10.14309/ctg.0000000000000025

INTRODUCTION

Liver cirrhosis is a growing health care burden, and the management of its complications is challenging, whereas mortality in many other pathologies is declining (1). Sarcopenia is defined as pathological muscle loss in patients with chronic diseases, and its role in the outcome of patients with cirrhosis is widely accepted (2). Different methods have been proposed to diagnose sarcopenia using cross-sectional imaging (2–8). Most methods

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Received December 11, 2018; accepted February 8, 2019; published online March 29, 2019

evaluated computed tomography (CT) and require special software, which may be time consuming and difficult to implement in clinical routine (4,7). A simpler and fast method uses the right transversal psoas muscle thickness normalized by height (TPMT/height), which is an independent predictor of mortality for patients with cirrhosis on the waiting list for liver transplantation (5,9). Similar to sarcopenia, TPMT/height may also be influenced by a number of factors. Sex, in particular, seems to influence the muscle structure and its distribution in the body and thus possibly influences the diagnosis and the pattern of sarcopenia in cirrhosis (10). Cumulative data emphasize the role of sex in the sarcopenia pattern suggesting different cutoffs for female and male patients (2,8).

Patients with cirrhosis with acute decompensations (ADs), in particular, are at a higher risk of death and require more health care resources (11–16). AD can lead to a systemic inflammatory response and progress to acute-on-chronic liver failure (ACLF), a syndrome with high short-term mortality. Systemic inflammation has been associated with age-related sarcopenia and development of ACLF (17,18). Although a number of risk factors for the development of ACLF have been discussed, the relationship of sarcopenia with ACLF and systemic inflammation has not been investigated yet (19–21).

Therefore, we conducted this analysis of the prospective Noninvasive Evaluation Program for TIPS and Follow Up Network (NEPTUN) study to evaluate the role of sarcopenia in ACLF development of patients with cirrhosis receiving transjugular intrahepatic portosystemic shunt (TIPS) using sex-specific TPMT/height.

METHODS

Study population

For this study, we included patients from the NEPTUN study, which prospectively included patients with decompensated cirrhosis who underwent the TIPS procedure in a structured monocentric follow-up program. Noninvasive methods for risk stratification were evaluated. For inclusion in this analysis, CT had to be available. Exclusion criteria were lack of available or poor-quality CT.

The primary end point was 1-year mortality after TIPS. Secondary end points were development of ACLF stratified by fatal and nonfatal at 1 and 2 years and ADs (ascites and overt hepatic encephalopathy (HE)) during follow-up after TIPS. ACLF and overt HE were defined according to the European Association for the Study of the Liver guideline (12,22).

Biochemical blood analyses were performed using standard laboratory tests. The local ethics committee of the University of Bonn approved the study (029/13), and all patients agreed to and signed informed written consent in accordance with the Declaration of Helsinki for the procedures they underwent. This study is part of the NEPTUN cohort registered at ClinicalTrials.gov (identifier: NCT03584204).

Assessment of muscle parameters

For all examinations, commercially available clinical CT imaging systems (Philips Brilliance 64 or Philips Brilliance 256 iCT; both Philips Healthcare, Best, the Netherlands) were used. We analyzed the transversal psoas muscle thickness (TPMT) as previously described in cross-sectional images on the level of the umbilicus (5). Briefly, the maximum transverse diameter of the right psoas muscle was measured in millimeters and normalized for height (in meters) to calculate TPMT/height (see Figure 1b, Supplementary Digital Content 1, http://links.lww.com/CTG/A22). We chose the umbilicus because it is easy to identify in CT and it was used as a landmark in the aforementioned description of the method (5). The umbilicus in this cohort was located at the level of L4 in 70%, L5 in 20%, and L3 in 10% of patients (data not shown). The median time between CT and TIPS was 542 ± 88 days. The assessments were performed by 2 hepatologists (M.P. and C.C.) who had been trained by an expert radiologist (C.M.).

Statistical analysis

We performed descriptive statistics for all variables. Nonparametric testing was used to compare different groups when suitable. Paired nonparametric testing was used to compare data before and after the TIPS procedure of the same patients. For the selection of cutoff values of TPMT/height, receiver operating characteristic (ROC) analysis with 1-year survival as end point was calculated. To examine the impact of muscle indexes on survival and ACLF, we used the Kaplan-Meier curve with the log-rank test. Univariate and multivariate risk factor analyses were performed with Cox regression for 1-year mortality, fatal and nonfatal ACLF, occurrence of ascites, and episodes of HE as end points. Multivariate analysis included all values with $P < 0.05$ from univariate Cox regression. Dependent variables such as bilirubin and model of end-stage liver disease (MELD) and MELD-sodium (MELD-Na) were included separately in multivariate analysis to avoid collinearity. Concordance of the sarcopenia definitions was expressed by calculating concordance (C-index). Continuous variables are presented as median (range). Categorical variables are presented as absolute cases or percentage. All data were analyzed using SPSS (version 24; IBM, Armonk, NY). Prism (version 5; GraphPad, LaJolla, CA) was used for data plotting.

RESULTS

General patient characteristics

In this study, 186 patients with decompensated cirrhosis from the NEPTUN study were included (see Figure 1a, Supplementary Digital Content 1, http://links.lww.com/CTG/A22). Of these 186 included patients, 109 (59%) were men. The median age at TIPS procedure was 56 (18–80) years. Alcohol was the most common etiology of cirrhosis (129 patients, 69%), whereas 24 patients (13%) had chronic viral hepatitis B and/or C infection and 18% other etiologies. Ninety-six patients (52%) received TIPS for refractory ascites, and 90 patients for variceal bleeding (48%). The median MELD score was 11 (Table 1). The median follow-up period was 2.1 years (0–24 years).

Sex-specific sarcopenia classification

As TPMT/height has been reported to predict waiting list mortality, we performed ROC analysis of TPMT/height with 1-year survival as the end point. This resulted in an area under the curve (AUC) of 0.732 (confidence interval (CI) 0.648–0.816, $P < 0.001$), which is in line with previous reports. The reported unisex cutoff of 16.8 mm/m was used to classify sarcopenia (see Figures 1b and c, Supplementary Digital Content 1, http://links.lww.com/CTG/A22) (4,5).

To evaluate whether sex-specific differences and therefore sex-specific cutoff values would improve the method, we performed

Table 1. General characteristics at baseline

Parameter	Baseline
Sex-specific TPMT classification	All n = 186
Clinical	
Age (yr)	56 (18–80)
Sex (male/female)	109/77 (59/41%)
Etiology of cirrhosis (alcohol/viral/other)	129/24/33 (69/13/18%)
Indication for TIPS (bleeding/ascites/both)	90/92/4 (48/50/2%)
PSPG before TIPS	19 (3–38)
PSPG after TIPS	7 (0–30)
TPMT/height	19.2 (9.6–29.4)
Scores	
MELD	11 (6–32)
MELD-Na	14 (6–32)
Child-Pugh	8 (5–12)
Child-Pugh grade (A/B/C)	41/112/33 (22/60/18%)
CLIF-C-AD	49 (23–71)
Laboratory	
Sodium (mmol/L)	137 (119–147)
Creatinine (mg/dL)	1.0 (0.5–7.8)
Bilirubin (mg/dL)	1.3 (0.2–14.7)
gGT (U/L)	128 (12–1,166)
AST (U/L)	38 (11–1,439)
ALT (U/L)	24 (7–1,439)
Albumin (g/L)	31 (8–54)
INR	1.2 (0.9–1.9)
WBC (G/μL)	6.9 (1.6–31.5)
Hb (mg/dL)	10.2 (5.9–16.7)
Platelets (G/μL)	125 (10–725)
Outcome	
Ascites	143 (77%)
HE	42 (23%)
Mortality at 1-year follow-up	41 (22%)
ACLF at 1-year follow-up (all/fatal/nonfatal)	41/35/6 (22/19/3%)
ACLF at 2-year follow-up (all/fatal/nonfatal)	52/42/10 (28/23/5%)
Follow-up time	25 (0–288)

ACLF, acute-on-chronic liver failure; ALT, alanine transaminase; AST, aspartate transaminase; CLIF-C-AD, Chronic Liver Failure Consortium Acute Decompensation; gGT, gamma-glutamyl transferase; INR, international normalized ratio; MELD, model of end-stage liver disease; PSPG, portosystemic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt; TPMT, thickness normalized by height; WBC, white blood count.

sex-specific ROC analysis. This revealed an optimal cutoff of 17.8 mm/m (AUC 0.754, CI 0.654–0.854, $P < 0.001$) for men and 14.0 mm/m (AUC 0.740, CI 0.606–0.874, $P < 0.010$) for women for 1-year mortality (see Figures 1d and e, Supplementary Digital Content 1, http://links.lww.com/CTG/A22).

With sex-specific classification, misclassification is lower compared with unisex classification. For 1-year mortality, sex-specific classification has a higher C-index and therefore a higher diagnostic accuracy.

Sarcopenia and survival

A Kaplan-Meier survival curve for 1-year mortality showed a significantly increased mortality in sarcopenic patients (Figure 1a). Interestingly, sex-specific classification provided superior discrimination compared with unisex classification of sarcopenia (Figure 1a). There was no significant difference regarding the causes of death between the sarcopenia and the nonsarcopenia groups (data not shown).

Cox regression analysis for 1-year mortality revealed Child-Pugh, MELD, MELD-Na, Chronic Liver Failure Consortium (CLIF-C) AD score, creatinine, bilirubin, international normalized ratio (INR), and age, as well as TPMT/height and unisex and sex-specific sarcopenia classification as dependent risk factors. Only sex-specific sarcopenia classification was shown to be an independent predictor alongside CLIF-C AD score, age, serum creatinine, and bilirubin (Table 2). Unisex classification did not reach statistical significance.

Interestingly, sarcopenic patients receiving TIPS for refractory ascites had a higher risk of 1-year mortality compared with those with variceal bleeding as indication for TIPS (hazard ratio 5.296 vs 2.832).

Sarcopenia and development of ACLF

Sarcopenic patients showed significantly higher rates of nonfatal ACLF development compared with nonsarcopenic patients (Figure 1b). Also, ACLF with fatal outcome occurred significantly more often in sarcopenic patients (Figure 1c). With sex-specific classification, misclassification is lower compared with unisex classification for development of ACLF at 1-year follow-up (C-index 0.66 vs 0.73) (see Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A22).

We performed univariate Cox regression to identify risk factors for 1-year ACLF development. Apart from the expected prognostic markers Child-Pugh, MELD, MELD-Na, CLIF-C AD score, creatinine, bilirubin, INR, and age, this also revealed TPMT/height and unisex and sex-specific sarcopenia classification as dependent predictors of ACLF development. In multivariate Cox regression analysis, unisex classification failed. Sex-specific cutoff-defined sarcopenia, CLIF-C AD score, age, serum creatinine, and INR were independent predictors of 1-year ACLF development (Table 3). Stratified for indication for TIPS, sarcopenic patients with refractory ascites had a higher of development of ACLF than sarcopenic patients with variceal bleeding as indication for TIPS (hazard ratio 6.845 vs 3.439).

Univariate and multivariate Cox regression analyses were performed separately for nonfatal ACLF and fatal ACLF. In multivariate analysis, only sex-specific classification and CLIF-C AD score were found to be significant (see Table 3, Supplementary Digital Content 1, http://links.lww.com/CTG/A22). For nonfatal ACLF, only sex-specific classification and age were independent predictors (see Table 4, Supplementary Digital Content 1, http://links.lww.com/CTG/A22).

Sarcopenia and AD

Absence of sarcopenia was associated with faster resolution of ascites after TIPS, whereas sarcopenic patients displayed a longer response to ascites despite patent TIPS (Figure 2a). Furthermore, sarcopenic patients had a significantly higher rate of episodes of HE compared with nonsarcopenic patients (Figure 2b). For the 2

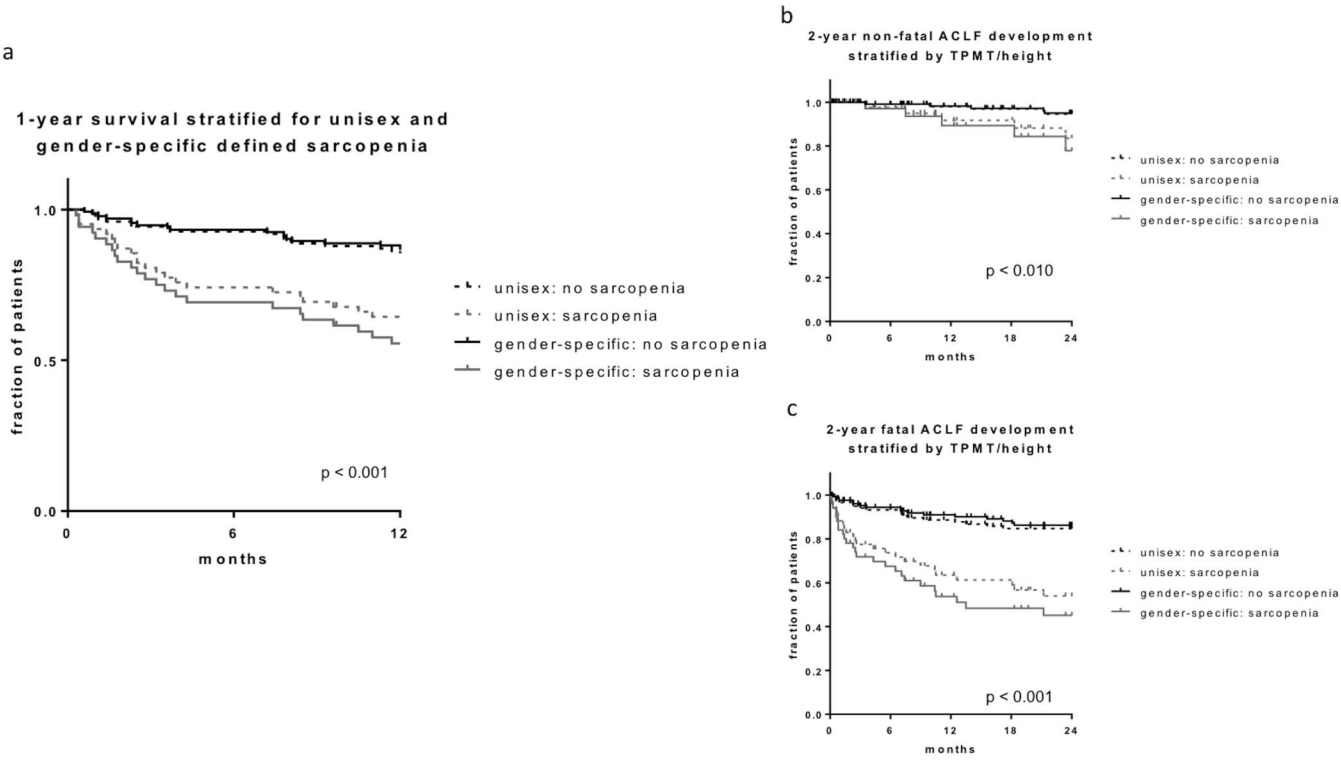

Figure 1. (**a**) Kaplan-Meier curve for 1-year survival stratified by unisex and sex-specific sarcopenia classification. (**b**) Kaplan-Meier curve for development of nonfatal acute-on-chronic liver failure (ACLF) at 2-year follow-up stratified by unisex and sex-specific sarcopenia classification. (**c**) Kaplan-Meier curve for development of fatal ACLF at 2-year follow-up stratified by unisex and sex-specific sarcopenia classification. CLIF-C-AD, Chronic Liver Failure Consortium Acute Decompensation; HE, hepatic encephalopathy; MELD, model of end-stage liver disease.

end points, ascites and HE, the sex-specific cutoff showed an improved discrimination compared with the unisex cutoff.

Sarcopenia and scores and systemic inflammation

The sarcopenia group showed a higher fraction of alcoholic etiology and ascites as indication for TIPS compared with the nonsarcopenia group. MELD, MELD-Na, CLIF-C AD, and Child-Pugh score were significantly higher in the sarcopenia group. After TIPS, increase in MELD and MELD-Na score was higher in sarcopenic patients than in nonsarcopenic patients. In fact, the CLIF-C AD score showed a decrease in nonsarcopenic patients, whereas it increased in sarcopenic patients (Figure 2c).

At follow-up, all prognostic scores (MELD, MELD-Na, Child-Pugh, and CLIF-C AD score) were significantly worse in the sarcopenia group. Interestingly, in the nonsarcopenia group, MELD, Child-Pugh, and CLIF-C AD score improved at follow-up, resulting in a significantly lower risk of decompensations in this group (see Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A22).

Apart from the prognostic scores, especially white blood cell count, as a marker of systemic inflammation, levels of INR and hemoglobin were significantly better in the nonsarcopenia group during follow-up (see Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A22).

DISCUSSION

The present study demonstrates that sex-specific TPMT/height-defined sarcopenia in the NEPTUN cohort identifies patients at risk of development of ACLF and risk of death.

In real life, patients with cirrhosis usually seek medical attention, including CT, at the time of decompensating events. In addition, CT is performed for evaluation and planning of interventions, such as TIPS or liver transplant. In these situations, the potential to predict outcome is extremely important to stratify patient care. Using these imaging methods, different measures of muscle mass have been described. TPMT/height is an easy-to-assess measure of muscle mass (5). It was previously reported that TPMT/height could predict survival in patients on the waiting list for liver transplantation (5). Interestingly, in that cohort, the authors elaborated only 1 cutoff for both male and female patients. There is growing evidence of the importance to recognize the sex differences in sarcopenic patients (2,4,23–25). Females tend to have significantly lower muscle indices, which is in line with our results and supports our data (2,8,26). These previous data explain, in part, our findings that the sex-specific cutoff is superior to the unisex cutoff used previously (5). There are several possible explanations for these discrepant findings. First, patients listed for liver transplantation have a higher MELD score than patients receiving TIPS, which was also the case in a previously published cohort with a mean MELD score of 19 (5), whereas in our cohort, the patients were not as advanced with a median MELD score of 11. Second, another key difference in patient characteristics is the rather low proportion of females in the previously published cohort of 21% (5), whereas in our cohort, it is 41%. These differences in characteristics possibly explain the inferior diagnostic accuracy of unisex cutoff compared with the sex-specific cutoff in our cohort. Therefore, sex-specific cutoff values should be applied to minimize misclassification. This is

Table 2. Univariate and multivariate Cox regression analyses for 1-year survival

1-year mortality	Univariate Cox regression				Multivariate Cox regression			
Parameter	*P*	HR	CI		*P*	HR	CI	
Age (yr)	0.016	1.035	11.006	1.064	0.010	1.046	1.011	1.081
Sex	0.488							
TPMT/height (mm/m)	<0.001	0.834	0.770	0.902	<0.001	0.835	0.764	0.912
Unisex classification	0.001	2.963	1.598	5.494				
Sex-specific classification	0.000	4.095	2.207	7.597	<0.001	3.462	1.808	6.631
HE at baseline	0.034	2.010	1.054	3.836				
Ascites at baseline	0.182	1.804	0.758	4.289				
Child-Pugh at baseline	0.004	1.311	1.093	1.574				
MELD at baseline	<0.001	1.125	1.074	1.178				
MELD-Na at baseline	<0.001	1.118	1.069	1.170				
CLIF-C-AD at baseline	<0.001	1.119	1.078	1.161	<0.001	1.105	1.064	1.147
Sodium at baseline (mmol/L)	0.087	0.942	0.879	1.009				
Creatinine at baseline (mg/dL)	0.004	1.356	1.103	1.666	<0.001	1.552	1.224	1.969
Bilirubin at baseline (mg/dL)	0.001	1.161	1.061	1.270	0.009	1.150	1.036	1.275
INR at baseline	0.028	4.775	1.183	19.282				

CI, confidence interval; CLIF-C-AD, Chronic Liver Failure Consortium Acute Decompensation; HR, hazard ratio; INR, international normalized ratio; MELD, model of end-stage liver disease; TPMT, thickness normalized by height.

emphasized even more by our results, which identify sex-specific sarcopenia classification as an independent predictor of mortality, whereas the unisex cutoff failed in the multivariate analysis. Further multicentric studies with large patient cohorts are needed to determine comparable sex-specific cutoff values (2,4,5,9,27–29). This is especially important regarding the relatively low negative predictive value of our classification in this cohort. It may well be higher in larger cohorts with lower prevalence of 1-year mortality.

Table 3. Univariate and multivariate Cox regression analyses for development of ACLF at 1-year follow-up

1-year ACLF	Univariate Cox regression				Multivariate Cox regression			
Parameter	*P*	HR	CI		*P*	HR	CI	
Age (yr)	0.003	1.044	1.015	1.073	0.003	1.056	1.019	1.094
Sex	0.286							
TPMT/height (mm/m)	<0.001	0.807	0.745	0.875	<0.001	0.808	0.736	0.886
Unisex classification	<0.001	3.492	1.874	6.509				
Sex-specific classification	<0.001	5.765	3.047	10.909	<0.001	5.285	2.660	10.499
HE at baseline	0.222							
Ascites at baseline	0.057							
Child-Pugh at baseline	0.002	1.334	1.114	1.596				
MELD at baseline	<0.001	1.108	1.060	1.157				
MELD-Na at baseline	<0.001	1.101	1.055	1.150				
CLIF-C-AD at baseline	<0.001	1.107	1.068	1.148	<0.001	1.093	1.052	1.136
Sodium at baseline (mmol/L)	0.186							
Creatinine at baseline (mg/dL)	0.009	1.328	1.074	1.642	<0.001	1.488	1.169	1.894
Bilirubin at baseline (mg/dL)	0.006	1.134	1.037	1.240				
INR at baseline	0.007	5.914	1.620	21.596	0.003	10.151	2.257	45.647

ACLF, acute-on-chronic liver failure; CI, confidence interval; CLIF-C-AD, Chronic Liver Failure Consortium Acute Decompensation; HR, hazard ratio; INR, international normalized ratio; MELD, model of end-stage liver disease; TPMT, thickness normalized by height.

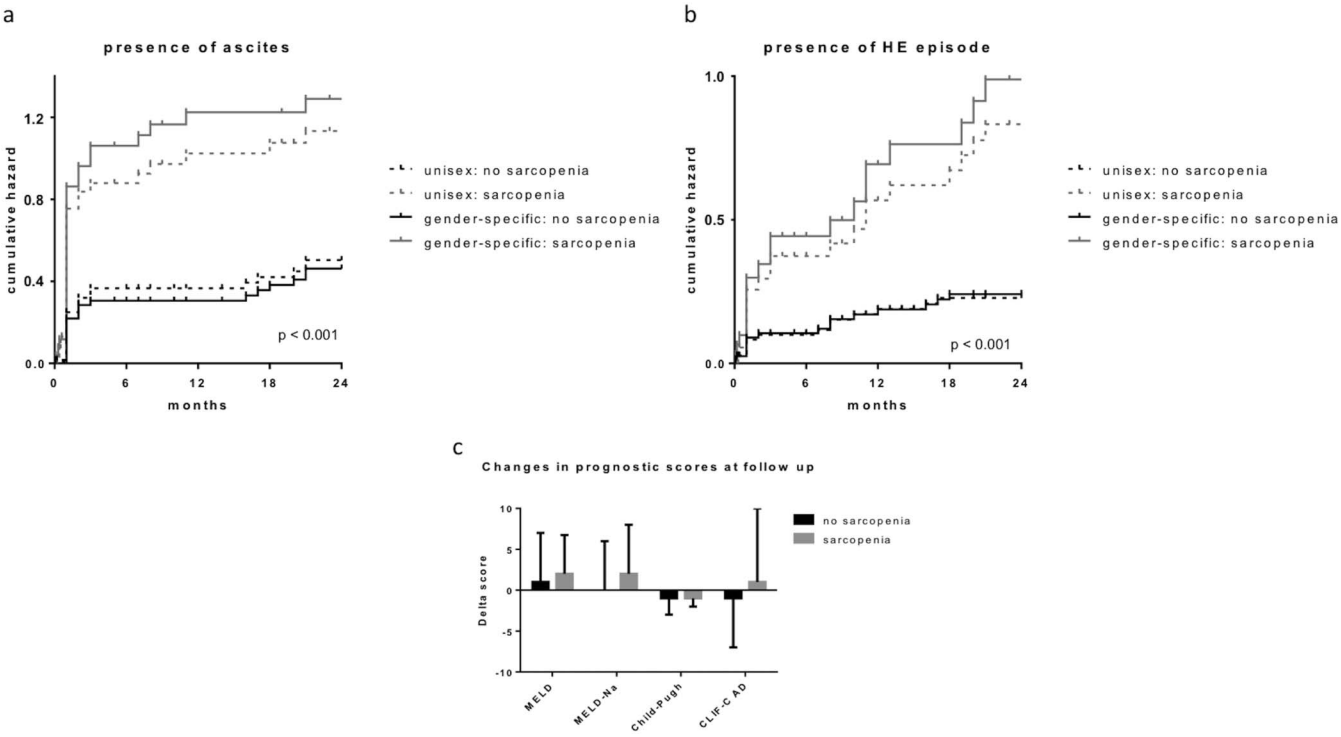

Figure 2. (**a**) Cumulative hazard function for the presence of ascites (persistence and/or reoccurrence) after TIPS stratified by unisex and sex-specific sarcopenia classification. (**b**) Cumulative hazard function for the occurrence of episode of hepatic encephalopathy after TIPS stratified by unisex and sex-specific sarcopenia classification. (**c**) Diagram showing changes in prognostic scores before and after TIPS. ACLF, acute-on-chronic liver failure; TPMT, thickness normalized by height.

Apart from the prediction of survival in these patients, another example is that TPMT/height-defined sarcopenia is associated with higher rates of overt HE. This has been supported by another study using skeletal muscle index at L3 vertebra (L3-SMI) requiring special software in a smaller cohort (30), underlining the robustness of our study. Moreover, the association of sarcopenia with survival and HE is important because this facilitates the caregiver to select patients who may benefit from additional therapeutic options, such as dietary strategies in sarcopenic patients (31–33).

The limitations of this study are in line with the nature of all retrospective studies, namely that selection bias cannot be excluded despite the cohort showing fairly representative characteristics for patients with cirrhosis in a TIPS program. However, probably not all decompensating events, including nonfatal ACLF, are recorded because we do not have all the information about admissions to other hospitals. This possibly explains the lower accuracy of prediction of nonfatal ACLF compared with fatal ACLF in our cohort. However, we are confident that we have detected all ACLF developments with fatal outcome, which seems to be the more severe clinical entity in our patients.

Although the relationship of sarcopenia with survival has been established on several different occasions, the main novel finding of this study is the association of sarcopenia with development of ACLF. Recently, ACLF has been characterized as a syndrome with very high short-term mortality, which may also develop in outpatients with cirrhosis (34). Interestingly, the presence of sarcopenia predicts—independent of other factors—the development of ACLF in TIPS patients. Further factors known to be associated with the development of ACLF and death were CLIF-C AD score, creatinine, and INR, predicting the development of ACLF in TIPS patients. This stresses the robustness of our data. However, both presence of sarcopenia and TMPT/height outperform the MELD score in the prediction of ACLF, which has been designed to predict mortality after TIPS. This finding might be also due to the chosen time frame as the development of ACLF in TIPS patients might occur at a later stage, while MELD predicts a 3-month mortality. ACLF is a dynamic syndrome, which can reverse rapidly, especially in the earlier stages.

To avoid the overrepresentation of ACLF due to laboratory value fluctuations, progressive ACLF—ending with death—was defined in this study as fatal ACLF and was evaluated separately. Importantly, half of the patients with sarcopenia developed fatal ACLF during the first year after TIPS, whereas less than 10% of the patients without sarcopenia developed ACLF, indicating that sarcopenia might play at least a predisposing and probably also a pathogenic role in the development of ACLF.

Through the secretion of soluble peptides, or myokines, skeletal muscle interacts in metabolic processes with other organs such as the liver. In turn, metabolic cues from these organs are received by skeletal muscle, adapting their response accordingly. Cross-talking between anabolic and catabolic pathways characterizes the signaling. Systemic inflammation evokes a catabolic reaction in skeletal muscle leading to excessive energy expenditure and ultimately sarcopenia (35). Systemic inflammation has also been identified in the pathogenesis of ACLF development (17,18,36). It is conceivable that sarcopenia is therefore a clinical expression of underlying chronic systemic inflammation, which might facilitate development of ACLF. Interestingly, in this cohort, leukocyte count, a surrogate of systemic inflammation, is

significantly higher in sarcopenic patients, further underlining the tight association of systemic inflammation with sarcopenia and ACLF. The question of whether sarcopenia predisposes for systemic inflammation and ACLF development or systemic inflammation causes sarcopenia and ACLF is beyond the scope of this study. This needs to be investigated in the future because it could also offer therapeutic or preventive approaches. Nevertheless, these results demonstrate that especially the early identification of sarcopenic patients is of clinical relevance because these patients are at risk of developing ACLF. In these patients, shorter follow-up periods might help to better monitor their progress.

Recently, a plethora of different techniques for estimation of muscle mass and frailty has been published. TPMT/height has been debated for the asymmetrical shape of the psoas muscle and because this method chooses the umbilicus as anatomical landmark, whereas other techniques use, e.g., the psoas muscle area or L3-SMI (4,5). The umbilicus as a landmark shows some variability and has a limitation in patients with giant umbilical hernia. However, in the current literature, there are conflicting data on the different performance of psoas muscle compared with other muscle parameters, where L3-SMI seems to perform better in cohorts with high fraction of hepatocellular carcinoma (4,5,37). In our cohort, hepatocellular carcinoma was excluded before treatment with TIPS. A test battery to perform frailty assessment was not possible in this retrospective study (38). However, despite its limitations, this study shows the value of TPMT/height in predicting ACLF and death. Finally, the requirement of CT for this study represents a selection bias, which led to the exclusion of several patients. The variable time between CT and TIPS might represent a limitation, and CT performed just before the TIPS procedure would have been ideal and should be considered in future prospective studies.

As for the clinical routine, we emphasize the simplicity and convenience of the method, as cross-sectional imaging is routinely performed in cirrhotic patients, e.g., for evaluation for liver transplantation or TIPS procedure. Hence, no additional cost for evaluation of sarcopenia is needed. The measurement itself is fast and reproducible, which is the main limitation for the clinical use of anthropometric parameters, such as mid-arm muscle circumference (8,9).

In conclusion, this study shows that the use of sex-specific cutoffs offers an improvement of prognostic value of TPMT/height. Furthermore, this study, for the first time, demonstrates the association of TPMT/height defined with the development of ACLF.

CONFLICTS OF INTEREST

Guarantor of the article: Jonel Trebicka, MD, PhD.

Specific author contributions: Michael Praktiknjo, MD and Caroline Clees, MD contributed equally as first authors. M.P. and C.C.: acquisition of data, analysis and interpretation of data, drafting of the manuscript, and statistical analysis. A.P., S.F., B.L., and V.K.K.: acquisition of data and analysis and interpretation of data. C.P.S. and M.M.: administrative support. C.M.: study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript regarding important intellectual content, and study supervision. J.T.: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript regarding important intellectual content, funding recipient, administrative, technical, and material support, and study supervision.

Financial support: The authors were supported by grants from the Deutsche Forschungsgemeinschaft (SFB TRR57), Cellex Foundation and European Union's Horizon 2020 research and innovation program GALAXY study (No. 668031), LIVERHOPE (No. 731875), MICROB-PREDICT (No. 825694) and by Challenge Grant "MicrobLiver" grant number NNF15OC0016692 from the Novo Nordisk Foundation. The funders had no influence on study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Potential competing interests: None.

ACKNOWLEDGEMENTS

We thank Gudrun Hack, Silke Bellinghausen, Nadine Köstlmeier, and Kristin Gehrmann for their excellent technical assistance and Sabine Dentler for critical reading.

Study Highlights

WHAT IS KNOWN

- ✓ ACLF is a syndrome with high short-term mortality occurs in decompensated cirrhosis.
- ✓ Sarcopenia is related to mortality in cirrhosis.
- ✓ TPMT/height reflects sarcopenia and predicts survival in cirrhosis.

WHAT IS NEW HERE

- ✓ Sarcopenic patients after TIPS develop more frequently ACLF, especially fatal ACLF.
- ✓ Sarcopenia is an independent predictor of ACLF and mortality in patients with cirrhosis after TIPS.
- ✓ TPMT/height performs better in the prediction of ACLF and mortality when sex-specific cutoffs are implemented.

TRANSLATIONAL IMPACT

- ✓ Sex-specific TPMT/height can be used in stratification of follow up timing.

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2.3 Die Rolle der MRT-definierten Sarkopenie als Risikofaktor bei Leberzirrhose

"Fat-free muscle mass in magnetic resonance imaging predicts acute-on-chronic liver failure and survival in decompensated cirrhosis."
Praktiknjo M, Book M, Luetkens J, Pohlmann A, Meyer C, Thomas D, Jansen C, Feist A, Chang J, Grimm J, Lehmann J, Strassburg CP, Abraldes JG, Kukuk G, Trebicka J. Erschienen in ***Hepatology***. *2018 Mar;67(3):1014-1026.*

Zur erstmaligen Etablierung von Muskelparametern aus MRT-Untersuchungen wurden retrospektiv MRT von 116 Patienten mit dekompensierter Leberzirrhose und TIPS aus der NEPTUN Kohorte des Universitätsklinikums Bonn untersucht. Die Ergebnisse der Muskelmessungen wurden mit dem klinischen Verlauf der Patienten (medianes Follow-Up 10 Monate) korreliert (Abb. 2.3.1).

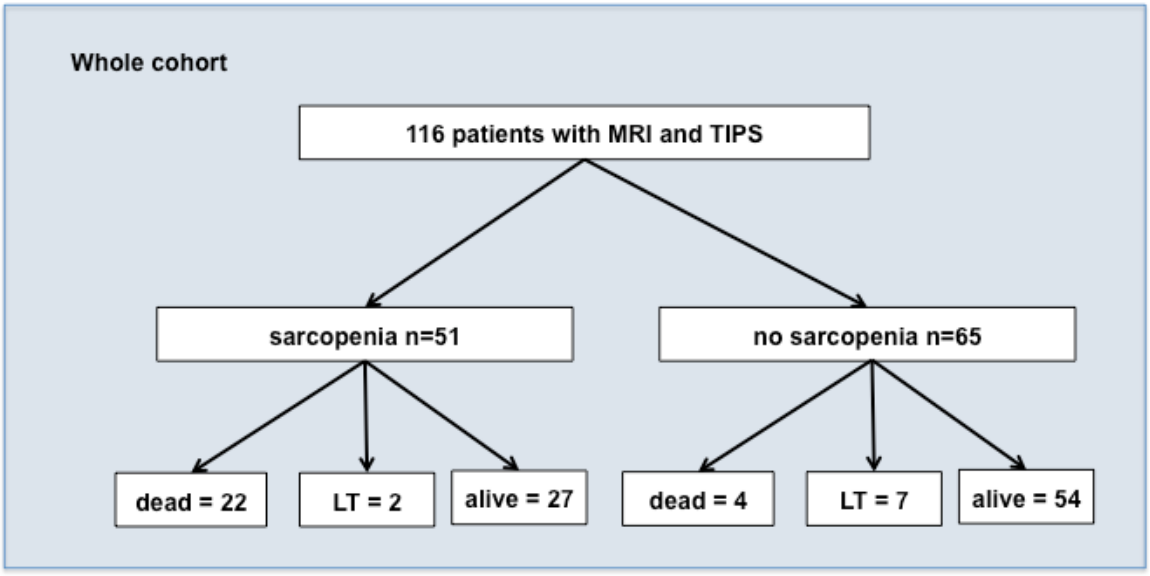

Abbildung. 2.3.1: Flowchart der eingeschlossenen Patienten. Es wurde 116 Patienten aus der eigenen Kohorte in Bonn untersucht. MRI (Magnetresonanztomographie), LT (Lebertransplantation).

T2-gewichtete TSE Sequenzen wurden für die Muskelmessungen gewählt. Die paraspinale Muskulatur (M. erector spinae) auf Höhe des Abgangs der A. mesenterica superior wurde identifiziert und mittels spezieller Software (Image J) das hyperintense intramuskuläre Fettgewebe markiert. Hierdurch wurde die fettfreie Muskelfläche (FFMA) als Surrogat der physiologisch aktiven Muskulatur, im Gegensatz zur Gesamtmuskelfläche, bestimmt (Abb. 2.3.2).

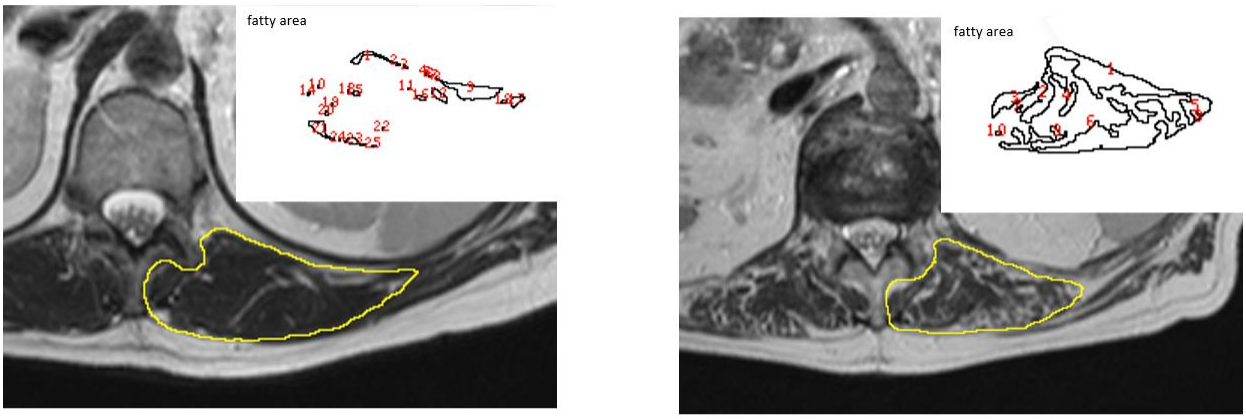

Abbildung. 2.3.2: Exemplarisches MRT Schnittbild der paraspinalen Muskulatur (gelb umrandet) eines Patienten mit geringer (links) und ausgeprägter (rechts) Fettdegeneration. Rechts oben Detailansicht des automatisiert erfassten intramuskulären Fettanteils. In Rot sind die Nummern der Inseln des intramuskulären Fettgewebes dargestellt.

Die Kohorte wurde zunächst in eine Trainingskohorte (n=71 mit verfügbarer CT-Untersuchung) und eine interne Validierungskohorte (n=45) aufgeteilt. Die Receiver Operating Characteristics (ROC) Analyse von FFMA für das 3-Jahresüberleben der Patienten zeigte eine gute Diskriminierung mit einer geschlechtsspezifischen Fläche unter der Kurve (AUC) von je 0.817 und 0.804 für Männer und Frauen. Hieraus wurden geschlechtsspezifische Grenzwerte der FFMA von 3197 mm^2 für Männer und 2895 mm^2 für Frauen ermittelt und die Patienten entsprechend in die Sarkopenie bzw. Nicht-Sarkopenie Gruppe klassifiziert.

Überleben und ACLF stratifiziert nach FFMA

Eine Kaplan-Meier Kurve für das Überleben zeigt ein signifikant reduziertes Überleben der Sarkopenie Gruppe im Vergleich mit der Nicht-Sarkopenie Gruppe. Dieses Ergebnis konnte in der Validierungskohorte bestätigt werden (Abb. 2.3.3).

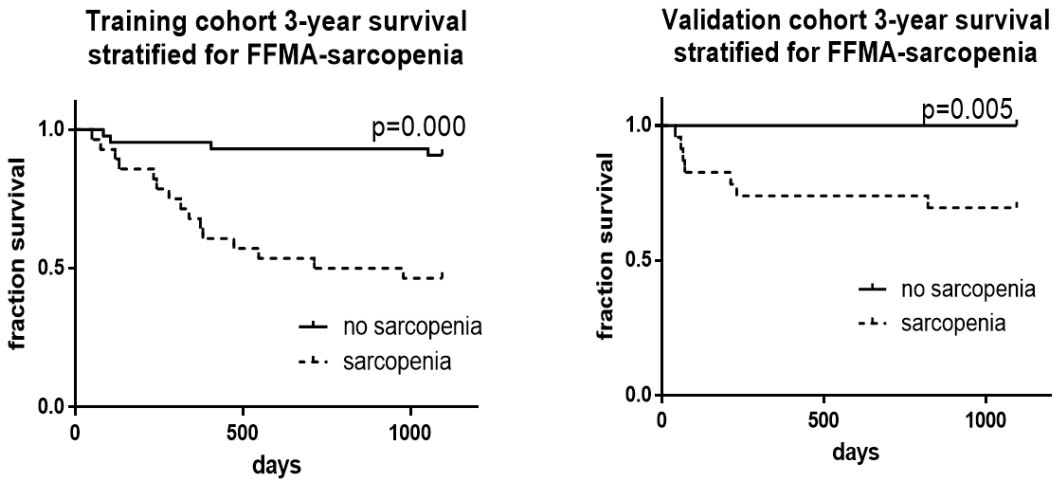

Abbildung. 2.3.3: Kaplan-Meier Kurve für das 3-Jahresüberleben in der Trainingskohorte (links) und Validierungskohorte (rechts). Die Sarkopenie Gruppe (gestrichelte Kurve) zeigt ein signifikant niedrigeres Überleben im Vergleich zu der Nicht-Sarkopenie Gruppe (durchgezogene Kurve). FFMA (fettfreie Muskelfläche). P durch log-rank Test.

Eine uni- und multivariate Cox Regressionsanalyse zeigte FFMA und nicht die Gesamtmuskelfläche als einen unabhängigen Prädiktor für das Überleben der Patienten. Die mit Abstand häufigste Todesursache war ACLF (78%) in beiden Gruppen.

HEPATOLOGY, VOL. 67, NO. 3, 2018

Fat-Free Muscle Mass in Magnetic Resonance Imaging Predicts Acute-on-Chronic Liver Failure and Survival in Decompensated Cirrhosis

Michael Praktiknjo,[1*] Marius Book,[1*] Julian Luetkens,[2] Alessandra Pohlmann,[1] Carsten Meyer,[2] Daniel Thomas,[2] Christian Jansen,[1] Andreas Feist,[2] Johannes Chang,[1] Jochen Grimm,[3] Jennifer Lehmann,[1] Christian P. Strassburg,[1] Juan Gonzalez Abraldes,[4] Guido Kukuk,[2**] and Jonel Trebicka [1,5–7**]

Muscle mass seems to be a prognostic marker in patients with liver cirrhosis. However, reported methods to quantify muscle mass are heterogeneous, consented cutoff values are missing, and most studies have used computed tomography. This study evaluated fat-free muscle area (FFMA) as a marker of sarcopenia using magnetic resonance imaging (MRI) in patients with decompensated cirrhosis with transjugular intrahepatic portosystemic shunt (TIPS). The total erector spinae muscle area and the intramuscular fat tissue area were measured and subtracted to calculate the FFMA in 116 patients with cirrhosis by TIPS and MRI. The training cohort of 71 patients compared computed tomography–measured transversal psoas muscle thickness with FFMA. In 15 patients MRI was performed before and after TIPS, and in 12 patients follistatin serum measurements were carried out. The results on FFMA were confirmed in a validation cohort of 45 patients. FFMA correlated with follistatin and transversal psoas muscle thickness and showed slightly better association with survival than transversal psoas muscle thickness. Gender-specific cutoff values for FFMA were determined for sarcopenia. Decompensation (ascites, overt hepatic encephalopathy) persisted after TIPS in the sarcopenia group but resolved in the nonsarcopenia group. Sarcopenic patients showed no clinical improvement after TIPS as well as higher mortality, mainly due to development of acute-on-chronic liver failure. FFMA was an independent predictor of survival in these patients. *Conclusion:* This study offers an easy-to-apply MRI-based measurement of fat-free muscle mass as a marker of sarcopenia in decompensated patients; while TIPS might improve sarcopenia and thereby survival, persistence of sarcopenia after TIPS is associated with a reduced response to TIPS and a higher risk of acute-on-chronic liver failure development and mortality. (HEPATOLOGY 2018;67:1014-1026).

Portal hypertensive complications such as refractory ascites and variceal bleeding are frequent causes of acute decompensation in liver cirrhosis.[1] In selected patients, the complications of portal hypertension can be effectively treated with transjugular intrahepatic portosystemic shunt (TIPS).[2-4] However, acute decompensation may still lead to a systemic inflammatory response and progress to acute-on-chronic

Abbreviations: ACLF, acute-on-chronic liver failure; AUC, area under the curve; CLIF-C AD, European Foundation for the Study of Chronic Liver Failure Consortium acute decompensation score; CT, computed tomography; FFMA, fat-free muscle area; HE, hepatic encephalopathy; INR, international normalized ratio; LT, liver transplantation; MA, total muscle area; MELD, Model for End-Stage Liver Disease; MELD-Na, MELD including sodium; MRI, magnetic resonance imaging; TIPS, transjugular intrahepatic portosystemic shunt; TPMT, transversal psoas muscle thickness.

Received July 5, 2017; accepted October 16, 2017.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.29602/suppinfo.

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***These are co-last authors.*

Supported by the Deutsche Forschungsgemeinschaft (SFB TRR57), the Cellex Foundation, and the European Union's Horizon 2020 research and innovation program (668031). The funders had no influence on study design, data collection and analysis, decision to publish, or preparation of the manuscript.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.29602

Potential conflict of interest: Nothing to report.

liver failure (ACLF), a recently described syndrome with high short-term mortality.[5,6] In this patient population, meticulous selection and management require good clinical markers. Sarcopenia is common in these decompensated patients, and methods to evaluate muscle mass have recently proposed cutoffs, especially for patients on the waiting list for liver transplantation (LT).[7-9] Especially, cross-sectional imaging, e.g., magnetic resonance imaging (MRI) and computed tomography (CT), could evaluate skeletal muscle mass and diagnose sarcopenia.[10] This is convenient because MRI or CT scans are routinely performed for several clinical reasons in decompensated patients.

It has been proposed that CT scans of different muscle parameters enable diagnosis of sarcopenia, e.g., the psoas cross-sectional area,[11] the transversal psoas muscle thickness (TPMT) normalized by height,[12] and the third lumbar vertebra muscle index.[13-16] In several methods, special software is required. CT has several drawbacks, such as radiation exposure and the risk of inducing or aggravating kidney injury (contrast-induced nephropathy) due to iodinated contrast agents.[17] For specific medical scenarios (e.g., accurate detection of hepatocellular carcinoma), MRI is nowadays increasingly used in chronic liver disease.[18] Moreover, not only total muscle mass but also quality or activity of the muscle seem to be important, as reflected by different myokines, such as follistatin, which has been used as a surrogate parameter.[19-21] To the best of our knowledge, no study has used MRI and specifically examined the quality of the muscles as a read-out for sarcopenia in decompensated cirrhosis to date.

This study aimed to (1) offer an MRI method to accurately assess sarcopenia and (2) explore the prognostic value of this method to predict ACLF and survival in patients with decompensated cirrhosis receiving TIPS.

Patients and Methods

STUDY POPULATION

For this retrospective study, we screened 677 patients receiving TIPS from December 1993 to September 2014 to identify 116 patients with MRI (Fig. 1A). A total of 561 patients were excluded, 556 without abdominal MRI and 5 due to poor image quality. The follow-up period was documented for 3 years after the TIPS procedure. Biochemical blood analyses were performed using standard tests. The local ethics committee of the University of Bonn approved the study (029/13), and all patients agreed and signed an informed written consent in accordance with the Helsinki Declaration for the procedures they underwent.

In order to compare the novel techniques with published data on sarcopenia, in 71 patients the muscle area (MA) was assessed in addition to cross-sectional MRI, also using TPMT in the CT scan.[12] Moreover, of the patients who underwent a TIPS procedure from June 2007 to May 2014, 15 had received MRI before and after TIPS (Table 1) and in 12 patients additional blood samples were collected to analyze follistatin (Fig. 1A). A validation cohort of 45 patients with only MRI was used to validate the MRI findings (Fig. 1A).

Finally, the whole cohort of 116 patients with MRI was analyzed (Fig. 1B). Mean and median follow-up after MRI were 17 ± 2 months (no sarcopenia group 20 ± 2 months, sarcopenia group 13 ± 2 months) and 10 (0-68) months (no sarcopenia group 13 [0-80] months, sarcopenia group 7 [0-65] months), respectively (Table 2).

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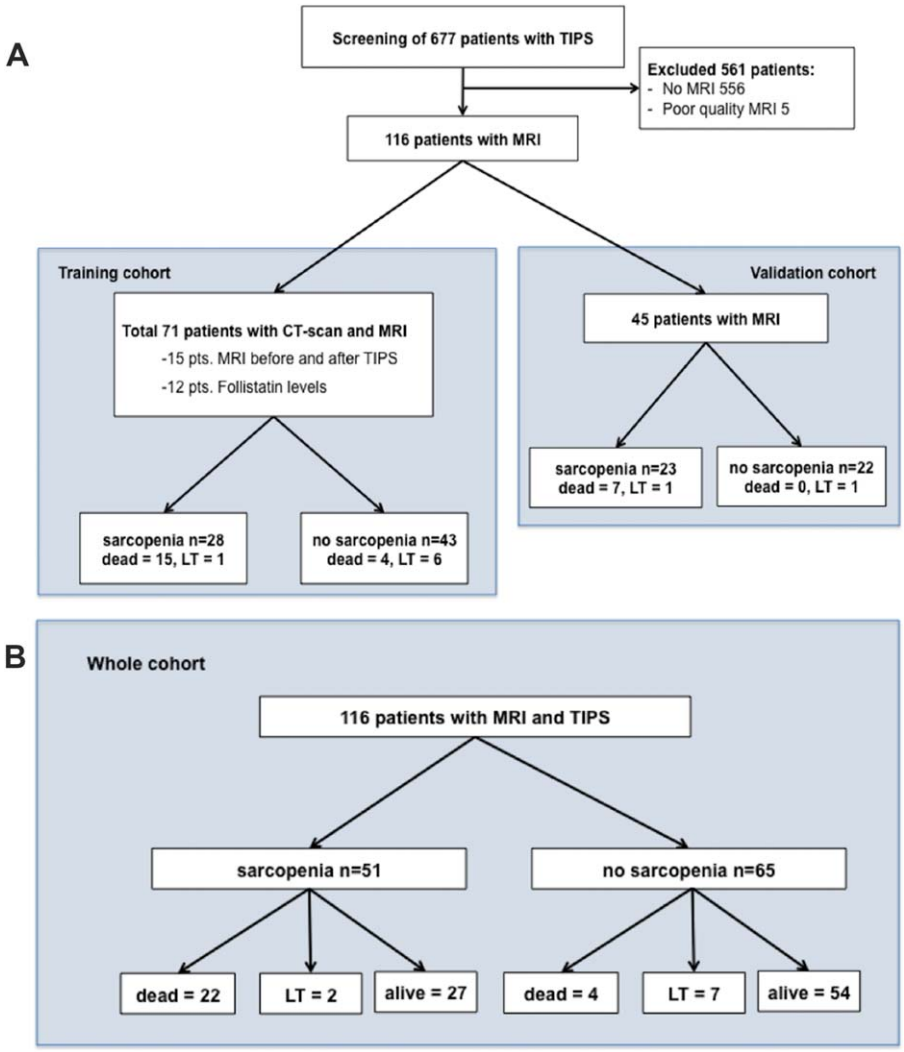

FIG. 1. (A) Flowchart of patient selection of the training and the validation cohorts. (B) Flowchart of patient selection of the whole cohort.

ASSESSMENT OF SKELETAL MA IN MRI

A commercially available clinical 3.0-Tesla MRI system (Ingenia 3.0 T; Philips Healthcare, Best, The Netherlands) or a 1.5-Tesla MRI system (Ingenia 1.5 T; Philips Healthcare) was used. The different magnetic field strengths (3.0 or 1.5 T) did not impact the results because both are equally effective at depicting the anatomy and thus muscle fat distribution. All patients underwent a standardized MRI sequence protocol, including axial T2-weighted turbo spin echo sequences with and without spectral presaturation attenuated by inversion recovery for fat suppression, axial T1-weighted fast field echo in-phase and opposed-phase sequences, diffusion-weighted imaging, and axial dynamic contrast-enhanced fat-suppressed T1-weighted gradient echo sequences. For image analysis, T2-weighted turbo spin echo sequences were transferred to a separate workstation. Sequence parameters for T2-weighted turbo spin echo were as follows: echo time, 80 ms; repetition time, dependent on respiratory rate; acquired voxel size, $1.5 \times 1.5 \times 5$ mm. The sequences were examined by four physicians (M.P., M.B., J.L., G.K.). The interreader variability was very low (intraclass correlation coefficient for the assessment of MA was 0.986 (95% confidence interval 0.970-0.994; $P = 0.000$). Agreement on classification of sarcopenic and nonsarcopenic

TABLE 1. Clinical and Laboratory Parameters Before and After TIPS

	All (n = 15)		Muscle Gain (n = 11)		Muscle Loss (n = 4)	
Parameter	Baseline	Last Follow-Up	Baseline	Last Follow-Up	Baseline	Last Follow-Up
MELD score	9 (7-15)	12 (7-40)	9 (7-14)	10 (7-20)	12 (8-15)	18 (16-40)††
MELD-Na score	12 (7-17)	13 (6-40)	11 (7-16)	8 (6-16)	13 (11-17)	22 (16-40)††
Child-Pugh score	8 (5-12)	7 (5-12)	8 (5-11)	6 (5-7)	8 (5-12)	10 (9-12)†
CLIF-C AD score	47.6 (33.5-92.9)	51.0 (25.1-77.3)	47.7 (33.5-92.9)	46.0 (25.2-56.2)	44.1 (41.6-60.7)	63.6 (52.4-77.2)†
Serum sodium (mmol/L)	139 (131-145)	141 (132-145)	141 (131-145)	142 (135-145)	137 (136-140)	136 (132-141)
Serum creatinine (mg/dL)	1.2 (0.6-4.0)	1.1 (0.4-2.0)	0.9 (0.6-2.0)	1.0 (0.6-1.5)	1.2 (1.1-1.6)	2.0 (0.9-4.0)
Serum bilirubin (mg/dL)	1.1 (0.4-2.0)	1.4 (0.7-18.5)	1.0 (0.4-1.6)	1.0 (0.7-5.5)	1.5 (0.7-2.0)	4.2 (1.0-18.5)
Serum albumin (g/L)	31 (10-41)	33 (17-39)	32 (10-41)	36 (24-39)	31 (16-38)	28 (17-28)†
INR	1.1 (0.9-1.5)	1.2 (1.0-4.0)	1.1 (0.9-1.5)	1.1 (1.0-1.3)	1.2 (1.1-1.3)	2.3 (1.4-4.0)††
White blood cell (g/L)	6.2 (2.2-12.3)	6.2 (1.0-24.4)	6.4 (2.2-11.0)	5.1 (1.0-14.9)	5.4 (2.8-12.3)	14.8 (6.2-24.4)†
C-reactive protein (mg/L)	7 (1-41)	13 (1-87)	17 (1-41)	4 (1-87)	4 (2-6)	75 (16-81)
Ascites	60%	33.3%	63.3%	27.3%	50%	50%
HE	60%	20%*	63.3%	9.1%*	50%	50%

Baseline versus last follow-up: *$P < 0.05$.
Nonsarcopenia versus sarcopenia at last follow-up: †$P < 0.05$, ††$P < 0.01$.

patients was 1.000 ($P < 0.001$). Also, the differences between 1.5T and 3T were negligible.

We chose a cross section, which is routinely captured in imaging of the liver, not prone to high variability and easy to identify. In 90% of our patients the position of the superior mesentery artery was located at the level of the L1 vertebra, while in 5% of our patients it was located at Th12 or L2. Consequently and due to the fact that main visceral arteries are largely immobile and rarely show interindividual differences, the radix of the superior mesenteric artery was chosen as a landmark for the measurement of the erector spinae muscle (Fig. 2A).[22,23]

We measured both sides to avoid confounders due to individual local inflammatory or degenerative processes or differences between the two sides resulting from dominant use of one side, postural fitness, and preferences. We evaluated side differences of the erector spinae muscle area (fat-free muscle area [FFMA]) and found that in 13 patients the right MA and left MA were similar, 48 patients had more pronounced MA on the left side (FFMA left – FFMA right = 6.2% [1.0-27.4%]), while 55 patients had more muscle on the right side (FFMA left – FFMA right = –6.7% [1.2-58.2%]).

The resulting DICOM images were analyzed with Image J software (Wayne Rasband, National Institutes of Health), which enables calculation of defined cross-sectional areas (square millimeters). It also allows distinction between striated muscular and fatty tissue within the total MA, which we used to determine myosteatosis. Muscle and fat tissue were semiautomatically quantified based on MRI signal, i.e., hypointense for striated muscle and hyperintense for fat. Next, the images were transformed into binary files, and the fatty tissue area was calculated by adding up tissue pixels and multiplying by pixel surface area. The interobserver variability was negligible. The identified area of fatty tissue was then subtracted from the total MA to obtain the FFMA (Fig. 2B,C). Mean distance of pre-TIPS MRI to TIPS was 47 ± 12 days, while mean distance of TIPS to post-TIPS MRI was 519 ± 50 days.

ASSESSMENT OF SKELETAL MUSCLE AREA IN CT

Commercially available CT imaging systems (Philips Brilliance 64 or Philips Brilliance 256 iCT; Philips Healthcare) were used. As it is the simplest parameter to obtain without special software, we examined the TPMT normalized by height as described in cross-sectional

TABLE 2. Patient Characteristics (Whole Cohort)

Parameter	All (n = 116)	No Sarcopenia (n = 65)	Sarcopenia (n = 51)	P
Age	59 (18-79)	54 (18-79)	61 (20-76)	0.101
Sex (male/female)	69/47	40/25	29/22	0.612
Etiology of cirrhosis (alcohol/viral hepatitis/other)	73/18/25	37/12/16	36/6/9	0.153
Indication for TIPS (variceal bleeding/refractory ascites/other)	36/62/18	28/26/11	8/36/7	0.032
Nominal stent diameter (8/10/12/14 mm)	10/83/22/1	6/45/13/1	4/38/9/0	0.758
Stent type (bare metal/covered)	26/90	13/52	13/38	0.511
Portal hepatic pressure gradient before TIPS	19 (7-35)	20 (8-30)	18 (7-35)	0.049
Portal hepatic pressure gradient after TIPS	7 (0-29)	8 (0-19)	7 (0-29)	0.815
Mean follow-up after MRI (months)	17 ± 2	20 ± 2	13 ± 2	0.040
Median follow-up after MRI (months)	10 (0-80)	13 (0-80)	7 (0-65)	0.040

images on the level of the umbilicus.[12] In our cohort, the umbilicus was located at the level of L4 in 70%, L5 in 20%, and L3 in 10% of patients. The mean time interval between CT and MRI was 117 ± 16 days.

ASSESSMENT OF FOLLISTATIN

In 12 patients, follistatin levels were assessed in peripheral blood using enzyme-linked immunosorbent assay (R&D Systems DY 669 Human Follistatin; Bio-Techne GmbH, Wiesbaden, Germany) according to the manufacturer's guidelines.

STATISTICAL ANALYSIS

Descriptive statistics were computed for all variables. Nonparametric testing was used to compare different groups when suitable. Paired nonparametric testing was used to compare data before and after the TIPS procedure of the same patients. Metric variables were correlated using Spearman's correlation. Inter-reader variability was analyzed by intraclass correlation coefficient. Agreement on classification of sarcopenia and no sarcopenia between the raters was assessed using kappa statistics. The prognostic value and selection of cutoff values of skeletal muscle area were analyzed using receiver operating characteristics with 3-year survival as the endpoint. Kaplan-Meier curves with log-rank tests were used to examine the impact of MA on survival. Univariate and multivariate risk factor analyses were performed with Cox regression. Multivariate analysis included all values with $P < 0.05$. Continuous variables are presented as median (range), if not otherwise specified. Categorical variables are presented as absolute cases or percentage. All data were analyzed using SPSS (version 24; IBM, Armonk, NY) and plotted using Prism (version 6; GraphPad, La Jolla, CA).

Results

GENERAL CHARACTERISTICS AND SARCOPENIA DIAGNOSED BY MRI AND CT IN TRAINING COHORT

The training cohort of 71 patients (42 men) had a median age of 58 and a range of 18-78 years. The main etiology of liver cirrhosis was alcoholic liver disease in 51 patients and chronic viral hepatitis in 9 patients. The indication for TIPS placement was refractory ascites in 34 patients and variceal bleeding in 26, and 11 patients received TIPS for both indications (Supporting Table S1). To confirm findings from the training cohort, a validation cohort of 45 patients was included. Between the validation and the training cohorts no major significant changes were found in general demographics, except for etiology. Briefly, the validation cohort included 27 male patients with a median age of 59 and a range between 26 and 79 years. Twenty-two patients had alcoholic cirrhosis, a significantly lower portion than in the training cohort, and 9 patients presented with chronic viral hepatitis. Reason for TIPS was refractory ascites in 28 patients, variceal bleeding in 10 patients, and both indications in 7 patients (Supporting Table S1). Laboratory parameters, such as serum sodium, creatinine, bilirubin, albumin, international normalized ratio (INR), white blood cell count, C-reactive protein, and prognostic scores (Model for End-Stage Liver Disease [MELD], MELD including sodium [MELD-Na], Child-Pugh, European Foundation for the Study of Chronic Liver Failure Consortium acute decompensation score

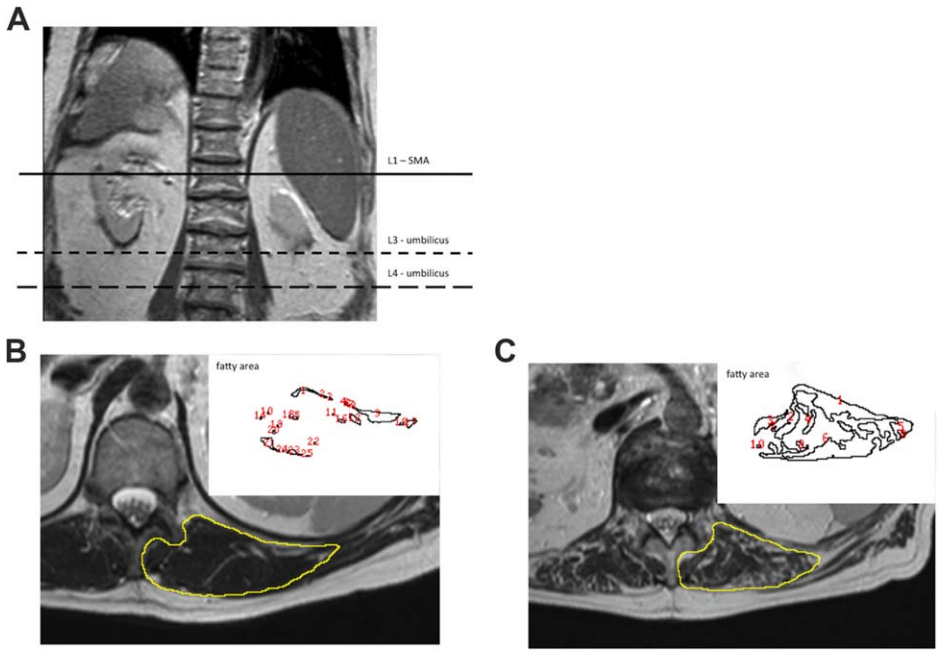

FIG. 2. (A) MRI in coronal plane of a patient displaying the levels of muscle examination of different methods (straight line L1, dotted line L3, discontinued line L4). (B) Exemplary MRI image of cross section of the spinal muscles in a patient with partially low fatty degeneration. Image detail in the upper right-hand corner depicts detected intramuscular fat tissue area. Numbers numerate islets of intramuscular fat tissue areas that accumulate to total intramuscular fat tissue area. (C) Exemplary MRI of cross section of the spinal muscles in a patient with partially high fatty degeneration. Image detail in the upper right-hand corner depicts detected intramuscular fat tissue area. Numbers numerate islets of intramuscular fat tissue areas that accumulate to total intramuscular fat tissue area. Abbreviation: SMA, superior mesenteric artery.

[CLIF-C AD]) did not differ significantly between the training and the validation cohorts (Supporting Table S1).

Receiver operating characteristics analysis (Fig. 3A) with 3-year survival as the endpoint showed similar areas under the curve (AUC) for both MRI parameters (MA and FFMA), while CT-assessed TPMT showed the lowest AUC. While TPMT was normalized for height,[12] the normalization for height, weight, or body mass index of the MRI parameters MA and FFMA did not improve their AUC (data not shown). Using the gender-specific receiver operating characteristic curves, we received even higher AUC for FFMA (AUC male patients, 0.817; 95% confidence interval, 0.684-0.949; $P < 0.001$; AUC female patients, 0.804; 95% confidence interval, 0.592-1.000; $P < 0.05$). We then determined gender-specific cutoff values. In male patients MA <3,523 mm^2 and FFMA <3,197 mm^2, and in female patients MA <3,153 mm^2 and FFMA <2,895 mm^2 were found optimal to diagnose sarcopenia. TPMT cutoff values were chosen at 16.8 cm/m for both male and female patients as described. Diagnosis of sarcopenia in the three different techniques was associated with significantly higher 3-year mortality (Fig. 3B-D). Regarding diagnosis of sarcopenia using MA and FFMA, 1 patient was misclassified, while comparison between FFMA and TPMT identified that 4 patients were misclassified.

VALIDATION OF FFMA

Using the above-mentioned cutoff values for MA and FFMA, in the validation cohort sarcopenia identified patients with significantly worse 3-year survival (Fig. 4A,B), while FFMA performed slightly better than MA and was therefore used for further analysis.

FFMA BEFORE AND AFTER TIPS

In 15 patients, FFMA before and after TIPS was assessed (Table 1). FFMA after TIPS increased significantly compared to FFMA before TIPS (2,677 mm^2 [1,563-5,083] versus 3,463 mm^2 [1,600-5,106]; $P < 0.05$) (Fig. 4C). Of 15 patients, 11 had an increased

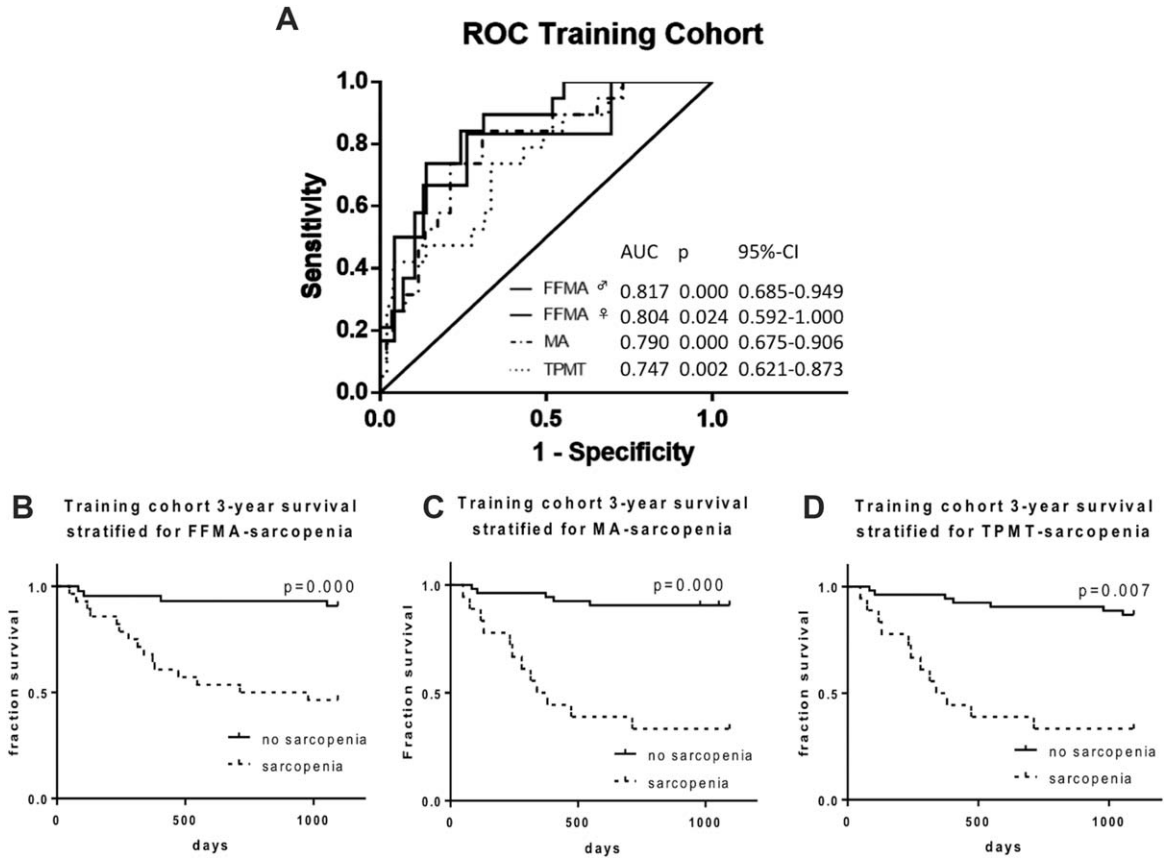

FIG. 3. (A) Graph of the results of an analysis using receiver operating characteristics to compare FFMA (male and female) in solid line, MA (dotted line), and TPMT (thin dotted line) in the training cohort. Detail contains corresponding AUC data, *P* values, and confidence intervals. (B) Graph of Kaplan-Meier survival curve of training cohort stratified for FFMA-defined sarcopenia. Patients with sarcopenia (dotted line) show significantly impaired survival compared to patients with out sarcopenia (solid line). (C) Graph of Kaplan-Meier survival curve of training cohort stratified for MRI-based, MA-defined sarcopenia. Patients with sarcopenia (dotted line) show significantly impaired survival compared to patients with out sarcopenia (solid line). (D) Graph of Kaplan-Meier survival curve of training cohort stratified for CT-based, TPMT-defined sarcopenia. Patients with sarcopenia (dotted line) show significantly impaired survival compared to patients with out sarcopenia (solid line). Abbreviations: CI, confidence interval; ROC, receiver operating characteristic.

median gain in MA of 605 mm^2 (234-2,001), while 4 had decreased MA or a median loss in MA of 283 mm^2 (176-612) after TIPS. Interestingly, patients with muscle loss after TIPS showed significantly worse survival (Fig. 4D). Three out of 4 patients with muscle loss died during follow-up compared to only 1 of 11 patients with muscle gain after TIPS ($P < 0.05$). After TIPS, 5 patients were still classified as sarcopenic and 10 patients were classified as nonsarcopenic according to the FFMA cutoffs mentioned above. Nonsarcopenic patients showed significantly better survival, suggesting that persistence of sarcopenia after TIPS is associated with worse survival (Fig. 4E). Between patients with muscle gain and muscle loss after TIPS, there was no significant difference in demographics, laboratory parameters, prognostic scores, and clinical features (hepatic encephalopathy [HE], ascites) before TIPS. However, after TIPS, patients with muscle loss showed significantly worse laboratory parameters (serum albumin, INR, white blood cell count) as well as higher MELD, MELD-Na, Child-Pugh, and CLIF-C AD scores (Table 1). Importantly, in patients with muscle gain, the occurrence of HE decreased, whereas this was not the case in patients with muscle loss (Table 1).

MRI-MEASURED MA CORRELATES WITH FOLLISTATIN LEVELS

Follistatin levels from blood samples of 12 patients taken at the time of the TIPS procedure strongly

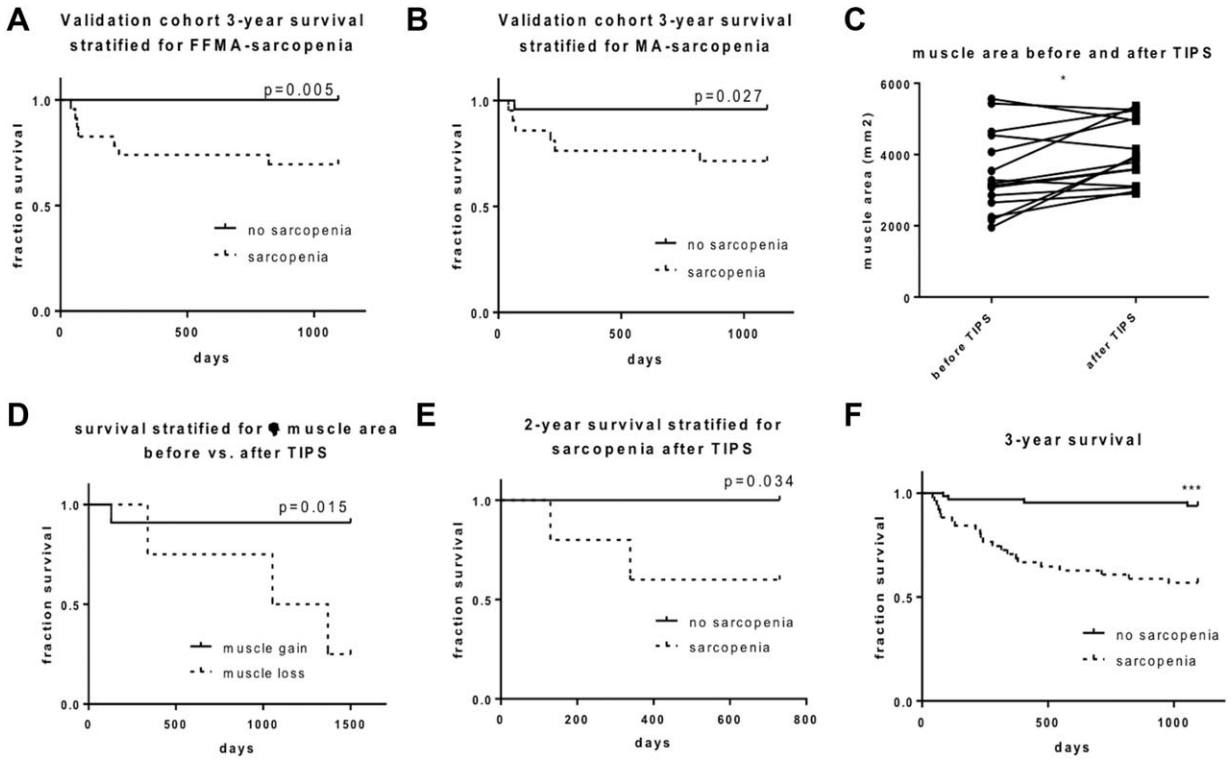

FIG. 4. (A) Graph of Kaplan-Meier survival curve of validation cohort stratified for MRI-based, FFMA-defined sarcopenia. Patients with sarcopenia (dotted line) show significantly impaired survival compared to patients with out sarcopenia (solid line). (B) Graph of Kaplan-Meier survival curve of validation cohort stratified for MRI-based, MA-defined sarcopenia. Patients with sarcopenia (dotted line) show significantly impaired survival compared to patients with out sarcopenia (solid line). (C) Graph depicting the comparison of the total MA in patients before and patients after TIPS. (D) Graph of Kaplan-Meier survival curve stratified for delta MA. Patients with muscle loss (dotted line) show significantly impaired survival compared to patients with muscle gain (solid line) after TIPS. (E) Kaplan-Meier curve of impaired 2-year survival in patients who maintained or developed sarcopenia (dotted line) after TIPS compared to nonsarcopenic patients (solid line). (F) Kaplan-Meier curve of overall 3-year survival after TIPS in sarcopenic (dotted line) versus nonsarcopenic (solid line) patients in the whole cohort. $^{*}P < 0.05$, $^{***}P < 0.001$.

correlated to left ($R = 0.7$, $P = 0.1$), right ($R = 0.9$, $P = 0.04$), and total ($R = 0.9$, $P = 0.04$) MA assessed using MRI, suggesting that this method assessed active muscle amount in these patients.

FFMA-DEFINED SARCOPENIA IS ASSOCIATED WITH ORGAN DYSFUNCTION AND ACLF AFTER TIPS

For further analyses the training and validation cohorts were merged to provide a larger cohort of 116 TIPS patients with MRI (Table 2). The general demographics and etiologies of cirrhosis did not significantly differ between sarcopenic and nonsarcopenic patients. The only differences were in indication for TIPS and portal systemic pressure gradient, whereby a larger proportion of sarcopenic patients received TIPS for refractory ascites and therefore had lower portal systemic pressure gradient before TIPS than nonsarcopenic patients (Table 2). Absence of sarcopenia was associated with a better response to ascites and recovery of serum sodium and albumin levels after TIPS, while in sarcopenic patients ascites persisted and neither serum sodium nor albumin levels recovered (Supporting Fig. S1A; Table 3). This was paralleled by a strong correlation of FFMA with serum protein levels (Supporting Fig. S1B). Similarly, serum bilirubin, INR, and alanine aminotransferase levels increased significantly in sarcopenic patients, while in nonsarcopenic patients INR and alanine aminotransferase remained stable and bilirubin increased to a lesser degree (Table 3).

The incidence of episodes of overt HE was significantly higher in sarcopenic patients before and after TIPS. Interestingly, TIPS significantly reduced the

TABLE 3. Clinical and Laboratory Parameters Before and After TIPS

Parameter	All (n = 116)		Nonsarcopenia (n = 65)		Sarcopenia (n = 51)	
	Baseline	Last Follow-Up	Baseline	Last Follow-Up	Baseline	Last Follow-Up
MELD score	11 (6-32)	14 (6-40)***	10 (6-25)	13 (6-40)*	12 (6-32)	15 (6-40)***‡
MELD-Na score	14 (6-33)	15 (6-40)	12 (6-27)	13 (6-32)	16 (6-33)††	16 (6-40)‡
Child-Pugh score	7 (5-12)	6 (5-10)**	7 (5-12)	6 (5-9)**	8 (5-12)††	5 (5-10)
CLIF-C AD score	48.6 (30.5-92.9)	46.9 (30.5-77.3)	47.8 (30.5-92.9)	44.1 (30.5-65.3)	51.5 (32.7-71.4)†	51.2 (35.5-77.3)†
Serum sodium (mmol/L)	137 (125-145)	139 (126-163)**	138 (125-145)	140 (133-163)**	136 (128-145)††	137 (126-146)‡‡
Serum creatinine (mg/dL)	1.2 (0.5-6.4)	1.0 (0.5-10.0)	1.0 (0.5-3.2)	1.0 (0.8-10.0)	1.3 (0.5-6.4)†	1.1 (0.5-5.6)
Serum bilirubin (mg/dL)	1.2 (0.1-10.7)	2.4 (0.1-24.4)***	1.3 (0.1-6.8)	2.0 (0.1-7.4)*	1.1 (0.2-10.7)	3.3 (0.7-24.4)***‡
AST (U/mL)	40 (10-297)	51 (15-1824)*	40 (10-163)	47 (15-105)	42 (11-297)	56 (23-1824)*
ALT (U/mL)	22 (8-200)	30 (2-577)**	26 (8-118)	26 (2-68)	20 (8-200)†	32 (8-577)***
Serum albumin (g/L)	31 (10-56)	36 (7-49)*	32 (11-56)	38 (27-49)**	29 (10-54)	29 (7-47)‡‡
INR	1.1 (0.9-1.9)	1.2 (1.0-3.2)*	1.1 (0.9-1.8)	1.2 (1.0-1.7)	1.1 (0.9-1.9)	1.2 (1.0-3.2)**
White blood cell (g/L)	6.3 (1.6-20.3)	6.0 (0.6-31)	6.0 (1.6-15.6)	6.0 (2.2-17.4)	7.3 (2.3-20.3)	7.2 (0.6-31)‡
CRP (mg/L)	15.6 (0.3-104)	8.3 (0.3-115)	13.4 (1-104)	7.9 (1.1-115)	17.7 (0.3-77)	9.2 (0.3-87)
Ascites	76.7%	28.4%***	69.2%	16.9%***	86.3%†	43.1%***‡‡‡
HE	48.3%	27.8%**	40.0%	18.5%**	58.8%†	48.0%‡‡

Baseline versus last follow-up: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.
Nonsarcopenia versus sarcopenia at baseline: $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$.
Nonsarcopenia versus sarcopenia at last follow-up: $^{\ddagger}P < 0.05$, $^{\ddagger\ddagger}P < 0.01$, $^{\ddagger\ddagger\ddagger}P < 0.001$.
Abbreviations: ALT, alanine transferase; AST, aspartate aminotransferase; CRP, C-reactive protein.

frequency of episodes of overt HE in the nonsarcopenia group, while no change was observed in the sarcopenia group (Supporting Fig. S1C; Table 3). Moreover, FFMA strongly correlated to performance on the number connection test for assessment of minimal HE (Supporting Fig. S1D).

The increase of the MELD and the MELD-Na scores after TIPS procedure was higher in the sarcopenia group than in the nonsarcopenia group (Supporting Fig. S2A,B; Table 3). Interestingly, sarcopenic patients presented a higher white blood cell count (Table 3), which was also associated with a higher CLIF-C AD score, associated with higher risk of developing ACLF. Importantly, after TIPS, the CLIF-C AD score decreased in nonsarcopenic patients but remained high in sarcopenic patients (Supporting Fig. S2C).

SARCOPENIA IS ASSOCIATED WITH HIGHER RISK OF ACLF AND DEATH AFTER TIPS

Overall, 26 patients died and 9 were transplanted (Fig. 1B). Sarcopenic patients showed worse 3-year survival compared to nonsarcopenic patients (Fig. 4F). Most patients died of ACLF (78%), which was triggered in 60% by infection, in 8% by bleeding, and in 10% by circulatory failure. The other deceased patients died from unknown reasons or carcinoma. There was no significant difference in the causes of death or TIPS dysfunction between the sarcopenia and the nonsarcopenia groups ($P > 0.05$, data not shown).

Univariate Cox regression analysis identified MA and FFMA as significantly associated with survival, *inter alia* with the expected prognostic scores (MELD, MELD-Na, and CLIF-C AD) and age (Table 4). Multivariate Cox regression analysis, including all significant parameters from univariate analysis, identified FFMA and the CLIF-C AD score as independent predictors of mortality. Of note, MA was not independently associated with mortality, although classification for sarcopenia or nonsarcopenia was similar when using MA and FFMA.

Only 9 patients underwent LT; therefore, competing risk analysis with LT as the endpoint was not performed.

Discussion

This study demonstrates in a training cohort and a validation cohort that MRI assessment of FFMA

TABLE 4. Univariate and Multivariate Cox Regression Analysis for Survival

	Univariate Cox Regression				Multivariate Cox Regression			
Parameter	*P*	HR	CI		*P*	HR	CI	
Age	0.009	1.048	1.012	1.085				
Sex	0.567							
Total MA (including fat; cm^2)	0.001	0.906	0.860	0.954				
FFMA (cm^2)	0.000	0.906	0.866	0.948	0.001	0.920	0.877	0.965
Fat area (cm^2)	0.167							
Sarcopenia	0.000	7.574	2.874	19.962	0.001	5.624	2.066	15.312
Number connection test before TIPS	0.000	1.026	1.011	1.040				
HE before TIPS	0.044	2.216	1.023	4.802				
Hepatorenal syndrome before TIPS	0.012	2.620	1.239	5.540				
Ascites before TIPS	0.056							
MELD before TIPS	0.016	1.074	1.014	1.139				
MELD-Na before TIPS	0.009	1.077	1.019	1.139				
CLIF-C AD before TIPS	0.004	1.043	1.013	1.074	0.015	1.053	1.010	1.096
Sodium before TIPS	0.089							
Creatinine before TIPS	0.148							
Bilirubin before TIPS	0.234							
INR before TIPS	0.392							

Abbreviations: CI, confidence interval; HR, hazard ratio.

identifies clinically relevant sarcopenia in a large cohort of patients with decompensated cirrhosis receiving TIPS. Besides describing and confirming the clinical impact of sarcopenia, this study shows that persistence of sarcopenia after TIPS impairs response to TIPS and increases the risk of developing ACLF and death.

For assessment of sarcopenia, a cross-sectional MA is usually described.[10] However, its assessment has been performed in different muscle groups and at different levels, mainly using CT scans.[8,11,12,14] The definition of reference values is a clinical requirement as stated by the European Working Group on Sarcopenia.[7] Simple anthropometric tests lack reproducibility and precision because in patients with cirrhosis they may be influenced by ascites and edema.[8] Although MRI is more demanding and costly than a CT scan, on many occasions CT scans may not be appropriate in these patients. Also, performing a CT scan with the intention of analyzing sarcopenia may be considered unethical due to radiation exposure. However, routine contrast-enhanced imaging CT or MRI for hepatocellular carcinoma screening or evaluation for LT or TIPS is clinically required in almost all patients with decompensated cirrhosis. In a number of patients, a CT scan might even be dangerous due to the risk of contrast medium–induced renal failure.[15] Therefore, liver MRI has been emerging as a more suitable imaging method in patients with cirrhosis. However, data regarding sarcopenia in decompensated liver cirrhosis are scarce.[24] This study provides an easy and useful marker of sarcopenia using MRI of the erector spinae muscle area on the level of the radix of the superior mesenteric artery, which is always in the window of liver MRI. Indeed, choosing this landmark for use in the analysis was motivated by the fact that this structure is easy to identify and that it is always in the MRI window of liver imaging. Importantly, to reduce the possible confounding role of ascites due to possible artifacts in the MRI, we selected the region less prone to ascites accumulation even in the supine position, as shown.[25,26] In contrast to the iliopsoas muscle, which is in the vicinity of the peritoneal cavity, the erector spinae muscle is located outside the peritoneal cavity and thus is not influenced by the persistence of ascites. Taking these considerations into account, the suggested measurements are available in all liver MRIs performed in patients with cirrhosis and easy to elaborate on. Importantly, these measurements might reflect active muscle mass as suggested by the correlation with follistatin, a myokine which, among secretions by different cell types, is involved in muscle hemostasis and sarcopenia,[21,27] and the good correlation with the widely used TPMT, which has been described as a very good marker of sarcopenia.[12]

Apart from practical issues, such as the availability of MRI or CT scans, MRI is suitable to dissect the quality of muscle because it is able to differentiate muscle tissue from fat tissue inside the muscle. In CT scans, lower attenuation by skeletal muscle has been associated with increased lipid infiltration of the muscle in diabetic and elderly patients.[28,29] However, these findings have never been applied to patients with

cirrhosis. Tsien et al. provided data on reduced CT attenuation in a cohort of 57 TIPS patients.[30] However, criteria for upper and lower cutoff values for Hounsfield units to define intramuscular fat tissue have not yet been standardized.[31] CT attenuation alone might depend on hydration as, e.g., fluid overload or ascites could influence the results.[32,33] With MRI it is possible to clearly and visually differentiate fat tissue areas within the total MA and exclude it to identify FFMA.[34] Taking this advantage of MRI into account and investigating a cohort of patients twice as large, the present study is the first to establish a distinct relationship between FFMA measured in MRI and TIPS response, the ACLF risk, and gender-specific cutoffs for the FFMA to define sarcopenia.

Furthermore, the present study demonstrated that failure to increase MA after a TIPS procedure was associated with worse outcome, as demonstrated in other studies.[30,35] This could further confirm this method's robustness as well as its adequacy in the assessment of sarcopenia. Indeed, after a TIPS procedure, sarcopenic patients performed worse, with a lower ascites resolution rate, a higher HE rate, generally worse renal and hepatic function, and protein metabolism. This clearly confirms that the FFMA reflects metabolically active muscle and that it is influenced by impaired liver function. Impaired protein and albumin hemostasis in sarcopenic patients possibly contributes to the persistence of ascites after TIPS.[36] Moreover, this study clearly demonstrates that after TIPS the rate of HE decreases in patients without sarcopenia, while in patients with sarcopenia HE episodes occur more frequently, possibly due to the fact that muscle is an important site of ammonia reduction. This is a confirmation of a recent study in 26 TIPS patients which found that sarcopenia assessed using CT scan predicted development of HE after TIPS.[37] The present study not only confirms this report on clinically assessed overt HE in a much larger set of patients[38] but also expands it to minimal (covert) HE assessed by neuropsychometric testing. All together, these findings demonstrate the prognostic value of FFMA assessed in a routine MRI in patients who received TIPS, which could be useful to identify patients at risk of complications, who might require closer management and/or allocation to LT. Indeed, at least in our cohort, the sarcopenic patients received fewer LTs than the nonsarcopenic patients, suggesting that, among other reasons, worse outcome predicted by the presence of sarcopenia is not reflected in the current allocation system of LT, which is mainly MELD score–based.

Patients with decompensation and complications of cirrhosis, even after sufficient treatment of portal hypertension with TIPS, have a very limited prognosis. In these patients, the FFMA seems to be associated with mortality and appears to be an independent predictor of mortality, as demonstrated in the present study. Of note, while the total muscle mass, which was assessed in several other studies investigating sarcopenia using non-MRI techniques in TIPS patients, also correlated with mortality, it is not an independent predictor of mortality. This suggests that in liver cirrhosis functional muscle mass might be more important than the total MA itself. This assumption is in line with a recent report suggesting an impact of myosteatosis measured indirectly by CT attenuation in a cohort of patients evaluated for LT.[39] In fact, in the present study, analyzing only nonsarcopenic patients, no predictive markers were assessed, which underlines that in TIPS patients decreased fat-free muscle mass is closely linked to decompensation and death.

This does not come as a surprise because sarcopenic patients after TIPS showed a higher CLIF-C AD score,[1] indicating a higher risk of ACLF development, and higher levels of systemic inflammation indicated by white blood cell count.[40] Indeed, in these patients, the leading cause of death was development of fatal ACLF, mainly due to sepsis.

Although our cohort is well characterized, this study has several limitations, mainly due to the retrospective nature of the analysis and the absence of a healthy control group. Nevertheless, this study demonstrates the impact of FFMA on survival using a two-step approach (a training cohort and a validation cohort) despite the fact that we only have MRI data of 15 patients before and after TIPS. Another limitation is that follistatin levels might be unspecific in relation to muscle mass. Moreover, other studies elaborated their cutoff values based on healthy or obese oncologic patients[41-44] and found similar cutoff levels for sarcopenia as we did,[8,45] rendering our technique and our data robust and valid.

Another limitation is that our training cohort and our validation cohort were not matched. Yet, these cohorts did not differ in terms of general characteristics, laboratory parameters, or prognostic scores, except for a significantly lower proportion of alcoholic etiology in the validation cohort. This, however, might also be considered one of the study's strengths as it demonstrates the importance of FFMA for different cohorts with differently distributed etiologies of cirrhosis.

Finally, we are aware that introducing a new method does not contribute to standardization of the already

diverse imaging-based definitions of sarcopenia. However, a recent approach, published as a letter to the editor, reported an intraclass coefficient correlation of 0.98 in retrospectively analyzed MA using CT and MRI of patients in a living LT donor program,[46] suggesting validity of sarcopenia diagnostics across techniques. There is no evidence for choosing the radix of the superior mesenteric artery (L1) as a landmark. However, umbilicus, L3 or L4, as previously used in CT studies, is not always in the scanning field of liver MRI. Therefore, choosing L1 contributes to a reduction in MRI investigation time and, consequently, costs. Another technical issue might arise by artifacts in MRI induced by massive ascites.[47] Due to this general MRI limitation we adapted the technique as follows: (1) L1 is more suitable than L3 and L4 because less ascites is located in the scanning field and (2) the erector spinae muscle, in contrast to the psoas muscle, is located extra-abdominally. Therefore, the results are less prone to disturbances by ascites-related artifacts, not mentioning the fact that massive ascites is usually drained before imaging.

In conclusion, this study demonstrates that MRI-assessed FFMA represents active muscle, is associated with outcome after TIPS, and predicts decompensation, ACLF risk, and death in decompensated patients with cirrhosis receiving TIPS. It could be a useful tool to stratify risk in decompensated patients, especially those receiving TIPS.

Acknowledgment: We thank Gudrun Hack and Silke Bellinghausen for their excellent technical assistance and Sabine Dentler for critical reading.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.29602/suppinfo.

2.4 Systemische Inflammation als Risikofaktor bei Leberzirrhose

“Cardiodynamic state is associated with systemic inflammation and fatal acute-on-chronic liver failure.”
Praktiknjo M, Monteiro S, Grandt J, Kimer N, Madsen JL, Werge MP, William P, Brol MJ, Turco L, Schierwagen R, Chang J, Klein S, Uschner FE, Welsch C, Moreau R, Schepis F, Bendtsen F, Gluud LL, Møller S, Trebicka J.
Erschienen in ***Liver International.*** *2020 Jun;40(6):1457-1466.*

In dieser Arbeit untersuchten wir das Risiko der Entwicklung von ACLF in Abhängigkeit verschiedener hämodynamischer Kreislaufsituationen und deren Assoziation mit zirkulierenden Markern systemischer Inflammation.

Für diese Untersuchung wurden 224 Patienten mit Leberzirrhose prospektiv am Department of Clinical Physiology and Gastro Unit Hvidovre Hospital in Kopenhagen, Dänemark untersucht. Bei den Patienten wurde mittels Katheterisierung der A. femoralis das Herzzeitvolumen (cardiac output, CO) via Indikator-Dilutionstechnik nach Injektion von 150 kBq of ^{125}I-markiertem humanen Albumin (IFE IT. 205, Institute of Energy Technique, Kjeller, Norway) in das rechte Atrium gemessen. CI wurde aus CO/Körperoberfläche errechnet und in L/min/m^2 dargestellt.

Aus den entnommenen Blutproben wurden am hiesigen Labor für Leberfibrose und Portale Hypertension, Medizinische Klinik und Poliklinik I, mittels Elisa die Serumspiegel von proinflammtorischen Interleukinen (IL) IL-6, IL-8 und löslichem IL-33-Rezeptor (sIL-33R) gemessen.

Primärer Endpunkt war die Entwicklung von ACLF.

Die Entwicklung von ACLF stratifiziert nach hämodynamischem Zustand

Die kumulative Wahrscheinlichkeit der ACLF-Entwicklung von Patienten mit hyperdynamischer, hypodynamischer und normodynamischer Kreislaufsituation lag bei jeweils 35%, 25% und 14 % in 5 Jahren. Ein ähnliches Bild zeigt sich bei Betrachtung der Gesamtmortalität (Abb. 2.4.1).

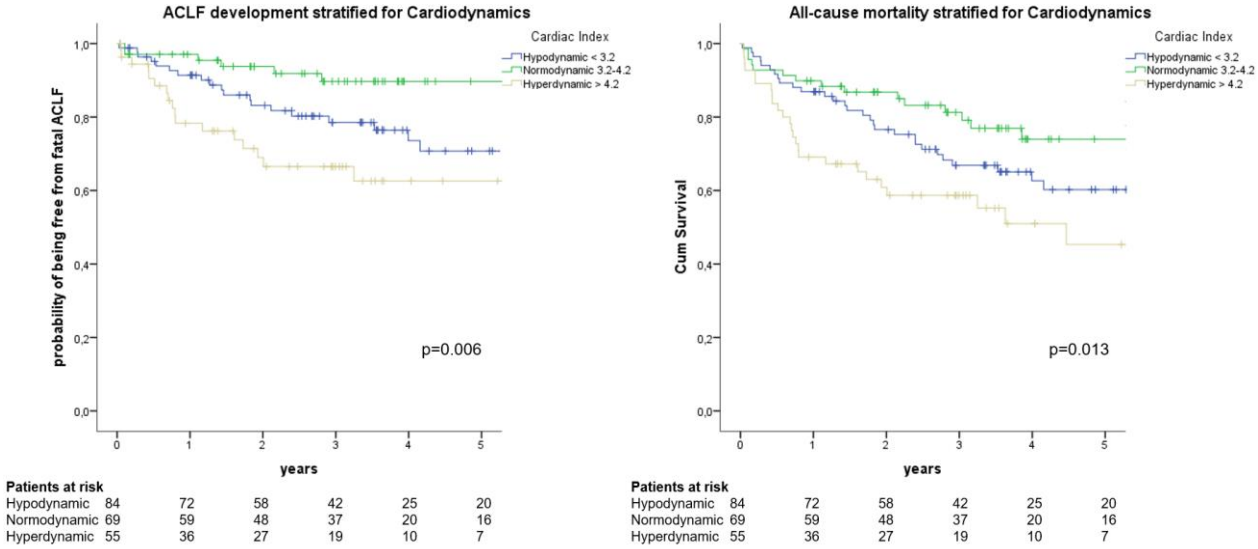

Abbildung. 2.4.1: Kaplan-Meier Kurve für die ACLF-Entwicklung (links) und Gesamtmortalität (rechts) stratifiziert nach hämodynamischer Situation. Es zeigt sich eine signifikant erhöhte Rate an ACLF-Entwicklungen bei Patienten mit hyper- und hypodynamischer Kreislaufsituation. Normodynamisch (grün), Hypodynamisch (blau), Hyperdynamisch (gelb). P durch log-rank Test. ACLF (Akut-auf-Chronisches Leberversagen).

Systemische Inflammation und hämodynamische Situation

Die höchste Detektionsrate der untersuchten proinflammatorischen Mediatoren (IL-6, IL-8, sIL-33R) war in Patienten mit hyperdynamischer Kreislaufsituation nachweisbar. Zwischen Patienten mit normo- und hypodynamischer Kreislaufsituation war kein signifikanter Unterschied in der Detektierbarkeit der proinflammatorischen Mediatoren nachweisbar (Abb. 2.4.2).

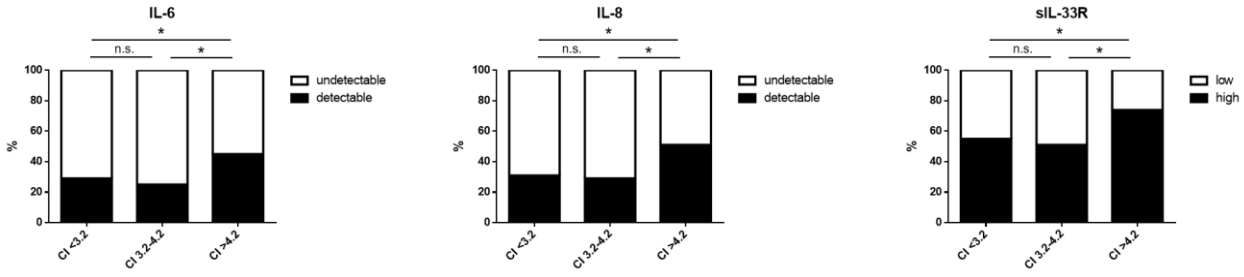

Abbildung. 2.4.2: Detektionsraten von proinflammatorischen Mediatoren IL-6 (links), IL-8 (mitte), sIL-33R (rechts). Es zeigen sich durchgehend erhöhte Raten an detektierbaren Spiegeln (schwarze Balken) in Patienten mit hyperdynamischer Kreislaufsituation (CI>4.2) verglichen mit normo- und hypodynamischer Kreislaufsituation (CI 3.2-4.2 und CI <3.2). *p<0.05, n.s. (nicht signifikant). CI (Herzindex).

Die systemische Inflammation und ACLF-Entwicklung

Zur Analyse der Rolle von hämodynamischer Kreislaufsituation und systemischer Inflammation im Hinblick auf die Entwicklung eines ACLF wurde eine Cox Regressionsanalyse durchgeführt. Univariat zeigten sich v.a. ein hyperdynamischer Kreislauf sowie IL-6 und sIL-33R mit der ACLF-Entwicklung assoziiert. Die multivariate Analyse konnte jedoch nur für IL-6 eine unabhängige Assoziation bestätigen (Tabelle 2.4.1).

Tabelle 2.2.1: Univariate und multivariate Cox Regressionsanalyse für ACLF-Entwicklung.

Parameter	Univariate Cox Regression				Multivariate Cox Regression		
	p	HR	95%-CI		*p*	HR	95%-CI
Age	0.010	1.257	1.057 – 1.494		0.024	1.044	1.006 – 1.083
Era (cat)	0.211						
NSBB	0.519						
Child-Pugh	0.011	1.179	1.039 – 1.337				
MELD	0.004	1.104	1.032 – 1.181				
CLIF-C AD	0.000	1.096	1.049 – 1.145				
Hb	0.013	0.835	0.725 – 0.962				
Bilirubin	0.026	1.201	1.022 – 1.411				
Albumin	0.000	0.903	0.860 – 0.948		0.001	0.907	0.857 – 0.961
INR	0.050	2.293	1.001 – 5.255				
MAP	0.023	0.975	0.954 – 0.996				
CI	0.157						
Hypodynamic (cat)	0.845						
Hyperdynamic (cat)	0.017	2.014	1.135 – 3.576				
HVPG ≥16 (cat)	0.005	2.484	1.320 – 4.677				
SVRI	0.028	0.999	0.999 – 1.000				
IL-6 (cat)	0.000	3.093	1.768 – 5.411		0.006	2.428	1.295 – 4.553
IL-8 (cat)	0.090						
sIL-33R (cat)	0.011	2.336	1.217 – 4.484				
Ascites (cat)	0.002	2.727	1.462 – 5.088				

AD (akute Dekompensation); AP (alkalische Phosphatase); ca,(kategorial); CI (Herzindex); CLIF-C (European Foundation for the study of chronic liver failure consortium); Hb (Hämoglobin); HVPG (hepatic venous pressure gradient); IL (Interleukin); INR (international normalized ratio); MELD (Model for end-stage liver disease); NSBB (nicht-selektive Betablocker); sIL-33R (soluble Interleukin-33 Receptor); SVRI (systemic vascular resistance index). Kategoriale Variablen: Era (2002-2011 vs. 2012-2016), Ascites: klinisch oder mit Ultraschall nachgewiesen. IL-6: ≥9.38 pg/ml (Detektionsniveau), IL-8: ≥31.2 pg/ml (Detektionsniveau), sIL-33R: ≥7380.2 pg/mL; Hyperdynamisch und Hypodynamisch mit Normodynamisch als Referenz. *kursiv* – in multivariates Modell aufgenommen. Child-Pugh, CLIF-C AD score (wegen Multikollinearität mit MELD) und MAP (wegen Multikollinearität mit hyperdynamischem Kreislauf) wurden nicht in das multivariate Modell aufgenommen.

Received: 15 December 2019 | Revised: 17 February 2020 | Accepted: 2 March 2020

DOI: 10.1111/liv.14433

ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

Cardiodynamic state is associated with systemic inflammation and fatal acute-on-chronic liver failure

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Abstract

Background & Aims: Acute-on-chronic liver failure (ACLF) is characterized by high short-term mortality and systemic inflammation (SI). Recently, different cardiodynamic states were shown to independently predict outcomes in cirrhosis. The relationship between cardiodynamic states, SI, and portal hypertension and their impact on ACLF development remains unclear. The aim of this study was therefore to evaluate the interplay of cardiodynamic state and SI on fatal ACLF development in cirrhosis.

Results: At inclusion, hemodynamic measures including cardiac index (CI) and hepatic venous pressure gradient of 208 patients were measured. Patients were followed prospectively for fatal ACLF development (primary endpoint). SI was assessed by proinflammatory markers such as interleukins (ILs) 6 and 8 and soluble IL-33 receptor (sIL-33R). Patients were divided according to CI (<3.2; 3.2-4.2; >4.2 L/min/m^2) in hypo- (n = 84), normo- (n = 69) and hyperdynamic group (n = 55). After a median follow-up of 3 years, the highest risk of fatal ACLF was seen in hyperdynamic (35%) and hypodynamic patients (25%) compared with normodynamic (14%) (P = .011). Hyperdynamic patients showed the highest rate of SI. The detectable level of IL-6 was an independent predictor of fatal ACLF development.

Conclusions: Cirrhotic patients with hyperdynamic and hypodynamic circulation have a higher risk of fatal ACLF. Therefore, the cardiodynamic state is strongly associated with SI, which is an independent predictor of development of fatal ACLF.

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALT, alanine transaminase; BSA, body surface area; CI, cardiac index; CLIF-C, European Foundation for the study of chronic liver failure consortium; CO, cardiac output; CRP, C-reactive protein; CSPH, clinically significant portal hypertension; Hb, haemoglobin; HR, heart rate; HVPG, hepatic venous pressure gradient; IL, interleukin; ILs, interleukins; MAP, mean arterial pressure; MELD, model of end-stage liver disease; NSBB, non-selective beta blockers; p, p-value; PC, principal component; RAP, right atrial pressure; ROC, Receiver Operating Characteristic; SI, systemic inflammation; sIL-33R, soluble interleukin-33 receptor; SVR, systemic vascular resistances; SVRI, systemic vascular resistance index.

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Funding information
The authors received funding by the European Union's Horizon 2020 research and innovation program's GALAXY study (No. 668031), LIVERHOPE (No. 731875), MICROB-PREDICT (No. 825694), and the Cellex Foundation and the Ernst und Berta Grimmke Foundation (Lfd.Nr5/19). The funders had no influence on study design, data collection and analysis, decision to publish or preparation of the manuscript.

Handling Editor: Virginia Hernandez-Gea

KEYWORDS
acute-on-chronic liver failure, circulation, cirrhosis, hemodynamic, inflammation

1 | INTRODUCTION

In the natural history of cirrhosis, acute decompensations (AD) are frequent and often lead to development of acute-on-chronic liver failure (ACLF),[1,2] a syndrome characterized by organ failure and high short-term mortality.[2,3] The pathophysiological pathways leading to this syndrome are only partly understood but systemic inflammation (SI) seems to play a crucial role.[4] SI can occur in the setting of chronic inflammation via translocated proinflammatory signals from the intestinal lumen to the systemic circulation.[5-8] A full-blown burst of proinflammatory mediators has been found in patients with ACLF.[9] Portal hypertension is a prerequisite for AD and can be quantified by measurement of the hepatic venous pressure gradient (HVPG).[10,11]

In patients with clinically significant portal hypertension (CSPH), SI measured by C-reactive protein (CRP) and hypodynamic [defined by cardiac index (CI) <3.2 L/min/m^2] and hyperdynamic (defined by CI >4.2 L/min/m^2) cardiodynamic states have been independently associated with an increased risk of first ascites development and mortality.[12] In addition, SI as assessed by IL-6 and IL-8 plays a crucial role in AD.[4,9] In outpatients with cirrhosis, arterial hypotension, as an element of cardiocirculatory dysfunction, has also been identified as an independent risk factor for ACLF development.[13]

To date, neither the interplay between cardiodynamic states or markers of SI, other than CRP, nor their relation with ACLF development have been studied.[14]

The aim of this study was therefore to evaluate the risk of fatal ACLF development in different cardiodynamic states and their association with SI. We hypothesize that a hypo- as well a hyperdynamic circulatory state represents a risk factor for the development of ACLF.

Key points

- Acute-on-chronic liver failure (ACLF) is suggested to be associated with systemic inflammation (SI).
- The impact of systemic circulation (cardiodynamic state) and SI on ACLF development is not fully elucidated.
- This study shows that cirrhotic patients with hyperdynamic and hypodynamic circulatory state have a higher risk of fatal ACLF.
- Hyperdynamic state is strongly associated with SI, which independently predicts fatal ACLF development.

2 | PATIENTS AND METHODS

2.1 | Patients and data collection

In this retrospective analysis of a prospectively observed patient cohort from a single centre study, 224 outpatients with cirrhosis were referred to the Department of Clinical Physiology and Gastro Unit Hvidovre Hospital, Denmark, between 2002 and 2016 for per protocol hemodynamic assessment. Inclusion criteria were as follows: age above 18 years; diagnosis of cirrhosis based on histological findings or clinical, biochemical, ultrasonographic and/or endoscopic findings; and hemodynamic evaluation including HVPG and cardiac output (CO). Exclusion criteria were as follows: age under 18 years; variceal bleeding, refractory ascites, hepatorenal syndrome, bacterial infection, at time of inclusion and malignancy. Cardiovascular disease was ruled out. Fulfilment of ACLF criteria was not evaluated at

inclusion and records of non-fatal ACLF were therefore not primarily recorded.[3]

Blood samples were collected at the time of the enrolment and patients were followed until October 2017. Primary endpoint was fatal ACLF defined as ACLF leading to death. The ACLF definition according to the CLIF consortium was established in 2013 and the ACLF diagnosis was therefore established retrospectively.[3] Causes of death that were recorded as liver failure, sepsis and multiorgan failure were classified as fatal ACLF. Non-specified shock, cardiovascular disease, malignancy and unknown causes were classified as non-ACLF deaths.

Biochemical blood analyses were performed using standard tests.

Written informed consent was obtained from included patients; the study was approved by the local ethics committee and Data Protection Agency (J-No.2008-41-2020 and HVH-2011-02).

2.2 | Assessment of circulating levels of biomarkers

After collection, blood samples were centrifuged at 4°C and serum samples were stored at −80°C. Serum concentrations of interleukins (ILs) IL-6, IL-8 and the soluble IL-33 receptor (sIL-33R) were assessed. The analyses were performed with DuoSet® Elisa kits (R&D Systems) according to the manufacturer's instructions (Table S1), at the Department of Internal Medicine I, Bonn, Germany. The ILs and sIL-33R levels were quantified in undiluted serum samples. On all ELISA plates, two patient serum samples were used as controls accessing variability within plates. CRP as a common marker of SI was not part of the routine analysis in this study.

Undetectable levels were assigned a value equal to lower limit of detection,[4,15] whereas for values higher than the upper limit of detection concentrations were extrapolated using GraphPad Prism version 5.00 (GraphPad Prism Software) according to the plotted standard curve.

2.3 | Assessment of hemodynamic parameters

All patients underwent a hemodynamic investigation in the morning after an overnight fast and at least 1-hour rest in the supine position under local analgesia. None of the patients received diuretics or beta blockers in the 24 hours preceding investigations.

Catheterization of the hepatic veins and right atrium was performed as previously described.[16] A Swan-Ganz catheter, size 7F, was guided to the hepatic veins and right atrium via the femoral route under fluoroscopy control. Pressures were measured by a capacitance transducer (Simonsen & Weel, Copenhagen, Denmark) in the wedged and free hepatic vein position in at least three different vessels, the midaxillary line being zero pressure level. Mean values of repetitive measurements were used. HVPG was determined as wedged minus free hepatic venous pressure. Right atrial pressure (RAP) was measured directly.

A small indwelling polyethylene catheter was placed in the femoral artery by the Seldinger technique and advanced to the aortic bifurcation, and the systolic, diastolic and mean arterial (MAP) blood pressures were measured directly. All the pressures were expressed in millimetres of mercury.

Cardiac output (expressed in L/min) was measured by the indicator dilution technique after a bolus injection of 150 kBq of ^{125}I-labeled human serum albumin (IFE IT. 205, Institute of Energy Technique) into the right atrium, followed by arterial sampling. CI was calculated as CO/body surface area (BSA) and expressed in L/min/m^2.

Systemic vascular resistance [SVR = ((MAP − RAP)/CO) × 80; expressed in dynes·s/cm^{-5}], and systemic vascular resistance index [SVRI = ((MAP − RAP)/CI) × 80; expressed in dynes·s/cm^{-5}/m^2] were also calculated. Heart rate was determined by electrocardiography.

2.4 | Statistical analysis

Data are presented as median and ranges or absolute frequency and percentage, if not otherwise specified.

Mann-Whitney, Kruskal-Wallis and Chi-square tests were used for unpaired comparisons. Receiver operating characteristic (ROC) analysis was used to calculate cut-off values. Kaplan-Meier curves and log-rank tests were used to analyse rates of fatal ACLF development and all-cause mortality. Spearman's correlation was used to evaluate the relationship between inflammatory markers and hemodynamic parameters. Univariate Cox regression was used to identify predictors of ACLF. Parameters with a P value < .05 (P-in) and P-out value of .1 entered the multivariate, forward step-wise regression model. To avoid multicollinearity in multivariate regression, model of end-stage liver disease (MELD) and European Foundation for the study of chronic liver failure consortium (CLIF-C AD) scores and their included variables, main systemic hemodynamic parameters and their dependent parameters (such as the calculated systemic vascular resistance) were included separately. Principal components analysis was performed to reduce number of variables that influence regression analysis. In principal component analysis, linear combinations of all available variables were created. Patients were then plotted according to the created principal components.

The significance level for all tests was set at P-value < .05. Statistical analyses were performed using SPSS V25 (IBM SPSS Statistics for Macintosh, Version 25.0: IBM Corp). Principal components analysis was performed using R (R core team, Version 3.6.0).

3 | RESULTS

3.1 | General characteristics of patients

In total, 208 patients (73% male, 77% alcoholic cirrhosis and median age 60 years) were included in the final analyses (Table 1). Median Child-Pugh, MELD and CLIF-C AD scores were 7, 11 and 50 points. At inclusion, none of the patients with alcoholic cirrhosis had acute alcoholic liver injury according to NIAAA criteria (at least 3 of the following: active alcoholism of 6 months >40 g/d for female or >60 g/d for male, bilirubin >3 mg/dL, AST >50IE, AST/alanine transaminase (ALT)

TABLE 1 General characteristics of all patients and stratified by cardiodynamic state

	Parameter median (range) or absolute (%)	All patients (n = 208)	Hypodynamic CI <3.2 (n = 84)	Normodynamic CI 3.2-4.2 (n = 69)	Hyperdynamic CI >4.2 (n = 55)
General Condition	Age [years]	60 (31-81)***	62 (34-81)§	60 (31-75)	57 (35-74)$^{\#\#\#}$
	Gender [male/female]	151 (73)/57 (27)	64 (76)/20 (24)	51 (74)/18 (26)	36 (64)/19 (35)
	Aetiology of cirrhosis [alcohol/viral/other]	171 (77)/21 (10)/26 (13)	63 (75)/7 (8)/14 (17)	52 (75)/12 (18)/5 (7)	46 (84)/2 (4)/7 (13)
	BMI [kg/m^2]	25 (13-45)	25 (13-45)	25 (16-37)	26 (16-41)
	All Beta blockers	47 (23)	23 (27)	14 (20)	10 (18)
	Non-selective Beta blockers	39 (19)	18 (21)	13 (19)	8 (15)
	Diuretics	118 (57)	48 (57)	34 (49)	36 (65)
Baseline Scores	MELD$^{\Delta}$	11 (6-25)***	10 (6-20)	10 (6-21)¶¶¶	12 (6-25)$^{\#\#\#}$
	Child-Pugh [A/B/C]	76 (37)/61 (29)/71 (34)	28 (33)/27 (32)/29 (35)	29 (42)/21 (30)/19 (28)	19 (35)/13 (24)/23 (42)
	Child-Pugh	7 (5-12)	7 (5-12)	6 (5-11)	7 (5-12)
	CLIF-C AD$^{¥}$	50 (33-67)	49 (38-67)	50 (34-66)	50 (33-64)
Baseline Laboratory	Hb [g/dL]	12.2 (6.8-16.9)**	12.6 (7.6-16.9)	12.4 (6.8-16.3)¶¶	11.3 (6.9-14.7)$^{\#\#}$**
	WBC [G/L]$^{¥}$	7.0 (1.8-23.3)	6.7 (2.4-17.5)	7.0 (1.8-23.3)	7.3 (2.0-21.9)
	Platelets [G/L]†	145 (29-647)	154 (29-647)	145 (39-495)	132 (47-448)
	Sodium [mmol/L]	137 (114-145)	137 (114-143)	137 (125-145)	137 (117-145)
	Creatinine [mg/dL]	0.9 (0.4-2.7)	0.9 (0.5-2.2)	0.8 (0.4-1.8)	0.8 (0.4-2.7)
	Bilirubin [mg/dL]$^{\Delta}$	1.0 (0.1-12.7)***	0.8 (0.1-6.4)	0.8 (0.2-6.4)¶¶¶	1.4 (0.4-12.7)$^{\#\#\#}$
	ALT [U/L]$^{\Delta}$	31 (7-41)	32 (7-104)	29 (8-240)	31 (13-136)
	Albumin [g/L]$^{\Delta}$	31 (15-45)***	33 (17-44)	33 (18-45)¶¶¶	29 (15-40)$^{\#\#}$
	INR	1.3 (1.0-2.6)***	1.3 (1.0-2.6)	1.3 (1.0-2.5)¶¶	1.5 (1.0-2.2)$^{\#\#\#}$
Hemodynamics	MAP [mmHg]	90 (57-146)**	89 (57-130)§§	97 (71-122)¶¶	88 (64-146)
	HR [/min]	74 (47-117)***	69.5 (47-101)	72 (51-103)¶¶¶	80 (51-117)$^{\#\#\#}$
	HVPG [mmHg]	16 (6-33)***	15 (6-26)	15 (6-33)¶¶¶	18 (8-26)$^{\#\#\#}$
	CO [L/min]	6.5 (2.9-12.3)***	5.1 (2.9-7.5)§§§	7.1 (5.0-9.3)¶¶¶	9.0 (6.3-12.3)$^{\#\#\#}$
	CI [L/min/m^2]	3.4 (1.6-6.3)***	2.7 (1.6-3.1)§§§	3.5 (3.2-4.2)¶¶¶	4.7 (4.3-6.3)$^{\#\#\#}$
	SVR [dynes·s·cm^{-5}]$^{\Omega}$	1048 (444-2658)***	1334 (865-2658)§§§	1033 (720-1657)¶¶¶	706 (444-1349)$^{\#\#\#}$
	SVRI [dynes·s/cm^{-5}/m^2]	2020 (911-4715)***	2500 (1598-4715)§§§	2018 (1408-2727)¶¶¶	1338 (911-2639)$^{\#\#\#}$
Baseline Clinical	Ascites [no/grade 1/2/3]	101 (49)/41 (20)/36 (17)/30 (14)***	42 (50)/17 (20)/9 (10)/16 (19)	44 (64)/8 (12)/12 (17)/5 (7)¶¶¶	15 (27)/16 (27)/15 (27)/9 (16)$^{\#\#}$
	Oesophageal Varices [no—grade I/grade II-III]	159 (76)/49 (24)	68 (81)/16 (19)	51 (74)/18 (26)	40 (73)/15 (27)
Outcome	Mortality 1-year/overall	35 (17)**/82 (39)	11 (13)/32 (38)	7 (10)¶¶/22 (32)¶	17 (31)$^{\#}$/28 (51)
	Fatal ACLF development 1-year/overall	20 (10)**/50 (24)*	7 (8)/21 (25)	2 (3)¶¶/10 (14)¶¶	11 (20)$^{\#}$/19 (35)
	Time to ACLF development [months]	17 (0-137)	18 (0-92)	26 (1-88)	10 (0-137)
	Follow-Up time [years]	3 (0-15)	3 (0-11)	3 (0-15)¶¶	2 (0-14)$^{\#*}$

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALT, alanine transaminase; AP, alkaline phosphatase; BMI, body mass index; CI, cardiac index; CLIF-C, European Foundation for the study of chronic liver failure consortium; CO, cardiac output; Hb, haemoglobin; HR, heart rate; HVPG, hepatic venous pressure gradient; IL, interleukin; INR, international normalized ratio; MAP, mean arterial pressure; MELD, Model for end-stage liver disease; sIL-33R, soluble interleukin-33 receptor; SVR, systemic vascular resistances; WBC, white blood cells. Data are expressed as median (range) or absolute frequency (percentage).

$^{\Delta}$Data available in 205 patients, †Data available in 204 patients, $^{\Omega}$Data available in 200 patients, $^{¥}$Data available in 191 patients.

***P < .001, **P < .01, *P < .05, comparison of all three groups.

$^{\S\S\S}P$ < .001, $^{\S\S}P$ < .01, $^{\S}P$ < .05, for Hypodynamic vs Normodynamic.

$^{\P\P\P}P$ < .001, $^{\P\P}P$ < .01, $^{\P}P$ < .05, for Normodynamic vs Hyperdynamic.

$^{\#\#\#}P$ < .001, $^{\#\#}P$ < .01, $^{\#}P$ < .05, for Hypodynamic vs Hyperdynamic.

>1.4, AST or ALT >400 IE). Patients with viral hepatitis were untreated at inclusion.

Regarding comorbidities 44 patients (21%) were diabetic and 115 (55%) had arterial hypertension. Overweight and obesity were found in 69 (33%) and 38 (18%) patients respectively.

The median MAP was 90 mmHg (57-146), HVPG was 16 mmHg (6-33), CI was 3.4 L/min/m^2 (1.6-6.3) and median systemic vascular resistance index (SVRI) was 2020 dynes·s·cm^{-5}·m^2 (911-4715).

At inclusion, no patient had ACLF. Eighty-two patients died (39%) and 50 (24%) developed fatal ACLF. Median time to all-cause mortality was 18 months (0-137) and fatal ACLF was 17 months (0-137). None of the patients underwent liver transplantation or transjugular intrahepatic portosystemic shunt placement.

Plasma levels of IL-6, IL-8 and sIL-33R were detectable in 66 (32%), 74 (36%) and 208 (100%) patients as shown in Table 2. There was no significant difference in the levels of IL-6, IL-8 and sIL-33R between the time eras (2002-2011 vs 2012-2016), suggesting stability of the measured cytokines in the blood samples stored over the years of the study (Table S2).

3.2 | Characteristics of patients stratified by cardiodynamic state

Based on cut-offs of CI as previously applied,[12] 84 (40%) patients showed hypodynamic (<3.2 L/min/m^2), 69 (33%) patients normodynamic (3.2-4.2 L/min/m^2) and 55 patients (27%) hyperdynamic (>4.2 L/min/m^2) cardiodynamic state (Table 1).

Hypodynamic patients were significantly older compared with hyperdynamic patients. In comparison with hypo- and normodynamic patients, the hyperdynamic patients had significantly higher MELD, as well as lower blood haemoglobin (Hb) and lower plasma albumin concentrations and higher rate of ascites.

In total, 39 patients (19%) were treated with non-selective beta blockers (NSBB) and 8 patients (4%) received other beta blockers. The proportion of patients treated with NSBB was highest in the hypodynamic group (n = 18, 21%) and lowest in the hyperdynamic group (n = 8, 15%). There was no significant difference between the three cardiodynamic groups with respect to NSBB treatment.

The hypo- and hyperdynamic patients had similar level of arterial blood pressure, but MAP was lower than in the normodynamic patients. The SVRI was normal in 33%, 39% and 0% in hypodynamic, normodynamic and hyperdynamic patients. Hyperdynamic patients had higher HVPG (median 18 mmHg), than the remaining patients (median 15 mmHg).

ACLF was the cause of death in 68%, 66% and 45% of hyperdynamic, hypodynamic and normodynamic patients respectively (Table 3). The cumulative probability of fatal ACLF in the three groups was 35%, 25% and 14% (P = .006, Figure 1A). After 1 year, the numbers were 20%, 8% and 3% (P < .01) respectively. The all-cause mortality at the end of follow-up and after 1 year was also higher in the hyperdynamic group and lowest in the normodynamic group (Figure 1B, Table 1).

Most common known trigger of fatal ACLF was infection in 20%. There were no differences between ACLF triggers within cardiodynamic groups but a trend showing higher rates of infection-triggered ACLF in patients with hyperdynamic circulation (Table S3).

In other settings, normodynamic circulation has been defined as CI of 2.5-4.2 L/min/m^2.[17] We therefore stratified our patients

TABLE 2 Levels of inflammatory cytokines of all patients and stratified by cardiodynamic state

	Parameter		All patients n = 208	Hypodynamic CI <3.2 n = 84	Normodynamic CI 3.2-4.2 n = 69	Hyperdynamic CI >4.2 n = 55
Biomarkers	IL-6	[undetectable/ detectable]	142 (68)/66 (32)*	60 (71)/24 (29)	52 (75)/17 (25)¶	30 (55)/25 (45)#
		[pg/mL]	9.4 (9.4-1248.2)	9.4 (9.4-645.8)	9.4 (9.4-1248.2)¶	9.4 (9.4-890.5)
		[pg/mL] detectable	48.7 (10.2-1248.2)	44.5 (10.2-645.8)	63.5 (11.0-1248.2)	32.3 (11.0-890.5)
	IL-8	[undetectable/ detectable]	134 (64)/74 (36)*	58 (59)/26 (31)	49 (71)/20 (29)¶	27 (49)/28 (51)#
		[pg/mL]	31.2 (31.2-1464.4)*	31.2 (31.2-1464.4)	31.2 (31.2-880.3)¶¶	33.2 (31.2-926.6)#
		[pg/mL] detectable	79.8 (32.4-1464.4)	114.4 (32.6-1464.4)	61.6 (32.4-880.3)	76.4 (33.3-926.6)
	sIL-33R	[<7380.2/≥7380.2]Ψ	85 (41)/121 (59)*	38 (45)/46 (55)	33 (49)/35 (51)¶	14 (30)/40 (74)#
		[pg/mL]Ψ	15 917.2 (1430.6-15917.2)	15 917.2 (1430.6-15917.2)	7967.6 (2528.7-15917.2)¶	15 917.2 (1506.0-15917.2)

Abbreviations: IL, interleukin; sIL-33R, soluble interleukin-33 receptor.

ΨData available in 206 patients.

*P < .05, comparison of all three groups.

¶¶P < .01, ¶P < .05, for Normodynamic vs Hyperdynamic.

##P < .01, #P < .05, for Hypodynamic vs Hyperdynamic.

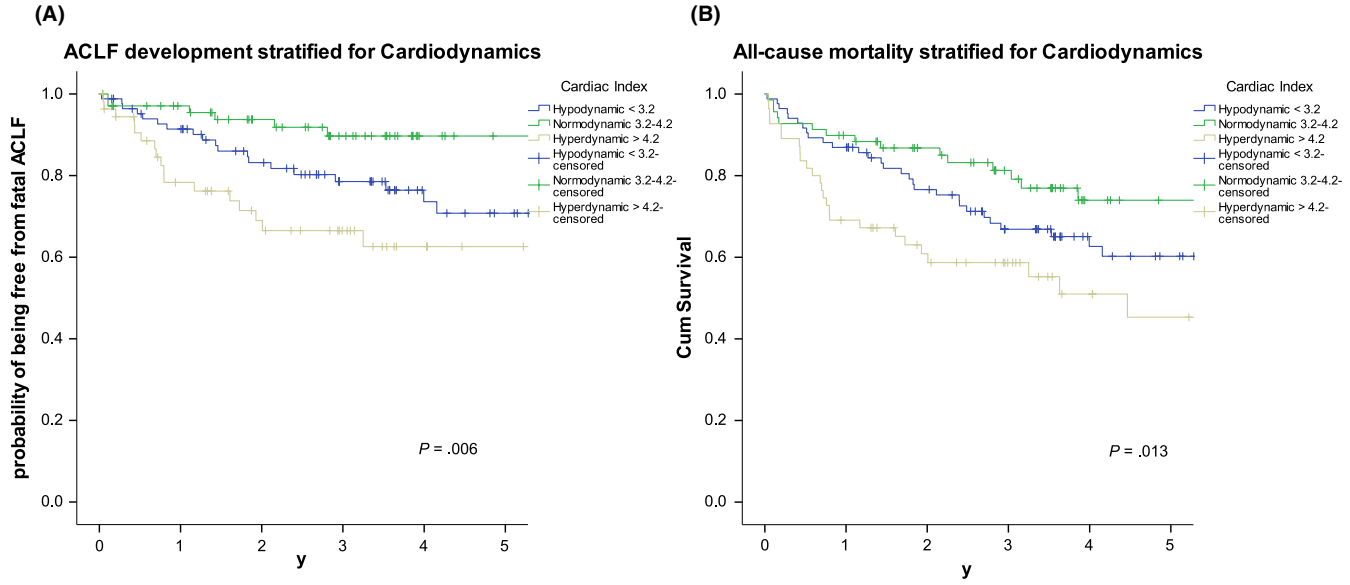

FIGURE 1 A, Kaplan-Meier survival curve with log rank test for development of fatal acute-on-chronic liver failure (ACLF) stratified by cardiodynamic state (hypodynamic <3.2 L/min/m^2 (blue line), normodynamic 3.2-4.2 L/min/m^2 (green line) and hyperdynamic >4.2 L/min/m^2 (yellow line)). B, Kaplan-Meier survival curve with log rank test for all-cause mortality stratified by cardiodynamic state (hypodynamic <3.2 L/min/m^2 (blue line), normodynamic 3.2-4.2 L/min/m^2 (green line) and hyperdynamic >4.2 L/min/m^2 (yellow line)). CI, cardiac index

according to those cut-offs as well. Kaplan-Meier plot for fatal ACLF development that hypodynamic circulation shows similar results with even worse outcome for patients with hypodynamic circulation. Normodynamic patients had the lowest while hyperdynamic patients the highest rate of fatal ACLF development (Figure S1).

3.3 | Inflammatory markers in different cardiodynamic states

In the assessment of the SI,[18-21] patients were divided into those with detectable and undetectable levels of IL-6 and IL-8 (Figure 2A,B). Among those with detectable levels, the IL-6 was 48.7 (10.2-1248.2) and IL-8 was 79.8 (32.4-1464.4) pg/mL (Table 2). The hyperdynamic group showed the highest rate of detection of inflammatory biomarkers, but no difference in detection rate was seen between the hypo- and normodynamic groups (Table 2). Similar results were obtained, when the patients were stratified for the 2.5-4.2 L/min/m^2 cut-offs (Table S4). sIL-33R levels were detectable in all patients 15 917.2 pg/ml (1430.6-15917.2). A cut-off of 7380.2 pg/ml was chosen based on the ROC analysis (Figure 2C). Across all cardiodynamic states patients, with ascites showed higher rates of detectable SI markers compared with patients without ascites (Figure 2D).

Looking at the concentrations of the inflammatory markers, in the hyperdynamic patients, levels of IL-8 and sIL-33R were higher compared with normodynamic patients, but the difference was not statistically significant. In hyperdynamic patients, levels of IL-8 were significantly higher compared with hypodynamic patients (Table 2).

IL-6, IL-8 and sIL-33R showed highly significant correlation with HVPG, whereas IL-8 was significantly correlated with CO. Inversely, SVR and MAP showed a negative correlation with IL-6 and IL-8 and sIL-33R respectively (Figure 2E).

To minimize confounding factors, we performed a principal component analysis and created linear combinations of all available variables for the presence of hypo- and hyperdynamic states. Inflammatory cytokines IL-6 and IL-8 transformed into principal component 1 (PC1 in Figure 2F). Hemodynamic parameters CO and SVR transformed with Hb into principal component 2 (PC2 in Figure 2F). Plotting of patients clearly showed that hyperdynamic patients cluster with each other as well as hypodynamic patients. The clusters are separated mostly on the axis representing the principal component 1 (x-axis). These results suggest a main contribution of inflammatory cytokines to distinguish between hypo- and hyperdynamic patients. By definition, hypo- and hyperdynamic patients are distinguished on the axis of principal component 2, which is consists of cardiodynamic parameters (CO and SVR) (Figure 2F).

3.4 | SI predicts development of fatal ACLF

Among the univariate analyses, predictors of fatal ACLF included age, MELD, Child-Pugh and CLIF-C AD scores, Hb, bilirubin, albumin, MAP, hyperdynamic state, SVRI, HVPG ≥16 mmHg (median), ascites, sIL-33R and IL-6 (Table 4). Owing to relatively long inclusion period we analysed time effects on survival, but time era of inclusion (2002-2011 vs 2012-2016) was not a significant predictor. Multivariate analysis including all significant factors from univariate analysis identified age, low albumin and detectable IL-6 as independent predictors of fatal ACLF. NSBB therapy was not significant in either analysis.

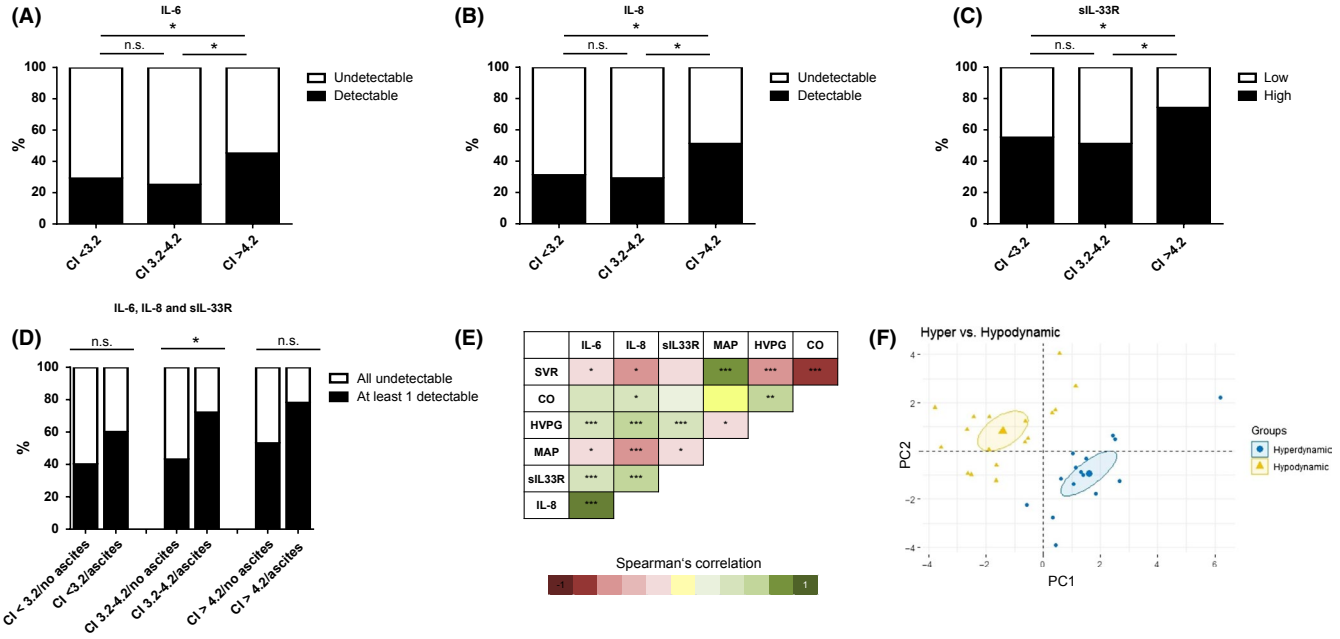

FIGURE 2 A, Percentage of patients with detectable (black fraction, lower limit detection of ELISA kit (9.38 pg/mL)) and undetectable (white fraction) levels of interleukin-6 stratified for cardiodynamic state (hypodynamic <3.2 L/min/m^2 (left column), normodynamic 3.2-4.2 L/min/m^2 (centre column) and hyperdynamic >4.2 L/min/m^2 (right column)). Highest fraction of detectable levels of interleukine-6 is found in hyperdynamic patients (right column). B, Percentage of patients with detectable (black fraction, lower limit detection of ELISA kit (31.2 pg/mL)) and undetectable (white fraction) levels of interleukin-8 stratified for cardiodynamic state (hypodynamic <3.2 L/min/m^2 (left column), normodynamic 3.2-4.2 L/min/m^2 (centre column) and hyperdynamic >4.2 L/min/m^2 (right column)). Highest fraction of detectable levels of interleukine-8 is found in hyperdynamic patients (right column). C, Percentage of patients with high (black fraction, >7380.2 pg/mL) and low (white fraction) levels of soluble IL-33 receptor—sIL-33R—stratified for cardiodynamic state (hypodynamic <3.2 L/min/m^2 (left column), normodynamic 3.2-4.2 L/min/m^2 (centre column) and hyperdynamic >4.2 L/min/m^2 (right column)). Highest fraction of high levels of soluble IL-33 receptor—sIL-33R—is found in hyperdynamic patients (right column). D, Percentage of patients with at least one detectable/high levels (black fraction) and undetectable/low (white fraction) levels of interleukine-6, -8 or soluble IL-33 receptor—sIL-33R—stratified for cardiodynamic state (hypodynamic <3.2 L/min/m^2 (left column), normodynamic 3.2-4.2 L/min/m^2 (centre column) and hyperdynamic >4.2 L/min/m^2 (right column)). Highest fraction of detectable/high levels of interleukine-6, -8 or soluble IL-33 receptor—sIL-33R—is found in hyperdynamic patients (right column). E, Spearman's correlation of inflammatory markers interleukine-6, -8 and soluble IL-33 receptor—sIL-33R—with hemodynamic parameters systemic vascular resistance (SVR), mean arterial pressure (MAP) and hepatic venous pressure gradient (HVPG). Correlation coefficient is colour coded (dark red—1, dark green—1). F, Plotting of patients and clustering according to principal components (PC) 1 and 2. Hypodynamic patients are coded in yellow and hyperdynamic patients are coded in blue. PC1 main variables: IL-6 and IL-8; PC2 main variables: CO, SVR and haemoglobin

4 | DISCUSSION

The main findings of our study are that in patients with cirrhosis the prevalence of fatal ACLF is high, significantly relating to all-cause mortality in hypo- and hyperdynamic states. The findings support the previous study by Turco et al showing that the cardiodynamic state is associated with the development of ascites and death. Moreover, the risk of developing of fatal ACLF seems related to both the type of cardiodynamic state and degree of SI.[12]

We found a strong circuital correlation among plasma ILs, HVPG and CO. Moreover, we showed that patients with a CI >4.2 L/min/m^2 had significantly higher rate of detectable circulating IL-6/-8 in comparison to patients with lower CI at baseline. This adds further granularity to previous findings that extreme cardiodynamic states and SI as determined by circulating CRP are independent predictors of outcomes in compensated patients and in those with ascites.[12] Indeed, CRP did not capture the differences in the degree of SI among cardiodynamic states.[12] This underlines the need for more specific markers of SI in this setting. Detectable levels of IL-6, which has been selected as an independent predictor of fatal ACLF development in our cohort, may be an appropriate candidate for such a purpose.

The interrelation between degree of portal hypertension and CO has been pivotal in the classical vasodilation hypothesis of portal hypertension in cirrhosis.[5-8] Moreover, this pathophysiological view represents the rational basis for the use of NSBB in the treatment and prevention of portal hypertensive complications.[22-24] Nevertheless, considering that CI >4.2 L/min/m^2 is found almost only in patients with CSPH, it is tempting to hypothesize that inflammation may be a main pathogenetic driver of disease progression in hyperdynamic cirrhotic patients.[25-29] As this study demonstrates the relationship between SI and cardiodynamic state, it points to the need of a better stratification of patients at risk for development of ACLF and delineation of potential therapeutic targets.

TABLE 3 Detailed cause mortality in different Hemodynamic states

Cause of death n (%)	All patients n = 82	Hypodynamic CI <3.2 n = 32	Normodynamic CI 3.2-4.2 n = 22	Hyperdynamic CI >4.2 n = 28
ACLF	50 (61)	21 (66)	10 (45)	19 (68)
HCC	5 (6)	2 (6)	2 (9)	1 (4)
Other cancer	5 (6)	2 (6)	2 (9)	1 (4)
Bleeding/shock	6 (7)	3 (9)	1 (5)	2 (7)
Cardiovascular disease	4 (5)	0 (0)	2 (9)	2 (7)
Unknown/ other	12 (15)	4 (13)	5 (23)	3 (11)

Abbreviations: ACLF, acute-on-chronic liver failure; HCC, hepatocellular carcinoma.

TABLE 4 Uni- and Multivariate Cox regression for fatal ACLF development

	Univariate Cox Regression			Multivariate Cox Regression		
Parameter	*p*	Hazard Ratio	95%-Confidence Interval	*p*	Hazard Ratio	95%-Confidence Interval
Age	.010	1.257	1.057-1.494	.024	1.044	1.006-1.083
Era (cat)	.211					
NSBB	.519					
Child-Pugh	.011	1.179	1.039-1.337			
MELD	.004	1.104	1.032-1.181			
CLIF-C AD	.000	1.096	1.049-1.145			
Hb	.013	0.835	0.725-0.962			
Bilirubin	.026	1.201	1.022-1.411			
Albumin	.000	0.903	0.860-0.948	.001	0.907	0.857-0.961
INR	.050	2.293	1.001-5.255			
MAP	.023	0.975	0.954-0.996			
CI	.157					
Hypodynamic (cat)	.845					
Hyperdynamic (cat)	.017	2.014	1.135-3.576			
HVPG ≥ 16 (cat)	.005	2.484	1.320-4.677			
SVRI	.028	0.999	0.999-1.000			
IL-6 (cat)	.000	3.093	1.768-5.411	.006	2.428	1.295-4.553
IL-8 (cat)	.090					
sIL-33R (cat)	.011	2.336	1.217-4.484			
Ascites (cat)	.002	2.727	1.462-5.088			

Note: Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; AP, alkaline phosphatase; cat, categorical; CI, cardiac index; CLIF-C, European Foundation for the study of chronic liver failure consortium; Hb, haemoglobin; HVPG, hepatic venous pressure gradient; IL, interleukin; INR, international normalized ratio; MELD, Model for end-stage liver disease; NSBB, non-selective beta blockers; sIL-33R, soluble interleukin-33 receptor; SVRI, systemic vascular resistance index.

Categorical variables: Era (2002-2011 vs 2012-2016), Ascites: present clinically or detected by ultrasound, IL-6: equal or above lower limit of detection (9.38 pg/mL), IL-8: equal or above lower limit of detection (31.2 pg/mL), sIL-33R: level ≥7380.2 pg/mL; hyperdynamic and hypodynamic with normodynamic as reference.

Italic—included in the multivariate model, following variable were not included Child-Pugh and CLIF-C AD score (multicollinearity with MELD) and MAP (multicollinearity with hyperdynamic circulation).

It has been shown that patients with decompensated cirrhosis are those with the most pronounced circulatory dysfunction (hyperdynamic/hypodynamic circulation).[30] At the same time, patients with decompensated cirrhosis are at higher risk of developing further AD and ACLF. Importantly, neither hyperdynamic circulation nor decompensated state (AD with previous ascites) was independent predictors of fatal ACLF development in our cohort, whereas SI (measured by IL-6) was. This suggests SI as an additional crucial risk factor for fatal ACLF development despite the association with decompensated states and hyperdynamic cardiodynamic states of cirrhosis.

However, patients with ascites had higher rates of detectable SI markers compared with patients without ascites, especially significant in the normodynamic group. This finding adds to recent studies that showed levels of SI markers in compensated cirrhosis were moderately altered compared with healthy controls and markedly increased in decompensated cirrhosis without ACLF.[9] Moreover, our data are supported by recent studies showing that CRP levels progressively increase from compensated to decompensated patients.[12,26] The cause-effect relationship between AD and SI remains unclear but current data suggest that SI is a prerequisite for development of the decompensated state and further progression to ACLF. However, in the presence of a similar activation of SI, patients with a hypodynamic circulatory state may face a higher risk of developing ACLF than those patients with a normodynamic circulation. These data outline the need of further exploration of the complex circuital interaction of hepatic and cardiac hemodynamics and inflammation in determining organ damage, AD and fatal ACLF in patients with hypodynamic features.

Hemodynamic assessments and cytokine levels represent a snapshot of the patients' current status. However, by definition, CI at rest in supine position is supposed to be stable in not acutely altered patients. Transitory conditions such as sepsis have been excluded at the time of catheterization. Favourably, future studies should perform repeated cardiodynamic assessments in case of availability of experimental treatments targeting the heart function or SI.

However, in clinical routine invasive hemodynamic assessment is resource intense. Among non-invasive methods, finometer is available for evaluation of CO. Moreover, echocardiography is widely available. Especially, more sophisticated techniques, such as speckle tracking echocardiography (STE), were shown to be able to predict ACLF development in patients with TIPS.[31,32] STE therefore seems to be a promising tool for non-invasive assessment of cardiodynamics and its impact on ACLF development should be investigated in future studies.

Interestingly, IL-6 was detectable in only 32% of patients in our cohort. A recent study by Clària et al comparing cytokine levels in healthy subjects, cirrhotic inpatients without ACLF and cirrhotic inpatients with ACLF showed lower rates of undetectable levels in both cirrhotic cohorts (eg IL-6 without ACLF 7.4%, with ACLF 0.8%), while showing high rates of undetectable levels in the healthy cohort (eg IL-6 healthy 87.5%).[4] Of note, the cirrhotic inpatients without ACLF had a much higher mean MELD of 17 compared with our outpatient cohort (median MELD 11). In our cohort of cirrhotic outpatients, we found undetectable rates of IL-6 of 55%-71% depending on cardiodynamic state. These detection rates fall right between the healthy group and cirrhotic inpatients of Clària et al suggesting an association of cytokine detection rates with progression of liver disease. The detection rates in our cohort therefore seem expected and reasonable. Moreover, this simple and natural cut-off (detectable vs undetectable) would allow for semi-quantitative testing to identify patients at risk.

Our study has several limitations. First, no data on cardiovascular diseases and cirrhotic cardiomyopathy were available. In addition, no data on alcohol consumption in follow-up, episodes of AD and non-fatal ACLF were collected and no data of trigger and degree of ACLF were available, which is a major limitation. Finally, even though NSBB were paused 24 hours before hemodynamic evaluation, it might not be completely eliminated at time of evaluation. Therefore, we cannot determine the hemodynamic state of those patients without any NSBB effect. Likewise, it is equally possible that NSBB have a detrimental effect in some and a protective one in other patients in terms of fatal ACLF development. It is likely that some patients originally hyper- or normodynamic have been classified as hypodynamic after introducing NSBB. Patients who were already hypodynamic are unlikely to be "good cardiac responders" to NSBB. Patients sensitive to NSBB would develop severe hypotension and/or intolerance to incremental dosages. Patients insensitive to NSBB might have impaired cardiosystemic response to stress either way.

5 | CONCLUSION

This study shows that in patients with cirrhosis the risk of developing fatal ACLF is independently associated with the degree of SI, which is associated with cardiodynamic state. Accordingly, further stratification may help in the identification of novel therapeutic targets.

ACKNOWLEDGEMENTS

We thank Gudrun Hack for his excellent technical assistance and Sabine Dentler for critical reading.

CONFLICT OF INTEREST

No conflict of interest exists.

AUTHOR CONTRIBUTIONS

MP, SM: acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis. JG, NK, JLM, MPW, PW, MB, LT, RS, JC, SK, FEU, CW, RM, FS, FB, SM: acquisition of data, analysis and interpretation of data, critical revision of the manuscript regarding important intellectual content, funding recipient. LLG, SM, JT: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript regarding important intellectual content, funding recipient, administrative, technical and material support, study supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Praktiknjo M, Monteiro S, Grandt J, et al. Cardiodynamic state is associated with systemic inflammation and fatal acute-on-chronic liver failure. *Liver Int*. 2020;40:1457–1466. https://doi.org/10.1111/liv.14433

3. Diskussion

In dieser Arbeit wurden bei Patienten mit Leberzirrhose aus medizinisch angezeigten Untersuchungen wie Schnittbildgebung (CT und MRT) und Blutentnahmen neuartige Biomarker für die Entwicklung von ACLF identifiziert und validiert. Diese Biomarker können dabei helfen Hochrisikopatienten frühzeitig zu identifizieren und entsprechend präventive Maßnahmen zu ergreifen. Vor dem Hintergrund der aktuell noch stark limitierten Behandlungsoptionen des ACLF scheint dies entscheidend für das Outcome dieser Patienten.

Im klinischen Alltag werden CT-Untersuchungen bei Patienten mit dekompensierter Leberzirrhose nicht selten durchgeführt, u.a. zur Planung von Interventionen wie TIPS oder einer Lebertransplantation. In diesen Situationen können zusätzliche Parameter gemessen werden, um das Risiko und entsprechend die Patientenversorgung besser einzuschätzen.

Unsere Ergebnisse bzgl. der SPSS bauen auf vorangegangene Studien auf, die ein erhöhtes Risiko für Komplikationen der Leberzirrhose bei Patienten mit großen SPSS zeigten (Simón-Talero et al., 2018). Die vorliegende Studie bestätigt diese Ergebnisse nicht nur, sondern erweitert sie durch Demonstration der TSA als prognostischen Marker für das Überleben von Patienten. Beim Vorliegen multipler SPSS könnte TSA das portosystemisch geshuntete Blutvolumen besser abbilden als der SPSS-Durchmesser und somit Einblick in für das Überleben wichtige Prozesse bei fortgeschrittener Leberzirrhose mit portaler Hypertension geben. Dieses gilt insbesondere für Patienten, die multiple SPSS aufweisen, welche etwa ein Drittel der Patienten in unserer und auch anderen Kohorten darstellen (Berzigotti et al., 2008; Praktiknjo et al., 2020a; Simón-Talero et al., 2018; Zardi et al., 2009).

Der negative Einfluss von portosystemischem Shunting (spontan oder therapeutisch) scheint ab einem gewissen Grad additiv zu sein, da das Vorliegen von SPSS bei Patienten mit TIPS mit mehr Komplikationen assoziiert ist als das Vorliegen eines TIPS allein (Borentain et al., 2016; He et al., 2018). Ferner suggeriert eine zunehmende Anzahl von Studien, dass weniger Komplikationen auftreten, wenn Patienten TIPS Stents mit kleinerem Durchmesser implantiert bekommen bzw. der Stent nicht vollständig aufdilatiert

wird (Praktiknjo M et al., 2018; Sauerbruch et al., 2015; Schepis et al., 2018; Trebicka et al., 2019b; Wang et al., 2017). Die Ergebnisse unserer Arbeit zeigen einen klaren Grenzwert von 83 mm^2 mit dem Hochrisikopatienten identifiziert werden können. Die manuelle Messung und Berechnung von SPSS und TSA ist aufwendig und zeitintensiv für den klinischen Alltag. Ein Problem, welches wir durch die Entwicklung einer Applikation zur Computer-assistierten Messung und Berechnung von TSA lösen konnten (Praktiknjo et al., 2020b).

Neben den SPSS bzw. der TSA können auch Muskelparameter zusätzlich aus CT-Untersuchungen gemessen werden. Diesbezüglich zeigen unsere Daten, dass geschlechtsspezifische, CT-definierte Sarkopenie im Allgemeinen und TPMT im Speziellen, Patienten mit hohem Risiko für die Entwicklung von ACLF und erhöhte Mortalität identifiziert.

Ein Vorteil der Messung des TPMT gegenüber anderen Methoden ist die Einfachheit der Bestimmung der Muskelmasse. Interessanterweise wurde für TPMT in einer Kohorte von Patienten auf der Warteliste zur Lebertransplantation nur ein einziger Grenzwert für Männer und Frauen vorgeschlagen (Durand et al., 2014). Unsere Daten und auch zunehmend andere Studien zeigen die Bedeutung von geschlechtsspezifischen Unterschieden bei sarkopenen Patienten (Golse et al., 2017; Montano-Loza et al., 2012; Peng et al., 2018; Prado et al., 2008; Praktiknjo et al., 2018a). Frauen zeigen im Vergleich zu Männern per se signifikant niedrigere Muskelindizes, was unsere Daten nun auch für Patienten mit dekompensierter Leberzirrhose bestätigen (Giusto et al., 2015; Praktiknjo et al., 2018a; Tachi et al., 2018). Die Evaluation und Bestimmung von Grenzwerten wurde explizit von der Europäischen Arbeitsgemeinschaft der Sarkopenie als Forschungsziel definiert (Cruz-Jentoft et al., 2010). Durch unsere Arbeit wurden erstmalig geschlechtsspezifische Grenzwerte für TPMT definiert, die die Risikostratifizierung gegenüber dem bisher üblichen unisex Grenzwert für TPMT verbessern.

Bei unseren Analysen aus CT-Untersuchungen kann ein Selektionsbias nicht ausgeschlossen werden. Insbesondere Patienten mit eingeschränkter Nierenfunktion und somit Kontraindikationen gegen CT-Kontrastmittel wurden nicht eingeschlossen.

Für diese Patienten können MRT-Untersuchungen im Vergleich zu CT-Untersuchungen als Bildgebung geeigneter sein, obwohl sie zeit- und kostenintensiver sind. Hierzu liegen jedoch keine Daten für Patienten mit dekompensierter Leberzirrhose vor. Ein Vorteil der Muskelmessung im MRT ist die Möglichkeit der genauen Trennung des intramuskulären Fettgewebes, was die Berechnung der physiologisch aktiven fettfreien Muskulatur erlaubt (Smith et al., 2016). Die vorliegenden Daten zeigen eine bessere Diskriminierung der Patienten durch Stratifizierung mittels FFMA als durch die der Gesamtmuskelfläche, was die besondere Bedeutung der funktionellen Muskelmasse in Zirrhosepatienten unterstreicht. Zwar sind für die CT Rückschlüsse auf den muskulären Fettgehalt durch die Hounsfield Einheiten des Gesamtmuskels beschrieben, jedoch sind diese Grenzwerte bislang in Patienten mit Zirrhose nicht validiert und konsentiert (Aubrey et al., 2014; Tsien et al., 2013).

Die Assoziation von Sarkopenie mit dem Gesamtüberleben ist bereits beschrieben. Eine entscheidende Neuheit dieser Arbeit ist die Beziehung der Sarkopenie mit der Entwicklung von ACLF. Unter den sarkopenen Patienten entwickelte die Hälfte ein fatales ACLF innerhalb eines Jahres, während es unter den nicht-sarkopenen Patienten weniger als 10 % waren. Dies suggeriert eine entscheidende Rolle der Sarkopenie bei der ACLF-Entwicklung oder zumindest eine erhöhte Suszeptibilität hierfür durch eine Sarkopenie. Analog zu unseren Ergebnissen der CT-definierten Sarkopenie können wir durch unsere Arbeit erstmalig (geschlechtsspezifische) Grenzwerte für MRT-definierte Sarkopenie identifizieren.

Als Limitation der Studien zu den bildgebenden Biomarkern ist das retrospektive Design zu nennen. Pathophysiologische Mechanismen hinter der Entwicklung von SPSS bzw. der Sarkopenie konnten nicht näher beleuchtet werden. Zukünftige Studien sollten zudem longitudinale Daten zu den Biomarkern erheben, um ihre Dynamik im natürlichen Verlauf der Zirrhose zu untersuchen.

Eine Gemeinsamkeit von ACLF und Sarkopenie ist, dass für beide Zustände eine erhöhte systemische Inflammation beschrieben ist. Die systemische Inflammation wurde als pathogenetischer Faktor bei der ACLF-Entwicklung identifiziert (Dalle et al., 2017; Ferrucci and Fabbri, 2018; Laleman et al., 2018). Eine systemische Inflammation führt aber auch zu einem katabolen Stoffwechsel mit erhöhtem Energiebedarf und

konsekutivem Abbau von Skelettmuskulatur (Pérez-Baos et al., 2018). Es ist möglich, dass die Sarkopenie lediglich die klinische Manifestation einer zugrundeliegenden, chronisch erhöhten systemischen Inflammation darstellt, welche wiederum die Entwicklung von ACLF ermöglicht. Die Hypothese wird dadurch unterstützt, dass in unserer Kohorte sarkopene Patienten signifikant höhere Leukozytenzahlen, als Surrogat von systemischer Inflammation, aufweisen.

Unsere Daten zu Markern der systemischen Inflammation zeigen eine hohe Rate an ACLF-Entwicklung bei Zirrhosepatienten mit hyper- und hypodynamischem Kreislauf. Ferner deuten diese Daten auf einen Zusammenhang des Grades systemischer Inflammation und Hämodynamik mit dem Risiko der ACLF-Entwicklung hin (Turco et al., 2018b). Diese Arbeit erweitert somit das Verständnis über extreme hämodynamische Kreislaufzustände und systemische Inflammation. Dies zeigt sich vor allem in den signifikant erhöhten Spiegeln von IL-6 und IL-8 in Patienten mit hyperdynamischem, aber nicht normo- und hypodynamischem Kreislauf. Das in einer vorigen Studie gemessene CRP zeigt keine Unterschiede zwischen den verschiedenen hämodynamischen Kreislaufzuständen (Turco et al., 2018b). Dies unterstreicht die Notwendigkeit spezifischerer Marker der systemischen Inflammation als das C-reaktive Protein. Diese Arbeit zeigt, dass IL-6 als unabhängiger Prädiktor für das Auftreten von ACLF ein geeigneter Biomarker sein könnte.

Aktuelle Studien deuten darauf hin, dass eine systemische Inflammation eine wichtige Voraussetzung für das Auftreten von ACLF ist (Mortensen et al., 2012; Turco et al., 2018b). Dennoch scheint das Risiko für ein ACLF bei gleicher Aktivierung der systemischen Inflammation für Patienten mit hyperdynamischem Kreislauf höher zu sein, verglichen mit Patienten mit normodynamischem Kreislauf. Weitere Studien zur Untersuchung des komplexen Zusammenspiels von kardialer und hepatischer Hämodynamik sowie systemischer Inflammation und ACLF sind jedoch notwendig.

4. Zusammenfassung

Zusammenfassend habe ich in dieser Arbeit neuartige nicht-invasive Biomarker für das Auftreten von ACLF bei Patienten mit Leberzirrhose evaluiert. Hierzu wurden aus medizinisch angezeigten Untersuchungen, wie Schnittbildgebungen (CT und MRT) und Blutentnahmen, Biomarker, die mit Entwicklung von ACLF assoziiert sind, identifiziert und validiert. Diese Biomarker können dabei helfen Hochrisikopatienten frühzeitig zu identifizieren und entsprechend präventive Maßnahmen zu ergreifen. Vor dem Hintergrund der aktuell noch stark limitierten Behandlungsoptionen des ACLF scheint dies entscheidend für das Outcome dieser Patienten.

In CT-Untersuchungen zeigte sich die Gesamtfläche spontaner portosystemischer Shunts (TSA) als prognostisch wichtiger Faktor für das Überleben von Patienten mit Leberzirrhose. Diese Arbeit legt nahe, dass ein Grenzwert für das portosystemisch geshuntete Blutvolumen existiert, ab dem die nachteiligen Effekte eines Shunts gegenüber den vorteilhaften überwiegen. Ob ein interventioneller Verschluss im Falle einer Überschreitung der Grenzwerte einen Vorteil für die Patienten darstellt, muss in weiteren Studien untersucht werden.

Ebenso konnte gezeigt werden, dass aus CT-Untersuchungen die Muskelmasse mittels transversaler Psoasmuskeldicke (TPMT) quantifiziert werden kann. Diese Arbeit ermittelte erstmalig geschlechtsspezifische Grenzwerte, die die prognostische Wertigkeit von TPMT verbessern. Ferner konnte erstmalig eine Assoziation von CT-definierter Sarkopenie mit der Entwicklung von ACLF bei Patienten mit dekompensierter Leberzirrhose gezeigt werden.

Für Patienten mit Kontraindikationen gegen die Durchführung einer CT wurde in dieser Arbeit MRT-definierte Muskelparameter evaluiert. Eine fettfreie Muskelfläche (FFMA), als Surrogat von physiologisch aktiver Muskulatur, zeigte sich signifikant mit dem Outcome von Patienten mit dekompensierter Leberzirrhose assoziiert. Insbesondere konnte auch erstmalig eine unabhängige Assoziation mit der Entwicklung von ACLF demonstriert werden. FFMA könnte daher zur Risikostratifizierung dieser Patienten Verwendung finden.

Abschließend beschäftigte ich mich in dieser Arbeit mit den zirkulierenden Markern systemischer Inflammation (IL-6, IL-8, sIL-33R) und untersuchte die prognostische Bedeutung für die Entwicklung von ACLF. IL-6 konnte als unabhängiger Prädiktor von ACLF identifiziert werden und ist wiederum mit der kardialen Hämodynamik assoziiert. Entsprechend ergeben sich sowohl mit der kardialen Hämodynamik als auch mit der systemischen Inflammation zwei potentielle therapeutische Ziele zur Behandlung des ACLF.

5. 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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7. Danksagung

Meine wissenschaftliche Tätigkeit begann während meines Studiums in der Arbeitsgruppe von Prof. Dr. Nico Schäfer (Chirurgie, UKB). Bei ihm und meinem Betreuer PD Dr. Thomas Pech bedanke ich mich für die intensive Einführung in das wissenschaftliche Arbeiten. Ich denke, dass in dieser Zeit die Saat für die wissenschaftliche Laufbahn gepflanzt wurde. Dennoch hätte ich zu dieser Zeit nicht gedacht, eines Tages meine eigene Habilitationsschrift zu verfassen, zumal ich mich nach dem Studium ausschließlich an nicht-akademischen Krankenhäusern bewarb. Wie so vieles im Leben ist es wohl Göttliche Führung gewesen, dass ich zunächst keine Anstellung fand. Und so möchte ich mich bei Prof. Dr. Tilmann Sauerbruch bedanken, der mir als einziger eine Stelle anbot und mir somit eine Chance gab. Viel mehr bin ich ihm auch zu Dank verpflichtet für die Ermunterung zur Bewerbung und Unterstützung bei der Einwerbung meiner ersten Drittmittel, und das lange nach seiner wohlverdienten Emeritierung. Prof. Dr. Christian Strassburg, seinem Nachfolger, danke ich ganz herzlich für die Ermöglichung der Habilitation, für seine stete Unterstützung und für Möglichkeiten Vorträge zu halten und so meine natürliche Scheu vor Publikum zu reden abzulegen.

Nachdem ich in den ersten Jahren als Assistenzarzt ausschließlich klinisch tätig war und mein Vorhaben in der Nephrologie Fuß zu fassen glücklos war, war es Prof. Trebicka, der mich in seine Arbeitsgruppe aufgenommen hat und von Anfang an an mich glaubte. Für die Chance, das Vertrauen und das Mentoring bin ich ihm von ganzem Herzen dankbar. Ich sehe ihn als Vorbild, nicht nur aufgrund seines unermüdlichen Engagements und seiner positiven Art Menschen zu begeistern, sondern auch für seine Weisheit nicht zu vergessen, was außerhalb der Kliniksmauern wichtig ist – die Familie. Über seinen Ruf nach Frankfurt a.M. habe ich mich mit einem lachenden Auge für ihn sehr gefreut, aber mit einem weinenden Auge bedauert meinen Mentor nicht mehr vor Ort zu wissen.

In dieser Zeit wäre es ohne Dr. Johannes Chang sicherlich nicht möglich gewesen das Labor wiederaufzubauen. Ich danke ihm für vielen wissenschaftlichen Gespräche, seine Kameradschaft und Freundschaft. An dieser Stelle möchte ich mich auch bei Professor Dr. Ulrich Spengler bedanken, der nicht nur immer ein offenes Ohr, sondern auch einen guten Rat für mich hatte, obwohl ich nie in seiner Arbeitsgruppe tätig war.

Die hervorragende technische Unterstützung von Frau Jennifer Söhne, Frau Franziska Füllmann und Frau Nadine Köstlmeier möchte ich ganz besonders erwähnen. Durch ihren unermüdlichen Einsatz und ihren unglaublichen Fleiß nehmen sie in meiner wissenschaftlichen Arbeit eine ganz besondere Stelle ein, die ein großes Stück zu dem Erfolg meiner Arbeit beitrug.

Meine wissenschaftliche Tätigkeit hat mich gelehrt, dass man zusammen mehr erreicht. Ich bedanke mich bei allen Kollegen und Doktoranden, die mir außerordentlich geholfen haben. Ich danke Dr. Christian Jansen, Dr. Carsten Meyer, PD Dr. Guido Kukuk, PD Dr. Julian Luetkens, PD Dr. Claus Pieper und PD Dr. Felix Jansen für die immer fruchtbare Zusammenarbeit. Ich bedauere nicht alle namentlich in dieser Schrift erwähnen zu können. Nicht zuletzt möchte ich für die Hilfen von Marius Book, Carolin Clees, Julia Römer, Viktoria Krabbe, Alexia Dumitrache, Sofia Monteiro, Antonia Witt, Isabel Korte, Katharina Böhm, Jasmin Abu-Omar, Alba Paar-Perez, Kim Krüger, Mara Diekhöner, Alexandra Decker, Maximiliane Krüsken, Julius Scheeben, Veronika Fraitzl, Anna-Lena Konicek, Katharina Kunz, Katharina Graf und Johanna Bergman danken.

Diese Arbeit wäre nicht zu Stande gekommen, wenn ich nicht das Vertrauen von den unterschiedlichsten Menschen und Institutionen erhalten hätte. Hier möchte ich ganz besonders das interne Förderprogramm BONFOR unserer medizinischen Fakultät sowie die Ernst-und-Berta Grimmke Stiftung erwähnen, welche meine Forschung unterstützten.

Ich danke Dr. Andreas Luu, der seit dem Studium ein Wegbegleiter und Freund ist und mich auf dem Weg zu dieser Arbeit stets motiviert hat. Meinen Freunden Dr. Alessandra Pohlmann und Dr. Jennifer Lehmann-Bell danke ich für die Korrektur dieser Arbeit.

Letzten Endes möchte auch ich nicht vergessen, was außerhalb der Kliniksmauern wichtig ist. Ich danke von ganzem Herzen meinen Eltern (Budhidharma und Shinta) für ihre selbstlose Liebe, die sie meinen Geschwistern und mir entgegenbrachten. Sie haben mich stets uneingeschränkt unterstützt und mich geprägt, in dem sie mir zeigten was man mit Fleiß, Ehrlichkeit und Demut erreichen kann. Ich danke ihnen und meinen Geschwistern Natalie und Matthew für ihre Geduld, ihren Glauben und dass sie in allen Lagen des Lebens mein Rückhalt sind.

Auf meinem Weg zu dieser Arbeit lernte ich den besonderen Wert der Weisheit gegenüber des Wissens: Wie mein alter Mentor nehme ich das Leben wie es ist, auch wenn manche Dinge auf den ersten Blick keinen Sinn ergeben. „Wo Hochmut ist, da ist auch Schande; aber Weisheit ist bei den Demütigen.“ Sprüche 11:2.