INTRA-ABDOMINAL HYPERTENSION IN THE CRITICALLY ILL PATIENT WITH LIVER CIRRHOSIS

RUI MANUEL ANTUNES DA CRUZ PEREIRA

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“The journey of a thousand miles begins with one step.”

Lao Tzu, Chinese philosopher.

To Sofia, my wife

To little Simão and Alice

To my parents Vasco e Maria Jesus

To my brother Nuno

To Professor Rui Perdigoto

To Professor Paulo Marcelino

To Professor Faouzi Saliba

To the patients

To my colleagues

To my friends along the way

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Abbreviations

AARC – American Association for Respiratory Care

ABC – Albumin Bilirubin Clotting

AbSeS - Abdominal Sepsis Study: Epidemiology of Etiology and Outcome

ACLF – Acute on Chronic Liver Failure

ACS - Abdominal Compartment Syndrome

ADQI - Acute Dialysis Quality Initiative

AhP - Abdominal Hypoperfusion

AKI - acute kidney injury

AKIN - Acute Kidney Injury Network

ALD – Alcoholic liver disease

aOR – Adjusted odds ratio

APACHE - Acute Physiology and Chronic Health Evaluation

APASL - Asian Pacific Association for the Study of Liver

APP - Abdominal Perfusion Pressure

APTT - Activated Partial Thromboplastin Time

ARF - Acute Renal Failure

aROC – area under the Receiver Operator Characteristic

AUC - Area Under the Curve

BCN - Bile Cast Nephropathy

CANONIC – Consortium Acute-on-Chronic Liver Failure in Cirrhosis

CCI - Charlson Comorbidity Index

CHULC - Centro Hospitalar Universitário Lisboa Central

CLD - Chronic Liver Disease

CLIF - Chronic Liver Failure

CLIF-C - Chronic Liver Failure Consortium

CO - Carbon Monoxide

CPP - Continuous Passive Paracentesis

CVVHD - Continuous Veno Venous Hemodialysis

DALY – Disability Adjusted Life Year

DAMPs – Damage Associated Molecular Patterns

DMC - Data Monitoring Committee

EASL - European Association for the Study of Liver

eGFR - Estimated Glomerular Filtration Rate

ESICM – European Society of Intensive Medicine

ESRD – End Stage Renal Disease

ET-1 - Endothelin-1

GCS – Glasgow Coma Scale

GOV - Gastroesophageal Varices

HBV - Hepatitis B

HCV - Hepatitis C

HE - Hepatic Encephalopathy

HPS - Hepatopulmonary Syndrome

HRS – Hepatorenal Syndrome

HSC - Hepatic Stellate Cells

HVPG - Hepatic Venous Pressure Gradient

IAH – Intra Abdominal Hypertension

IAP – Intra Abdominal Pressure

IAPC - Indwelling Abdominal Paracentesis Catheter

IBM – International Business Machines Corporation

ICA - International Club of Ascites

ICP - Increased Intracranial Pressure

ICU - Intensive Care Unit

IGC - Isolated Gastric Varices

IHVR - Intrahepatic Vascular Resistance

IMV – Invasive mechanical ventilation

INR - International Normalized Ratio

IROI – Incidence, Risk Factors, and Outcomes of Intra-Abdominal Hypertension

ITT – Intention To Treat

KDIGO - Kidney Disease: Improving Global Outcomes

LOS – Length of Stay

LSEC – Liver sinusoidal endothelial cell

LT – Liver Transplantation

LVP – Large Volume Paracentesis

MAP – Mean Arterial Pressure

MELD - Model for End Stage Liver Disease score

mPAP - Pulmonary Artery Pressures

NACSELD – North American Consortium for the Study of End-Stage Liver Disease

OF - Organ Failure

PA - Pulmonary Artery

PACD – Paracentesis Associated Circulatory Dysfunction

PAMPs – Pathogen Associated Molecular Patterns

PAVH - Peripheral Arterial Vasodilation Hypothesis

PAWP – Pulmonary wedge pressure

PCD - Percutaneous Catheter Drainage

PEEP – Positive End-Expiratory Pressure

P.I. - Principal Investigator

PH - Portal Hypertension

POPH - Portopulmonary Hypertension

PPCD – Post Paracentesis Circulatory Disfunction

PSS - Portosystemic Shunting

PT - Prothrombin Time

PV - Portal Vein

PVR - Pulmonary Vascular Resistance

PVT - Portal Vein Thrombosis

RAAS – Renin Angiotensin Aldosterone System

RCT - Randomized Controlled Trial

RIFLE – Risk, Injury, Failure, Loss, and End-stage

RRT – Renal Replacement Therapy

SAAG – Serum Ascites Albumin Gradient

SAPS – Simplified Acute Physiology Score

SBP - Spontaneous Bacterial Peritonitis

SCr - Serum Creatinine Concentration

SD – Standard deviation

SIBO - Small Intestinal Bacterial Overgrowth

SOFA - Sequential Organ Failure Assessment

SPSS – Statistical Package for Social Science

SS - Septic Shock

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology

TIPS - Transjugular Intrahepatic Portosystemic Shunt

VTE – Venous thromboembolism

WBC – White Blood Cell

WGO - World Gastroenterology Organization

WH – West-Haven

WSACS - World Society of Abdominal Compartment Syndrome

Abstract

Liver cirrhosis is a common cause of death and a worldwide public health problem linked to alcohol consumption and viral hepatitis. Patients with advanced liver disease in the stage of cirrhosis develop complications and are prone to critical illness with acute organ failure (OF).

The patient with cirrhosis in intensive care poses a clinical challenge due to high mortality rates. These patients develop the acute-on-chronic liver failure syndrome (ACLF), with acute decompensation, OF as defined in the seminal CANONIC study using the Chronic Liver Failure – Sequential Organ Failure Assessment (CLIF-SOFA) score, and high 28-day mortality rate.

Intra-abdominal hypertension (IAH) is defined by the World Society of Abdominal Compartment Syndrome (ACS) and is well studied in multiple clinical settings (i.e. major abdominal surgery, ruptured abdominal aortic aneurism, major burns, major trauma, acute pancreatitis, and mechanical ventilation). However, there is paucity of data regarding IAH in the patient with cirrhosis.

Patients with cirrhosis are at risk of developing elevated intra-abdominal pressure (IAP), due to the presence of portal hypertension and the formation of ascites. The occurrence of IAH is frequently underdiagnosed in these patients, and is subjectively termed "tense ascites". In patients with ascites refractory to medical treatment, repeated large-volume paracentesis (LVP) is a therapeutic option. Furthermore, the treatment of IAH through LVP results in short-term improvement of renal and respiratory dysfunction in patients with cirrhosis and ascites in intensive care.

Intra-abdominal hypertension is an underappreciated cause of organ dysfunction/failure, and may play an important role in the development of acute kidney injury (AKI) in patients with

cirrhosis. However, fundamental data regarding the impact of IAH on clinical outcomes in critically ill patients with cirrhosis and ascites is scarce.

In this thesis we aimed to comprehensively study IAP, ACS and abdominal perfusion pressure (APP) in critically ill patients with cirrhosis. To achieve this objective we conducted a series of five studies with distinct methodologies in different populations of patient with cirrhosis in intensive care.

In the first, retrospective study we analyzed the clinical characteristics, mortality and risk factors in a cohort of 71 patients between March 2013 and December 2016. The typical patient was under 60 years-old, male, with alcoholic liver cirrhosis presenting with septic shock and multiorgan failure ACLF grade 3 at intensive care unit (ICU) admission. The 28-day mortality rate (49%) was higher than in the reference literature, and risk factors included a high total number of OF at admission, and arterial blood lactate and international normalized ratio at the third day of stay.

In the second, multicentric, retrospective study we characterized IAP, determined the prevalence, severity and risk factors of IAH, as well as the outcomes in 95 patients between January 2009 and October 2019. There was a very high prevalence (82%) of IAH and the distribution mode was grade II (33%), as assessed by the maximum IAP value. Risk factors for IAH were alcoholic etiology of liver disease, hepatic encephalopathy (HE) West-Haven score and, surprisingly, higher oxygenation ratio PO2/FiO2 at admission. Additionally, ACS had a prevalence of 23% and infection as precipitant event of critical illness was a risk factor. Increased IAP was associated with increased 28-day mortality, and maximum IAP was a risk factor after adjusting for clinical severity SAPS II score.

In the third, prospective study we analyzed APP, the prevalence and risk factors of abdominal hypoperfusion (AhP), as well as the outcomes in 101 patients between October 2016 and December 2021. The mean APP was 63 (± 15) mmHg with a 47% prevalence of AhP at ICU admission. Abdominal hypoperfusion during the first week was independently associated with higher clinical severity of ACLF and with a higher likelihood of paracentesis performed at admission. Additionally, total bilirubin and SAPS II score at admission were independent risk factors for 28-day mortality.

In the fourth, post-hoc analysis of the prospective study we determined the impact of APP on the development of acute renal failure (ARF), defined as stage 3 International Club of Ascites (ICA) - AKI in 58 patients. The prevalence of AhP was 75% during the first week of ICU stay, and in 29% of cases we observed persisting AhP during this 7-day period. There was a high prevalence of ARF (48%) during this period, and risk factors included higher serum urea and white blood cell count at admission, as well as lower persisting APP. Furthermore, we observed an optimal cut-off value of persisting APP <70 mmHg to predict ARF that may be useful in clinical practice.

Consequently, in the fifth study, we designed and implemented a clinical trial to compare a continuous passive paracentesis (intervention) versus an intermittent LVP (control) strategy in the prevention and treatment of IAH in the critically ill patient with cirrhosis and ascites in intensive care. In this investigator-initiated, open label, randomized controlled trial (RCT), 70 patients will be allocated to study groups, in a 1:1 ratio, within 24h of admission. The primary endpoint is serum creatinine concentration, and secondary endpoints include IAP, stage 3 ICA-AKI and multiorgan dysfunction CLIF-SOFA score, assessed at day 7 after enrollment, as well

as 28-day mortality rate. The trial was initiated in August 2022 with an expected duration of 36 months.

Furthermore, liver transplant in critically ill patients with cirrhosis was performed in an important proportion (15%) of patients within 28 days of ICU admission in our aggregate cohorts.

In conclusion, the majority of patients were male with alcohol-related liver disease. Infection was the most frequent precipitant event for acute decompensation and patients presented with multiorgan failure at ICU admission. Twenty-eight day mortality was high and risk factors were related to OF, systemic inflammation and metabolic dysfunction. Liver transplant was an effective treatment for selected patients. The prevalence of IAH during the ICU stay was high, and alcoholic cirrhosis, HE and oxygenation ratio at admission were risk factors. Infection as a precipitant event was a risk factor for ACS. Higher IAP was associated with higher 28-day mortality rate, and maximum IAP was a risk factor. Abdominal perfusion pressure was low in patients with cirrhosis, and lower APP was associated with worst vital outcome. Initial higher ACLF severity was a risk factor for AhP, and patients with AhP were more likely to be submitted to paracentesis at admission. Critically ill patients with cirrhosis presented a high prevalence of ARF, and risk factors were serum urea, WBC count and low persisting APP with a predictive cut-off value of <70 mmHg that may be clinically useful. The prevention and treatment of IAH in patients with cirrhosis and ascites may improve clinical outcomes, and consequently a RCT has been implemented to compare the clinical outcomes of two therapeutic paracentesis strategies.

Resumo

A cirrose hepática está associada ao consumo de álcool e hepatite viral, é uma causa comum de morte e um problema de saúde pública em todo o mundo. Os doentes com doença hepática avançada na fase de cirrose desenvolvem complicações e encontram-se propensos a contrair doenças agudas críticas com falências de órgão (FO). O doente com cirrose na unidade de cuidados intensivos (UCI) representa um desafio clínico devido a elevadas taxas de mortalidade. Estes doentes desenvolvem a síndrome *acute-on-chronic liver failure* (ACLF), com descompensação aguda e FO, conforme definido no original estudo CANONIC através da escala de gravidade clínica *Chronic Liver Failure - Sequential Organ Failure Assessment* (CLIF-SOFA) e de uma elevada taxa de mortalidade aos 28 dias.

A hipertensão intra-abdominal (IAH) (pressão intra-abdominal [PIA] ≥12 mmHg) e a síndrome de compartimento abdominal (SCA) são definidas pela *World Society of Abdominal Compartment Syndrome* e estão bem estudadas em diversos contextos clínicos (cirurgia abdominal major, rutura de aneurisma de aorta abdominal, queimaduras graves, trauma grave, pancreatite aguda e ventilação mecânica). No entanto, são escassos os dados sobre IAH no doente com cirrose. Os doentes com cirrose estão em risco de desenvolver PIA elevada, devido à presença de hipertensão portal e à formação de ascite. A ocorrência de IAH é, frequentemente, sub-diagnosticada nestes doentes e, subjetivamente, denominada "ascite tensa". Em doentes com ascite refratária ao tratamento médico, a paracentese de grande volume (PGV) repetida é uma opção terapêutica. Além disso, o tratamento da IAH através de PGV resulta na melhoria das disfunções renal e respiratória a curto prazo em doentes com cirrose e ascite na UCI. A HIA é uma causa subestimada de disfunção e FO e pode desempenhar um papel importante no

desenvolvimento de insuficiência renal aguda (IRA) em doentes com cirrose. No entanto, há uma escassez de dados fundamentais sobre o impacto da IAH nos resultados clínicos dos doentes críticos com cirrose e ascite.

Nesta tese, de forma abrangente, pretendeu-se estudar a PIA, a SCA e a pressão de perfusão abdominal (PPA) em doentes críticos com cirrose. Para alcançar este objetivo, realizamos uma série de cinco estudos com metodologias distintas em várias populações de doentes com cirrose.

No primeiro estudo, retrospetivo, analisámos as características clínicas, mortalidade e fatores de risco numa coorte de 71 doentes, entre março de 2013 e dezembro de 2016. O doente típico apresentava menos de 60 anos, sexo masculino e cirrose alcoólica, com choque séptico e falência multiorgânica, com ACLF 3 na admissão. A taxa de mortalidade a 28 dias (49%) foi mais alta do que na literatura de referência, e os fatores de risco incluíram um elevado número total de FO na admissão, lactato arterial e o índice internacional normalizado (INR) no terceiro dia de UCI.

No segundo estudo, retrospetivo, multicêntrico, caracterizámos a PIA, determinámos a prevalência, a gravidade e os fatores de risco da IAH, bem como os resultados clínicos em 95 doentes, entre janeiro de 2009 e outubro de 2019. Observou-se uma prevalência de IAH muito alta (82%) e a moda da sua distribuição foi o grau II (33%), conforme avaliado pelo valor máximo de IAP. Os fatores de risco para IAH foram a etiologia alcoólica da doença hepática, o grau de encefalopatia hepática (HE) pela escala de West-Haven e, surpreendentemente, uma maior razão de oxigenação (PO2/FiO2) no dia de admissão na UCI. Adicionalmente, a SCA apresentou uma prevalência de 23%, e teve a infeção como evento precipitante de doença crítica como fator de risco. O aumento da IAP esteve associado a uma maior taxa de mortalidade a 28 dias, e a IAP máxima foi um fator de risco independente da gravidade clínica na admissão, tal como avaliada pela escala SAPS II.

No terceiro estudo, prospetivo, analisámos a pressão de perfusão abdominal (PPA), a prevalência e os fatores de risco da hipoperfusão abdominal (hPA) (PPA <60 mmHg), bem como os resultados clínicos em 101 doentes, entre outubro de 2016 e dezembro de 2021. A PPA média foi de 63 (±15) mmHg, com uma prevalência hPA de 47% no dia de admissão na UCI. A hPA durante a primeira semana na UCI apresentou-se associada de forma independente a uma maior gravidade clínica, aferida pelo grau de ACLF, e a uma maior probabilidade de realização de paracentese no dia de admissão. Além disso, a bilirrubina total e a escala SAPS II na admissão foram fatores de risco independentes para a mortalidade a 28 dias.

No quarto estudo, um análise pós-hoc do estudo prospetivo, determinámos o impacto da PPA no desenvolvimento de falência renal aguda (FRA), definida como o grau 3 de IRA de acordo com o *International Club of Ascites* (ICA), em 58 doentes. A prevalência de hPA foi de 75% durante a primeira semana na UCI, e em 29% dos casos observamos hPA persistente durante esse período de 7 dias. Houve uma elevada prevalência de FRA (48%) durante este período, e os seus fatores de risco incluíram a elevação da ureia sérica e da contagem de leucócitos na admissão, bem como uma reduzida PPA persistente. Adicionalmente, observámos um valor de corte de PPA persistente <70 mmHg otimizado para a previsão de FRA, que poderá ser útil na prática clínica.

Consequentemente, para o quinto estudo, desenhámos e implementámos um estudo clínico para comparar a paracentese passiva contínua (intervenção) versus a PGV intermitente (controlo) na prevenção e tratamento da IAH no doente critico com cirrose e ascite na UCI. Neste estudo clínico controlado com aleatorização, iniciado em agosto de 2022, e com uma duração prevista de 36 meses, 70 doentes serão alocados aos grupos de estudo, numa razão de 1:1, nas 24 horas iniciais após a admissão. O "outcome" primário é a concentração de creatinina sérica, e os

"outcomes" secundários incluem a PIA, FRA e a escala de CLIF-SOFA avaliados ao 7º dia após a admissão, bem como a taxa de mortalidade em 28 dias.

De forma suplementar, observou-se que o transplante hepático foi realizado numa proporção significativa (15%) dos doentes críticos com cirrose, durante os 28 dias após a admissão na UCI.

Em conclusão, a maioria dos doentes era do sexo masculino, com doença hepática relacionada com o consumo de álcool. A infeção foi o evento precipitante mais frequente na descompensação aguda, e os doentes apresentaram-se com falência multiorgânica na admissão na UCI. A taxa de mortalidade a 28 dias foi elevada, e os fatores de risco relacionaram-se com a FO, inflamação sistémica e disfunção metabólica. O transplante hepático foi um tratamento eficaz em doentes selecionados. A HIA apresentou uma prevalência elevada durante o internamento na UCI, e os seus fatores de risco foram a cirrose alcoólica, o elevado grau de HE e a razão de oxigenação na admissão. A infeção foi um fator de risco para SCA. A PIA elevada encontrou-se associada a uma maior taxa de mortalidade aos 28 dias, e o valor máximo de PIA foi um fator de risco. A PPA foi baixa em doentes críticos com cirrose, e a reduzida PPA esteve associada a um pior desfecho vital. A maior gravidade da ACLF na admissão foi um fator de risco para hPA, e os doentes com hPA apresentaram maior probabilidade de ser submetidos a paracentese na admissão. Os doentes críticos com cirrose apresentaram uma elevada prevalência de FRA, cujos fatores de risco foram a elevação da ureia sérica e da contagem de leucócitos na admissão e a reduzida PPA persistente, com um respetivo valor de corte <70 mmHg preditivo de FRA, que pode ser clinicamente útil. A prevenção e o tratamento da HIA em doentes críticos com cirrose e ascite poderão melhorar os resultados clínicos e, consequentemente, um estudo clínico foi implementado para comparar os resultados de duas estratégias de paracentese terapêutica.

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Chapter 1

Introduction

1.1. Liver Cirrhosis

1.1.1. Epidemiology

Liver disease accounts for approximately 2 million deaths per year worldwide and cirrhosis is responsible for half of these deaths (1).

Cirrhosis is an advanced stage of liver disease with fibrosis resulting from a chronic pathophysiological inflammatory response to liver injury. The stage of liver cirrhosis features impaired hepatocyte function and increased intra-hepatic vascular resistance, with typical portal vein hypertension, hemodynamic changes, compensatory mechanisms and clinical complications, including hepatocellular carcinoma, leading to impaired quality of life and patient death in the absence of liver transplantation (1,3). Nowadays, cirrhosis is the 11th most common cause of death globally (4). It burdens the individual patient and public health with major economic costs (4-9). Therefore disability-adjusted life-year (DALY), the sum of years of life lost due to premature death and years of life lived with disability, is a metric for public health burden. The more DALYs attributable to a disease, the greater its burden on public health. In a recent study, cirrhosis was responsible for 560 age-standardized DALYs per 100,000 population globally, excluding deaths from hepatocellular carcinoma, although most of these cancers develop in patients with cirrhosis (8). By comparison, in the same study, liver cancer was responsible for 151 DALYs, chronic obstructive pulmonary disease for 926, depressive disorders for 578, dementia for 339, and inflammatory bowel disease for 20 (8).

1.1.2. Causes and risk factors

Common etiologies of liver cirrhosis include hepatitis B (HBV) and hepatitis C (HCV), alcohol-related liver disease and non-alcoholic fatty liver disease. The etiologies of cirrhosis can

be classified into viral, alcohol-related, metabolic and genetic, autoimmune, biliary, vascular, drug-related (long-term use) and cryptogenic of uncertain cause (1) (Figure 1).

The reported worldwide dominant etiology of cirrhosis from 1993 to 2021 varies widely according to the examined regions (10,11). The combined prevalence of HBV and HCV infection exceeded 50% in most Asian and African regions, while the contribution of heavy alcohol use was highest in Europe, and in the Americas (10).

The biggest risk factors for cirrhosis are alcohol consumption, HBV and HCV and non-alcoholic fatty liver disease, which is strongly associated with metabolic risk factors, such as obesity and diabetes (12).

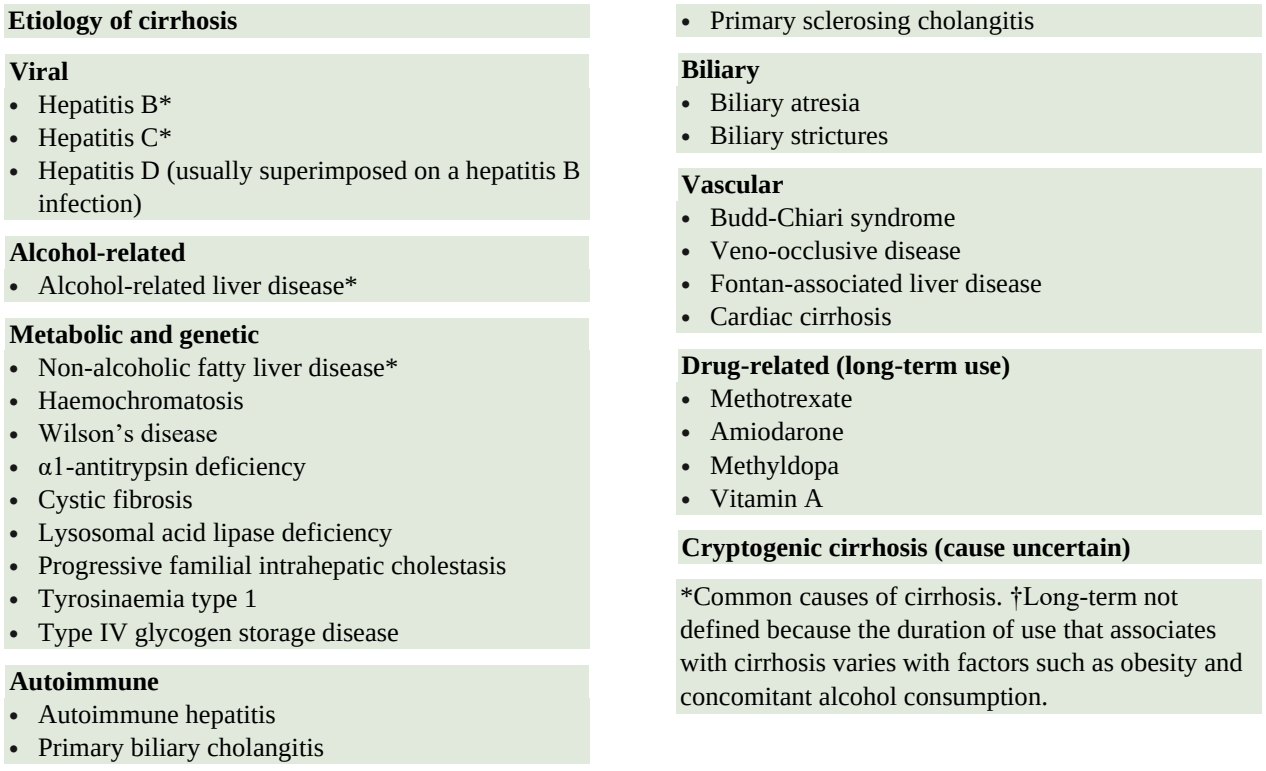

Figure 1. Etiology of cirrhosis. Reprinted with permission from Elsevier (License Number 5538090408009) (1).

The prevalence of these risk factors varies across the regions of the globe. In the World Health Organization European region, prevalence and mortality data indicate that increasing cirrhosis and liver cancer may be linked to dramatic increases in harmful alcohol consumption in Northern European countries, and viral hepatitis epidemics in Eastern and Southern European countries, while countries with historically low levels of liver disease may experience a future increase in non-alcoholic fatty liver disease, given the rise of obesity across most European countries (6).

1.1.3. Pathophysiology

Inflammation and fibrosis are responsible for the structural alterations observed in chronic liver disease (13). Persisting inflammation produces activation and cellular phenotype alteration, with dysfunction of liver sinusoidal endothelial cells (LSECs), activated hepatic stellate cells (HSCs) and macrophages, while increased extracellular matrix turnover and accumulation produce fibrosis (14). Histologically, this is characterized by a distortion of the normal hepatic architecture due to the development of regenerative nodules and encapsulating fibrotic septa (2). These phenomenon increases liver stiffness and structural resistance to hepatic blood flow.

Furthermore, dynamic sinusoidal blood flow is regulated by SECs and HSCs. One of the most prominent features of HSCs activation is an increase in the expression of smooth muscle α actin, pointing to HSCs as liver specific myofibroblasts (15,16). Furthermore, in response to liver injury LSECs produce fibronectin, resulting in a potent positive paracrine feedback for endothelin-1 (ET-1) production (15,17,18). Particularly, in the context of liver injury where vascular disorder ensues, vasoconstriction by HSC overproduction of ET-1 and reduction of

endothelial cell-derived nitric oxide (NO) leads to increased intra-hepatic resistance and development of complications, such as portal hypertension (PH) (13,19,23).

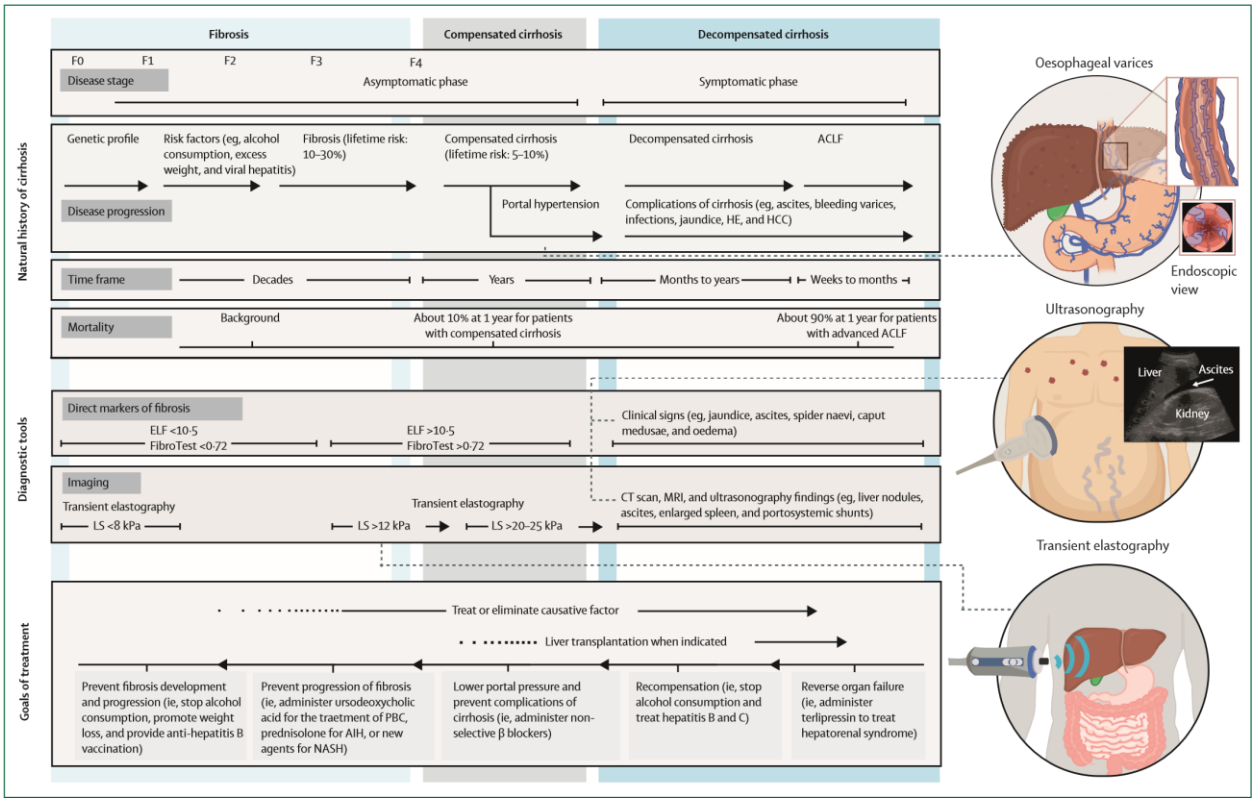

Figure 2. The clinical spectrum of chronic liver disease. Reprinted with permission from Elsevier (License Number 5538090408009) (1).

1.1.4. Diagnosis

Chronic liver disease may have an asymptomatic course for decades, as fibrosis progresses into a compensated cirrhosis phase, before it becomes decompensated cirrhosis due to a symptomatic complication (1). The natural history of cirrhosis, the diagnostic tools and the goals of treatment are illustrated in the following Figure 2 (1).

Ultrasound elastography, such as transient elastography Fibroscan™, measure liver stiffness and are first-line, non-invasive, screening tests to assess hepatic fibrosis that perform particularly well in the stages of advanced fibrosis and cirrhosis (24,25). Liver biopsy is the

gold standard for diagnosis of cirrhosis, and is an invasive method used to determine the cause of liver disease in selected cases. Other test and biomarkers can be used in combination for differential diagnosis, to confirm or exclude certain etiologies of liver disease and cirrhosis, as exemplified in Table 1 (1).

Table 1. Etiology and diagnosis of the most common causes of cirrhosis by risk factor.

	Causative factors	Main drivers or contributing factors	Risk of cirrhosis*	Primary tests	Confirmatory tests†	Main differential diagnosis
Metabolism	Alcohol consumption	Lifestyle	5–10%	Alcohol use disorder identification test; blood tests for γ-glutamyltransferase, aspartate aminotransferase, alanine aminotransferase, and mean corpuscular volume; liver elastography‡	Urinalysis for ethyl glucuronide, liver biopsy, and liver elastography‡	Any other cause mentioned in this table
Metabolism	Obesity, type 2 diabetes, metabolic syndrome	Genetic polymorphisms (ie, mutations in the *PNPLA3* gene) and alcohol consumption	1–2%	Body-mass index, HbA_{1c}, aspartate aminotransferase, alanine aminotransferase, fibrosis-4 index, and liver elastography‡	Liver biopsy to detect non-alcoholic steatohepatitis, and liver elastography‡	Any other cause mentioned in this table
Infection	Hepatitis B (90% of infants and 5–10% of adults infected with the hepatitis B virus develop chronic hepatitis)	Living in high-endemicity areas (>2% prevalence), including prisons; high-risk sexual behaviours; intravenous drug use; immunosuppressive therapy; haemodialysis	Up to 40% if untreated	HBsAg testing	Presence of hepatitis B virus DNA	Any other cause mentioned in this table
Infection	Hepatitis C (75–80% of all infected patients with the hepatitis C virus develop chronic hepatitis)	Living in high-risk environments (eg, prisons); high-risk sexual behaviours; intravenous drug use; immunosuppressive therapy; haemodialysis; working with blood products or needles	10–20% if untreated	Anti-hepatitis C virus antibodies testing	Presence of hepatitis C virus RNA	Any other cause mentioned in this table
Genetic predisposition	Haemochromatosis, mutations in the *HFE* gene	..	2–4%	Serotransferrin (also known as transferrin) saturation >45% (screening test); high serum ferritin	*HFE* test for Cys282Tyr homozygosity or other *HFE* genotypes	High alcohol consumption, metabolic syndrome, hepatitis B, hepatitis C, inflammatory states, iron supplementation, and frequent blood transfusions
Genetic predisposition	α-1 antitrypsin deficiency, mutations in the *SERPINA1* gene	..	15% with a ZZ genotype for α-1 antitrypsin	Low serum levels of α-1 antitrypsin	*SERPINA1* test for ZZ, SZ, or MZ genotypes	High alcohol consumption, amyloidosis, glycogen storage disease
Genetic predisposition	Wilson's disease, mutations in the *ATP7B* gene	..	Insufficient data available	Low serum ceruloplasmin	Urinary copper in 24 h, liver biopsy, genetic analysis	Any other cause mentioned in this table
Host and environmental triggers	Autoimmune hepatitis	Female sex (male to female prevalence ratio: approximately 1:3)	Insufficient data available	Alanine aminotransferase, IgG, ANA, smooth muscle antibody, liver-kidney microsomal antibody, liver cytosolic antigen type 1	Liver biopsy	Non-alcoholic steatohepatitis, hepatitis B, hepatitis C, primary sclerosing cholangitis, primary biliary cholangitis, Wilson's disease
Host and environmental triggers	Primary biliary cholangitis	Female sex (male to female prevalence ratio: approximately 1:4)	Approximately 33% if untreated	Elevation of serum alkaline phosphatase, γ-glutamyltransferase, conjugated bilirubin, or all	Serum antimitochondrial antibodies, primary biliary cholangitis-specific ANA, normal MRCP, and liver biopsy§	Primary sclerosing cholangitis, secondary sclerosing cholangitis, IgG4-associated cholangitis
Host and environmental triggers	Primary sclerosing cholangitis	Male sex (male to female prevalence ratio: approximately 2:1); two-thirds of patients with primary sclerosing cholangitis have concomitant inflammatory bowel disease	Most patients will require liver transplantation for complications	Elevation of serum alkaline phosphatase and γ-glutamyltransferase	MRCP, liver biopsy§, ERCP§	Secondary sclerosing cholangitis

ERCP=endoscopic retrograde cholangiopancreatography. HbA_{1c}=glycated haemoglobin. MRCP=magnetic resonance cholangiopancreatography. *Risk of cirrhosis is defined as the percentage of people in the population with the corresponding risk factor who will receive a diagnosis of cirrhosis at any time in their life. †To assess the severity of fibrosis, presence of cirrhosis, or portal hypertension, all patients must be assessed with abdominal ultrasound and elastography. ‡Although useful, liver elastography is not available as primary test in most countries. §Not essential for diagnosis, but can be useful for differential diagnosis.

1.1.5. Complications of cirrhosis

During the course of liver cirrhosis typical complications occur and these aggravate the vital prognosis (26). It is estimated that approximately 58% of patients with compensated cirrhosis will develop clinical decompensation within 10 years of their disease course (27). These include PH, hyperdynamic circulation, ascites, hepatorenal syndrome (HRS) spontaneous bacterial peritonitis (SBP) and other infections, furthermore, hyponatremia, coagulopathy, variceal bleeding, cirrhotic cardiomyopathy, hepatopulmonary syndrome and portopulmonary hypertension and hepatic encephalopathy (HE).

1.1.5.1. Portal hypertension

Portal hypertension derives primarily from the development of a marked increase in intrahepatic vascular resistance (IHVR) and secondarily to increased portal blood flow, due to splanchnic vasodilatation and hyperkinetic circulation (13). The portal vein (PV) is responsible for approximately 75% of the liver's blood supply and results from the confluence of the splenic and superior mesenteric veins, connecting the splanchnic blood outflow from the gastrointestinal tract, gallbladder, pancreas and spleen (27).

From a physics perspective, PH can be explained by the hydraulic equivalent of Ohm's Law (15): (pressure = flow × resistance). This means that the portal pressure gradient (ΔP) is directly proportional to the amount of blood flow circulating through the portal venous system (Q) and the resistance (R) opposing this flow ($\Delta P = Q \times R$). Hence, an increase in portal pressure can be considered secondary to an increase in resistance, an increase in blood flow, or a combination of both factors (28).

Wedge hepatic venous pressure and hepatic venous pressure gradient (HVPG) measurements are established surrogate measurements of, respectively, portal venous pressure and portal pressure gradient, respectively (29). Direct measure of PV pressure was originally performed by Thompson et al. in 1937, by inserting a needle directly into a branch of PV during surgery (30,31). Portal pressures ranges from 7 to 12 mmHg in normal fasted subjects at rest and in the supine position (32).

Portal hypertension is defined as a sustained increase in the pressure gradient between the portal vein and systemic circulation. The method for indirect measuring of portal pressure by occlusive catheterization of a hepatic vein was described by Myers and Taylor in 1951 (33). However, only in 1979 did Groszmann and colleagues described the method that involved the inflation of a balloon catheter (wedge) that would occlude the hepatic vein and obtain measures of free and occluded pressure without the need to move the catheter (31,34). The HVPG is the gold-standard measure for the diagnosis of PH in patients with liver disease (13,35,36). It is obtained by introducing a catheter into one hepatic vein and by measuring the difference in blood pressure between the occluded-catheter position and the free-catheter position (37) (Figure 3).

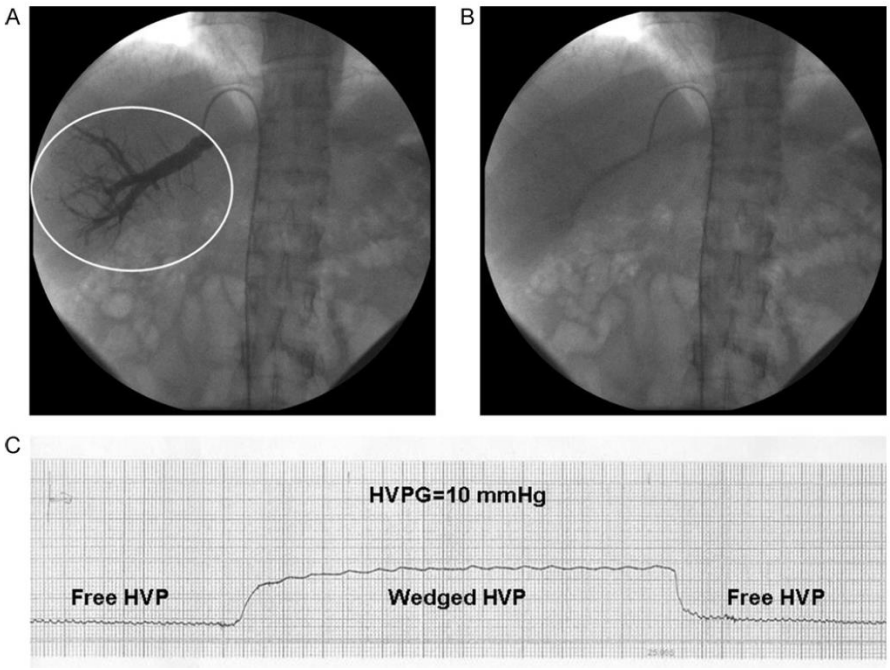

Figure 3. Hepatic venous pressure gradient measurement with a balloon catheter. The catheter is inserted into the hepatic vein and pressure recordings (HVP) obtained in the occluded (A) and free positions (B) (personal data). HVPG is obtained by calculating the difference in pressure in the occluded and free positions (C). The white circle (A) indicates the hepatic area the measurement pertains to. Reprinted with permission from Elsevier (License Number 5558111106455) (37).

Cirrhotic PH is the intra-hepatic type and arises at the sinusoidal capillary level. Due to the absence of collaterals between hepatic veins and the presence of collaterals between venules in the portal tract, the occlusion of one hepatic vein blocks blood flow in the hepatic veins and in the sinusoids, thus blood pressure in the occluded position equals to pressure in the sinusoids. In turn, this equals to portal pressure in sinusoidal or post-sinusoidal PH (29,37).

Portal hypertension can be classified in different etiologies, according to the original site of increased vascular resistance to portal blood flow, as prehepatic, intrahepatic (presinusoidal, sinusoidal and postsinusoidal), and posthepatic, as described in Table 2 (31).

Table 2. Portal hypertension classification by etiology.

Portal hypertension classification			
Type	**Most Common Causes**	**Clinical Presentation**	**Hemodynamic Characteristics**
Prehepatic	Portal vein occlusion (thrombosis or neoplasm) Splenic vein occlusion (thrombosis or neoplasm) Portal vein stenosis	Splenomegaly GEVs Collaterals Variceal bleeding	Normal HVPG Normal WHVP Normal FHVP
Intrahepatic			
Presinusoidal	Schistosomiasis Primary biliary cholangitis (early stages) Primary sclerosing cholangitis Focal nodular hyperplasia Idiopathic PH Sarcoidosis	Splenomegaly GEVs Collaterals Variceal bleeding	Normal HVPG Normal or slightly elevated WHVP Normal FHVP
Sinusoidal	Cirrhosis (viral, alcoholic, NASH-related) Alcoholic hepatitis Primary biliary cholangitis (advanced stages)	Splenomegaly GEVs Collaterals Variceal bleeding Ascites Hepatic encephalopathy	Elevated HVPG Elevated WHVP Normal FHVP
Postsinusoidal	Venoocclusive disease	Splenomegaly Collaterals Ascites	Normal HVPG Elevated WHVP Elevated FHVP
Posthepatic			
Vascular obstruction	Hepatic vein thrombosis (Budd-Chiari syndrome)	Ascites Intrahepatic collaterals	Not possible to catheterize hepatic veins
Liver congestion	Chronic right heart failure Chronic constrictive pericarditis Restrictive cardiomyopathy Tricuspid insufficiency	Ascites	Normal HVPG Elevated WHVP Elevated FHVP

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Risk stratification in cirrhosis and PH is crucial for appropriate management and prognostic evaluation. Hepatic venous pressure gradient measurement is useful for risk stratification in low, intermediate, and high-risk cirrhosis (13,35-38). Low-risk cirrhosis (HVPG < 10 mmHg) patients exhibit minimal signs of PH and tend to be asymptomatic or have mild manifestations. The prognosis is generally favorable with a mortality rate at one year

less than 1%, and the risk of variceal bleeding is low. Intermediate-risk cirrhosis (HVPG 10-16 mmHg) patients are at an increased risk of developing varices and/or ascites. Variceal bleeding typically occurs at HVPG ≥ 12 mmHg (39,40). High-risk (HVPG > 16 mmHg) cirrhosis patients exhibit clinically decompensated cirrhosis and more severe clinical manifestations, including variceal bleeding, refractory ascites, SBP, HRS, hyponatremia and HE with a poorer prognosis. Several studies found an increased mortality risk in patients with HVPG beyond the threshold of 16 mmHg (41–44) and an HVPG ≥ 20 mmHg identifies patients at high risk of early rebleeding and bleeding related mortality (45). The risk classification of cirrhosis based on HVPG measurements allows for tailored management strategies, including pharmacological therapy, endoscopic interventions, or liver transplantation.

1.1.5.2. Hyperdynamic circulation

Cirrhosis and PH lead to a splanchnic and peripheral arterial vasodilatation with development of a hyperdynamic circulatory state (46).

The peripheral arterial vasodilation hypothesis (PAVH) identifies effective hypovolemia secondary to splanchnic arterial vasodilation as the primary pathogenetic mechanism responsible for the cardinal manifestations of cirrhosis, such as ascites formation and renal dysfunction (47).

Hyperdynamic circulation in liver cirrhosis is a complex hemodynamic alteration characterized by increased cardiac output and reduced systemic vascular resistance. Portal hypertension, arterial vasodilation, decreased systemic vascular resistance, enhanced myocardial contractility, altered neurohumoral regulation, endothelial dysfunction, and altered nitric oxide metabolism are key contributors to this pathophysiological state (48-50).

The release of various vasodilatory substances into the systemic circulation, including NO, carbon monoxide (CO), endocannabinoids, and vasodilatory prostaglandins causes systemic arterial vasodilation, particularly in the splanchnic circulation. This leads to a reduction in systemic vascular resistance, primarily observed in the splanchnic and peripheral arterial beds, reducing overall systemic arterial pressure. The decrease in systemic vascular resistance triggers compensatory mechanisms to maintain arterial blood pressure and organ perfusion. The neurohumoral response involves activation of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), and the release of vasopressin. These mechanisms aim to restore arterial pressure and systemic vascular resistance, resulting in an increased cardiac output. This compensatory increase in cardiac output is the result of enhanced myocardial contractility and increased heart rate. The increased venous return from the splanchnic circulation, facilitated by arterial vasodilation and decreased systemic vascular resistance, leads to increased preload and subsequently increased stroke volume. Additional factors directly contribute to enhanced myocardial contractility, such as an increase in circulating catecholamines due sympathetic activation and the presence of endogenous vasodilators, previously mentioned. Furthermore, the diseased liver releases pro-inflammatory cytokines and oxidative stress mediators, which impair endothelial function, along with the increased production of NO, primarily from the endothelium and activated macrophages, and impaired clearance thereof, promotes vasodilation, increased capillary permeability, and contributes to the hyperdynamic state. The long-term overactivation of these systems can lead to further systemic vasodilation and fluid retention.

The hyperdynamic state results in a hyperdynamic multi-organ syndrome that affects many organ systems, including the cardiovascular system with development of a cirrhotic

cardiomyopathy, autonomic dysfunction, and renal dysfunction as part of a cardiorenal syndrome (46).

1.1.5.3. Cirrhotic cardiomyopathy

Cirrhotic cardiomyopathy reveals as a state of low systemic vascular resistance, low central blood volume with high peripheral volume, a state of neurohormonal activation and high cardiac output, which may adversely affect cardiac reserve under stress (51,52). It was first described in 1953, as cirrhosis-associated cardiomyopathy, and described as a state of hyperdynamic circulation in patients with alcohol-related cirrhosis (53). In 2005, the World Congress of Gastroenterology in Montreal defined cirrhotic cardiomyopathy as "chronic cardiac dysfunction in patients with cirrhosis, characterized by blunted contractile responsiveness to stress, and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease", with diagnostic and supportive criteria, and a protocol for liver transplant candidates assessment (54). Clinically, cirrhotic cardiomyopathy may display subtle electrocardiographic and echocardiographic abnormalities, most commonly as prolonged QT interval and diastolic dysfunction, however, it may progress to fulminant myocardial failure under hemodynamic stress (i.e., liver transplant, sepsis or systemic inflammatory response syndrome), aggravated by the concomitant use of commonly prescribed medication (beta-blockers, mineralocorticoid antagonists, diuretics) (52).

1.1.5.4. Ascites

Ascites is defined as the presence of more than 25 ml of fluid in the peritoneal cavity, and the initial evaluation of a patient with ascites should include history, physical examination, abdominal ultrasound, and laboratory assessment of liver function, renal function, serum and urine electrolytes, as well as an analysis of the ascitic fluid (55-57).

Ascites is the first and most frequent clinical decompensation event in patients with cirrhosis, occurring in the context of PH and renal sodium retention (58–60). The development of ascites in cirrhosis indicates a poor prognosis with a mortality rate of approximately 40% at 1 year and 50% at 2 years (61).

The Forward Theory of Ascites Formation is based on the pathophysiological Peripheral Arterial Vasodilation hypothesis. The arterial vasodilation in the splanchnic circulation would induce the formation of ascites by simultaneously impairing the systemic circulation (hyperdynamic), leading to sodium and water retention, and the splanchnic microcirculation (portal hypertension), leading to the leakage of fluid into the abdominal cavity (62,64). The process of ascites formation is secondary to arterial splanchnic vasodilation, decreased effective arterial blood volume, activation of arterial and cardiopulmonary volume receptors, vasoconstrictor and sodium-retaining systems, such as the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), hyperdynamic circulation, inflammation and endothelium dysfunction, as previously described (56,60).

Ascites rarely develops in patients with a HVPG below 12 mmHg (39). In this context, increased hydrostatic pressure is critical, while decreased oncotic pressure and low plasma albumin concentrations may be of minor importance for the rate of ascites formation (55,65,66). Protein-rich fluid will not spill over into the peritoneal cavity, as long as transsinusoidal filtration, through fenestrated hepatic capillaries, conducts balance with local lymphatic drainage, though the thoracic duct. When transsinusoidal filtration exceeds lymphatic drainage, a small fraction (0.5 l per 24 h) of protein-rich fluid will accumulate in the peritoneal cavity, and equilibrate (dilute) according to hydrostatic and oncotic dynamics,

resulting in a relatively protein-poor ascitic fluid (55). Ascites due to PH present serum–ascites albumin gradient (SAAG) greater than or equal to 1.1 g/dl (or 11 g/L), with approximately 97% accuracy (67,68). Patients with total ascitic protein concentration lower than 15 g/L have an increased risk of SBP (56,59).

The majority of ascitic fluid is drained into the right lymphatic duct with relative low flow rate (1.5 l per 24 h). Increased PH raises hydrostatic pressure and peritoneal membrane filtration, along with diffusive transport of low-molecular components (water, electrolytes, glucose, creatinine, antibiotics, etc.) into the peritoneal cavity. Therefore, clinically significant ascites formation depends on the balance between upraised peritoneal transvascular filtration and relatively low lymph drainage (55).

The classification of ascites can be defined as:

Grade 1 - mild ascites only detectable by ultrasound;

Grade 2 – moderate ascites evident by moderate symmetrical distension of abdomen;

Grade 3 – large or gross ascites with marked abdominal distension (56).

Whereas, refractory ascites is defined as ‘‘ascites that cannot be mobilized or the early recurrence of which (i.e., after LVP) cannot be satisfactorily prevented by medical therapy”, according to the criteria of the International Ascites Club (ICA) (69).

Ascites in early stages can be treated with progressive restriction of sodium intake, aldosterone antagonists and loop diuretics, although as cirrhosis progresses it is estimated that from 5 to 10% of ascitic patients develop ascites that is refractory to standard medical

treatment each year (56,60,69,70). When ascites becomes refractory to medical therapy, then repeated LVP, combined with the administration of albumin (8 g per liter of ascitic fluid removed) to prevent paracentesis-associated circulatory dysfunction (PACD) is indicated for symptomatic relief. Additional therapies for PH with refractory ascites include insertion of transjugular intrahepatic portosystemic shunt (TIPS), and liver transplantation (56).

1.1.5.5. Hepatorenal syndrome

The broad definition of the term acute renal failure (ARF) has been refined over time and has mostly been replaced by the more accurate term acute kidney injury (AKI). Three consensus initiatives have defined AKI, either due to structural or functional injury, to produce evidence-based results and improve patient outcomes in the twenty-first century.

The Acute Dialysis Quality Initiative (ADQI) group developed, in 2004, the expert consensus-based RIFLE system for diagnosis and classification of a broad range of acute impairment of kidney function. The acronym RIFLE stands for the Increasing severity classes Risk, Injury, and Failure; and the two outcome classes, Loss and End-Stage Renal Disease (ESRD) (71).

Around the same time, in 2005, the Acute Kidney Injury Network (AKIN) was established as an independent international collaborative network to facilitate and pursue improved outcomes in patients with or at risk for AKI, resulting in a three-stage AKI classification system (72). Both these systems included serum creatinine concentration (sCr) and urine output for diagnosis and classification of AKI.

The Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group produced a comprehensive set of Clinical Practice Guidelines in 2012, analogous to the

AKI definitions and classification of the RIFLE and AKIN systems (73). The KDIGO guidelines define AKI as any of the following: 1) increase in sCr by ≥0.3 mg/dl within 48 hours; or 2) increase in sCr to ≥1.5x baseline, which is known or presumed to have occurred within the prior 7 days; or 3) urine volume <0.5ml/kg/h for 6 hours.

Hepatorenal syndrome is a specific type of AKI that develops in patients with liver cirrhosis. It has been long recognized and described by clinicians, although its pathogenesis and classification remains challenging (74). The history of AKI in liver cirrhosis can be traced back to the 19th century (75). Richard Bright (1789–1858) wrote on "dropsy" (edema) in his original 1827 "Report of Medical Cases". He remarked, that the liver, in case of dropsy due to kidney disease, was "seldom perfectly health" with "a tendency to granulation". In 7 cases of dropsy due to liver disease, urine was described as "scanty," diminishing, "high colored," with "pink sediment" that did not coagulate on heating case. In one case the kidney was described as "rather pale, with irregular vascularity but in structure normal," and in another it was said to be "large, unhealthy." (76). One of the first studies to describe renal pathology in patients with liver cirrhosis was Friedrich Frerichs (1819–1885) in his classic "A Clinical Treatise on Diseases of the Liver," published in 1858. This work describes the oliguria of liver failure, in the absence of significant changes in renal pathology, and was referred to as "cholemic nephropathy" (77,78). Around the same time, in 1863, Austin Flint (1812–1886) reported on 46 liver cirrhosis patients with ascites, where he conducted 11 autopsies and found 6 to presented extrahepatic organ involvement with renal "nephrosis", due to degenerative lesions, rather than inflammatory (79). Later in the twentieth century, in 1916, the French physician Prosper Jean Merklen (1874–1939), described 15 patients with acute hepatic failure, jaundice, and ascites who developed an "acute nephritis" with rapidly progressing oliguria which he termed "hépato-

néphrite aigue" (acute hepatonephritis) (80). Subsequently, Maurice Dérot in his 1937 monograph "Les Hépatonéphrites," described "hépatonéphrite simple" (simple hepatonephritis) and that of "hépatonéphrite chronique" (chronic hepatonephritis) or "syndrome hépatorenaux" (81).

The application of modern radiologic imagery techniques, and selective renal arteriography in HRS allowed the confirmation of a significant reduction in renal blood flow, preferentially, affecting the cortical perfusion (82,83).

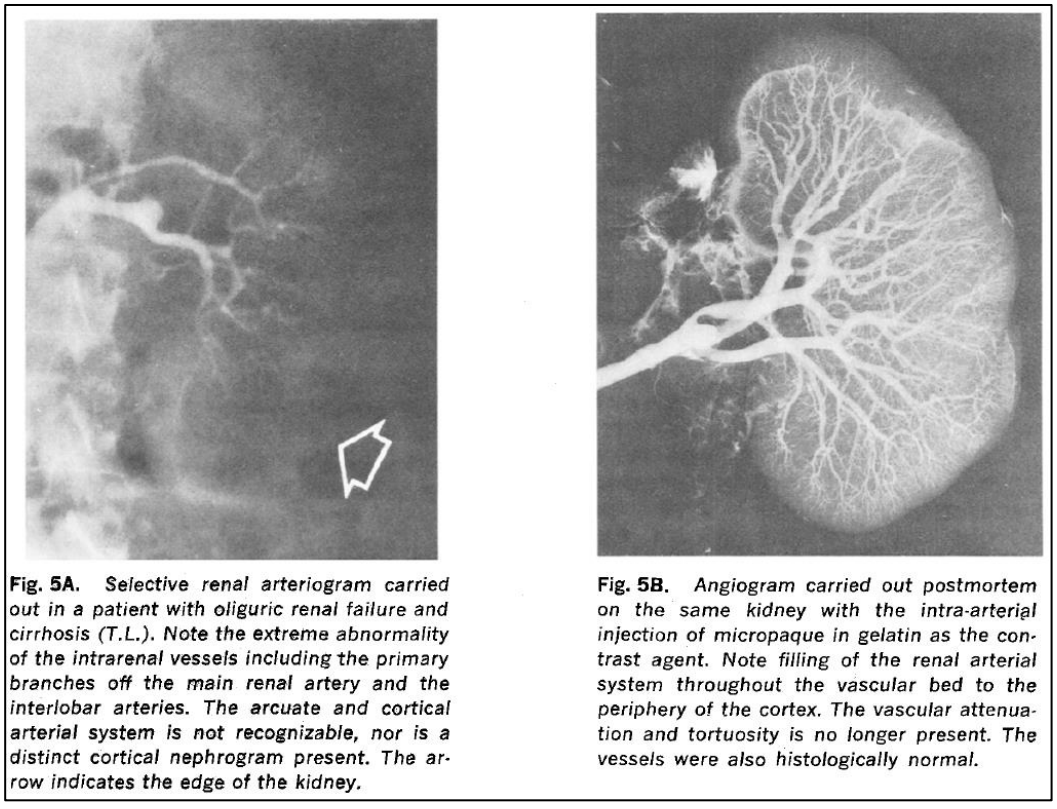

Fig. 5A. *Selective renal arteriogram carried out in a patient with oliguric renal failure and cirrhosis (T.L.). Note the extreme abnormality of the intrarenal vessels including the primary branches off the main renal artery and the interlobar arteries. The arcuate and cortical arterial system is not recognizable, nor is a distinct cortical nephrogram present. The arrow indicates the edge of the kidney.*

Fig. 5B. *Angiogram carried out postmortem on the same kidney with the intra-arterial injection of micropaque in gelatin as the contrast agent. Note filling of the renal arterial system throughout the vascular bed to the periphery of the cortex. The vascular attenuation and tortuosity is no longer present. The vessels were also histologically normal.*

Figure 4. Renal arteriography in hepatorenal syndrome. Reprinted with permission from Elsevier (License number 5583591141800) (83).

The impaired renal perfusion in a patient with liver cirrhosis with oliguric HRS was no longer present in the post-mortem study, suggesting "*a functional basis for the renal failure*" (Figure 4).

The first consensus conference to define and propose diagnostic criteria for HRS was held in Sassari, Italy, in 1978, resulting in a set of major and minor criteria (69,84). The ICA was created in 1990 with the aim of studying the mechanisms of circulatory and renal disfunction in liver diseases and the pathogenesis and treatment of ascites, HRS and SBP. Since its creation it has produced several consensus documents with revised definitions of HRS and updated clinical guidelines (69,85-87).

In 2007, the ICA classified HRS into type 1 (HRS-1), a rapidly deteriorating renal function that often occurs because of a precipitating event, and type 2 (HRS-2), a moderate and stable or slowly progressive renal dysfunction that often occurs without an obvious precipitant.

The HRS classification has been recently reviewed and modified (88). Hepatorenal syndrome type 1 was renamed HRS-AKI and included changes in urinary output (UO) for improved diagnostic and prognostic ability (89). Hepatorenal syndrome type 2 was renamed HRS-non-AKI (HRS-NAKI), and further distinguished acute kidney disease (HRS-AKD) that does not meet the criteria for AKI and lasts for <90 days, and HRS in patients with known chronic kidney disease (HRS-CKD).

The current ICA consensus definition and classification of AKI in patients with cirrhosis was modified to align with KDIGO criteria (86):

• Stage 1 defined as an increase in sCr ≥0.3mg/dl or an increase in sCr ≥1.5-2x from baseline;
• Stage 2 defined as an increase in sCr >2-3x from baseline; and
• Stage 3 defined as an increase of sCr >3x from baseline or sCr ≥4.0 mg/dl, with an acute increase ≥0.3 mg/dl or initiation of renal replacement therapy.

The current ICA criteria for HRS-AKI diagnosis are defined as (88):

• Presence of cirrhosis, acute liver failure or acute-on-chronic liver failure.
• Increase in sCr ≥0.3mg/dl within 48 hours or ≥50% from baseline value (using the last available value of outpatient sCr within 3 months) and/or UO =< 0.5 mL/kg body weight (BW) ≥6 hours (requires a urinary catheter);
• No full or partial response, according to ICA consensus document, after at least 2 days of diuretic withdrawal and volume expansion with albumin (the recommended dose of albumin is 1 g/kg of BW per day to a maximum of 100mg/day);
• Absence of shock;
• No current or recent treatment with nephrotoxic drugs;
• Absence of parenchymal disease as indicated by proteinuria >500mg/day, microhematuria (>50 red blood cells per high power filed), urinary injury biomarkers (if available) and/or abnormal renal ultrasonography (not included in cases of known pre-

existing structural chronic kidney disease);
• Suggestion of renal vasoconstriction with fractional excretion of sodium of <0.2% (with levels <0.1% being highly predictive).

The current ICA criteria for HRS-NAKI subtype diagnosis and classification are defined as (88):

HRS-AKD:
• Estimated Glomerular Filtration Rate (eGFR) <60 ml/min per 1.73m2 for <3 months in the absence of other (structural) causes.
• Percent increase in sCr <50% using the last available value of outpatient sCr within 3 months as the baseline value.
HRS-CKD:
• eGFR <60 ml/min per 1.73 m2 for ≥3 months in the absence of other (structural) causes.

Acute kidney injury HRS is currently recognized as a potentially reversible functional AKI due to multiple factors, including severe renal vasoconstriction, endotoxin-mediated inflammation, bile acid-induced tubular toxicity and true tubular ischemia (90,91). The treatment of AKI-HRS in based on volume expansion, including albumin, vasoconstrictor drugs or with liver transplantation (Figure 5) (91–93).

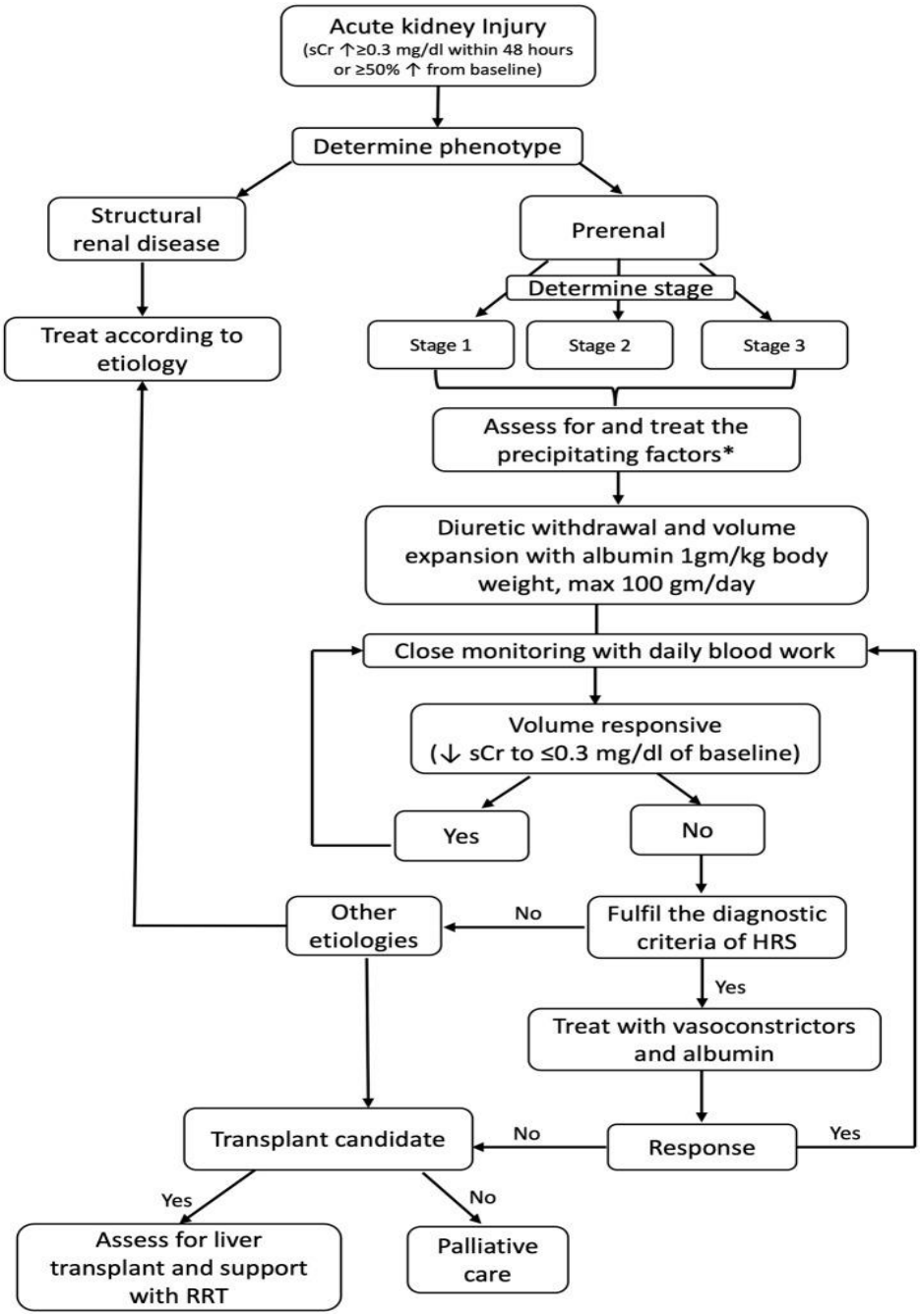

Figure 5. Clinical management algorithm for acute kidney injury including hepatorenal syndrome. Abbreviations: HRS, hepatorenal syndrome; max, maximum; RRT, renal replacement therapy; sCr, serum creatinine. *Precipitating factors: infections, excessive diuretics use, use of nephrotoxic drugs or radiologic contrast, sepsis, gastrointestinal blood loss, diarrhea secondary to lactulose, alcoholic hepatitis (93).

The management of AKI-HRS is based on excluding/treating hypovolemia with fluid challenge, including albumin infusion 1g/kg/day for two days, withdrawal of nephrotoxic, diuretic and negative inotropic drugs, treatment of any precipitant events and vasoconstrictors. Liver transplant is the ultimate treatment to cure AKI-HRS. Other therapeutic options can be considered on a case-by-case basis, such as the investigational role of transjugular intrahepatic portosystemic shunt, and RRT (does not improve survival AKI-HRS) as a bridge to decision to transplant (91,93,94).

1.1.5.6. Spontaneous bacterial peritonitis

Globally, the most frequent bacterial infections in hospitalized patients with cirrhosis are SBP (13-27%), urinary tract infections (20-29%), pneumonia (10-19%), bacteriemia (8-13%), skin and soft tissue infections (8-12%), depending on the cohort and varying according to the region of study (95-97). In hospitalized patients with cirrhosis infections are more frequently caused by Gram-negative bacteria (96,98,99). However, an increasing trend towards Gram-positive bacterial infections has been reported, particularly, in those with previous hospital admissions, prophylactic treatment with quinolones and submitted to invasive procedures (95,100-102). Furthermore, infections are more frequent in case of ACLF, acting as precipitant events, when compared to patient with cirrhosis hospitalized with acute decompensation. This is particularly significant in the case of pneumonia (7.7% vs 3%, p=0.015), secondary peritonitis (2.6% vs 0%, p=0.009) and in the more severe cases of ACLF grade 3 (52%, p=0.016) (97,103).

Spontaneous bacterial peritonitis is a bacterial infection in the peritoneum, with no apparent intra-abdominal source of infection. It is very common in patients with cirrhosis and ascites and presents in approximately 10% of hospitalized cases (56). Patients with SBP have

elevated risks of developing HE, sepsis and AKI (104). It is recommended that a diagnostic paracentesis should be carried out in all patients with cirrhosis and ascites at hospital admission to rule out SBP. Additionally, it should also be performed in patients that develop gastrointestinal bleeding, shock, fever, or other signs of systemic inflammation, gastrointestinal symptoms, as well as in patients with worsening liver and/or renal function, and HE. Spontaneous bacterial peritonitis is diagnosed thru the use of ascitic fluid cell analysis, when a neutrophil count is equal or greater than 250/mm3 or with a positive ascitic fluid bacterial culture. Patients with an ascitic fluid neutrophil count equal or greater than 250 cells/mm3 and negative culture have culture-negative SBP and should be treated in a similar manner. Empirical antibiotics should be started immediately following the diagnosis of SBP, taking into consideration risk factors for bacterial resistance to antibiotics, such as prophylaxis against SBP, high prevalence of antibiotic resistance or in case of nosocomial SBP (56).

Bacterascites refers to a patient with positive ascitic fluid culture with normal ascitic neutrophil count (<250/mm3), usually with general symptoms and signs of infection (56). In some asymptomatic patients, bacterascites may represent a transient and spontaneously reversible colonization of ascites, although in the presence of symptoms (abdominal pain, fever) it may represent the initial development of SBP. It is recommended that if there are signs of systemic inflammation or infection, the patient should be treated with antibiotics. Otherwise, the patient should undergo a second paracentesis when culture results come back positive. Patients in whom the repeat ascitic neutrophil count is >250/mm3 should be treated for SBP, and the remaining patients (i.e., neutrophils <250/mm3) should be followed up (56).

1.1.5.7. Hepatic encephalopathy

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting (PSS); it is revealed as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma (105).

The diagnosis of HE is clinical and through exclusion of other causes of neurologic dysfunction. Clinical signs include a wide spectrum of abnormal neuropsychological testes, cognitive/behavioral decay, disorientation and coma. Neurologic imaging does not add to the diagnosis of HE, however, it usually is part of the diagnostic workup in first-time HE (106). Laboratorial testing typically presents increased blood ammonia concentration, without diagnostic, staging or prognostic value for HE in patients with chronic liver disease (CLD), although a normal value should indicate a diagnostic reevaluation (105-107).

One of the first classification systems for HE correlated clinical signs with electroencephalographic findings into 4 grades (A-D) with increasing severity (108,109). The West-Haven (WH) HE clinical grading scale was latter introduced by Conn et al., named after West Haven Connecticut Veterans Affairs Hospital, where Conn practiced his clinical research in hepatology (109-111).

The current classification of HE takes into consideration (105):

1) the underlying disease, and subdivides into type A in acute liver failure, type B in portosystemic bypass or shunting, and type C in cirrhosis;

2) the severity of manifestations from the WH scale, distinguishing between covert (minimal or grade I) and overt (grades II-IV);

3) the time course, subdivided into episodic, recurrent (with a time interval of 6 months or less) and persistent (always present and interspersed with relapses of overt HE); and

4) the existence of precipitating factors: non-precipitated or precipitated (in nearly all bouts of episodic HE type C).

Table 3. West Haven classification for hepatic encephalopathy.

WHC including MHE	ISHEN	Description	Suggested operative criteria	Comment
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	**Covert**	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change.	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis. Local standards and expertise required
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioural decay with respect to his/her standard on clinical examination, or to the caregivers	Clinical findings usually not reproducible
Grade II	**Overt**	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season or year) ± the other mentioned symptoms	Clinical findings variable but reproducible to some extent
Grade III		• Somnolence to semi-stupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to pain stimuli	Comatose state usually reproducible

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Additionally, the Glasgow Coma Scale (GCS) is widely used in critical patients in intensive care, providing an operative, robust description of altered consciousness (Table 4). In patients with WH grade III-IV the GCS should be added (105,106, 112).

Table 4. Glasgow Coma Scale.

	GCS					
	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	n.a.	n.a.
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	n.a.
Motor	Makes no movements	Extension to painful stimuli (decerebrate response)	Abnormal flexion to painful stimuli (decorticate response)	Flexion/withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

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Minimal HE or covert HE occurs in 20%–80% of patients with cirrhosis, and overt in 16%–21% in those with decompensated cirrhosis (105,113,114). Hepatic encephalopathy is associated with poor survival and a high risk of recurrence (115). The treatment of HE is based on treating any precipitating factors, the administration of oral lactulose and, additionally, rifaximin for the prevention of recurrences (106).

1.1.5.8. Coagulopathy

Coagulopathy is common in the patients with cirrhosis, presenting with thrombocytopenia, prolongations in the prothrombin time (PT) and activated partial thromboplastin time (APTT), and decreased plasma fibrinogen (116).

Hemostasis is a complex process in which platelets adhere to the injured vessel wall and coagulation factors are activated to form cloth and stop bleeding. In clinical practice two common in vitro tests of coagulation measure time (seconds) required to form a cloth. The PT is measured in plasma to form a clot, via extrinsic and common coagulation pathways, and the International normalized ratio (INR) (INR = patient PT/control PT) serves as a reference value taking into account in PT measurement in device related variations, type of reagents used, and sensitivity differences in the TF activator (117). It is clinically used to monitor vitamin K

antagonist anticoagulant therapy. The APTT estimates the activity of the intrinsic and common coagulation pathways. It is clinically used to screen for coagulation factor deficiency, monitor unfractionated heparin therapy and detect the presence of lupus anticoagulant (118).

The clinically stable cirrhotic patient features the concept of a "rebalanced hemostasis" state (119). Cirrhosis affects the whole spectrum of procoagulants and anticoagulants, which are associated with both platelet hyperactivity and increased levels of von Willebrand factor (120). The liver is responsible for the synthesis of most procoagulant (i.e., prothrombin, factor V, and X) and anticoagulant (i.e., protein C, protein S, and antithrombin) factors, fibrinogen, as well as thrombopoietin, which regulates the production of platelets from megakaryocytes (116,121,122). Patients with cirrhosis present laboratorial changes that have classically been interpreted as a state of hypocoagulability. However, this notion has been progressively changing, particularly since portal vein thrombosis (PVT) is more frequent in patients with cirrhosis, as well as thrombotic events in liver disease patients when compared to the general population. In a prospective observational study the cumulative incidence of PVT was 3.7% and 7.6%, respectively, at 1 and 3 years, and previous decompensations of cirrhosis and thrombocytopenia were predictive of PVT development (123). A case-control study in hospitalized patients with cirrhosis and venous thromboembolism (VTE) revealed that traditional markers of coagulation such as INR and platelet count were not predictive of VTE, and that approximately 0.5% of admissions involving patients with cirrhosis resulted in a new thromboembolic event (124). Furthermore, in a large nationwide registry case-control study patients with liver disease presented nearly twice the risk for VTE and pulmonary embolism than population controls (125). This rebalanced hemostasis, however, appear fragile and patient

with decompensated liver disease can readily experience both hemostasis related bleeding and thrombotic events (126).

1.1.5.9. Variceal bleeding

Upper gastrointestinal variceal bleeding in the patient with cirrhosis is typically a consequence of ruptured gastric and esophageal varices. These varices are due to PH and can be found in more than half of the patients with compensated cirrhosis, and in the majority of patients with decompensated cirrhosis (127,128). Acute variceal bleeding is associated with a high 6-week mortality of 15–20% (129). An HVPG >10 mmHg is the strongest predictor of the development of varices and, therefore, sets the threshold for clinically-significant PH (128,130,131). Upper gastrointestinal varices in the patient with cirrhosis are classified into four types according to Sarin et al.: Gastroesophageal Varices (GOV) type 1-2 and Isolated Gastric varices (IGC) type 1-2 (132). The clinical guidelines and recommendations for prevention and management of acute variceal hemorrhage in the patient with cirrhosis include adequate hemodynamic resuscitation, restrictive red blood cell transfusion policy, vasoactive drugs, antibiotic prophylaxis, proton pump inhibition, endoscopic hemostasis and transjugular intrahepatic portosystemic shunt (TIPS), and are addressed in the Baveno Cooperation consensus meetings (133).

1.1.5.10. Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is characterized by intrapulmonary vascular dilatations resulting in ventilation-perfusion mismatch, diffusion restriction and arteriovenous shunts, causing impaired gas exchange in patients with liver disease (134). Typical symptoms include dyspnea on exertion or at rest and the classical signs of platypnoea (dyspnea worsening

when moving from supine to upright position) and orthodeoxia (>5% or >4 mmHg decrease in partial pressure of arterial oxygen [PaO2] after changing from supine to upright position). Patients are frequently asymptomatic and underdiagnosed, however, it affects 10–30% of patients evaluated for a liver transplantation and is associated with twice the risk of death, as well as worse functional status and quality of life (135). Diagnostic criteria for HPS include 1) liver disease (usually cirrhosis with PH), 2) positive contrast-enhanced transthoracic echocardiography and elevated alveolar-arterial oxygen gradient (AaO2) ≥ 15 mmHg (or ≥ 20 mmHg if age > 64 years) while breathing room air in the sitting position at rest. The severity of HPS is determined by the degree of hypoxemia and graded as mild (PaO2 ≥ 80 mm Hg), moderate (PaO2 = 60-79 mm Hg), severe (PaO2 = 50-59 mm Hg), and very severe (PaO2 < 50 mm Hg) (136). Management of HPS is supportive with supplemental oxygen. Because there are no medical therapies LT should be considered before the development of severe disease, and severe HPS should be considered an indication for LT (137).

1.1.5.11. Portopulmonary hypertension

Portopulmonary hypertension (POPH) refers to pulmonary artery (PA) hypertension in the setting of PH (138). Clinical features of POPH include dyspnea, fatigue and progressive signs of right heart failure (139). Diagnostic criteria are made by hemodynamic criteria via right heart catheterization measurements with an increase in mean PA pressure (mPAP) due to increased pulmonary vascular resistance (PVR) in the setting of a normal PA wedge pressure (PAWP) and exclusion of other causes of PH (140). Impaired PA blood flow can be due to contributions of vasoconstriction, proliferation of endothelium/smooth muscle, and platelet aggregation. Mediators associated with POPH include increased circulating ET-1 and estradiol levels and deficiency of prostacyclin synthase in pulmonary endothelial cells. The severity of

POPH is based on mPAP and graded as mild (25 ≤ mPAP < 35 mmHg), moderate (35 ≤ mPAP < 45 mmHg), and severe (mPAP ≥ 45 mmHg). Pulmonary artery hypertension approved therapies may be useful in improving hemodynamics and exercise capacity in patients with POPH and should be initiated in moderate severity POPH. Regardless of therapy, severe POPH is an absolute contraindication to LT due to the risk of heart failure during surgery (137).

1.1.5.12. Hyponatremia

Hyponatremia is the most common electrolyte abnormality in hospitalized patients (141). Practically half (49%) of hospitalized patients with cirrhosis present low serum sodium concentration as defined by a concentration ≤135 mmol/L. This is associated with severe ascites and frequent use of LVP, impaired renal function and HRS, HE and SBP (142). It may occur due to hypovolemia or dilutional hypervolemia and can be influenced by multiple factors, including dietary restriction and diuretics (143). The pathogenesis of hyponatremia in the patient with cirrhosis includes PH with systemic vasodilation, solute-free water imbalance, activation of the RAAS and sympathetic nervous systems and antidiuretic hormone, leading to retention of sodium and water (143).

Hyponatremia is an important predictor of mortality in patients with liver cirrhosis on the waiting list for liver transplantation, as it identifies the subgroup of patients with severe fluid retention and a higher risk of death. The impact of hyponatremia on Model for End-Stage Liver Disease score (MELD) score is enough to make a real difference in the probability of receiving a liver transplant and avert death, particularly in patients with lower severity, as the effect of hyponatremia gradually diminished as the MELD score increases (144). Additionally, it has been associated with increased morbidity and mortality in the immediate postoperative period of liver transplantation, related to central pontine myelinolysis (145–146).

1.1.6. Prognostic scores

The Child-Pugh score was originally developed to predict the 6-month mortality of patients with cirrhosis who underwent esophageal surgical ligation for bleeding varices but is now generally used to determine the 6-month mortality risk for all patients with complicated cirrhosis. It comprises the assessment of the following characteristics (ranging each from 1 [least severe] to 3 [most severe] and overall from 5 to 15): INR, bilirubin, albumin, HE, and ascites (147).

The MELD score was initially developed to predict 3-month mortality for patients with cirrhosis and PH who underwent a transjugular intrahepatic portal shunt (TIPS) procedure, but it is widely used to assess the 3-month mortality risk of these patients while on the waitlist for LT. It is based on the analytical evaluation of liver (INR and bilirubin) and renal (creatinine) function (146). In the United States, the MELD score was used to determine priorities for organ allocation in liver transplantation since 2002, and was replaced in 2016 by the MELD. Na score, as follows (148-150).

Candidates who are at least 12 years old receive an initial MELD(I) score equal to: 0.957 x Log^e (creatinine mg/dL) + 0. 378 x Log^e (bilirubin mg/dL) + 1.120 x Log^e (INR) + 0.643. Laboratory values less than 1.0 will be set to 1.0 when calculating a candidate's MELD score. The following candidates will receive a creatinine value of 4.0 mg/dL if: 1) creatinine value is >4.0 mg/dL, 2) two or more dialysis treatments within the prior 7 days, or 3) if 24 hours of continuous veno-venous hemodialysis (CVVHD) within the prior 7 days. The maximum MELD score is 40. The MELD score derived from this calculation will be rounded to the tenth decimal place and then multiplied by 10. For candidates with a MELD(i) score greater than 11, the MELDNa score is then re-calculated as follows: MELDNa = MELD(i) + 1.32*(137-Na) –

[0.033*MELD(i)*(137-Na)]. Sodium values less than 125 mmol/L will be set to 125, and values greater than 137 mmol/L will be set to 137.

1.2. Abdominal Compartment Syndrome

1.2.1. Historical overview

The history of compartment syndromes have long been recognized (151). Since medieval ages has *hydrops abdominis*, or abdominal ascites, been recognized as a pathological entity that needed interventional treatment. Guy de Chauliac (1298-1370) recognized hydrops abdominis, often combined with swollen legs, as a serious disease that required surgical treatment, namely paracentesis by means of cauterization, and from the 16-17th century onwards different types of trocars were used to drain ascites (151-153). A specific device proposed by doctor Nicolas Tulp in 1650 allowed to hold the abdominal trocar in place during drainage of the ascitic fluid (153). In 1667, Niels Stensen experimentally induced in dogs a pathological condition that mimicked the etiological principles of compartment syndromes, namely regional ischemic phenomena that subsided after blood flow restauration, and attributed this to neurological causes (154). It was until the year 1850 that muscular compartment syndrome was scientifically described by Hamilton and attributed to vascular cause (151). One year later, in 1851, the same principles were proposed for abdominal compartment syndrome (ACS) (155).

In the era of measurable pressures, Paul Bert described the elevation of intra-abdominal pressure (IAP) due to diaphragmatic descent during inspiration, through the use of tracheal and rectum tube insertion (156). Similar measures were performed by Christian Wilhelm Braune and correlated with urine output by E.C. Wendt (157,158). Ernst Odebrecht and Mosso & Pellacani then introduced intravesical pressure measures as surrogate of IAP (159,160). Subsequently, IAP was measured in multiple physiological and pathophysiological conditions. In 1911 Haven Emerson published “epoch-making” experimental results correlating signs of

cardiovascular collapse with strongly elevated IAP and noted that “relief of the laboring heart is constantly seen after removal of ascitic fluid” (161,162).

The concept of surgical decompression of muscular compartment syndrome in extremities was introduced by Bernhard Bardenheuer in 1906, and in 1940 Sir Heneage Ogilvie described the advantages of laparostomy in cases of extensive abdominal war wounds, avoiding the consequences of elevated IAP resulting from wound closure (163-165). The event of laparoscopic procedures with induced elevated IAP led Kron et al. to evaluate IAP in aortic repair surgery and to demonstrate the benefit of timely abdominal decompressive laparostomy on urine output (166,167). These studies described the Kron technique for methodological intravesical pressure measurements: “*The wall of the urinary bladder behaves as a passive diaphragm when the bladder volume is between 50 and 100 ml. Pressure measurements recorded simultaneously through a transurethral urinary bladder catheter and a peritoneal dialysis catheter were equal during several infusions of peritoneal dialysis solution. This unity is confirmed for pressures ranging from 5 to 50 mmHg and verifies that intra-abdominal pressure can be accurately measured through an indwelling urinary bladder catheter. This technique is now employed routinely in our surgical intensive care unit, and it appears that intra-abdominal pressure averages 3-15 mmHg after abdominal surgery*”. This method developed by Kron has subsequently modified over the years and the measure of IAP became more frequent in critically ill patients in intensive care (168,169). It should be noted that the Kron method had placed the reference point at the symphysis pubis, in contrast to the current standard method that uses the phlebostatic axis, corresponding to the right atrium, for zeroing the IAP pressure monitor device.

One of the first grading system of IAP was described by Burch et al. in 1996 with four grades: I, 10-15 mmHg; II, 16-25 mmHg; III, 26-35 mmHg; and IV >35 mmHg (170). Surgical decompression became mandatory in patients with grade III-IV intra-abdominal hypertension (IAH) (171).

1.2.2. Definitions

A milestone for the study of IAH and ACS was the creation of the World Society of Abdominal Compartment Syndrome (WSACS) in 2004. The WSACS has published a series of consensus definitions recognizing the clinical needs of patients with IAH/ACS (172-175).

The current definitions, accepted by the 2013 WSACS consensus panel, reaffirmed the reference standard for IAP measurement, normal and pathological IAPs (mmHg), grades and types of IAH, and introduced new definition, as follows (174):

1. IAP is the steady-state pressure concealed within the abdominal cavity.
2. The reference standard for intermittent IAP measurements is via the bladder with a maximal instillation volume of 25 mL of sterile saline.
3. IAP should be expressed in mmHg and measured at end expiration in the supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the midaxillary line.
4. IAP is approximately 5–7 mmHg in critically ill adults .
5. IAH is defined by a sustained pathological elevation in IAP ≥12 mmHg.

6. ACS is defined as a sustained IAP >20 mmHg (with or without an abdominal perfusion pressure [APP] <60 mmHg) that is associated with new organ dysfunction/failure.

7. IAH is graded as follows:

- Grade I, IAP 12–15 mmHg
- Grade II, IAP 16–20 mmHg
- Grade III, IAP 21–25 mmHg
- Grade IV, IAP >25 mmHg

8. Primary IAH or ACS is a condition associated with injury or disease in the abdominopelvic region that frequently requires early surgical or interventional radiological intervention.

9. Secondary IAH or ACS refers to conditions that do not originate from the abdominopelvic region.

10. Recurrent IAH or ACS refers to the condition in which IAH or ACS redevelops following previous surgical or medical treatment of primary or secondary IAH or ACS.

11. Abdominal perfusion pressure (APP) = MAP – IAP.

12. A polycompartment syndrome is a condition where two or more anatomical compartments have elevated compartmental pressures.

13. Abdominal compliance is a measure of the ease of abdominal expansion, which is determined by the elasticity of the abdominal wall and diaphragm. It should be

expressed as the change in intra-abdominal volume per change in IAP.
14. The open abdomen is one that requires a temporary abdominal closure due to the skin and fascia not being closed after laparotomy.
15. Lateralization of the abdominal wall is the phenomenon where the musculature and fascia of the abdominal wall, most exemplified by the rectus abdominus muscles and their enveloping fascia, move laterally away from the midline with time.

Additionally, the consensus statement categorized risk factors for IAH/ACS:

1. Diminished abdominal wall compliance: abdominal surgery, major trauma major burns, prone positioning.
2. Increased intra-luminal contents: gastroparesis/gastric distention/ileus, ileus, colonic pseudo-obstruction, volvulus.
3. Increased intra-abdominal contents: acute pancreatitis, distended abdomen, hemoperitoneum/pneumoperitoneum or intra-peritoneal fluid collections, intra-abdominal infection/abscess, intra-abdominal or retroperitoneal tumors, laparoscopy with excessive insufflation pressures, liver dysfunction/cirrhosis with ascites, peritoneal dialysis.
4. Capillary leak/fluid resuscitation: acidosis, damage control laparotomy, hypothermia, increased APACHE II or SOFA score, massive fluid resuscitation or positive fluid balance, polytransfusion.
5. Others/miscellaneous: age, bacteremia, coagulopathy, increased head of bed angle, massive incisional hernia repair, mechanical ventilation, obesity or increased body mass

index, peep>10, peritonitis, pneumonia, sepsis, shock or hypotension.

The WSACS guidelines presented a set of consensus management statements regarding the clinical management of IAH /ACS, including:

Recommendations:
i. measuring IAP when any known risk factor for IAH/ACS is present in a critically ill or injured patient.
ii. studies should adopt the trans-bladder technique as the standard IAP measurement technique.
iii. use of protocolized monitoring and management of IAP versus not.
iv. efforts and/or protocols to avoid sustained IAH as compared to inattention to IAP among critically ill or injured patients.
v. No recommendation could be made regarding use of APP in the resuscitation or management of the critically ill or injured.

Suggestions:
i. that clinicians ensure that critically ill or injured patients receive optimal pain and anxiety relief.

ii. brief trials of neuromuscular blockade as a temporizing measure in the treatment of IAH/ACS.
iii. that the potential contribution of body position to elevated IAP be considered among patients with, or at risk of, IAH or ACS.
iv. liberal use of enteral decompression with nasogastric or rectal tubes when the stomach or colon are dilated in the presence of IAH/ACS.
v. using a protocol to try and avoid a positive cumulative fluid balance in the critically ill or injured patient with, or at risk of, IAH/ACS after the acute resuscitation has been completed and the inciting issues have been addressed.
vi. use of percutaneous catheter drainage (PCD)to remove fluid (in the setting of obvious intraperitoneal fluid) in those with IAH/ACS when this is technically possible compared to doing nothing. We also suggest using PCD to remove fluid (in the setting of obvious intraperitoneal fluid) in those with IAH/ACS when this is technically possible compared to immediate decompressive laparotomy as this may alleviate the need for decompressive laparotomy.

Furthermore, the WSACS guidelines include an IAH/ACS medical management algorithm that summarizes the consensus management statements, depicted in the figure below.

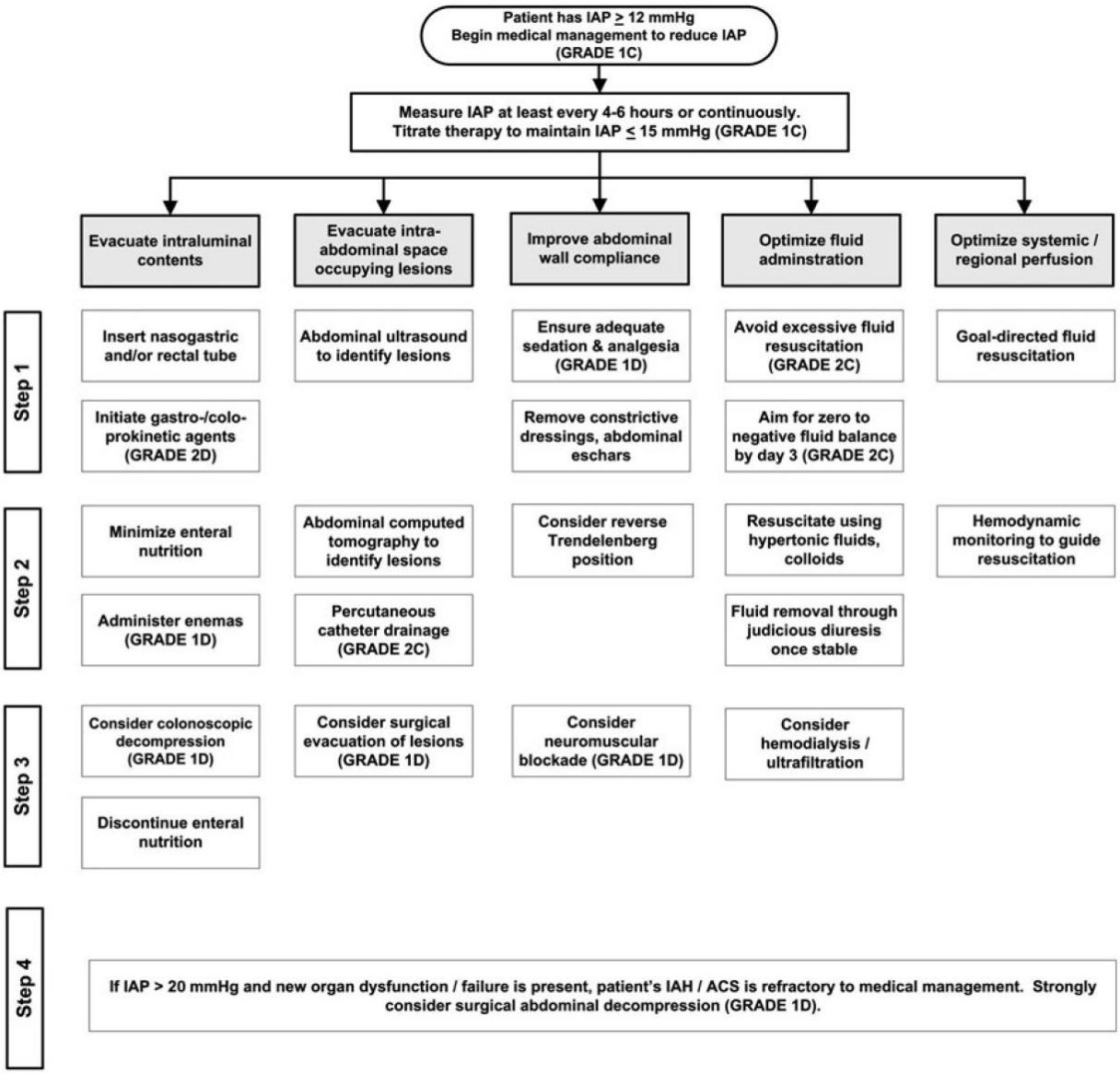

Figure 6. A medical management algorithm for IAH/ACS. IAH Intra-abdominal hypertension, ACS abdominal compartment syndrome, IAP intra-abdominal pressure. (176)

Particularly, it is noted that although paracentesis has long been a diagnostic and therapeutic procedure among those without documented IAH, the insertion of an indwelling PCD catheter in an attempt to improve IAP and associated patient-important outcomes among those with IAH/ACS was only first suggested in 2001 (176,177).

1.3. Acute-on-Chronic Liver Failure

1.3.1. Historic overview

Acute-on-chronic liver failure (ACLF) is an heterogenous clinical syndrome that affects patients with chronic liver disease following an acute insult or precipitating event resulting in an increase in short term mortality. The history of the clinical ACLF syndrome began in the last decade of the twentieth century. As it continued to be progressively acknowledged by clinicians, multiple definitions were proposed and, currently, international definitions present regional differences that preclude a universal definition.

The term ACLF was first used in Japan, in 1995, by Ohnishi H. et al. to describe a clinical condition where both an acute and a chronic insult coincided (178).

A decade later, a first international expert-based consensus definition of this clinical syndrome was presented (2009) by the Asian Pacific association for the study of liver (APASL) (179). This ACLF definition stated " acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease". Liver failure in ACLF was deemed mandatory to present: 1) jaundice (serum bilirubin ≥5 mg/dl) and coagulopathy (INR ≥1.5 or prothrombin activity <40%); and 2) ascites and/or encephalopathy as determined by physical examination. The acute event was classified into: 1) infectious, 2) noninfectious and 3) unknown hepatotoxic etiology. The underlying CLD included 1) compensated cirrhosis of any etiology, 2) chronic hepatitis, 3) nonalcoholic steatohepatitis, 4) cholestatic liver disease and 5) metabolic liver disease. Furthermore, the pathophysiology of ACLF recognized a central role of systemic inflammation, sepsis, HVPG and systemic hemodynamics, liver histology,

prognostic scores and liver transplantation. The consensus definition was latter updated in 2014 and 2019 to include prospective ACLF patient data from the APASL ACLF Research Consortium (AARC) with nearly 1400 patients (180,181). One of the major changes was the inclusion of short term (28 days) prognosis in the definition. Other specific aspects were refined, including the reclassification of acute events into 1) infectious (hepatotropic and non-hepatotropic), 2) drug-induced liver injury, 3) auto-immune liver disease, 4) acute variceal bleeding and 5) vascular liver diseases, and the qualification of underlying CLD as 1) cirrhotic and 2) non-cirrhotic.

The first evidence-based definition of ACLF was presented in 2013 by the European Association for the study of Liver (EASL) Chronic Liver Failure CONSORTIUM (CLIF-C) defining the syndrome's diagnostic criteria and assessing its natural history from a prospective cohort of 1343 patients with cirrhosis with AD (97). The EASL CLIF-C definition of ACLF definition deemed that acute decompensation was necessary with the onset of acute organ failure (OF) and presented a high 28-day mortality rate. A high 28-day "short-term" mortality rate was predefined to be greater than 15% for one OF, and the clinical severity Sequential Organ Failure Assessement (SOFA) score was specifically modified into the CLIF-SOFA score to differentiate organ disfunction from OF, and ACLF from simple acute decompensation ("non-ACLF") in cirrhotic patients.

1.3.2. Definitions

The original Sepsis Organ Failure Assessment (SOFA) score described by Vincent et al., included a subscore for six organic systems (liver, kidney, cerebral, coagulation, circulation, lungs), ranging from normal function to increasing disfunction and failure, respectively 0 to 4 (182).

Table 5. Chronic Liver Failure – Sequential Organ Failure Assessment score.

Organ/system	0	1	2	3	4
Liver (bilirubin, *mg/dL*)	<1.2	≥1.2 to ≤2.0	≥2.0 to <6.0	≥6.0 to <12.0	**≥12.0**
Kidney (creatinine, *mg/dL*)	<1.2	≥1.2 to <2.0	**≥2.0 to <3.5**	**≥3.5 to <5.0**	**≥5.0**
				or use of renal replacement therapy	
Cerebral (HE grade)	No HE	I	II	**III**	**IV**
Coagulation (international normalized ratio)	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	**≥2.5 or platelet count ≤20×10^9/L**
Circulation (mean arterial pressure, *mm Hg*)	≥70	<70	**Dopamine ≤5 or dobutamine or terlipressin**	**Dopamine >5 or E ≤0.1 or NE ≤0.1**	**Dopamine >15 or E >0.1 or NE >0.1**
Lungs					
PaO/FiO_2 or	>400	>300 to ≤400	>200 to ≤300	**>100 to ≤200**	**≤100**
SpO_2/FiO_2	>512	>357 to ≤512	>214 to ≤357	**>89 to ≤214**	**≤89**

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The CLIF-SOFA score was modified to address cirrhotic patient specificities, namely, the use of WH score for neurologic assessment of HE, the use of INR for coagulation and terlipressine for the cardiovascular subscores. It provided a definition for OF in patients with cirrhosis, clearly differentiating from organ dysfunction, in each subgroup.

Accordingly, single OF was defined as:

1) Liver: bilirubin ≥ 12.0 mg/dL,
2) Kidney: creatinine ≥ 3.5 mg/dL or use of renal replacement therapy (RRT),
3) Central nervous system: WH grade III-IV,
4) Coagulation: INR ≥ 2.5 or platelet count ≤ 20.000 10^6/L,
5) Cardiovascular: use of dopamine, dobutamine, terlipressine or noradrenaline,
6) Respiratory: PaO2/FiO2 ≤ 200 or SpO2/FiO2 ≤214.

The aggregated score ranges from 0 to 24 and provides overall clinical severity.

Additionally, the authors observed that patients with one OF at study enrollment had a significant higher 28-day mortality if there was concomitant kidney dysfunction (creatinine equal or greater than 1.2 mg/dL and lesser than 2.0 mg/dL) or neurologic dysfunction (HE grade I-II).

The classification of ACLF grade was, therefore, based on the number of OF.

a) Grade 1, with one OF included 3 subgroups.
i. patients with single kidney failure.
ii. patients with single cerebral failure, plus renal disfunction.
iii. patients with single OF, plus renal and/or neurologic disfunction.
b) Grade 2, with two OFs.
c) Grade 3, with three or more OFs.

The 28-day mortality rates in patients with ACLF were 23.3% for grade 1, 31.3% for grade 2, and 74.5% for grade 3, while for patients without ACLF it was 1.9%. Furthermore, the results emphasized that the absence of a prior history of acute decompensation, specific age, CLD etiology and precipitating events were consistent with an intense systemic inflammatory responses in parallel with the severity of ACLF.

Overall, the prevalence of ACLF in patients with AD was 30% and was associated with a short-term mortality rate approximately 15 times higher than that in patients with acute decompensation alone. Thus, the CLIF-C ACLF combined the CLIF-OF scores plus two additional independent predictors of mortality, age and WBC count, with a high predictive ability for mortality, both in the short (28 days) and long (12 months) term (183,184).

A working definition of ACLF proposed in 2015 by the World Gastroenterology Organization (WGO) tried to establish a bridge between the East (APASL) and West (EASL), respectively, recognizing that the definitions reflected a liver-centered versus an OF-centered understanding of the ACLF syndrome (185). Some of these differences in ACLF definitions rely on the thresholds of total bilirubin, INR and HE grade, the types of acute precipitant events such as sepsis or acute variceal bleeding, the presence of extra-hepatic OF, compensated CLD or cirrhosis without acute decompensation, and the prior history of clinical decompensation (185). These differences result in different CLD populations depending from where they are drawn(185-188). This becomes evident when we consider the regional differences of CLD etiologies with a greater proportion of viral hepatitis in the East and alcoholic liver disease in the West as previously described.

The WGO defined ACLF as “syndrome in patients with CLD with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure with jaundice and prolongation of the INR and one or more extrahepatic OFs that is associated with increased mortality within a period of 28 days and up to 3 months from onset” (185). Furthermore, it classified three types of ACLF, according to the clinical stage of CLD:

Type A – non-cirrhotic chronic liver disease with an acute flare;

Type B – well compensated cirrhosis with an acute insult;

Type C – cirrhosis with previous hepatic decompensation.

Thus, this definition includes patients with chronic hepatitis, compensated cirrhosis as well as cirrhosis with previous decompensation. Hence, in this proposed definition, non-cirrhotic chronic liver disease, type A ACLF may be indistinguishable from acute or sub-acute liver failure, including reactivation of hepatitis B, hepatitis A or E superimposed on chronic hepatitis B, autoimmune hepatitis, and hepatitis E infection in patients at risk for NASH (185-189).

The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) is a consortium of sixteen tertiary-care hepatology centers in the United States of America and Canada, was initially formed in 2011 to study the role of infection in patients with cirrhosis, and later expanded to include both infected and non-infected cirrhotics (190). In 2018, the NACSELD defined ACLF as ≥2 OFs from the following (95):

• brain failure was determined to be a 3 or 4 WH grade of encephalopathy,
• renal failure was the need for RRT,
• respiratory failure was assessed as the need for bilevel positive airway pressure non-invasive ventilation or invasive mechanical ventilation, and
• shock, defined as the need for pressor support or a mean arterial pressure (MAP) < 60 mm Hg or a reduction of > 40 mmHg in systolic blood pressure from baseline despite adequate fluid resuscitation (95).

The NACSELD-ACLF clinical score has been validated in a large multinational prospective cohort and considered to be a simple, reliable bedside tool to predict 30-day survival in hospitalized cirrhotics (95). In this study 30-day survival was analyzed in 2675 patients and the number of OF was observed as the strongest predictor of decreased survival, independently from age, white blood cell count, serum albumin, MELD score and the presence of infection.

1.3.3. Systemic inflammation

The Systemic Inflammation Hypothesis positions inflammation as a core factor in the development of decompensation and organ dysfunction in cirrhosis (47). It is widely accepted that cirrhosis is associated with systemic inflammation as assessed by increases in white cell count, activated circulating neutrophils and monocytes, plasma C-reactive protein, pro-inflammatory cytokines, markers of macrophage activation and systemic oxidative stress (191-193).

Small intestinal bacterial overgrowth (SIBO) and qualitative dysbiosis initiate and sustain systemic inflammation in cirrhosis (47). In addition, SIBO is common in cirrhosis, more often detected in patients with more severe cirrhosis, and is associated with ascites, minimal HE, malnutrition, SBP and bacterial translocation (194).

A first mechanism of chronic "sterile" systemic inflammation would be the release of pathogen-associated molecular patterns (PAMPs) into the systemic circulation and peripheral organs, resulting from the interaction of bacterial translocation from the intestinal lumen and their neutralization in the intestinal mucosa (195,196). A second "sterile" source of

inflammation would be acute hepatic inflammatory processes with the systemic release of damage-associated molecular patterns (DAMPs) and subsequent activation of immune cells (47). A final, third inflammatory mechanism of systemic inflammation would be overt bacterial infections leading to an exaggerated inflammatory response given the state of pre-activation of the innate immune system due to chronical bacterial translocation and other pro-inflammatory stimuli (197,198).

These critical factors contribute to the grade of systemic inflammation in cirrhosis that parallels the severity of clinical decompensations, of liver, circulatory and renal dysfunction, HE and ACLF, ultimately leading to death (97,199,200).

1.4. A preliminary study

1.4.1. Introduction

Due to the growing interest and recognition of ACLF as a distinct clinical syndrome, a study to characterize the clinical presentation, evolution, and outcomes of a population of ACLF patients was conducted at our center (201).

1.4.2. Methods

This was a single-center retrospective cohort study of ACLF patients admitted to the intensive care unit (ICU) at Hospital de Curry Cabral between 2013 and 2015.

Inclusion criteria were adult patients with age ≥18 years and with a known diagnosis of cirrhosis. Exclusion criteria were patients with age >85 years, prior liver and/or kidney transplant; end-stage renal disease on a regular dialysis program, pregnancy, hepatocellular carcinoma outside the Milan criteria, and known human immunodeficiency virus infection.

ACLF was diagnosed and classified in accordance with the EASL CLIF-C criteria (97). Different causes of decompensation were categorized into bacterial infectious insults, such as pneumonia, SBP, and urinary tract infections, and nonbacterial infectious insults, such as active HCV, upper gastrointestinal bleeding, portal vein thrombosis, acute cardiac failure, and carcinoma of the ampulla of Vater. Additionally, AKI was diagnosed using the adaptation of the AKIN criteria to define AKI in patients with cirrhosis, as proposed by the ADQI along the ICA (202,203). According to these criteria, AKI was defined as an increase in the serum creatinine (Scr) level of ≥ 0.3 mg/dL within 48 h or an increase in the Scr level by ≥ 50% from baseline that is known or presumed to have occurred within the prior 7 days.

The MELD scoring system was used to estimate the severity of the hepatic dysfunction for the different grades of ACLF (204). The outcome of patients was evaluated 28 and 90 days after ICU admission. The prognostic impact of the different grades of ACLF, of intrahepatic versus extrahepatic ACLF precipitant event, of AKI and RRT, and of liver transplant were analyzed. Statistical analysis included the Kruskal-Wallis test and the Exact Fisher's test and the statistical software SPSS (v.18. Chicago: SPSS Inc.) was used.

1.4.3. Results

Sixty-two patients were admitted in the ICU with a new episode of acute decompensation of cirrhosis and a total of 29 patients were included in the analysis.

Considering these 29 patients, 90% were male (n = 26) with a median age of 50 years, a minimum of 18 and a maximum of 81 years.

Regarding the etiology of cirrhosis, 41% of patients had alcoholic liver cirrhosis alone, 24% had cirrhosis due to both HCV infection and alcoholic liver disease, 21% had liver disease due to HCV infection alone, and cirrhosis due to primary sclerosing cholangitis, cryptogenic hepatic cirrhosis, hepatocellular carcinoma and hemochromatosis with alcoholic liver disease each had a frequency of 3.4%.

The precipitant ACLF event was a bacterial infection in 48.3% (14) patients versus 51.7% (15) with nonbacterial infectious event, as described in Table 6.

Table 6. Bacterial infections and other insults identified as causes of ACLF.

Bacterial infectious insult	Nonbacterial infectious insult
Pneumonia (n = 8; 27.5%)	Upper gastrointestinal bleeding (n=11; 38%)
Spontaneous bacterial peritonitis (n = 2; 6.9%)	Acute cardiac failure (n=1; 3.4%)
Urinary tract infections (n = 4; 13.8%)	Ampulla of Vater carcinoma (n=1; 3.4%)
	Active hepatitis C virus (n=1; 3.4%)
	Portal vein thrombosis (n=1; 3.4%)

A higher MELD score was associated with higher grade of ACLF ($p < 0.04$), especially when comparing ACLF grade 1 with 2 and 3, with a less notorious MELD difference between ACLF grades 2 and 3 (Figure 7).

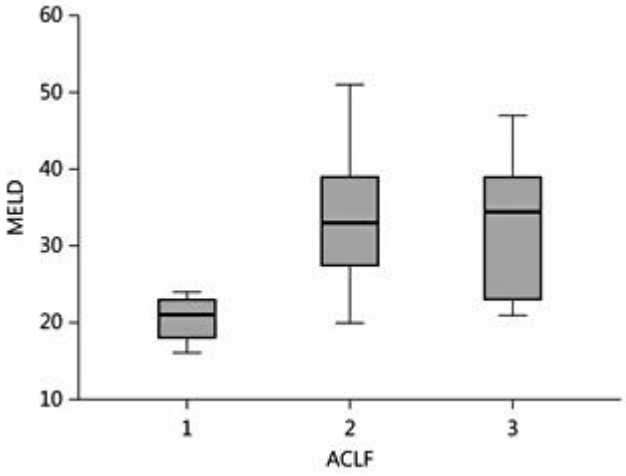


Figure 7. Comparison of MELD score between ACLF grades. Kruskal-Wallis test. ACLF, acute-on-chronic liver failure; MELD, model for end-stage liver disease.

The overall mortality was 69%, equal in both 28 and 90 days as described in Table 7.

Table 7. Outcome of patients by ACLF grade.

ACLF	Outcome at 28 and 90 days		Total
	Alive	Deceased	
Grade 1	4	0	4
Grade 2	4	7	11
Grade 3	1	13	14
Total	9	20	29

Higher grades of ACLF were associated with increased mortality ($p < 0.02$).

Patients with bacterial infectious as precipitant event had a 90-day mortality rate of 64.3%, versus 73.0% in those with non-infectious event, without statistically significant difference (p=0.9).

Twenty-four patients (83%) developed AKI and RRT was required in 12 of these patients, with a 92% 28-day mortality rate in this subgroup of patients. All patients with ACLF due to bacterial infectious insult developed AKI.

Finally, LT was performed in 3 patients and they were alive at 90-day follow-up.

1.4.4. Discussion

This was the first study of the ACLF syndrome in Portuguese patients. Acute-on-chronic liver failure syndrome patients composed a heterogeneous population with multiple etiologies of cirrhosis, precipitant events and high mortality rates.

The most frequent etiology of cirrhosis was alcoholic liver cirrhosis, in accordance with data from the European region (7,11,97,205).

There was a wide diversity of ACLF precipitating events, particularly upper gastrointestinal bleeding (non-infectious) and pneumonia (infectious).

The MELD score varied significantly between ACLF grade, more prominently when comparing grade 1 with higher grade of ACLF. This may be due to the fact that ACLF is a systemic disorder, and the MELD is an indicator of hepatic dysfunction. As the syndrome progresses, its outcome may be more impacted with the degree of multi-organ failure than with the severity of the hepatic disease.

Acute-on-chronic liver failure is life-threatening condition, reaching two thirds of deceased patients at day 28 and 90 days in the most severe grades, as reported in the literature (97,206,207). We were not able to establish a difference between the outcome of ACLF caused by bacterial infection ACLF versus nonbacterial infectious mechanisms. Although infection status remains an important predictor of death, it was not identified as an independent risk factor for ACLF mortality (95).

Acute kidney injury presented in the majority of patients, and half of them required RRT, highlighting the importance of renal function in extrahepatic ACLF involvement (97,206-208). Interestingly, all patients with ACLF caused by infections developed AKI. This may be due to an increased systemic inflammation triggered by the infection, which has been suggested to contribute as a pathophysiological hallmark for the development of structural AKI in patients with ACLF (209). The main causes of AKI in patients with cirrhosis are functional changes, induced by pre-renal hypoperfusion from hypovolemia and accounting for approximately half of cases. This may be partly due to diuretic therapy and lactulose-associated diarrhea, but also due to critical states of shock. Approximately 15-20% are attributable to HRS. Intrinsic causes, such as glomerulonephritis, acute tubular necrosis and other forms of tubular dysfunction or

parenchymal disease, account for approximately 30% of cases. Less than 1% are of obstructive origin (74,86). Acute kidney injury secondary to structural changes is more common in ACLF patients, this being due to the presence of inflammation in the pathophysiological mechanisms (209). Histological findings of 127 post-mortem kidney biopsies of patients hospitalized with ACLF, or decompensated cirrhosis, with a diagnosis of AKI due HRS, showed that bile cast nephropathy (BCN), characterized as renal tubular epithelial injury together with intraluminal bile cast formation, was independently associated with direct bilirubin serum concentration and the presence of ACLF (210). The distinction between functional and structural AKI assumes a paramount importance, particularly, when the liver transplant is considered a therapeutic option, since functional AKI will probably subside after liver transplant, on the contrary, structural AKI may require simultaneous liver-kidney transplant (207,211).

1.4.5. Conclusion

ACLF is a heterogeneous syndrome with a variety of etiologies for cirrhosis, precipitant factors, and different grades of extrahepatic organ involvement. Early diagnosis and quick reference to a hepatic transplant center could be crucial in the management and success of this clinical situation. Most cases will have some degree of renal dysfunction, with an increased risk of mortality. Hepatic transplant may be an efficient form of therapy for this syndrome in selected patients.

1.5. Aims, objectives and hypothesis

Liver cirrhosis is a common cause of death and a worldwide public health problem linked to alcohol consumption and viral hepatitis (4,6,7,9). Patients with cirrhosis develop complications that include refractory ascites, SBP, or AKI-HRS, and precipitate acute critical illness with OF, comprehended by the ACLF syndrome (56,97). Patients with cirrhosis and ascites are at increased risk for the development of IAH/ACS (176), an underappreciated cause of organ dysfunction/failure, and may play a role in the development of AKI-HRS (74,91). The treatment of IAH/ACS through abdominal paracentesis results in short-term improvement of renal and respiratory dysfunction in these patients (212–214). However, ffundamental data is scarce regarding the impact of IAH/ACS on clinical outcomes in critically ill patients with cirrhosis and ascites in intensive care (176,215).

The aim of this thesis was to study critically ill patients with cirrhosis and IAH in intensive care.

The specific objectives were the following:

1. to characterize a cohort of ACLF patients and analyze mortality risk factors;
2. to determine the prevalence of IAH/ACS, risk factors and clinical outcomes;
3. to characterize APP, analyze the prevalence of AhP, risk factors and associated outcomes;
4. to determine the prevalence of AhP, and the impact of APP on ARF;
5. to test the hypothesis that continuous passive paracentesis for the prevention and treatment of IAH improves clinical outcomes when compared to standard intermittent LVP in patients with cirrhosis with ascites in intensive care.

Chapter 2

Critical Patient with Cirrhosis

2.1. Introduction

The critically ill patients with cirrhosis poses a challenge for intensive care specialists. Therapeutic advances such as albumin dialysis, high volume plasma exchange and transplantation in increasingly severe patients have brought critically ill patients with cirrhosis closer to the intensive care setting. Nonetheless, high mortality rates and advanced chronic liver disease, combined with acute critical illness, represent increased difficulty in determining which patients with cirrhosis benefit most from intensive care therapy (216-219).

Chronic liver disease patients hospitalized with acute decompensation can develop an inflammatory state with ensuing acute OF leading to ACLF syndrome (220-222).

Acute-on-chronic liver failure syndrome is clearly defined in the multicentric CANONIC study and represents a severe subgroup of decompensated patients with cirrhosis with acute OF, as assessed by the CLIF-SOFA score (222). These patients present a complex clinical course with high short-term mortality rates despite vital organ support (223-225) .

Liver transplantation (LT) may be an option for some patients, although the selection of potential candidates and the timing for this intervention remains complex (217,226).

Furthermore, ethical issues concerning futility of care while receiving vital organ support in the intensive care unit (ICU) increase the complexity of the clinical management of these patients(218,227-229).

2.1.1. Aims and objectives

We aimed to present epidemiologic data from a single center cohort of ACLF patients accepted in intensive care.

The primary objective of this study was to identify the all-cause 28-day mortality rate post-ICU admission, and the secondary objective was to analyze 28-day mortality risk factors assessed at ICU admission (day 0) and 72 hours (day 3) thereafter.

2.2. Methods

2.2.1. Design, settings and participants

This study was a retrospective analysis from a prospective registry of patients with ACLF from a general ICU, specialized in liver disease, situated at Hospital Curry Cabral, within a tertiary hospital center, Centro Hospitalar Universitário Lisboa Central, Lisboa, Portugal, with a regional LT program, between 03/2013 and 12/2016.

The inclusion criteria were as follows: age ≥18 years; previous diagnosis of cirrhosis, acute OF present or expected at ICU admission, and first ICU admission from the index hospital stay; and the exclusion criteria were as follows: acute liver failure, cirrhosis without OF during the ICU stay; history of previous LT; and ICU admission for surgical reasons.

2.2.2. Definitions, exposures and outcomes

Cirrhosis was defined as bridging fibrosis on previous liver biopsy or a composite of clinical signs and findings provided by laboratory tests, endoscopy, and radiologic imaging (220). Despite worldwide variations in the definition of ACLF, we defined OFs and ACLF as per the European Foundation for the Study of Chronic Liver Failure Consortium (CLIF-C) definitions (222).

The general ICU and specific cirrhosis clinical severity of illness scores considered upon ICU admission and at D3 were the following: the CLIF-SOFA score and ACLF grading system, the Child-Pugh score, the MELD score, and the APACHE II score.

All data on patient characteristics were retrieved from medical records and collected in an anonymous and protected database. The clinical data and variables were collected at ICU admission (day 0) and after 72 hours (day 3) for 28-day mortality risk factor analysis. The following clinical variables were assessed: age, sex, etiology of liver disease, previous decompensation and complications (ascites, portal vein thrombosis and HCC) of cirrhosis, precipitating event of acute illness (alcohol, infection, bleeding, and others), general laboratory parameters including complete hemogram, biochemical serum analyses and arterial blood lactate concentration, clinical severity scores at ICU admission day (D0) and at the third day (D3), and organ support (vasopressor use, mechanical ventilation and renal replacement therapy [RRT]).

Organ failure in this study used the CLIF-SOFA score definition. The calculation of the Delta CLIF-SOFA used D3 minus D0 scores. Bleeding - a category of the “precipitating event” variable - was transformed into a dichotomous variable for multivariate logistic regression.

2.2.3. Statistical analysis

Continuous and categorical variables were described as medians (interquartile ranges – IQRs) and frequencies (percentages - %), accordingly. The univariate analysis of 28-day mortality rate risk associations was performed using Mann-Whitney and Chi-square tests, where appropriate. The multivariate backward stepwise logistic regression included variables with $p < 0.10$ on univariate analysis and excluded variables with $p > 0,10$ from the final model.

Survival analysis used the Kaplan-Meier method. Statistical significance was defined as $p \leq 0.05$. Statistical analysis was performed using IBM Statistical Package for Social Science (SPSS), version 23 (IBM Corp, North Castle, NY, US).

2.2.4. Ethics

The Institutional Ethics Committee waived the need for individual informed consent for this noninterventional study. All study procedures followed the principles of the Declaration of Helsinki (230). The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (231).

2.3. Results

2.3.1. Patient characteristics

Patient characteristics at ICU admission and third day post-ICU admission, with associated univariate 28-day mortality rates, are detailed in Tables 8 and 9, respectively.

There were 71 ACLF patients with a median age of 59 (51 - 64) years; 81.7% were male. Alcohol consumption alone (53.5%) or combined with hepatitis C virus infection (11.3%) were the most frequent etiologies of cirrhosis, and the most common precipitating events of acute illness were infection (53.5%) and gastrointestinal bleeding (22.5%).

2.3.2. Clinical severity at admission

The median clinical severity scores at ICU admission were APACHE II, 21 (16 - 23); ACLF grade, 2 (1 - 3); CLIF-SOFA, 13 (11 - 15); Child-Pugh, 12 (10 - 13); and MELD, 27 (20 - 32).

The ACLF severity scores at ICU admission were as follows: no-ACLF, 11.3%; grade one, 14.1%; grade two 28.2%; and grade three 46.5%.

The proportion of OF at ICU admission was one: 4.2%; two: 42.3%; three: 32.4% four: 16.9% and five: 4.2%.

Table 8. Acute-on-chronic liver failure patient characteristics at admission and 28-day mortality.

Characteristics	Overall (n = 71)	Non-survivors at 28 days (n = 40)	Survivors at 28 days (n = 31)	p value	OR	95%CI Inferior	95%CI Superior
Age	59 (51-64)	60 (50-65)	59 (51-63)	0.29	1.0	1.0	1.0
Sex (male)	58 (81.7)	32 (80.0)	26 (83.9)	0.41	1.6	0.5	4.9
Etiology							
Alcohol	38 (53.5)	22 (55.0)	16 (51.6)	0.67	Ref.		
HCV	7 (9.9)	4 (10.0)	3 (9.7)	0.33	1.4	0.7	2.6
Alcohol + HCV	8 (11.3)	3 (7.5)	5 (16.1)	0.71	1.3	0.3	6.0
Other	18 (25.4)	11 (27.5)	7 (22.6)	0.48	0.6	0.1	2.5
Previous decompensation	61 (85.9)	35 (87.5)	26 (83.9)	1.00	1.0	0.3	3.5
Ascites	64 (90.1)	36 (90.0)	28 (90.3)	0.71	1.3	0.3	6.0
Hepatocellular carcinoma	7 (9.9)	4 (10.0)	3 (9.7)	0.32	1.3	0.8	2.1
Portal vein thrombosis	7 (9.9)	5 (12.5)	2 (6.5)	0.45	1.2	0.7	2.0
Precipitant events							
Alcohol	5 (7.0)	2 (5.0)	3 (9.7)	0.17	Ref.		
Infection	38 (53.5)	26 (65.0)	12 (38.7)	0.66	0.7	0.1	4.0
Bleeding	16 (22.5)	6 (15.0)	10 (32.3)	0.03	2.2	1.1	4.3
Other	3 (4.2)	2 (5.0)	1 (3.2)	0.32	0.6	0.2	1.7
Unknown	9 (12.7)	4 (10.0)	5 (16.1)	0.57	2.0	0.2	22
West-Haven score	3 (1-3)	3 (1-3)	3 (1-3)	0.90	1.0	0.7	1.4
Hemoglobin (g/dL)	9.3 (8.2-10.9)	9.6 (8.5-10.9)	8.9 (8.0-11.0)	0.27	1.0	1.0	1.1
Leucocytes (103/µl)	10.3 (5.5-15.9)	11.3 (5.0-16.3)	10.1 (5.5-15.9)	0.27	1.0	1.0	1.0
Platelets (103/µl)	92 (50-134)	86 (43-120)	97 (58-156)	0.91	1.0	1.0	1.0
Ammonia (µmol/L) (n = 46)	106 (81-180)	107 (79-192)	100 (77-160)	0.43	1.0	1.0	1.0
INR	2.0 (1.7-2.4)	2.2 (1.8-2.7)	1.8 (1.5-2.3)	0.09	1.2	1.0	1.5
Bilirubin (mg/dL)	5.4 (2.4-21.1)	9.2 (2.9-22.1)	4.0 (1.7-13.3)	0.13	1.0	1.0	1.1
Albumin (g/dL)	25 (21-31)	24 (20-31)	26 (21-31)	0.51	1.0	1.0	1.0
Creatinine (mg/dL)	1.5 (0.83-2.4)	1.5 (0.90-2.6)	1.1 (0.77-2.2)	0.49	1.1	0.9	1.3
Sodium (mmol/L)	135 (129-140)	134 (125-139)	136 (132-142)	0.35	1.0	1.0	1.0
CRP (mg/L) (n = 69)	34 (18-63)	37 (24-72)	20 (13-51)	0.04	1.0	1.0	1.0
Lactate (mmol/L) (n = 63)	2.3 (1.5-3.6)	2.7 (1.8-4.4)	1.9 (1.4-2.7)	0.03	1.2	1.0	1.4
Renal replacement therapy	8 (11.3)	3 (7.5)	5 (16.1)	0.17	1.4	0.9	2.3
Vasopressors	37 (52.1)	23 (57.5)	14 (45.2)	1.00	1.0	0.5	2.0
IMV	18 (25.4)	12 (30.0)	6 (19.4)	0.68	1.1	0.7	1.9
PaO_2/FiO_2	300 (218-382)	283 (157-390)	316 (222-381)	0.57	1.0	1.0	1.0

CLIF-SOFA	13 (11-15)	14 (12-16)	11 (9-14)	0.10	1.0	1.0	1.1
Child-Pugh	12 (10-13)	12 (11-13)	11 (9-12)	0.17	1.0	1.0	1.1
MELD	27 (20-32)	28 (23-35)	26 (17-31)	0.10	1.0	1.0	1.0
ACLF (grade)*	2 (1-3)	3 (2-3)	2 (1-3)	0.04	1.7	1.0	2.7
Organ failures*	2 (1-3)	3 (2-3)	2 (1-3)	0.01	2.0	1.2	3.4
APACHE II	21 (16-23)	21 (17-25)	20 (16-23)	0.14	1.0	1.0	1.0

*Definitions of organ failures based on Chronic Liver Failure-Sequential Organ Failure Assessment. Results expressed as n (%) or median (inter-quartile range).Abbreviations: OR - odds ratio; 95%CI - 95% confidence interval; PaO2/FiO2 - arterial oxygen partial pressure with oxygen inspiration fraction ratio; CLIF-SOFA - Chronic Liver Failure-Sequential Organ Failure Assessment; CRP, C-reactive protein; HCV, Hepatitis C virus; IMV, Invasive mechanical ventilation, INR, International normalized ratio; MELD - Model for End-Stage Liver Disease; ACLF - Acute-on-Chronic Liver Failure Score; APACHE II - Acute Physiology and Chronic Health Evaluation II.

2.3.3. Clinical severity at day 3

The third day analysis excluded 5 patients who died (n = 66) and the median ACLF grade was 2 (1 - 3), the median CLIF-SOFA score was 13 (9 - 17) with a Delta CLIF-SOFA of 0 (-2 - 3); the median Child-Pugh score was 12 (10 - 13) and the median MELD score was 26 (21 - 35).

Table 9. Acute-on-chronic liver failure patient characteristics at day 3 and 28-day mortality.

Characteristics	Overall † (n=66)	Non-survivors at 28 days (n=35)	Survivors at 28 days (n=31)	p value	OR	95%CI	
						Inf.	Sup.
Hepatic encephalopathy	2 (1-3)	3 (2-4)	2 (1-2)	0.03	1.5	1.0	2.1
Hemoglobin (g/dL)	8.5 (7.6-10.0)	8.8 (7.7-10.0)	8.4 (7.4-10)	0.90	1.0	0.8	1.3
Leucocytes (103/µl)	11.0 (5.4-13.7)	11.9 (7.5-17.1)	6.6 (5.0-12.7)	0.09	1.0	1.0	1.0
Platelets (103/µl)	63 (40-105)	46 (38.5-94)	68 (50-110)	0.23	1.0	1.0	1.0
Ammonia (µmol/L)(n=46)	83 (62-107)	74 (57-107)	99 (76-106)	0.44	1.0	1.0	1.0
INR	2.1 (1.6-2.8)	2.5 (1.9-3.3)	1.7 (1.4-2.0)	0.002	3.7	1.6	8.5
Bilirubin (mg/dL)	6.6 (2.1-19.7)	12.4 (3.2-21.9)	3.9 (1.4-14.3)	0.07	1.0	1.0	1.1
Creatinine (mg/dL)	1.0 (0.8-2.3)	1.0 (0.8-2.3)	0.9 (0.7-1.8)	0.63	1.1	0.7	1.7
Sodium (mmol/L)	137 (133-142)	135 (132-142)	140 (135-143)	0.09	0.9	0.9	1.0
CRP (mg/dL) (n=64)	49 (28-77)	57 (31-90)	36 (25-63)	0.05	1.0	1.0	1.0
Lactate (mmol/L) (n=61)	2.0 (1.4-3.3)	3.1 (1.8-5.3)	1.4 (1.1-2.0)	0.002	4.7	1.8	12.6
Renal replacement therapy	16 (23)	12 (75)	4 (25)	0.10	0.3	0.1	1.2
Vasopressors	37 (52)	26 (70.3)	11 (29.7)	0.02	0.3	0.1	0.8
IMV	23 (32)	18 (78.3)	5 (21.7)	0.01	0.2	0.1	0.7

PaO_2/FiO_2	263 (201-363)	230 (144-364)	300 (237-360)	0.04	1.0	1.0	1.0
CLIF-SOFA	13 (9-17)	15 (11-19)	9 (8-13)	<0.001	1.3	1.1	1.5
Child-Pugh	12 (10-13)	13 (11-13)	10 (9-12)	<0.001	1.7	1.2	2.3
MELD	26 (21-35)	31 (25-38)	25 (15-29)	0.003	1.1	1.0	1.2
ACLF (grade)*	2 (1-3)	3 (2-3)	1 (0-2)	<0.001	3.4	1.9	6.2
Organ failures *	2 (1-3)	3 (2-4)	1 (1-2)	<0.001	2.6	1.6	4.3
Delta CLIF-SOFA	0 (-2-3)	1 (-1-5)	-1 (-3-1)	0.004	1.3	1.1	1.5

* Definitions of organ failures based on CLIF-SOFA. † Five patients were dead by day 3 post ICU admission thus n=66. Results expressed as n (%) or median (inter-quartile range). Abbreviations: PaO2/FiO2 - arterial oxygen partial pressure with oxygen inspiration fraction ratio; CLIF-SOFA - chronic liver failure-sequential organ failure assessment; CRP - C-reactive protein; INR - International normalized ratio; IMV, Invasive mechanical ventilation, MELD - model for end-stage liver disease score; ACLF - acute-on-chronic liver failure score; OR – odds ratio.

The acute-on-chronic liver failure severity scored at the third day as follows: no-ACLF, 16.7%; grade one, 18.2%; grade two, 27.3% and grade three, 37.9%.

The proportion of OF at day 3 was zero, 12.7%; one, 19.7%; two, 25.4%; three, 18.3%; four, 12.7%; five, 5.6%; and six, 5.6%.

2.3.4. Outcomes

The 28-day mortality rate post-ICU admission was 56.3%, and the in-ICU mortality rate was 49.3%. The main causes of death were sepsis (54.7%) and bleeding (18.9%).

The observed mortality rates for each ACLF grade assessed upon ICU admission were as follows: 1, 30.0%; 2, 45.0%; and 3, 72.7%. The 28-day mortality rate by the total number of OFs at ICU admission and D3 are shown in Figure 8.

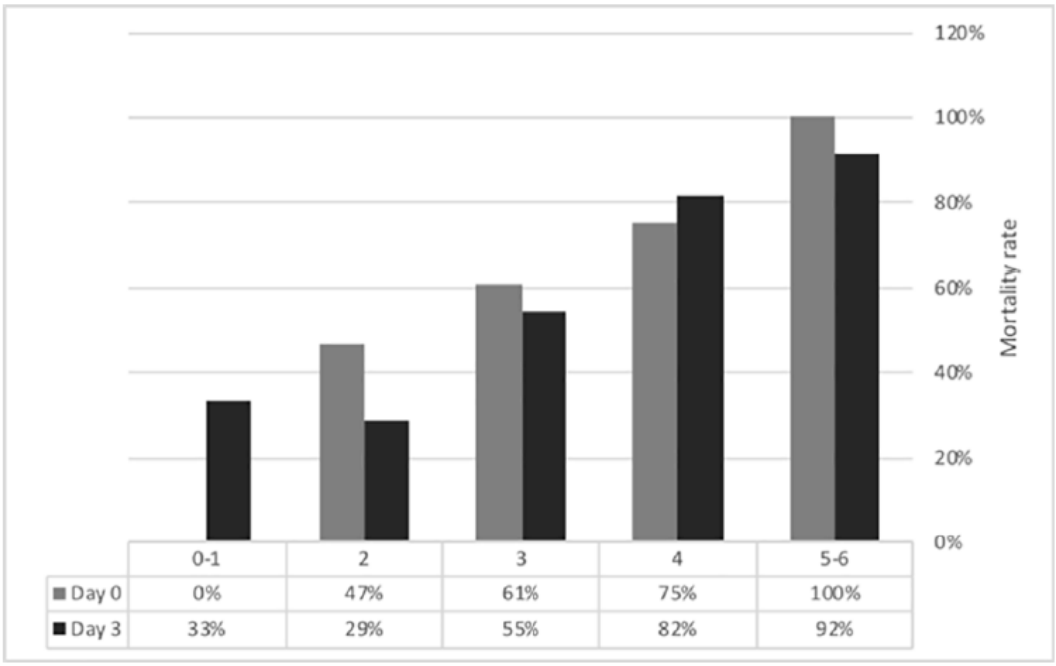


Figure 8. Number of failing organs in acute-on-chronic liver failure patients and 28-day mortality rate. (D0, n=71; D3, n= 66)

Figure 8 illustrates a linear relationship between the number of OF and mortality rates. No patients with OF ≥5 at ICU admission, nor lactate ≥3.2 at D3 survived in this cohort.

The Kaplan-Meier 28-day survival curve is depicted in Figure 9.

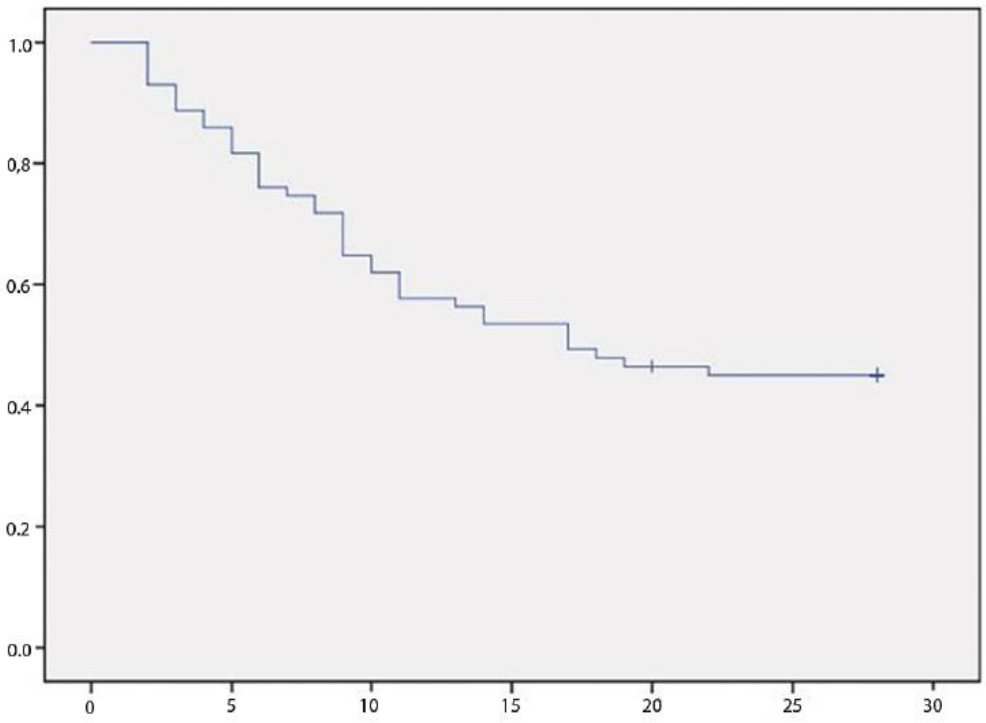


Figure 9. Kaplan-Meier 28-day survival curve for acute-on-chronic liver failure patients in the intensive care unit. (N = 71)

Figure 9 shows a decreasing survival rate that stabilizes approximately at the third week of ICU admission.

2.3.5. Mortality risk factors

Upon ICU admission day, a significant univariate association with 28-day mortality was found for bleeding as the precipitating event, C-reactive protein, arterial blood lactate, ACLF grade and OF number (Table 8). Variceal bleeding was significantly associated with lower mortality (p = 0.096, odds ratio - OR 0.37; 95% confidence interval - 95%CI 0.12 - 1.2) and was included in the multivariate analysis. The multivariate analysis (n = 61) of D0 variables found that OF number was the only independent risk factor for 28-day mortality (Table 10).

Table 10. Risk factors at ICU admission for 28-day mortality.

			95% C.I.	
n=61	**p value**	**Odds ratio**	**Inferior**	**Superior**
Organ Failure (n)	0,02	2,1	1,2	3,9
Lactate	0,14	1,3	0,9	1,9

Variables included in step 1: Bleeding (precipitant), INR, C-reactive protein, lactate, MELD, CLIFSOFA, ACLF grade, Organ Failure (number). Bleeding, as a precipitant event, was computed as a binary variable and included in this multivariate model. Logistic regression model's ROC AUC 0,76; p<0,001; 95% CI (0,64-0,88), Nagelkerke's R square 0,26 and Hosmer-Lemeshow test p=0,82

On the third day of intensive care, univariate associations with 28-day mortality found statistical significance for HE, INR, C-reactive protein, arterial blood lactate, renal replacement therapy, vasopressors, invasive mechanical ventilation, PaO2/FiO2 ratio, all clinical severity scores (CLIF-SOFA, Child-Pugh, MELD, ACLF grade), OF number and Delta CLIF-SOFA (Table 9).

The multivariate logistic regression (n = 55) found D3 arterial blood lactate concentration and INR to be independent risk factors (Table 11).

Table 11. Risk factors at day 3 of ICU stay for 28-day mortality.

			95% C.I.	
n=55	**p value**	**Odds ratio**	**Inferior**	**Superior**
Lactate	0.02	6.3	1.4	29
INR	0.03	10.2	1.3	83
Delta ClifSOFA	0.06	0.46	0.21	1.0
Organ Failure (n)	0.12	3.5	0.73	16
CLIFSOFA	0.14	1.8	0.84	3.7

Multivariate logistic regression variables included in step 1: hepatic encephalopathy, INR, lactate, C-reactive protein, invasive mechanical ventilation, vasopressor, RRT, PaO2/FiO2 ratio, CHILD, MELD, ACLF, OF number, CLIFSOFA, Delta ClifSOFA.
Logistic regression model's ROC AUC 0,91; p<0,001; 95% CI (0,83-0,98), Nagelkerke's R square 0,744 and Hosmer-Lemeshow test p=0,96

The multivariate analysis (n=61) combining D0 and D3 variables included: OF_{DO}, and $lactate_{D3}$, INR_{D3} and Delta $CLIFSOFA_{D3}$. The results identified that $lactate_{D3}$ and number of OF_{D1} were the two significant risk factors for 28-day mortality rate (Table 12).

Table 12. Combined risk factors at ICU admission and day 3 for 28-day mortality.

			95% C.I.	
n=61	**p value**	**Odds ratio**	**Inferior**	**Superior**
Lactate (day 3)	0.002	6.9	2.1	22.8
Organ Failure (n) (day 1)	0.012	3.1	1.3	7.3

Multivariate logistic regression (n=61) of intensive care admission day and day 3 variables for association with 28-day mortality in ACLF patients. Variables included in step 1: Organ Failure (day 1), lactate (day 3), INR (day 3) and Delta CLIF-SOFA (day 3).
Logistic regression prediction model's ROC AUC 0,884 (p<0,001; 95% CI 0,80-0,97). Nagelkerke's R square 0,59 and Hosmer-Lemeshow test p=0,42.

2.3.6. Liver transplant

There were 11 patients submitted to emergent LT within the initial 28 days of ICU admission with both 28-day and hospital survival rates of 64% (Table 13). The corresponding D0 ACLF grade were as follows: 1, 18% (n=2); 2, 27% (n=3) and 3, 55% (n=6).

Table 13. Liver transplant and vital outcome at 28 days.

Vital status at 28 days		**Survivors**	**Deceased**	**Total**
Liver transplant	No	25	35	60
	Yes	7	4	11
Total		32	39	71

By comparing 28-day mortality rates, there was no statistically significant difference between the vital outcome of between patients submitted to LT within the initial 28 days of ICU admission and rest of the cohort (n=60) (respectively, 36% vs. 58%; OR 0.4; 95%CI 0.11-1.5, p = 0.18).

2.4. Discussion

Our study analyzed the results of a 3-year cohort of ACLF patients admitted to a general ICU, specialized in liver disease at a tertiary hospital center with a regional LT program. The typical patient was a 60-year old, male, with alcoholic liver cirrhosis, presenting with septic shock, multiorgan failure and ACLF grade 3 at ICU admission.

Our study observed patients with overall higher clinical severity and higher mortality rates when compared to reference studies (222,225). Weil et al. conducted a recent large meta-analysis of 1904 patients with cirrhosis, including 369 ACLF patients, admitted to intensive care. The presence of ACLF criteria appeared to have had no significant impact on ICU mortality in this meta-analysis, although the authors admit limitations to this observation (225). Regarding this investigation, the typical patient with cirrhosis was younger, under 60 years-old, male with alcohol-related cirrhosis, and the primary reason for ICU admission was variceal bleeding. The proportions of patients with OF ≥ 2 was 47.7%, and 15.6% had OF ≥ 4, with an overall in-ICU mortality rate of 42.4%. Together, these proportions of OF, indicated less severe patients, and mortality rates were lower than in our study. Additionally, one of the findings of this study was that patients with variceal bleeding showed significantly lower mortality than those with infection as ACLF precipitant event (225). In our study infection was the most frequent precipitating ACLF event, and may have influenced an increase in our mortality rates.

In a seminal CANONIC study, Moreau et al. reported the outcomes in 415 ACLF patients and presented a definition for this syndrome (222). Acute-on-chronic liver failure was present in 303 patients at study enrollment, and importantly, this study included 208 ACLF patients who did not receive intensive care, which may have had an impact on the clinical outcomes. The precipitating events included bacterial infection (32.6%), gastrointestinal hemorrhage (13.2%), and unidentified causes (43.6%). The main causes of death were multiorgan failure without shock and both septic and hypovolemic shock types. The proportion of ACLF grade one was 48.8%, grade two was 36.6%, and grade three was 15.5% with mortality rates of 23.3%, 31,3% and 74,5%, respectively (222). Overall, their results also described less severe patients and presented lower mortality rates than in our cohort. Both of these multicenter reference studies reported less severe patients and lower mortality rates than our single-center study. The comparison of clinical results should be interpreted cautiously due to the large heterogeneity of the ACLF patients studied, including differences in clinical severity, clinical settings and primary precipitating events. Furthermore, our institution serves as a regional reference center for liver disease patients and LT, and we care for severe ACLF patients transferred from other acute care hospitals. This fact may help to explain and understand the increased burden of severity and mortality we report in our study. Subgroup analyses, including the diagnosis of the precipitating events, should provide more homogenous groups for future studies.

The number of OF was the only independent risk factor upon ICU admission for 28-day mortality in our cohort of patients. This finding was further explored by our colleagues Cardoso et al. in a recently published multicenter study of mortality prediction in ACLF patients in intensive care. In this study, a training set of 240 patients was used to derive the “LacOF” model using OF and arterial blood lactate concentration at ICU admission. This

model's mortality prediction results (area under the ROC curve 0.85) outperformed the CLIF-SOFA, CLIF-ACLF, MELD and APACHE II scores in a validation set of 237 patients (233). This stresses the clinical importance of discriminating the exact number of failing organs in multiorgan failure at ICU admission, whereas the "all inclusive" ACLF grade 3 does not discriminate between patients with three or more OFs.

On the third day our analysis revealed that lactate concentration and INR were also risk factors for 28-day mortality, both acting as surrogate markers of persistent metabolic and hepatic failure and inability to recover from the initial ACLF precipitant event.

Lactate undergoes hepatic metabolic clearance, and its concentration increases under liver failure and/or anaerobic stress conditions such as sepsis and shock. These conditions were highly frequent in our cohort, with more than half of patients requiring vasopressor support. Arterial blood lactate concentration is widely used as a surrogate marker for the general severity of critical illness, and prognostic scores for critically ill patients with cirrhosis have incorporated this variable into their scoring algorithms. These scores include the SOFA-lactate (234), Child-Pugh + lactate (235,236), albumin-bilirubin-clotting + lactate (237) and Royal Free Hospital algorithms (238). Furthermore, in the context of critical illness, the INR is a valuable biomarker of hepatic synthetic function, used to assess and monitor the degree of hepatic dysfunction and coagulopathy in the CLIF-SOFA score, and is used as a criterion for emergent LT (222, 236, 239). In our study, both lactate concentration and INR proved to be clinically useful for prognostic assessment in ACLF patients, providing an indication at D3 of ICU stay that may assist decisions regarding vital therapy. In our cohort, no patient survived with a D3 assessement including OF ≥ 5 or lactate concentration ≥ 3.2mmol/L.

Emergent LT in a small selected subset ACLF patients in intensive care presented clinically valuable hospital survival rates. We believe our results clearly benefit the decision to transplant well-selected patients as emergent vital therapy. The therapeutic concept of LT in severe ACLF patients has been demonstrated by Artru et al. in his work with 73 ACLF grade 3 patients receiving liver transplant while in the ICU, with a clear 1-year survival benefit when compared to non-transplanted controls (83.9 versus 7.9%, $p < 0.0001$). The observed high survival rate did not significantly differ from liver transplant matched controls with lower grades of ACLF. The authors emphasized the notion of a "transplantation window" where these severe patients could benefit from a rapid liver transplant decision process after initial ICU treatment and stabilization for their ACLF precipitating event (217) .

Finally, general and liver specific severity scores and their prognostic value throughout the first week of the ICU stay are well described in the literature. Whether clinical scores should serve as a rationale to determine the benefit of supportive therapy or discontinuation of intensive care due to futility, as suggested by Gustot et al. (when OF ≥ 4 at days 3 – 7), is a matter of debate (227, 240-242). In our cohort, two patients with 4 OF at D3 were alive 28 days after ICU admission and both were discharged home with clinical improvement. Clinical severity scores provide a basis for analysis but should not replace clinical judgment (224, 243). Decisions regarding vital support and liver transplant in critical patients remain complex and should include, and respect, the patients, families, and healthcare teams when setting goals of care and expectations.

Limitations in this study include the retrospective characteristic of the study and the relatively low number of patients, precluding a deeper analysis of mortality risk factors.

Furthermore, heterogeneity of the ACLF patients' clinical settings, precipitating events, clinical severity and outcomes reporting in the literature prevented a clear, direct comparison of results.

2.5. Conclusion

The typical patient in our study was a 60 year-old male with alcoholic liver disease admitted to the intensive care unit for septic shock and ACLF grade 3 multiorgan failure.

Our results presented overall higher clinical severity and mortality rates when compared to the literature. In our investigation, the number of OF upon ICU admission, and the arterial blood lactate concentration and INR on day 3, were independent risk factors for 28-day mortality. We consider essential that ACLF patients be treated in intensive care and that a timely clinical decision is vital for emergent LT in well-selected patients.

Chapter 3

Intra-Abdominal Hypertension

3.1. Introduction

Pathologic increases of IAP are associated with increased morbidity and mortality in the critically ill patient (176,243). Intra-abdominal hypertension (IAH), and ACS with acute OF, are recognized as independent mortality risk factors in several clinical settings, including major abdominal surgery, ruptured abdominal aortic aneurism, major burns, major trauma, acute pancreatitis, and mechanical ventilation (176,243).

In mixed populations of critically ill patients in intensive care the prevalence of IAH ranged between 31%-51% and mortality rates between 25–59% (244–246). Furthermore, ACS occurred in 4%-8% of these patients. Acute OF in the setting of elevated IAP can be caused by several mechanisms including reduced APP and reduced venous return with impaired organ perfusion. This may result in acute ischemic organ injury, impairing kidney, liver, gut and cardiovascular functions, as well as in transdiaphragmatic pulmonary compression, with elevated intrathoracic pressures, reduced respiratory volumes, and increased upper vena cava venous pressure, possibly leading to elevated intracranial pressure (247).

Patients with advanced liver cirrhosis are at high risk of developing IAH/ACS (176). Increased portal vein pressure and subsequent intra-abdominal ascites stipulate the need for symptomatic treatment (70). Ultimately, refractory ascites leads to chronically increased IAP and the need for repeated percutaneous drainage through paracentesis (56). There is, however, paucity of data regarding the incidence of IAH and ACS in critical patients with cirrhosis with acute medical illness.

3.1.1. Aims and objectives

The aim of this study was to assess the prevalence of IAH/ACS, analyze risk factors and the impact on clinical outcomes in the liver cirrhosis patient with acute medical (non-surgical) illness in intensive care.

3.2. Methods

3.2.1. Study design, settings and population

This was a multicentric, retrospective cohort study of patients with liver cirrhosis admitted in the ICU between 2009 and 2019.

Participating centers included two ICUs and pooled data from a multicentric study on intra-abdominal infection/sepsis (248). The study period length was determined by data availability while clinical guidelines remained largely unchanged regarding the management of IAH/ACS.

Center one was a general ICU, with 21 beds, specializing in liver disease at Hospital de Curry Cabral, Centro Hospitalar Universitário Lisboa Central, Lisboa, Portugal. Standard care included IAP measurement and patients were retrospectively screened for eligibility between October 2016 and October 2019.

Center two was a general ICU, with 10 beds, mostly treating emergency patients at Tartu University Hospital at Estonia. Standard care included IAP measurement and patients were retrospectively screened for eligibility between January 2009 and December 2018.

Supplemental patient enrollment was pooled from the “Abdominal Sepsis Study: Epidemiology of Etiology and Outcome” (AbSeS), a multicenter, prospective, observational,

epidemiological study, from the ESICM Trials Group Project, on adult ICU patients diagnosed with intra-abdominal infection (248).

Patients admitted in the ICU were screened for the following inclusion criteria: age ≥18 years, first ICU admission during the index hospital stay and a diagnosis of liver cirrhosis. The exclusion criteria were absence of IAP recordings and any type of surgical patient, since most surgical ICU patients may present anatomical changes to the chest and/or abdominal wall, interfering with the normal reference range for IAP. Therefore, this cohort was restricted to adult patients with cirrhosis with acute medical (non-surgical) conditions.

3.2.2. Baseline variables

Baseline variables were recorded on ICU admission day and included demographics, liver cirrhosis etiology, precipitant event of acute illness, arterial blood lactate concentration, vital organ support with vasopressor use and mechanical ventilation, and the following clinical severity scores according to the original formulas: APACHE II (250), SAPS II (251), MELD (204), MELDNA (252), SOFA (182), CLIF-SOFA (97). Renal replacement therapy during the ICU stay was also recorded. Acute-on-chronic liver failure syndrome and OF were defined as per the EASL CLIF-C (253). All data on patient characteristics were retrieved on site from medical records and collected in an anonymous and protected database.

3.2.3. Intra-abdominal pressure

Intra-abdominal pressure definitions, assessment method, and clinical management of IAH and ACS in these patients followed the updated guidelines published by the WSACS (176,173,172).

The patient's maximum IAP was determined using the single highest IAP value of all known measurements, and mean IAP was the average value calculated using all available measurements during the entire ICU stay.

The clinical management was performed by intensivists and complied with the guidelines for the treatment of precipitant events of clinical decompensation in cirrhosis and multiorgan system failure support (56,254,255).

3.2.4. Statistical analysis

Statistical analysis described discrete variables through count and percentage and continuous variables using mean (SD) or median (Q1, Q3), where appropriate. The Pearson coefficient was used to test correlations between continuous variables. Univariate analysis of continuous variables was performed using the t-test or the Mann-Whitney U test as a non-parametric alternative where appropriate. Chi-square and Fisher's exact tests were used for categorical variables. Multivariable analysis in backward stepwise logistic regression was performed using variables with p value ≤ 0.10 in univariable analysis. For multivariate statistical analysis the etiology of liver cirrhosis was dichotomized into "alcohol alone or combined" versus "all other causes" for comparison" and, similarly, precipitant events of clinical decompensation were categorized into "infection", "bleeding" and "other". Statistical significance was defined as p value ≤ 0.05. Statistical analysis was performed using IBM Statistical Package for Social Science (SPSS), version 23 (IBM Corp, North Castle, NY, US).

3.2.5. Ethics

The study has been approved by the Ethics Committee of both Centro Hospital Universitário Lisboa Central, E.P.E. and Tartu University Hospital. All study procedures followed the principles of the Declaration of Helsinki (255).

The reporting of this study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (257).

3.3. Results

3.3.1. Patient characteristics

A total of 9,345 ICU admissions were screened, of which 554 were adult patients with liver cirrhosis in their first ICU admission, and 459 were excluded either due to surgical type of patient and/or absence of IAP measure. Ninety-five patients were included in the study analysis. A patient flowchart is described in Figure 10.

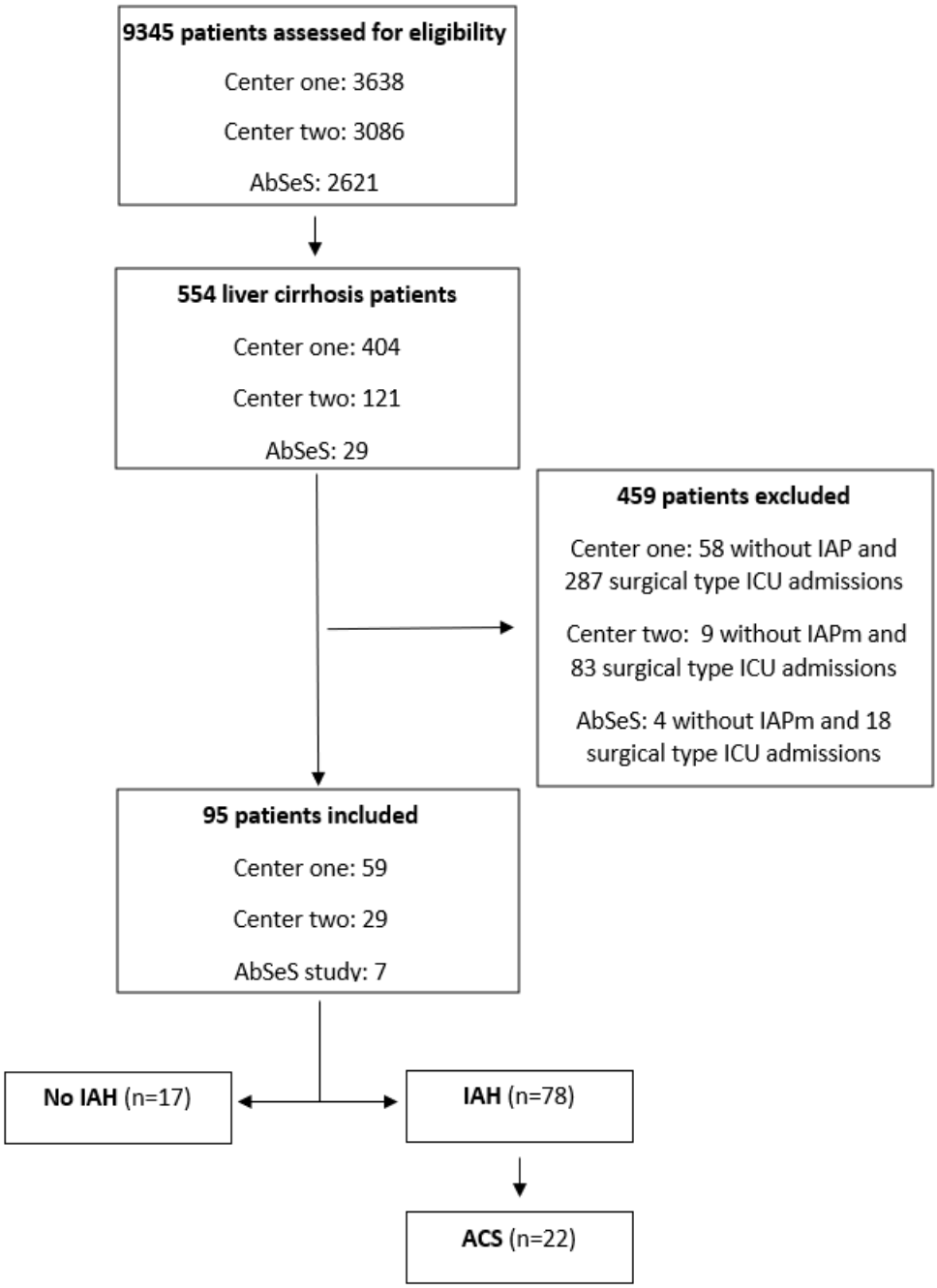


Figure 10. Study patient flowchart. Patients with liver cirrhosis were considered eligible and were excluded if they had a surgical condition at ICU admission or absence of IAPm. Abbreviations: AbSeS–Abdominal Sepsis Study: Epidemiology of Etiology and Outcome; ACS–Abdominal Compartment Syndrome; ICU–Intensive Care Unit; IAH–Intra-abdominal Hypertension; IAPm–Intra-Abdominal Pressure.

Table 14. Baseline characteristics of critical patients with cirrhosis and 28-day mortality.

Baseline variables	All patients (n = 95)	
Age (years)	56.7	±1.3
Male gender (n, %)	75	(79)
Etiology of liver cirrhosis (n, %)[a]		
Alcohol	43	(45)
Alcohol plus HCV	6	(6)
HCV	6	(6)
Other	37	(39)
Precipitant event (n, %)[b]		
Infection	25	(26)
Bleeding	20	(21)
Other	50	(53)
CCS (n=64)	5.4	±2.1
MELD (n=87)	26.2	±9.9
MELDNA (n=87)	27.7	±9
APACHE II (n=88)	25.3	±10.1
SAPS II (n=89)	48.5	±15.3
CLIF-SOFA (n=87)	12.8	±3.6
SOFA (n=83)	11.3	±3.4
Organ failure (n=87)	2.2	±1.2
Ascites (n = 64) (n, %)	59	(92)
West-Haven score (Q1-Q3)	1	(0, 3)
GCS (Q1-Q3) (n = 88)	14	(8, 15)
Ammonia (mmol/L)(Q1-Q3)(n=34)	153	(104, 237)
Hematocrit (%) (n=59)	24.4	±5.9
Leucocytes (10 x 10^9/mL) (n=94)	13.7	±8,6
Platelets (10 x 10^9/mL) (n=85)	118	±91
INR (n = 87)	2.4	±1.3
Bilirubin (mg/dl) (n=88)	8.5	±9.6
Creatinine (mg/dl) (n=88)	2.1	±1.5
Sodium (mEq/L) (n=95)	136	±7.9
C-reactive protein (mg/L) (n=58)	60.7	±60.1
Lactate (mmol/l) (n= 58)	4.1	±4.3
PaO2/FiO2 (n=83)	285	±111
Vital organ support (n, %) [b]	81	(85)
Vasopressors	68	(72)
IMV	63	(66)
RRT	19	(20)

Maximum IAP (mmHg)	16	±5.7
Mean IAP (mmHg)	12.1	±4.1
ICU LOS	10.8	±11.3

Number of observations (n) equals 95 and are presented in mean and SD unless otherwise stated.
[a] p value is provided for the comparison of "alcohol alone plus combined" versus all other liver cirrhosis etiologies.
[b] Vital organ support refers to single or combined vasopressor, IMV or RRT during the entire ICU stay.
Abbreviations: ACS—abdominal compartment syndrome; APACHE II—Acute Physiology and Chronic Health Evaluation II; CCS—Charlson Comorbidity Score; CLIF —Chronic Liver Failure; GCS—Glasgow Coma score; HCV—hepatitis C virus; IAP—intra-abdominal pressure; IAH—intra-abdominal hypertension; IAP—intraabdominal pressure; ICU—intensive care unit; INR—international normalization ratio; Q1- 1st quartile; Q3 – 3rd quartile; LOS—length-of-stay; MELD—Model for End Stage Liver Disease; MELDNA—Model for End Stage Liver Disease Sodium; SAPS II—Simplified Acute Physiology Score II; SD—standard deviation; SOFA— Sequential Organ Failure Assessment.

The etiology of liver cirrhosis included alcohol in 45.3% cases, alcohol plus HCV in 9.5%, HCV alone in 6.3%, other causes such as NASH, alfa-1-antitripsin deficiency and haemochromatosis corresponded to 21.0% of cases, and in 17.9% the cause remained unspecified. Comorbidities were reported in 66 patients with a mean Charlson Comorbidity Index (CCI) of 5.4±2.1. The comorbidities included cirrhosis with clinical signs of PH (86.4%), diabetes mellitus with and without end-organ damage (9.1% and 22.7%, respectively), solid cancer with metastasis (4.5%) and without metastasis (13.6%), hematologic cancer (1.5%) and chronic kidney disease (15.2%). Precipitant events of decompensated cirrhosis leading to ICU admission included infection (26.2%), bleeding (21.2%), alcohol intoxication (4.2%), AKI, HE and refractory ascites (each 3.2%). Baseline characteristics of patients at ICU admission are shown in Table 14.

The number of failing organs at ICU admission included cardiovascular shock (73%), renal (45%), hematologic (31%), respiratory (27%), neurologic (26%) and hepatic (22%) failures. Furthermore, vital organ function support was provided at baseline and included vasopressors in 72%, IMV in 66% and RRT in 20% of patients.

3.3.2. Intra-abdominal pressure

There were a total of 1,189 IAP measurements reported in 56 patients with a median of 18 (8, 30) measures per patient. In the remaining 39 patients, single mean and maximum values were reported without reference to the total number of IAP measurements performed.

The observed prevalence of IAH was 82.1%, and ACS was 23.2%, with a corresponding mean value of 16.0 ±5.7 mmHg, obtained from the maximum IAP measurements. Regarding the mean IAP value during the ICU stay, it presented an overall value of 12.1 ±4.1 mmHg. The IAH grade distributions of maximum and mean IAP during ICU stay are depicted in Figure 11.

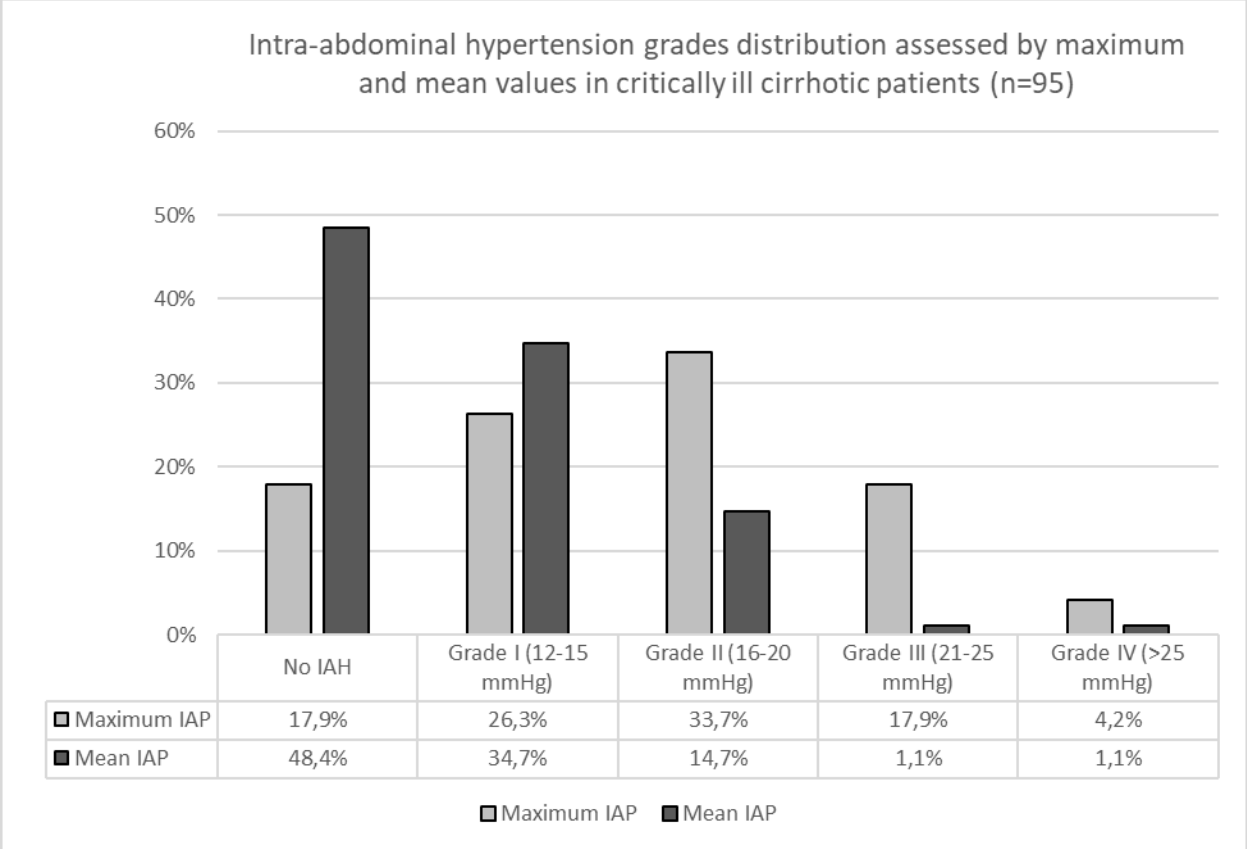


Figure 11. Comparison of IAH grades for maximum and mean IAP. Pressures where measures during the entire the ICU stay (n=95). Abbreviations: IAH – Intraabdominal Hypertension; IAP – Intra-abdominal Pressure.

Comparing the distribution of maximum and mean IAP (Figure 11), we can observe that maximum IAP had a central distribution of IAP grades with a statistical mode of IAH grade II (33.7%). Conversely, when analyzing mean IAP during the ICU stay, the absence of IAP (48.4%) was apparent, and IAH grade I (34.7%) was the most frequent.

3.3.3. Risk factors for intra-abdominal hypertension

Univariate associations with IAH are detailed in Table 15.

Table 15. Comparison of patients with and without intra-abdominal hypertension.

	No IAH (n=17) IAP <12mmHg		IAH (n=78) IAP ≥12mmHg		p value
Age (years)	56.5	±10.1	56.8	±10.6	0.90
Male gender (n, %)	15	(88)	60	(77)	0.51
Etiology of cirrhosis (n, %) [a]					0.2
Alcohol	10	(59)	33	(42)	
Alcohol plus HCV	3	(18)	6	(7,7)	
HCV	0	(0)	6	(7,7)	
Other	4	(24)	33	(42)	
Precipitant event (n, %) [b]					0.85
Infection	4	(24)	21	(27)	
Bleeding	3	(18)	17	(22)	
Other	10	(59)	40	(51)	
CCS (n = 64)	4.9	±2.0	5.5	±2.1	0.40
MELD (n = 87)	26.7	±9.0	26.0	±10.2	0.81
MELDNA (n = 87)	28.9	±8.1	27.4	±9.2	0.55
APACHE II (n = 88)	27.5	±15.2	24.8	±8.7	0.33
SAPS II (n = 89)	48.2	±12.3	48.5	±16.0	0.94
CLIF-SOFA (n = 87)	12.8	±3.1	12.8	±3.8	0.98
SOFA (n = 83)	10.4	±2.8	11.4	±3.5	0.28
Organ failure (n = 87)	2.2	±1.4	2.2	±1.2	0.94
Ascites (n = 64) (n, %)	11	(92)	48	(92)	1.00
West-Haven score (Q1-Q3)	0.0	(0, 1)	1.0	(0, 3)	0.04
GCS (Q1-Q3) (n = 88)	15	(14, 15)	14	(7, 15)	0.03
Ammonia (mmol/L)(Q1-Q3)(n = 34)	150	(94, 235)	155	(106, 243)	0.97
Hematocrit (%) (n = 59)	24.0	±6.7	24.4	±5.8	0.84
Leucocytes (10 x 10^9/mL) (n = 94)	14.4	±9.7	13.5	±8.4	0.69
Platelets (10 x 10^9/mL) (n = 85)	131	±136	116	±81	0.56

INR (n = 87)	2.5	±1.2	2.4	±1.4	0.73
Bilirubin (mg/dl) (n = 88)	7.4	±7.4	8.7	±10.1	0.63
Creatinine (mg/dl) (n = 88)	2.0	±1.4	2.1	±1.6	0.78
Sodium (mEq/L) (n = 95)	132	±9	137	±7	0.02
C-reactive protein (mg/L) (n = 58)	73	±65	56	±60	0.36
Lactate (mmol/l) (n = 58)	5.1	±5.2	5.1	±5.2	0.96
PaO2/FiO2 (mmHg) (n = 83)	242	±112	298	±119	0.10
Vital organ support (n, %) [c]	15	(88)	66	(85)	1.00
Vasopressors	11	(65)	57	(73)	0.56
IMV	12	(71)	51	(65)	0.78
RRT	3	(18)	16	(21)	1.00
Maximum IAP (mmHg)	7.9	±2.0	17.8	±4.6	<0,001
Mean IAP (mmHg)	7.2	±2.0	13.2	±3.5	<0,001
28-day mortality	7	(41)	43	(55)	0.42
ICU mortality	6	(35)	38	(49)	0.42
ICU LOS (days)	9.4	±10.8	11.1	±11.5	0.60

Number of observations (n) equals 95 and values are presented as mean (± SD) unless otherwise stated.
[a] p value is provided for the comparison of "alcohol alone plus combined" versus all other liver cirrhosis etiologies.
[b] p value is provided for the comparison of bleeding or infection versus all other precipitant events.
[c] Vital organ support refers to single or combined vasopressor, IMV or RRT during the entire ICU stay.
Abbreviations: ACS—abdominal compartment syndrome; APACHE II—Acute Physiology and Chronic Health Evaluation II; CCS—Charlson Comorbidity Score; CLIF —Chronic Liver Failure; GCS—Glasgow Coma score; HCV—hepatitis C virus; IAP—intra-abdominal pressure; IAH—intra-abdominal hypertension; IAP—intraabdominal pressure; ICU—intensive care unit; INR—international normalization ratio; Q1- 1st quartile; Q3 – 3rd quartile; LOS—length-of-stay; MELD—Model for End Stage Liver Disease; MELDNA—Model for End Stage Liver Disease Sodium; SAPS II—Simplified Acute Physiology Score II; SD—standard deviation; SOFA— Sequential Organ Failure Assessment.

Univariate associations with IAH were as follows: higher serum sodium concentration (p = 0.02), higher GCS (p = 0.03), and higher WH score (p = 0.04) (Table 15).

Multivariable analysis included alcoholic etiology of cirrhosis and PaO2/FiO2 ratio, and excluded GCS due to preference for WH encephalopathy score in the patient with cirrhosis. (Table 16)

Table 16. Risk factors at intensive care admission for intra-abdominal hypertension.

			95% Confidence interval	
(n=86)	***p* value**	**Odds ratio**	**Inferior**	**Superior**
Alcoholic cirrhosis	0.01	9.9	1.7	57
West- Haven HE	0.01	2.2	1.2	3.9
PaO2/FiO2 (mmol)	0.02	1.01	1.00	1.02
Sodium (mmol/L)	0.08	1.1	1.0	1.2

Multivariable backward stepwise logistic regression including alcoholic cirrhosis, PaO2/FiO2, West-Haven hepatic encephalopathy score and Sodium in the initial step.
Abbreviations: FiO2 - fraction of inspired oxygen; GCS - Glasgow coma score; PaO2 - Partial pressure of arterial oxygen.

Independent risk factors for the presence of IAH at ICU admission were alcoholic cirrhosis (p = 0.01), higher WH scores (p = 0.01), and higher PaO2/FiO2 ratio (p = 0.02) (Table 16).

3.3.4. Risk factors for abdominal compartment syndrome

The comparison of clinical characteristics between critically ill patients with cirrhosis with IAH grade I-II and III-IV (ACS), is detailed in Table 17.

Table 17. Clinical characteristics of patients with IAH grade I-II and III-IV (ACS).

	IAH grade I-II (n=56)		**IAH grade III-IV (ACS) (n=22)**		
	IAPmax [12–19] mmHg		**IAPmax ≥20mmHg**		**p value**
Age (years)	56.7	±10.8	57.2	±10.5	0.86
Male gender (n, %)	42	(75)	18	(82)	0.77
Etiology of cirrhosis (n, %) [a]					0.6
Alcohol	24	(43)	9	(41)	
Alcohol plus HCV	4	(7,1)	2	(9,1)	
HCV	3	(5,4)	3	(14)	
Other	25	(45)	8	(36)	
Precipitant event (n, %) [b]					0.03
Infection	12	(21)	9	(41)	
Bleeding	10	(18)	7	(32)	
Other	34	(61)	6	(27)	
CCS (n = 64)	5.3	±2.3	5.8	±2.0	0.45
MELD (n = 87)	24.4	±9.7	30.2	±10.4	0.03

MELDNA (n = 87)	26.0	±8.8	31.0	±9.5	0.04
APACHE II (n = 88)	24.7	±9.1	24.9	±7.7	0.95
SAPS II (n = 89)	48.1	±17.2	49.5	±12.7	0.75
CLIF-SOFA (n = 87)	12.9	±3.9	12.6	±3.5	0.74
SOFA (n = 83)	11.7	±3.5	10.8	±3.4	0.34
Organ failure (n = 87)	2.3	±1.1	2.1	±1.3	0.62
Ascites (n = 64) (n, %)	30	(94)	18	(90)	0.63
West-Haven score (Q1-Q3)	1.0	(0, 3)	1.0	(0, 3)	0.34
GCS (Q1-Q3) (n = 88)	14	(7, 15)	15	(9, 15)	0.14
Ammonia (mmol/L)(Q1-Q3)(n = 34)	157	(92, 243)	147	(117, 213)	0.78
Hematocrit (%) (n = 59)	23.5	±4.7	26.1	±7.1	0.13
Leucocytes (10 x 10^9/mL) (n = 94)	12.4	±8.1	16.1	±8.9	0.08
Platelets (10 x 10^9/mL) (n = 85)	111	±78	127	±89	0.48
INR (n = 87)	2.2	±1.1	2.7	±1.9	0.17
Bilirubin (mg/dl) (n = 88)	7.7	±9.4	11.4	±11.4	0.16
Creatinine (mg/dl) (n = 88)	2.0	±1.6	2.5	±1.6	0.28
Sodium (mEq/L) (n = 95)	137	±8	136	±6	0.53
C-reactive protein (mg/L) (n = 58)	51	±49	70	±83	0.23
Lactate (mmol/l) (n = 58)	5.1	±5.2	5.1	±5.5	0.97
PaO2/FiO2 (mmHg) (n = 83)	291	±126	315	±100	0.45
Vital organ support (n, %) [c]	51	(91)	15	(68)	0.31
Vasopressors	43	(77)	14	(64)	0.27
IMV	40	(71)	11	(50)	0.11
RRT	14	(25)	2	(9,1)	0.21
Maximum IAP (mmHg)	15.4	±2.5	23.8	±3.2	<0,001
Mean IAP (mmHg)	12.3	±2.6	15.7	±4.4	<0,001
28-day mortality	26	(46)	17	(77)	0.02
ICU mortality	24	(43)	14	(64)	0.13
ICU LOS (days)	11.4	±13.0	10.3	±6.1	0.71

Number of observations (n) equals 95 and values are presented as mean (± SD) unless otherwise stated.
[a] p value is provided for the comparison of "alcohol alone plus combined" versus all other liver cirrhosis etiologies.
[b] p value is provided for the comparison of bleeding or infection versus all other precipitant events.
[c] Vital organ support refers to single or combined vasopressor, IMV or RRT during the entire ICU stay.
Abbreviations: ACS—abdominal compartment syndrome; APACHE II—Acute Physiology and Chronic Health Evaluation II; CCS—Charlson Comorbidity Score; CLIF —Chronic Liver Failure; GCS—Glasgow Coma score; HCV—hepatitis C virus; IAP—intra-abdominal pressure; IAPmax – maximum IAP; IAH—intra-abdominal hypertension; IAP—intraabdominal pressure; ICU—intensive care unit; INR—international normalization ratio; Q1- 1st quartile; Q3 – 3rd quartile; LOS—length-of-stay; MELD—Model for End Stage Liver Disease; MELDNA—Model for End Stage Liver Disease Sodium; SAPS II—Simplified Acute Physiology Score II; SD—standard deviation; SOFA— Sequential Organ Failure Assessment.

Abdominal compartment syndrome was associated with higher MELD and MELDNA scores (respectively, p = 0.03 and p = 0.04), and precipitant event (p = 0.03) when comparing between patients with IAH grade I-II and grade III-IV (ACS) (Table 17).

Multivariate analysis (n = 71), including the aforementioned variables and white blood cell count, showed that the precipitant event "infection" (p = 0.048) was the only independent risk factor for ACS.

3.3.5. Outcomes

The overall 28-day mortality rate was 52.6%.

3.3.6. Mean IAP and outcomes

The distribution of IAH grades, regarding mean IAP during the ICU stay, and respective mortality rates are shown in Figure 12.

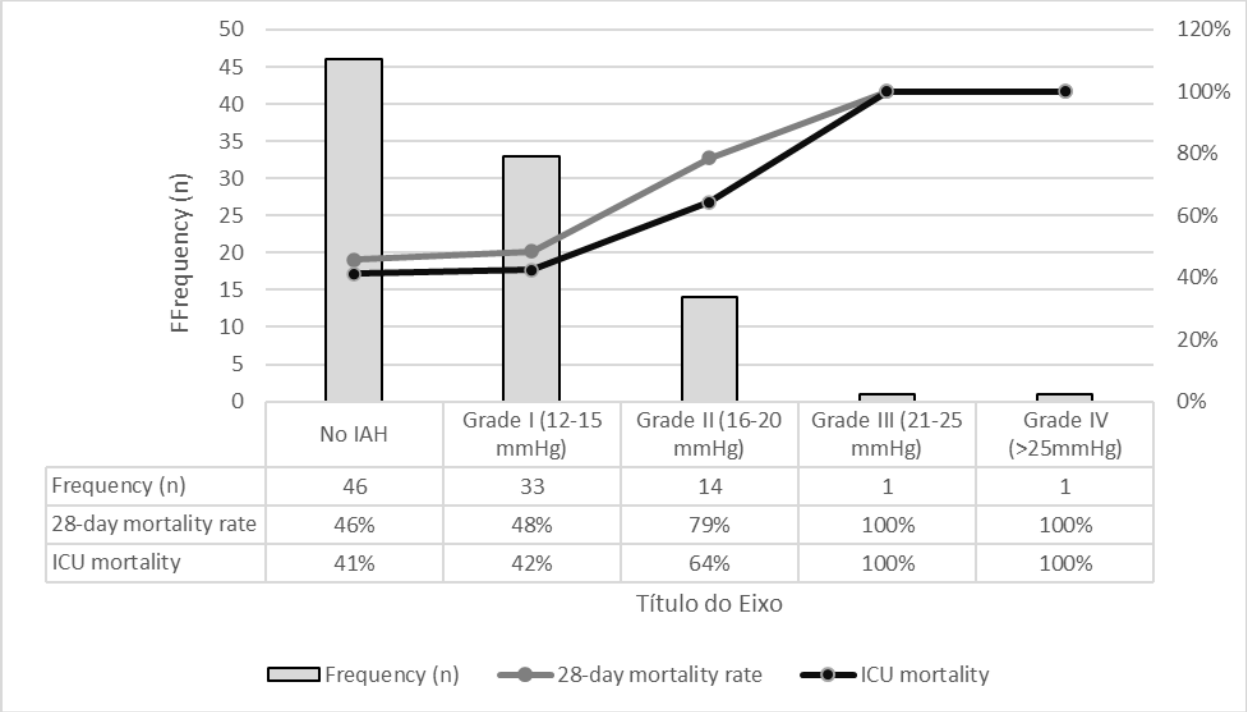
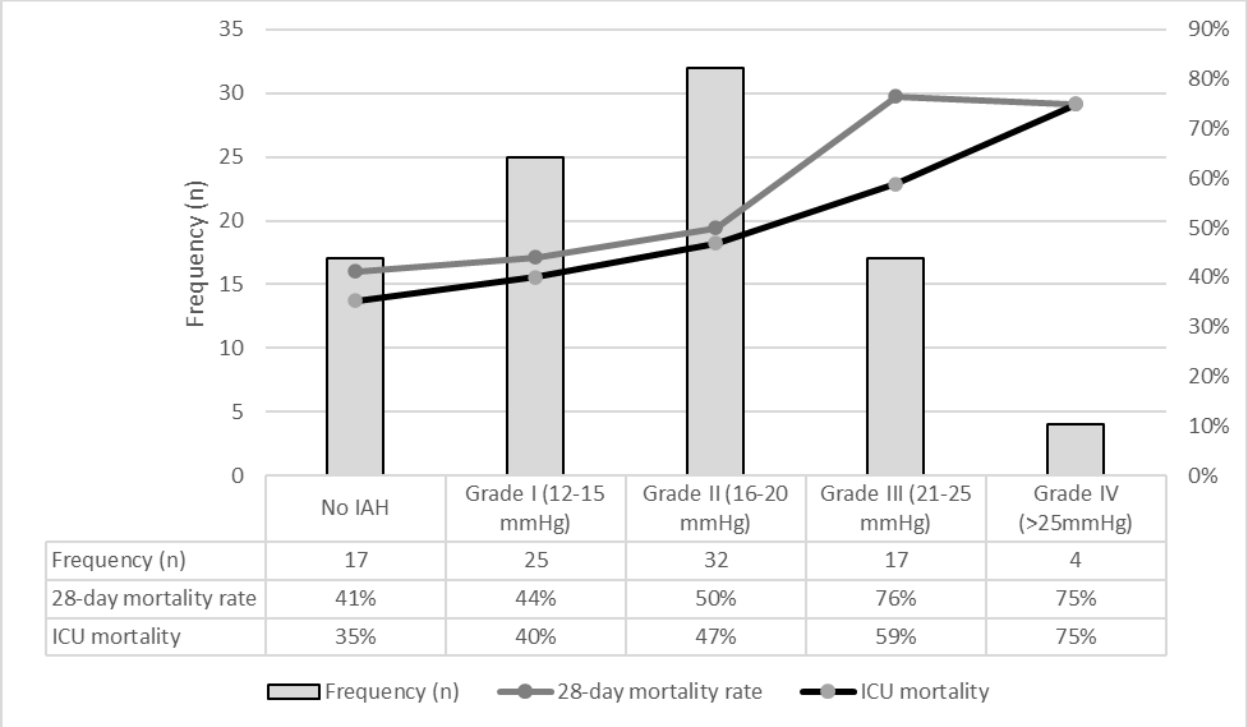


Figure 12. Distribution of IAH grades for mean IAP and mortality rates in the ICU. (n=95) Abbreviations: IAH–Intra-abdominal hypertension; ICU–intensive care unit.

Mean IAP during the ICU stay was associated with increased 28-day mortality rate for grade II IAH or higher. Comparing the mortality rate between grades of IAH, assessed by mean IAP, we found that there was a significant difference between patients without IAH and grade II IAH (46% vs. 79%, one-sided p=0.03). A similar result was observed for grade II + III + IV combined (46% vs. 81%, one-sided p=0.01). Nonetheless, there was no significant difference when comparing patients without IAH and IAH grade I.

3.3.7. Maximum IAP and outcomes

The distribution of IAH grades and respective mortality rates, regarding maximum IAP values, are shown in Figure 13.



	No IAH	Grade I (12-15 mmHg)	Grade II (16-20 mmHg)	Grade III (21-25 mmHg)	Grade IV (>25mmHg)
Frequency (n)	17	25	32	17	4
28-day mortality rate	41%	44%	50%	76%	75%
ICU mortality	35%	40%	47%	59%	75%

Figure 13. Distribution of IAH grades for maximum IAP and mortality rates. (n=95) Abbreviations: IAH–Intra-abdominal hypertension; ICU–intensive care unit.

Patients with higher IAH grade III-IV had significantly higher 28-day mortality when compared to those with lower IAH grades I–II (77% versus 46%, respectively, p = 0.02, assessed by maximum IAP) (Table 17).

Maximum IAP was associated with increased 28-day mortality rate for grade III IAH or ACS. Comparing the mortality rate between grades of IAH, assessed by maximum IAP as seen in Figure 13, we found that there was a significant difference between patients without IAH and those with grade III IAH (41% vs. 76%, one-sided p=0.04). The combination of grade III + IV, corresponding to patients with ACS, presented a similar significant difference (41% vs. 76%, one-sided p=0.03). Conversely, there was no significant difference when comparing to IAH grade I and II.

3.3.8. Mortality at 28 days

The comparison of patient characteristics at admission between 28-day survivors and non-survivors is specified in Table 18.

Table 18. Baseline characteristics of survivors and non-survivors at 28 days.

	Non-survivors (n = 44)		**Survivors (n = 50)**		**p value**
Age (years)	57.2	±11.0	56.3	±10.0	0.5
Male gender (n, %)	41	(93)	34	(68)	0.9
Etiology of liver cirrhosis (n, %)[a]					0.4
Alcohol	26	(59)	17	(34)	
Alcohol plus HCV	3	(7)	6	(12)	
HCV	3	(7)	3	(6)	
Other	18	(41)	19	(38)	
Precipitant event (n, %) [b]					0.6
Infection	14	(31)	11	(22)	
Bleeding	12	(27)	8	(16)	
Other	24	(55)	26	(52)	

CCS (n=64)	5.6	±2.1	5.1	±2.1	0.4
MELD (n=87)	30.4	±30.4	21.6	±7.5	<0,001
MELDNA (n=87)	31.4	±9.0	23.7	±7.1	<0,001
APACHE II (n=88)	28.2	±11.3	22.1	±7.7	0.004
SAPS II (n=89)	54.7	±15.1	41.5	±12.5	<0,001
CLIF-SOFA (n=87)	13.7	±3.7	11.8	±3.3	0.01
SOFA (n=83)	11.7	±3.4	10.8	±3.4	0.2
Organ failure (n=87)	2.5	±1.3	1.9	±1.0	0.01
Ascites (n = 64) (n, %)	32	(89)	27	(96)	0.4
West-Haven score (Q1-Q3)	1.0	(0, 3)	0.0	(0, 2)	0.2
GCS (Q1-Q3) (n = 88)	14.0	(8, 15)	15.0	(8, 15)	0.2
Ammonia (mmol/L)(Q1,Q3) (n=34)	155	(120, 221)	144	(74, 258)	0.3
Hematocrit (%) (n=59)	23.8	±5.8	25.1	±6.1	0.4
Leucocytes (10 x 10^9/mL) (n=94)	15.9	±9.5	11.3	±7.0	0.01
Platelets (10 x 10^9/mL) (n=85)	129	±80.1	106	±101	0.2
INR (n = 87)	2.9	±1.6	1.9	±0.6	<0,001
Bilirubin (mg/dl) (n=88)	11.3	±10.6	5.4	±7.3	0.003
Creatinine (mg/dl) (n=88)	2.3	±1.5	1.9	±1.5	0.2
Sodium (mEq/L) (n=95)	136	±7.8	137	±8	0.5
C-reactive protein (mg/L) (n=58)	55.8	±63.4	63.3	±58.9	0.6
Lactate (mmol/l) (n= 58)	6.6	±6.1	3.5	±3.4	0.004
PaO2/FiO2 (n=83)	311	±130.3	262	±99	0.06
Vital organ support (n, %) [c]	42	(84)	39	(87)	0.8
Vasopressors	37	(74)	31	(69)	0.7
IMV	35	(70)	28	(62)	0.5
RRT	12	(24)	7	(16)	0.4
Maximum IAP (mmHg)	17.3	±6.3	14.6	±4.7	0.02
Mean IAP (mmHg)	13.0	±4.8	11.2	±2.8	0.03
ICU LOS	8.7	±8.7	13.1	±13.4	0.07

Number of observations (n) equals 95 and are presented in mean and SD unless otherwise stated.

[a] p value is provided for the comparison of "alcohol alone plus combined" versus all other liver cirrhosis etiologies.

[b] p value is provided for the comparison of bleeding or infection versus all other precipitant events.

[C] Vital organ support refers to single or combined vasopressor, IMV or RRT during the entire ICU stay.

Abbreviations: ACS—abdominal compartment syndrome; APACHE II—Acute Physiology and Chronic Health Evaluation II; CCS—Charlson Comorbidity Score; CLIF —Chronic Liver Failure; GCS—Glasgow Coma score; HCV—hepatitis C virus; IAP—intra-abdominal pressure; IAH—intra-abdominal hypertension; IAP—intraabdominal pressure; ICU—intensive care unit; INR—international normalization ratio; Q1- 1st quartile; Q3 - 3rd quartile; LOS—length-of-stay; MELD—Model for End Stage Liver Disease; MELDNA—Model for End Stage Liver Disease Sodium; SAPS II—Simplified Acute Physiology Score II; SD—standard deviation; SOFA— Sequential Organ Failure Assessment.

Patients deceased by day 28 had a significantly higher maximum and mean IAP (p = 0.02 and p = 0.03, respectively) (Table 19).

Univariate analysis of 28-day mortality revealed that non-survivors had significantly worse clinical severity scores, except for the SOFA and Charlson Comorbidity Index, and significantly elevated values for laboratory variables bilirubin, INR, lactate, and WBC at admission (Table 18).

Multivariable analysis including lactate, WBC, PaO2/FiO2, maximum IAP, and MELD score (excluding bilirubin and INR as these variables are included in MELD score) identified MELD (p = 0.001), WBC (p = 0.03), PaO2/FiO2 (p = 0.03), and lactate (p = 0.04) as independent predictors of 28-day mortality (Table 19).

Table 19. Risk factors for 28-day mortality in critical patients with cirrhosis.

			95% Confidence interval	
Baseline (n=83)	***p* value**	**Odds ratio**	**Inferior**	**Superior**
Lactate (mmol/L)	0.04	1.15	1.01	1.31
WBC ($10x10^{9/mL}$)	0.03	1.09	1.01	1.17
PaO2/FiO2	0.03	1.01	1.00	1.01
MELD	0.001	1.11	1.05	1.18

Multivariate analysis for 28-day mortality risk factors in critically ill patients with cirrhosis. Multivariable backward stepwise logistic regression (n=83), lactate, WBC, PaO2/FiO2, maximum IAP and MELD score in the initial step (bilirubin and INR are included in MELD score and were therefore excluded from this analysis).
Abbreviations: FiO2 - fraction of inspired oxygen; IAP- intra-abdominal pressure; INR - international normalization ratio; PaO2 - partial arterial oxygen pressure; SAPS II - Simplified acute physiology score II; WBC - white blood cell.

Maximum IAP was associated with 28-day mortality when adjusted for SAPS II score (OR = 1.11; 95% CI: 1.01–1.22; p = 0.02 for n = 89) but not for MELD nor MELDNA (respectively, OR = 1.06; 95% CI: 0.97–1.15; p = 0.2; and OR = 1.07; 95% CI: 0.98–1–16; p = 0.1, n=87).

3.13.9. Organ failure

Distribution of number of OF at ICU admission and respective mortality rates are depicted in Figure 14.

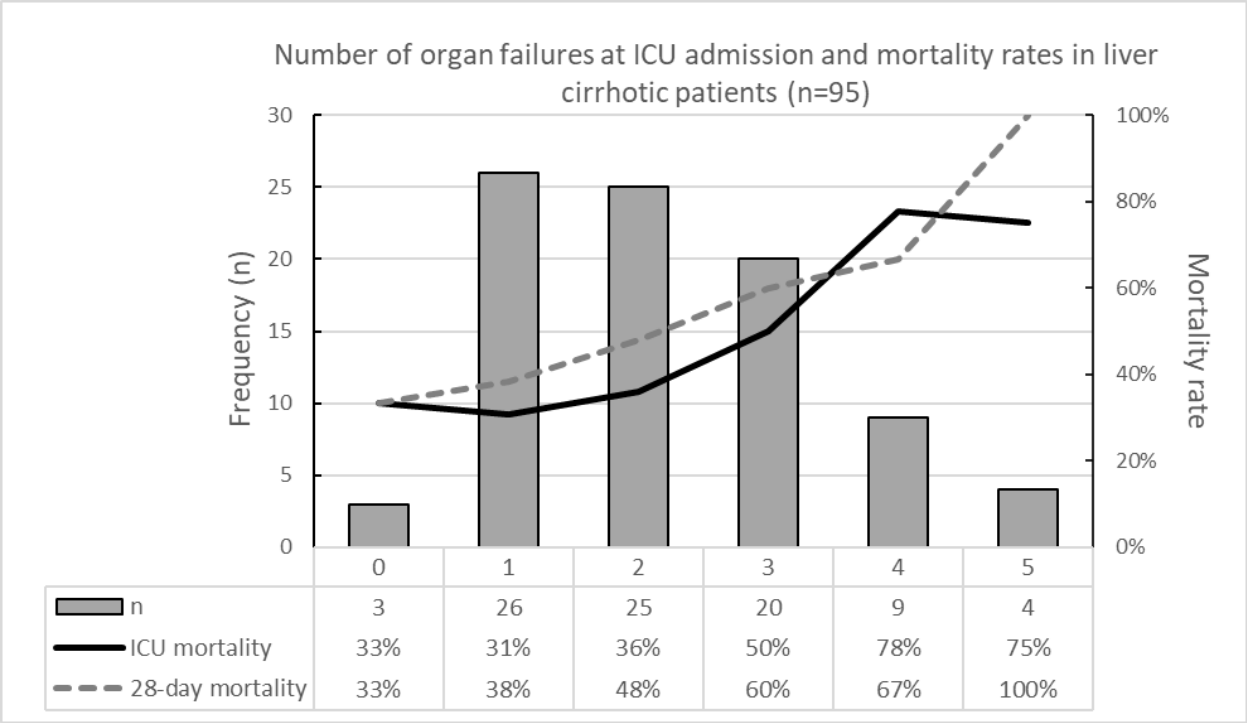


Figure 14. Number of organ failures at ICU admission and 28-day mortality. Abbreviations: OF – organ failure; ICU – intensive care unit.

There was a progressive relationship between OFs at ICU admission and increased 28-day mortality rate (Figure 14).

3.3.10. Liver transplant

Emergent LT after ICU admission was performed in 9 (15.3%) ACLF cases out of 59 patients from Center one (Table 20).

Table 20. Emergent liver transplant in ACLF patients and survival rates.

ACLF grade	n	28-day survivors	Hospital survivors
1	3	3	2
2	3	3	2
3	3	1	1
Total	9	7	5

Abbreviation: ACLF, acute-on chronic liver failure.

The ACLF severity of these LT patients was evenly distributed (33.3%) between grades 1-3. The survival rate at 28 days was 77.8%, and 55.6% where discharged home with improved condition (Table 20).

3.4. Discussion

This is the first multicentric study to analyze the prevalence and outcomes of IAH and ACS in patients with cirrhosis admitted in the ICU with acute medical illness.

3.4.1. Intra-abdominal hypertension

The typical patient in our cohort was under 60 year-old male patient with alcoholic liver cirrhosis, admitted in the ICU with shock due to infection or variceal bleeding.

The prevalence of IAH was very high, in more than three quarters, and ACS in nearly one quarter of the study population, as assessed by maximum IAP. Furthermore, the prevalence

of IAH remained high, in over half of the patients, when we consider mean IAP throughout the ICU stay.

Our results in patients with cirrhosis showed a higher prevalence of IAH/ACS when compared to studies in other mixed populations of intensive care patients. These reported prevalences of IAH between 32-59%, and ACS between 4.2-8.2% (234–236). In an international multicentre, prospective 1-day point-prevalence epidemiological study, 97 patients from a mixed medical-surgical population presented a prevalence of IAH of 58.8%, and 8.2% for ACS, with the only risk factor found for IAH being body mass index (244). In another international, multicenter, prospective study, in 265 consecutive patients from a mixed population in intensive care the prevalence of IAH was 32.1%, and 4.2% for ACS at ICU admission. Additionally, IAH on admission was associated with severe organ dysfunction, and during the ICU stay was an independent mortality predictor (245). Furthermore, in the recent IROI Study, an international, multicentric, prospective study in 491 mixed ICU patients, the prevalence of IAH was 48.9%, and 6.3% for ACS, during the first 2 weeks of the ICU stay (246).

The specific prevalence of IAH in the critically ill patient with cirrhosis has only been addressed in the single-center *post hoc* analysis from a randomized controlled trial for the use of low-dose hydrocortisone in septic shock (215,258). In their study, Al-Dorzi et al. observed 61 patients with cirrhosis and reported the presence of mean IAH in 82%, and ACS in 15% of them during ICU admission day. Furthermore, they reported a 97% prevalence of IAH, and 39% of ACS during the first week in the ICU. Noteworthy, ascites was present in nearly all (95.1%) patients. The authors recognized a likely overestimation of the prevalence of IAH/ACS since a modified Kron technique for IAP measure was used, with intravesical

pressure measurements performed with vesical instillation of a large volume (50–100 mL), and the zero-pressure reference point set at symphysis pubis. Current guidelines recommend an injection of 25 mL of sterile saline to prevent bladder overdistension and zero-pressure reference set at the phlebostatic axis in the mid-axillary line (166). Even so, and considering patient selection, the prevalence of IAH was remarkably high in the Saudi study. Despite the difference in the populations of patients with cirrhosis, and in IAP measure methodology, our results confirm a very high prevalence of IAH.

3.4.2. Risk factors for IAH and ACS

Our observations suggest a relationship between etiology, severity of hepatic disease, number of OFs and IAH.

Independent risk factors for the development of IAH were alcoholic cirrhosis, EH WH score and oxygenation ratio (PaO2/ FiO2) at ICU admission. This is in partial accordance with previous studies where liver dysfunction with the formation of ascites, severe acute illness (APACHE II ≥18 points), respiratory dysfunction (mechanical ventilation with positive end-expiratory pressure ≥7 cm), abdominal distension, ileus, positive fluid balance, obesity (body mass index >27 kg/m2), and abdominal surgery increase the likelihood of developing IAH (245,246).

Finding that IAH was associated with higher WH hepatic encephalopathy score deserves attention. A few studies have reported a correlation between IAH and increased intracranial pressure (ICP), even at low levels of increased IAP (255). Reversible disruption of the blood-brain barrier and increased ischemic mediators, indicating cerebral ischemia, due to IAH have been demonstrated (259-264). According to the Monro-Kellie hypothesis, two distinct pathways by which IAP could be transmitted to the central nervous system have been proposed

(265). First, due to backflow in the venous plexus of the spinal canal and the intracranial veins, and second, due to cranial excursion of the diaphragm causing elevated intrathoracic pressure and augmented central venous pressure with a decrease in venous drainage from the central nervous system via the jugular system (259,265,266). These mechanisms could represent an additional pathophysiologic rationale for HE in liver disease patients with increased IAP (259,266).

Strikingly, a higher oxygenation PaO2/FiO2 ratio was associated with IAH. The reason for this observation was not obvious to us and we speculate that higher levels of PEEP may have been used in mechanically ventilated patients with IAH, thus increasing the observed PaO2/FiO2, although, the available data could not confirm this.

Alcoholic cirrhosis was associated with IAH. Alcohol is as a co-factor for fibrosis progression in chronic liver disease of variable aetiology, as it negatively affects the outcome of most patients with liver disease. Despite a number of histological similarities, individual cases of alcoholic liver disease can be differentiated from other causes of liver disease (267). The fact that over half of the study population had alcohol-related cirrhosis and the remaining etiologies were either scarce in number or unspecified prevented us from drawing further conclusions.

3.4.3. Risk factors for ACS

Infection as a precipitant event of acute decompensation of cirrhosis was an independent risk factor for the presence of ACS among patients with IAH. When we looked at ACS patients' characteristics, we could see higher MELD, MELDNA scores and WBC count. Curiously, there was a noteworthy trend towards lower requirements of vital organ support, including IMV, vasopressor support and RRT in ACS patients. These findings reflected a

higher severity of chronic liver disease and systemic inflammation. The presence of infection may have led to a higher degree of PH, increased ascites formation and the development of ACS. Unfortunately, our data could not clarify whether spontaneous bacterial peritonitis, or any other type of infection, was responsible for the increased likelihood of ACS.

3.4.4. Outcomes

The distribution of IAH grades revealed that the distribution of mean IAP during the ICU stay was mostly restricted to grade I-II, which contrasts with a central distribution of grades of maximum IAP, as illustrated in Figure 11. This difference could may have been partly due to the initial clinical management of IAH at ICU admission and reflected a sustained reduction of IAP throughout the ICU stay. Furthermore, the central distribution of maximum IAP grades could indicate that this variable may be a better indicator of severity of disease.

Importantly, maximum IAP was a risk factor for 28-day mortality when adjusted for clinical severity SAPS II score. Increased IAP was associated with higher 28-day mortality, particularly in patients with ACS (Figure 13). The severity of IAH was associated with progressively higher mortality, which was similarly for IAH grades III and IV. This observation strengthens the clinical argument for merging grades III and IV together, as suggested by Blaser et al (246).

Mean IAP during the ICU stay presented higher mortality rates (Figure 12) than maximum IAP when we compared matching grades of IAH. The deleterious clinical impact of sustained (mean) IAP, more than episodical (maximum) IAH, may play a predominant role in the ultimate outcome, and highlights the importance of the duration of IAH and the time-dependence of its pathological effects on organ dysfunction. The effect of prolonged duration of IAH has been well demonstrated in critically ill surgical patients by Kyoung et al (243).

An overall high 28-day mortality rate was observed, and was comparable with other studies in critically ill liver cirrhosis patients showing short-term mortality rates ranging from 34.9% to 71.9% (268,201). The IROI study reported the presence and severity of IAH as an independent risk factor for increased mortality in a mixed population of critical patients (246). Similarly, IAH was reported to be associated with renal failure and RRT in septic shock liver disease patients and with longer ventilatory and vasopressor support (97). We showed that maximum IAP was associated with 28-day mortality when adjusted for SAPS II score. However, in multivariate analysis of 28-day mortality, MELD score, WBC count, PaO2/FiO2 ratio, and lactate concentration were risk factors for 28-day mortality, in line with previous studies (97,269,270,183). A possible explanation for this is an underpowered sample size to detect the effect of maximum IAP at ICU admission on 28-day mortality, and the complex, multifactorial nature of these patient's outcomes. Further research is needed to confirm these findings.

Clinical practice guidelines for the critically ill patient with IAH/ACS recommend a stepwise medical management algorithm to reduce and maintain IAP ≤15 mmHg. Importantly, ascites stands out as a fundamental common feature in critical liver disease patients with IAH. Studies in intensive care have reported the safety of LVP, potentially lowering IAP with beneficial effects on hepatosplenic blood flow, as well as in respiratory and renal dysfunction (214,213). Particular relevance should be assigned to the clinical management of patient with cirrhosis with ascites, given that paracentesis can treat and potentially prevent the recurrence of IAH and ACS during an ICU stay.

3.4.5. Limitations

Some noteworthy limitations in this study precluded more accurate reporting and interpretation of results. These included effective variables that were not available, such as APP, fluid balance, IAP trends during ICU stay. Additional data regarding the impact of specific therapeutic interventions aimed at lowering IAP, importantly, abdominal paracentesis, was not available. Possible selection and sampling biases were minimized due to the multicentric collection of data at each study site and the reasonably sized patient cohort. External validation of our results is required, although we believe them to be generalizable given the multicentric design of the study and the reasonable sample size.

3.5. Conclusions

Our study demonstrates a very high prevalence of IAH/ACS in the critically ill liver patient with cirrhosis with acute medical illness when compared to other populations of mixed intensive care patients. Increased IAP was associated with severity of disease and adverse outcomes. Risk factors for IAH were alcoholic cirrhosis, HE and PO2/FiO2 ratio, as well as infection for ACS. Particular relevance should be given to early diagnosis, treatment, and prevention of IAH and ACS as it might improve outcomes in the liver cirrhosis patient in the ICU.

Chapter 4

Abdominal Perfusion Pressure

4.1. Introduction

Cirrhosis increases intrahepatic resistance and leads to impairment of hepatosplanchnic blood flow. These changes result in chronic PH, further aggravated in advanced stages of the disease by compensatory splanchnic vasodilation, relative hypotension and the development of ascites.

The pathophysiologic aspects of intra-abdominal hypertension (IAH), in the decompensated patient with cirrhosis with ascites, have been previously studied, as well as the safety and immediate beneficial effects of therapeutic LVP on hemodynamic status and regarding renal, respiratory and hepatic functions (271-278).

In critically ill patients, APP resulting from the difference between MAP and IAP, correlates with improved survival (279). Furthermore, in the decompensated patient with cirrhosis, APP correlates with the clearance of indocyanine green, and may be predictive of organ dysfunction and outcome (280, 281). A few studies have reported various clinical cut-off values for APP, ranging from 50 to 72 mmHg, and potential resuscitation endpoints have been proposed (279, 281, 284). However, the clinical importance of APP, prevalence, risk factors and outcomes for AhP require specific research in the area of the critically ill patient with cirrhosis.

4.1.1. Aims and objectives

The objectives of this study were to characterize APP in a population of critically ill patients with cirrhosis, to analyze the prevalence and risk factors of AhP, clinical outcomes, including mortality rates at 28 and 90 days, intensive care unit (ICU) and hospital length-of-stay (LOS).

4.2. Methods

4.2.1. Design, settings, participants and definitions.

This was a single center prospective cohort study of patients with cirrhosis admitted to the ICU. The study was set in a general ICU, with 21 beds, specialized in liver disease, at Hospital de Curry Cabral, Centro Hospitalar Universitário Lisboa Central, Portugal.

Patients were recruited between October 2016 and December 2021 and followed-up to hospital discharge or to the last known date of patient record at the center.

Patient selection was performed using the following inclusion criteria: (1) age ≥ 18 years, (2) first ICU admission during the index hospital stay, and (3) medical type of admission (no surgery in the 4 weeks preceding the index ICU admission). The exclusion criteria considered: (1) any type of surgical ICU admission, (2) contra-indication for intravesical IAP measurements, (3) absence of recorded APP values, (4) patients with ICU stay duration inferior to 24 h and (5) patients with previous LT.

Abdominal compartment syndrome was defined as IAP > 20 mmHg in this population of critically ill patients.

For this study, “Paracentesis” refers to both diagnostic and LVP combined, unless otherwise stated. Large-volume paracentesis was defined for a volume ≥ 500 mL of drained ascites. Post-paracentesis circulatory disfunction (PPCD) was actively prevented with 20% albumin (8 g/L of drained ascites) infusion, according to clinical guidelines, and standard-of-care fluid therapy to ensure euvolemic state (285-289).

Pressure measures were performed every 6–8 h, and mean APP (APP = MAP − IAP) was calculated on each day for each patient. Values presented for IAP, APP and MAP in this study

correspond to daily mean value unless otherwise stated. The expressions "ICU admission" and "baseline" are interchangeable, and refer to the period corresponding to calendar day zero (0) plus day one (1) of ICU stay, to assure completeness of 24-h ICU stay data. Whenever a patient underwent emergent liver transplant during the ICU stay, IAP measure and APP calculation were halted due to the change in the type (surgical) of patient. These patients were included in the overall mortality analysis at 28-days.

Outcome measurements included survival data at 28 and 90 days, and length-of-stay in the ICU and hospital.

4.2.2. Statistical analysis

Chi-square test was used to compare the frequency of categorical variables for independent groups. Shapiro–Wilk test was used to assess for normal distribution of continuous variables. T-test was then used to compare the mean between two normally distributed groups and the median test to compare the median of non-normal continuous variables. Multivariate analysis was performed using backward stepwise logistic regression, and included variables based on clinical importance and with p value ≤ 0.10 in univariate analysis, after assessment of statistical assumptions, namely, independence of observations, absence of influential outliers, linearity in the logit for continuous variables and collinearity, using Kendall Tau coefficient to identify and exclude strongly (±0.35) correlated predicting variables (290). The area under the Receiver operator curve (aROC) was used to determine the ability of a continuous variable to discriminate between a dichotomous outcome and the Younden's J statistic (Younden index) was used to identify the optimal cut-off value. Statistical significance was considered for two-sided p value ≤ 0.05. Statistical software IBM SPSS Statistics for Windows (version 23.0) was used for analysis.

4.2.3. Ethics

The study protocol was approved by the Ethics Committee at Centro Hospitalar Universitário Lisboa Central (CES nº397/2017), and waived the need for individual informed consent for this observational study. All study procedures followed the principles of the Declaration of Helsinki (291).

4.3. Results

4.3.1. Overall

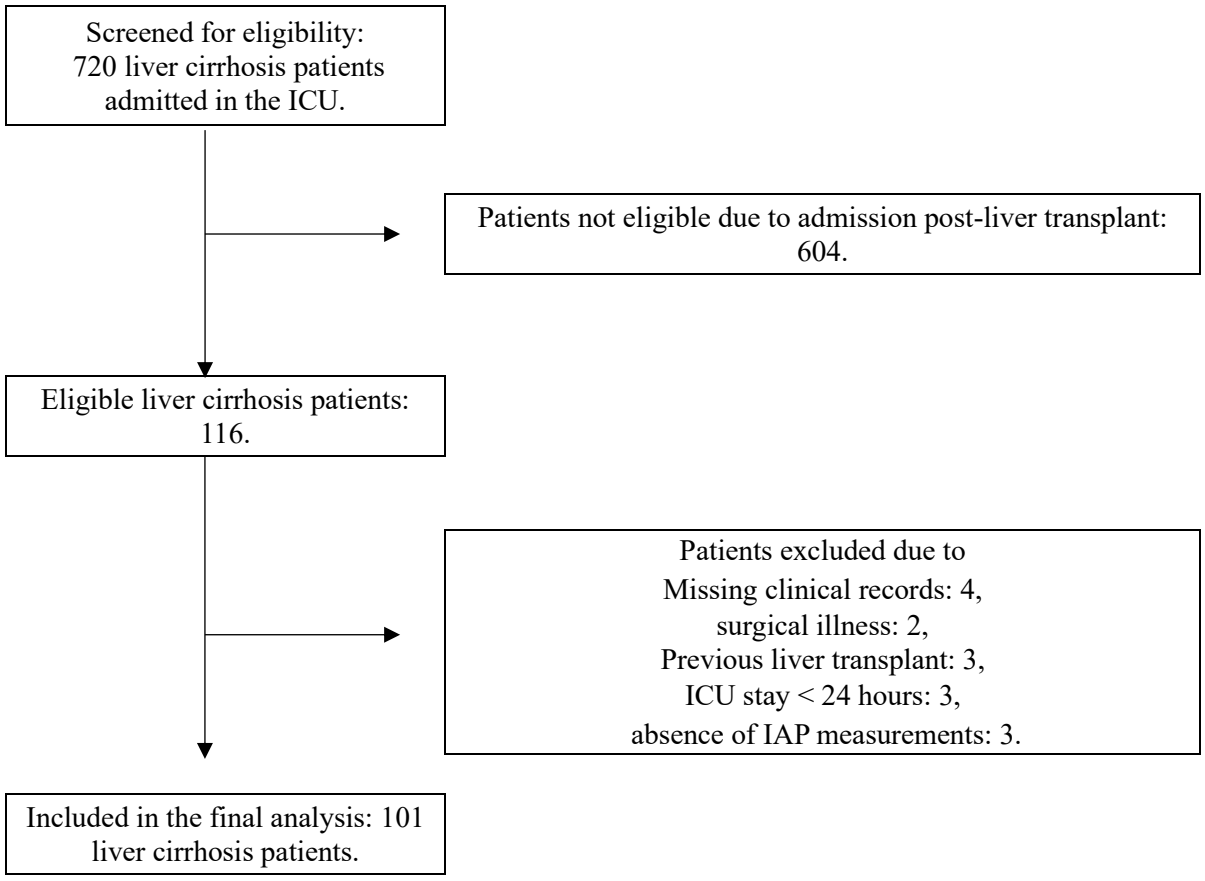


Figure 15. Study patient flowchart.

This study included 101 cirrhosis patients. A patient flowchart is depicted in Figure 15.

Patients presented a mean age of 57.2 (± 10.4) years and female gender represented 23.5% of the cohort. Liver disease etiology included alcohol alone (51.0%), alcohol plus HCV (13.7%), NASH (5.9%), HCV alone and non-C viral hepatitis (both 4.9%). There was a history of past liver disease decompensation in 62.7% of patients, and hepatic related comorbidities included any type of hepatic neoplasm (20.6%), portal vein thrombosis (18.6%) and ascites (88.2%). The most frequent precipitant events leading to index ICU admission were infection (37.3%), bleeding (23.5%), HE (7.8%) and AKI (6.9%). Clinical severity at ICU admission presented a mean SAPS II of 49 (± 15.0), median MELDNA of 31 [23, 37], mean CLIF-C of 53 (± 11) and ACLF grades (1-3) of 8.9%, 26.7% and 52.5%, respectively. The need for vasopressor therapy was present in 75% of patients at baseline, namely, noradrenaline (30%), or terlipressine (18%), or both in combination in 27% of cases.

The observed mortality rates were 48.1% in-ICU, 64.4% in-hospital, and 56.4% and 67.6%, respectively, at 28 and 90 days. Median (days) ICU stay was 8 [4, 12] and hospital stay 23 [14, 42] (Table 21). During the hospital stay liver transplant was performed in 18 (17.8%) cases after index ICU admission.

Table 21. Baseline clinical characteristics of patients with cirrhosis and 28-day mortality.

Baseline variables	Overall (n=101)	Non-survivors (n=57)	Survivors (n=44)	p
Age (years)	57.1 (10.4)	57.0 (11.3)	57.4 (9.4)	0.8
Male gender, n (%)	77 (76.2)	45 (78.9)	32 (72.7)	0.6
Liver disease etiology, n (%)				0.1
Alcohol	52 (51.5)	29 (50.9)	23 (52.3)	
Alcohol + HCV	14 (13.9)	5 (8.8)	9 (20.5)	
Precipitant, n (%)				0.6
AKI[a]	7 (6.9)	4 (7.0)	3 (6.8)	
Bleeding	24 (23.8)	13 (22.8)	11 (25.0)	
Encephalopathy	8 (7.9)	6 (10.5)	2 (4.5)	
Infection	38 (37.6)	23 (40.4)	15 (34.1)	
CRP (mg/L)	51 [18, 93]	50 [18, 93]	56 [18, 84]	0.9
WBC count (10^3/mL)	11.9 [6.4, 18.3]	13.5 [8.4, 19.1]	8.5 [5.4, 15.7]	0.02
Hematocrit (%)	23.9 (5.7)	23.8 (5.9)	24.0 (5.6)	0.9
INR	2.2 [1.7, 3.1]	2.40 [1.78, 3.60]	1.85 [1.60, 2.42]	0.004
Platelets (10^3/mL)	67 [42, 121]	67 [46, 146]	62 [38, 94.25]	0.3
Urea (mg/dL)	90 [55, 131]	97 [62, 146]	70.50 [45.75, 105]	0.03
Creatinine (mg/dL)	1.8 [0.9, 3.0]	2.1 [1.3, 3.1]	1.3 [0.8, 2.6]	0.04
Urine output (mL/24h)	1090 [498, 1823]	1005 [418, 1695]	1133 [805, 1924]	0.5
Bilirubin (total, mg/dL)	6.0 [2.3, 17.6]	11.1 [4.9, 24.5]	3.5 [1.9, 6.4]	< 0.001
Ammonia (ug/dL)	240 [159, 314]	243 [177, 230]	189 [137, 306]	0.2
West-Haven score	1 [0, 3]	3 [1, 3]	1 [0, 2]	0.001
PaO2/FiO2 ratio	257 [170, 356]	257 [166, 356]	249 [178, 354]	0.9
Arterial blood pH (minimum)	7.38 [7.30, 7.43]	7.35 [7.28, 7.42]	7.41 [7.35, 7.45]	0.03
Lactate (mmol/L)	2.6 [1.5, 4.3]	2.9 [1.9, 5.3]	2.2 [1.4, 3.5]	0.01
Fluid balance (mL)	1618 [433, 3623]	1699 [− 410, 3744]	1563 [715, 2908]	0.9
Ascites, n (%) (n = 98)	87 (86.1)	4885.7)	38 (90.5)	0.7
Paracentesis, n (%)	38 (37.6)	23 (40.4)	15 (34.1)	0.7
Paracentesis volume (mL)[b] (n = 21)	3000 [1800, 4500]	4000 [1825, 5575]	2300 [1640, 2900]	0.2
SAPS II score	49 (15)	53 (16)	43 (11)	< 0.001
MELD Na score	31 [23, 37]	34 [28, 40]	26 [17, 32]	< 0.001
ACLF grade	3 [2, 3]	3 [2, 3]	2 [1, 3]	< 0.001
AKI[a], n (%)	66 (65.3)	44 (77.2)	22 (50.0)	0.008
RRT, n (%)	24 (23.8)	16 (28.1)	8 (18.2)	0.4
IMV, n (%)	56 (55.4)	36 (63.2)	20 (45.5)	0.12
Vasopressors, n (%)	72 (71.3)	41 (71.9)	31 (70.5)	1
IAP (mmHg)	12 [8, 15]	13 [9, 15]	11 [8, 14]	0.2
MAP (mmHg)	72 [66, 81]	72 [63, 77]	75 [68, 90]	0.2
APP (mmHg)	63 (15)	60 (14)	67 (15)	0.050
Mortality at day 28, n (%)	57 (56.4)			
ICU LOS (days)	8 [4, 12]	7 [4, 10]	9 [6, 16]	0.06
Hosp stay (days)	24 [14, 42]	19 [8, 25]	39 [24, 65]	< 0.001

Normally distributed continuous variables are presented as mean (SD) and non-normal continuous variables as median [IQR]. IAP and MAP values are drawn from pooled APP data components. [a] Diagnosis of AKI as indicated in clinical records. [b] Paracentesis volume (mL) includes only large-volume paracentesis (≥ 500 mL), and excludes diagnostic paracentesis. Abbreviations: IAP intra-abdominal pressure, APP abdominal perfusion pressure, BMI body mass index, HCV Hepatitis C virus, ACLF acute-on-chronic liver failure, INR international normalization ratio, CRP C-reactive protein, PaFiO2 arterial oxygen partial pressure to fractional inspired oxygen ratio, IMV invasive mechanical ventilation, AKI acute kidney injury, RRT renal replacement therapy, SAPS II simplified acute physiology score II, CLIF-C Chronic Liver Failure Consortium, MELDNA Model For End-Stage Liver Disease—sodium, MAP mean arterial pressure, ICU intensive care unit, LOS length-of-stay, WBC white blood cell.

A total of 1274 APP measurements were recorded throughout the ICU stay, approximately, corresponding to a mean of 13 per patient. Measured pressures (mmHg) presented a median IAP of 12.4 [9.6, 13.9], a mean MAP of 78.2 (± 11.0) and a median APP of 65.9 [58.6, 72.0]. The distribution of IAH grades (I–IV) during the ICU stay and associated mortality rates are depicted in Figure 16.

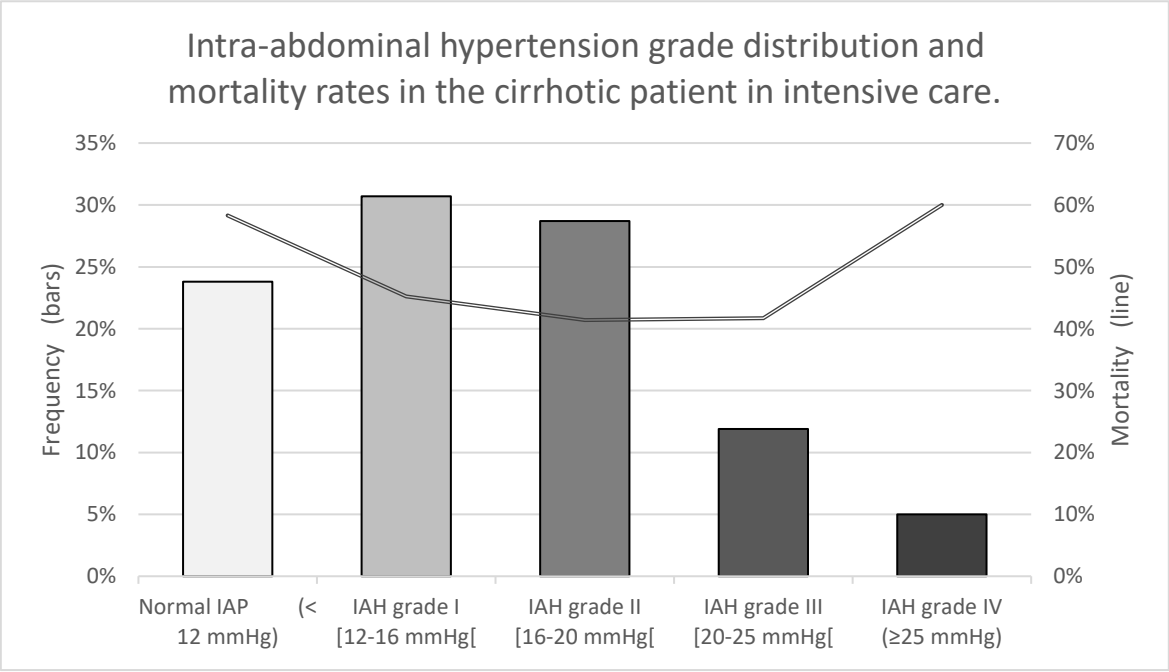


Figure 16. Intra-abdominal hypertension grades and 28-day mortality. Distribution of IAH grades during the entire ICU stay (n=101). Intra-abdominal hypertension grades take into account the highest daily mean value of intra-abdominal pressure throughout the ICU stay. Abbreviations: IAH, intra-abdominal hypertension.

4.3.2. Abdominal hypoperfusion

Baseline AhP had a prevalence of 47%, as illustrated in Figure 17.

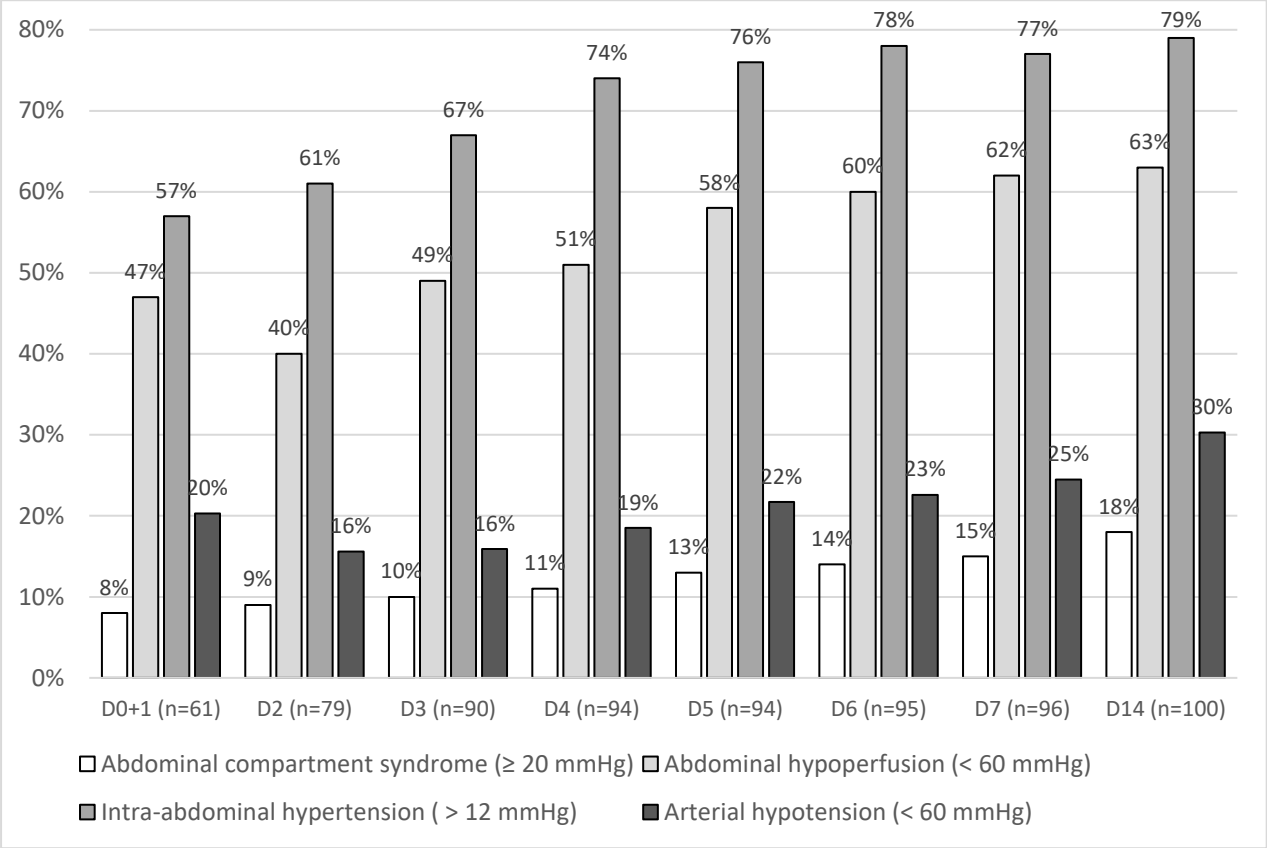


Figure 17. Cumulative prevalence of critical pressures in intensive care. The frequencies shown take into account the daily mean values. Abbreviations: D day, IAP intra-abdominal hypertension, APP abdominal perfusion pressure, MAP mean arterial pressure.

Baseline AhP was associated with higher serum urea concentration and clinical severity SAPS II score, lower arterial blood pH and the presence of paracentesis in univariate analysis (Table 22).

Table 22. Comparison of patients with cirrhosis with and without abdominal hypoperfusion.

	At ICU admission			During ICU stay		
Baseline variables	**APP < 60 mmHg**	**APP ≥ 60 mmHg**	**p**	**APP < 60 mmHg**	**APP ≥ 60 mmHg**	**p**
N (%)	28 (47.5)	31 (52.5)		67 (67.7)	32 (32.3)	
Age (years)	58 [52, 63]	58 [52, 63]	0.9	58 (11)	55 (9)	0.13
Male gender, n (%)	22 (78.6)	25 (80.6)	1.0	53 (79.1)	23 (71.9)	0.6
Liver disease etiology, n (%)			0.8			0.3
Alcohol	15 (53.6)	15 (48.4)		39 (58.2)	12 (37.5)	
Alcohol + HCV	4 (14.3)	4 (12.9)		9 (13.4)	5 (15.6)	
Precipitant, n (%)			0.9			0.2
AKI[a]	2 (7.1)	4 (12.9)		3 (4.5)	4 (12.5)	
Bleeding	5 (17.9)	5 (16.1)		13 (19.4)	10 (31.2)	
Encephalopathy	3 (10.7)	2 (6.5)		6 (9.0)	2 (6.2)	
Infection	12 (42.9)	11 (35.5)		26 (38.8)	12 (37.5)	
CRP (mg/L)	50 [23, 94]	27. [13, 66]	0.2	56 [18, 95]	47 [18, 88]	0.6
WBC count (10^3/mL)	13.2 [6.5, 20.0]	10.8 [6.5, 16.7]	0.3	12 [6.8, 18.4]	11.3 [6.4, 17.9]	0.7
Hematocrit (%)	24.8 (5.9)	23.4 (6.8)	0.4	24.40 (5.71)	23.0 (5.8)	0.2
INR	2.4 [1.7, 2.8]	2.2 [1.7, 2.9]	0.7	2.3 [1.7, 3.0]	1.9 [1.6, 3.5]	0.4
Platelets (10^3/mL)	70 [45, 126]	54 [43, 93]	0.3	69 [41, 99]	56 [41, 139]	0.9
Urea (mg/dL)	115 [78, 178]	72 [44, 110]	0.01	93 [62, 145]	66 [41, 98]	0.02
Creatinine (mg/dL)	2.3 [1.5, 2.9]	1.3 [0.8, 2.9]	0.10	2.1 [1.0, 3.2]	1.2 [0.8, 2.2]	0.01
Urine output (mL/24h)	975 [393, 2053]	1268 [898, 1933]	0.4	970 [409, 1503]	1330 [930, 1923]	0.03
Bilirubin (total, mg/dL)	6.2 [2.4, 12.0]	6.7 [3.4, 20.2]	0.5	5.70 [2.26, 13.96]	6.58 [2.52, 19.04]	0.8
Ammonia (ug/dL)	238 [170, 286]	255 [169, 308]	0.7	228 [159, 333]	255 [163, 294]	0.7
West-Haven score	2 [0, 3]	1 [0, 3]	0.6	1 [0, 3]	2 [0, 3]	0.3
PaO2/FiO2 ratio	253 [157, 354]	286 [166, 357]	0.6	257 [163, 355]	257 [197, 359]	0.7
Arterial blood pH (minimum)	7.34 [7.24, 7.40]	7.40 [7.32, 7.44]	0.03	7.36 [7.29, 7.42]	7.40 [7.36, 7.47]	0.02
Lactate (mmol/L)	2.9 [1.9, 9.1]	2.5 [1.3, 3.7]	0.09	2.7 [1.7, 4.3]	2.3 [1.5, 4.1]	0.2
Fluid balance (mL)	1565 [115, 4405]	819 [− 396, 2194]	0.3	1791 [273, 4104]	1426 [563, 2624]	0.4
Ascites, n (%)	27 (100)	27 (87.1)	0.2	54 (90.0%)	28 (84.8)	0.7
Paracentesis, n (%)	18 (64.3)	10 (32.3)	0.03	29 (43.2)	9 (28.1)	0.11
Paracentesis (mL)[b] (n=21)	3500 [1650, 5613]	3110 [2055, 4375]	0.9	3500 [1750, 5538]	2220[1850, 2600]	0.4
SAPS II score	56 (17)	43 (14)	0.004	50 (16)	46 (13)	0.3
MELD Na score	31 [26, 37]	29 [20, 38]	0.5	31 [25, 37]	28 [19, 40]	0.3
ACLF grade	3 [2, 3]	2 [1, 3]	0.06	3 [2, 3]	2 [1, 3]	0.03
AKI[a], n (%)	22 (78.6)	17 (54.8)	0.10	47 (70.1)	17 (53.1)	0.2
RRT, n (%)	6 (21.4)	8 (25.8)	0.9	18 (26.9)	6 (18.8)	0.5
IMV, n (%)	18 (64.3)	12 (38.7)	0.09	37 (55.2)	18 (56.2)	1.0
Vasopressors, n (%)	24 (85.7)	19 (61.3)	0.07	52 (77.6)	18 (56.2)	0.05
IAP (mmHg)	13 [11, 15]	11 [7, 14]	0.04	13 [9, 15]	9 [7, 14]	0.2
MAP (mmHg)	65 [60, 71]	81 [72, 92]	<0.001	71 [62, 79]	81 [74, 97]	0.002
APP (mmHg)	51 (7)	73 (11)	<0.001	59 (13)	76 (12)	<0.001
Mortality at day 28, n (%)	21 (75.0)	14 (45.2)	0.04	39 (58.2)	17 (53.1)	0.8
ICU LOS (days)	7 [2, 12]	8 [4, 11]	0.2	9 [5, 14]	7 [4, 9]	0.03

[a] Diagnosis of AKI as indicated in clinical records.

[b] Paracentesis volume (mL) includes only large-volume paracentesis (≥ 500 mL), and excludes diagnostic paracentesis.

Normally distributed continuous variables are presented as mean (SD) and non-normal continuous variables as median [IQR]. IAP and MAP values are drawn from pooled APP data components.
Abbreviations: IAP intra-abdominal pressure, APP abdominal perfusion pressure, BMI body mass index, HCV Hepatitis C virus, ACLF acute-on-chronic liver failure, INR international normalization ratio, CRP C-reactive protein, PaFiO2 arterial oxygen partial pressure to fractional inspired oxygen ratio, IMV invasive mechanical ventilation, AKI acute kidney injury, RRT renal replacement therapy, SAPS II simplified acute physiology score II, CLIF-C Chronic Liver Failure Consortium, MELDNA Model For End-Stage Liver Disease – sodium, MAP mean arterial pressure, ICU intensive care unit, LOS length-of-stay, WBC white blood cell.

Multivariate analysis (n = 59) revealed independent association between paracentesis (aOR 4.81, CI 95% 1.46–15.8, p = 0.01), and ACLF grade (aOR 2.41, CI 95% 1.20–4.85, p = 0.01) with AhP at baseline (Table 23).

Table 23. Risk factors for abdominal hypoperfusion in intensive care.

				95% CI	
	Baseline variables	**p**	**Odds ratio**	**Lower**	**Upper**
AhP at baseline (n = 59)[a]	Paracentesis	0.01	4.81	1.46	15.8
	ACLF grade	0.01	2.41	1.20	4.85
AhP up to day 7 (n = 92)[b]	Paracentesis	0.07	2.51	0.92	6.86
	ACLF grade	0.003	2.09	1.29	3.39

Abdominal hypoperfusion corresponds to a daily mean abdominal perfusion pressure < 60 mmHg. AhP abdominal hypoperfusion, C.I. confidence interval, ACLF acute-on-chronic liver failure. [a] Multivariate analysis included: urea, pH, lactate, invasive mechanical ventilation, ACLF grade and paracentesis. [b] Multivariate analysis included: creatinine, urine output, pH, paracentesis and ACLF grade.

During the ICU stay, AhP presented a cumulative prevalence of 63% (Figure 17) and was associated with higher creatinine and urea concentrations, urine output, ACLF grade and lower pH at baseline (Table 22).

Multivariate analysis (n = 92), with the addition of paracentesis at admission due to clinical relevance, revealed that higher ACLF grade was significantly associated with AhP during the first week of ICU stay, differently from paracentesis (Table 23).

4.3.3. Paracentesis

Paracentesis was performed in 38% of patients at ICU admission. Additionally, the frequency of paracentesis performed prior to ICU admission was 37%, and after ICU admission was 51%. In 27% of cases there was no record of paracentesis during the entire hospital stay and this was justified due to absent/minimal ascites (n = 16) or waived based on a confirmed clinical diagnosis (n = 9, including pneumonia, hydrothorax and ruptured esophageal varices).

At baseline, APP was significantly lower in patients submitted to LVP (60 ± 6.2 vs. 67 ± 14, p = 0.01) when compared to the rest of the patients and did not significantly differ throughout the rest of the study period days (Figure 19). The variation in APP from baseline to D2 was not significantly different between patients with/without LVP at ICU admission (p = 0.9).

Large-volume paracentesis (> 500 mL, n = 21) presented a median volume of 3000 mL [1800, 4500], and was not associated with baseline AhP (p = 0.3) nor with 28-day mortality (p = 0.4) in multivariate analysis.

4.3.4. Mortality

Baseline APP (mmHg) was lower in non-survivors at 28-days when compared to survivors (60 ± 14 vs. 67 ± 15, p = 0.050). Additionally, mortality was also associated with WBC count, bilirubin, urea, SAPS II score, lactate, WH score, paracentesis, INR, creatinine, pH and a clinical diagnosis of AKI at admission. (Table 21). Those with AhP had a higher 28-day mortality rate (75.0% vs. 45.2%, p = 0.04) (Table 22).

In multivariate analysis (n = 96) we observed that bilirubin and SAPS II score were independently associated with 28-day mortality (Table 24). Similar results were observed for 90-day mortality. When we included baseline AhP, due to clinical importance, in the multivariate analysis (n = 55) WH HE score was the only risk factor for 28-day mortality (Table 24).

Table 24. Risk factors at ICU admission for 28-day mortality.

	Baseline variables	p	Odds ratio	95% CI	
				Lower	Upper
Mortality at 28 days (n = 96)	Lactate	0.4	1.07	0.92	1.24
	C-reactive protein	0.07	1.01	1.00	1.02
	SAPS II	0.048	1.04	1.00	1.09
	Bilirubin	0.001	1.13	1.05	1.21
Variables included: white blood cell count, bilirubin, urea, SAPS II score, lactate, West-Haven score, paracentesis at admission					
Mortality at 28 days (n = 55)	Baseline AhP	0.09	0.31	0.08	1.20
	SAPS II	0.08	1.04	1.00	1.09
	West-Haven score	0.02	1.88	1.11	3.21
Variables included: white blood cell count, bilirubin, urea, SAPS II score, lactate, West-Haven score, paracentesis and AhP at baseline					

Multivariate analysis for 28-day mortality risk factors in liver cirrhosis patients in intensive care.
Paracentesis corresponds to both diagnostic and large-volume paracentesis. C.I. confidence interval; SAPS simplified acute physiologic score; AhP abdominal hypoperfusion.

Baseline APP presented a poor ability to discriminate between survivors and non-survivors at 28 days (Figure 18).

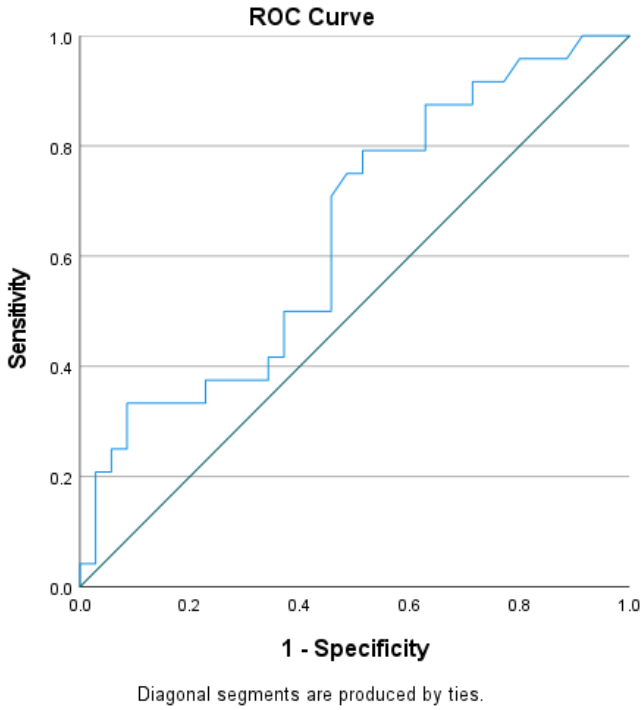


Figure 18. Receiver operator characteristic curve for the ability of baseline abdominal perfusion pressure to discriminate 28-day vital outcome. Area under the ROC curve 0.64 ±0.07, 95% CI 0.50-0.79, p=0.07.

The optimal cut-off value for APP was ≥ 59 mmHg (Younden index 0.28) to discriminate between survivors and non-survivors at day 28.

Daily critical pressures APP, IAP and MAP during the first week of ICU by groups of patients with and without LVP at baseline (D0+D1) and by vital outcomes at day 28 are illustrated in Figure 19.

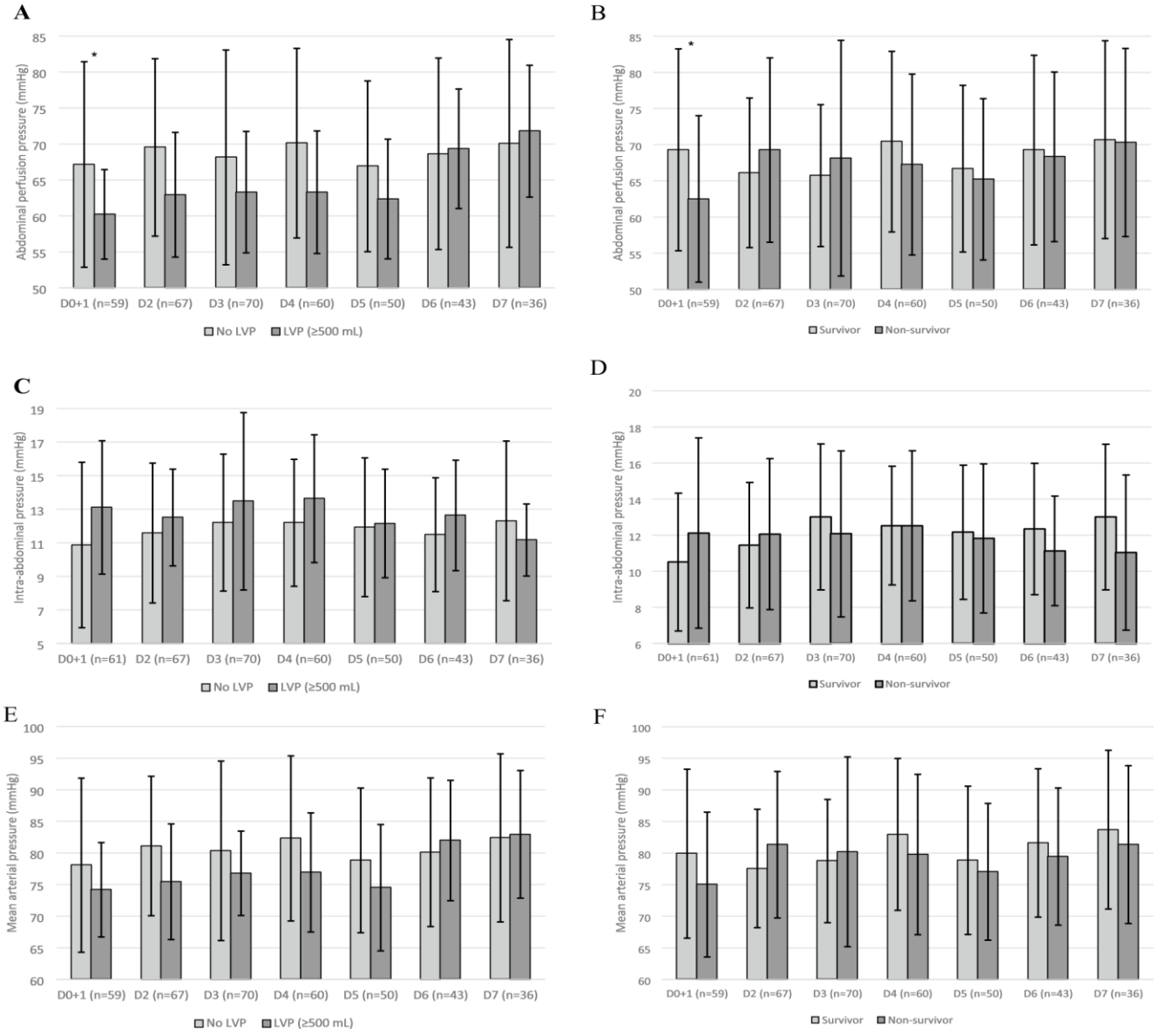


Figure 19. Critical pressures during the first 7 days of intensive care. Abdominal perfusion pressure (A and B), intra-abdominal pressure (C and D), mean arterial pressure (E and F).* Statistically significant ($p \leq 0.05$) intraday difference between groups. Large-volume paracentesis (≥500 mL) at baseline (n=21), was compared to all other study patients (n=79). Mortality was assessed at day 28; survivors: n=43, non-survivors: n=57. Error bars: ±1 standard deviation. Abbreviations: LVP, large-volume paracentesis; D, Day.

There was a significant difference in baseline APP between groups of patients with and without LVP and between survivors and non-survivors. (Figure 19)

Patients presenting AhP had a longer ICU LOS (days) (9 [5, 14] vs. 7 [4, 9], p = 0.03) (Table 25), compared to those without AhP.

4.3.5. Other results

Additional comparison of IAH groups, from our center's overall patient cohort is detailed in the following Table 25.

Table 25. Comparison of patients with and without intra-abdominal hypertension in the ICU.

	At ICU admission.			During the ICU stay		
Baseline variables	**IAP ≥ 12 mmHg**	**IAP < 12 mmHg**	**p**	**IAP ≥ 12 mmHg**	**IAP < 12 mmHg**	**p**
n	34 (55.7)	27 (44.3)		78 (77.2)	23 (22.8)	
Age	58.5 [51.3, 63.8]	57.0 [51.5, 61.5]	0.5	57.2 (10.8)	56.8 (9.1)	0.9
Male gender, n (%)	25 (73.5)	23 (85.2)	0.4	60 (76.9)	17 (73.9)	1.0
BMI (n=57)	25.9 [21.9, 27.5]	26.0 [20.8, 30.8]	0.7	25.7 [22.0, 28.6]	27.7 [24.2, 30.8]	0.4
Charlson Score	5 [4, 6]	5 [4, 7]	1.0	5 [4, 6]	5 [4, 8]	0.4
Liver disease etiology, n (%)			0.5			1.0
Alcohol	17 (50.0)	14 (51.9)		42 (53.8)	10 (43.5)	
Alcohol + HCV	5 (14.7)	3 (11.1)		10 (12.8)	4 (17.4)	
HCV	2 (5.9)	1 (3.7)		4 (5.1)	1 (4.3)	
NASH	3 (8.8)	2 (7.4)		4 (5.1)	2 (8.7)	
Ascites, n (%)	19 (55.9)	14 (51.9)	0.6	67 (85.9)	20 (87.0)	0.6
Tumor, n (%)	9 (26.5)	6 (22.2)	0.9	13 (16.7)	7 (30.4)	0.2
PVT/CT, n (%)	8 (23.5)	5 (18.5)	0.3	14 (17.9)	5 (21.7)	0.03
Chronic dialysis, n (%)	0	0	NA	1 (1.3)	1 (4.3)	0.9
Prior decompensation, n(%)[a]	21 (61.8)	18 (66.7)	0.4	44 (56.4)	19 (82.6)	0.07
Prior antibiotics (%)[a]	9 (26.5)	7 (25.9)	0.5	20 (25.6)	6 (26.1)	0.9
Prior hospitalization, n (%)[a]	16 (47.1)	8 (29.6)	0.3	29 (37.2)	6 (26.1)	0.5
Precipitant, n (%)			0.4			0.2
AKI	3 (8.8)	3 (11.1)		4 (5.1)	3 (13.0)	
Bleeding	6 (17.6)	5 (18.5)		18 (23.1)	6 (26.1)	
Encephalopathy	1 (2.9)	4 (14.8)		4 (5.1)	4 (17.4)	
Infection	13 (38.2)	10 (37.0)		32 (41.0)	6 (26.1)	

Albumin (mg/L)	27.3 (13.6)	24.2 (6.4)	0.5	25.3 (11.7)	25.65 (6.0)	0.9
CRP (mg/L)	42 [18, 64]	49 [15, 83]	0.7	55 [18, 96]	45 [23, 75]	0.9
WBC count (10^3/mL)	13.2 [7.3, 18.5]	11.9 [5.6, 16.9]	0.3	12.5 [7.3, 18.8]	7.0 [4.9, 14.6]	0.03
Hematocrit (%)	23.6 (6.1)	24.4 (6.7)	0.6	24.07 (5.92)	23.11 (4.99)	0.5
INR	2.2 [1.6, 3.0]	2.2 [1.7, 2.7]	0.9	2.2 [1.7, 3.0]	2.4 [1.7, 3.5]	0.6
Platelets (10^3/mL)	73 [47, 140]	59 [39, 75]	0.1	70 [46, 124]	53 [36, 98]	0.1
Urea (mg/dL)	93 [71, 157]	84 [51, 132]	0.3	90 [51, 125]	90 [60, 135]	0.8
Creatinine (mg/dL)	2.2 [1.3, 3.0]	1.5 [0.9, 2.5]	0.2	2.0 [0.8, 3.0]	1.6 [1.0, 3.1]	1.0
Urine output (mL)	1093 [416, 1959]	1215 [680, 2095]	0.5	1095 [561, 1668]	855 [441, 1905]	0.7
Bilirubin (total, mg/dL)	6.7 [2.6, 22.3]	4.7 [3.0, 13.3]	0.5	6.2 [2.3, 19.0]	5.7 [3.3, 11.3]	0.7
Ammonia (unit)	204 [157, 259]	260 [204, 360]	0.2	221 [158, 299]	245 [189, 376]	0.3
West-Haven score	2 [1, 3]	1 [0, 2]	0.1	2 [0, 3]	1 [0, 3]	0.3
PaO2/FiO2 ratio	316 [194, 411]	215 [138, 288]	0.006	296 [174, 383]	215 [156, 276]	0.05
pH min	7.36 [7.27, 7.41]	7.40 [7.29, 7.43]	0.4	7.38 [7.30, 7.43]	7.38 [7.30, 7.41]	0.6
Lactate (mmol/L)	2.5 [1.5, 3.6]	3.1 [1.4, 4.5]	0.8	2.5 [1.5, 4.1]	3.2 [1.7, 6.2]	0.3
Fluid balance (mL)	812 [-1098, 3201]	1699 [478.75, 3743]	0.2	1595 [430, 3398]	1640 [826, 3707]	0.7
Ascites, n (%)	19 (55.9)	14 (51.9)	0.6	67 (85.9)	20 (87.0)	0.6
Paracentesis, n (%)	17 (50.0)	6 (22.2)	0.006	27 (34.6)	3 (13.0)	0.08
Paracentesis volume (mL)	3000 [50, 5500]	1160 [238, 1880]	0.3	1800 [50, 4000]	220 [1510, 3110]	0.8
SAPS II score	50 (15)	48 (18)	0.6	47 (14)	55 (16)	0.03
CLIF OF score	11 [9, 13]	10 [8, 12]	0.3	10 [9, 12]	11 [9, 12]	0.9
CLIF C score	55 (11)	51 (11)	0.1	54 (11)	50 (11)	0.2
MELD Na score	31 [24, 39]	29 [24, 34]	0.3	30 [22, 37]	31 [25, 36]	0.8
ACLF grade	3 [2, 3]	3 [2, 3]	0.7	3 [2, 3]	3 [2, 3]	0.9
AKI, n (%)	24 (70.6)	17 (63.0)	0.7	51 (65.4)	15 (65.2)	1.0
RRT, n (%)	10 (29.4)	4 (14.8)	0.3	20 (25.6)	4 (17.4)	0.6
IMV, n (%)	16 (47.1)	15 (55.6)	0.7	39 (50.0)	17 (73.9)	0.07
Vasopressors, n (%)	26 (76.5)	19 (70.4)	0.8	56 (71.8)	16 (69.6)	1.0
IAP (mmHg)	15 [13, 17]	8 [6, 9]	<0.001	13 [11, 15]	7 [6, 8]	<0.001
MAP (mmHg)	72 [68, 82]	71 [62, 80]	0.3	72 [69, 86]	65 [58, 72]	0.03
APP (mmHg)	61 (14)	65 (15)	0.2	64 (14)	60 (16)	0.4
Survivor at day 28, n (%)	11 (32.4)	14 (51.9)	0.2	34 (43.6)	10 (43.5)	1.0
Survivor at day 90, n (%)	8 (23.5)	9 (33.3)	0.6	24 (30.8)	9 (39.1)	0.6
ICU LOS (days)	7 [3, 11]	6 [3, 12]	0.8	9 [5, 12]	5 [2, 7]	0.001
Hospital stay (days)	23 [18, 46]	25 [12, 47]	0.7	25 [18, 46]	15 [7, 24]	0.004

[a] In past three months prior to index hospitalization. Normally distributed continuous variables are presented as mean (SD) and non-normal continuous variables as median [IQR]. IAP and MAP values are drawn from pooled APP data components. Abbreviations - IAP: intra-abdominal pressure, IAH: intra-abdominal hypertension, APP: abdominal perfusion pressure, BMI: body mass index, HCV: Hepatitis C virus, NASH: Non-alcoholic steato-hepatitis, PVT/CT: portal vein thrombosis or cavernomatous transformation, ACLF: acute-on-chronic liver failure, INR: international normalization ratio, CRP: C-reactive protein, PaFiO2: arterial oxygen partial pressure to fractional inspired oxygen ratio, IMV: invasive mechanical ventilation, AKI: acute kidney injury, RRT: renal replacement therapy, SAPS II: simplified acute physiology score II , CLIF-C: Chronic Liver Failure Consortium, MELDNA: Model For End-Stage Liver Disease - sodium, IAP: intra-abdominal pressure, MAP: mean arterial pressure, ICU: intensive care unit, LOS: length-of-stay, WBC: white blood cell.

Patients with IAH at admission had higher PaO2/FiO2 ratio and higher frequency of paracentesis performed, whereas those with IAH during the entire ICU stay presented higher WBC count, higher PaO2/FiO2 ratio, lower SAPS II score and lower ICU and hospital LOS. Independent risk factors for IAH in this cohort of patients included paracentesis, higher CLIF-C score, PaO2/ratio, and WBC count, and there was a lesser likelihood of IAH in patients that were submitted to IMV at ICU admission, as detailed in the table below (Table 26).

Table 26. Risk factors for intra-abdominal hypertension in the ICU.

	Baseline variables	P value	Odds ratio	95% C.I. Lower	95% C.I. Upper
ICU admission (n=57) [a]	Paracentesis	0.03	4.32	1.11	16.8
	CLIF-C score	0.02	1.08	1.01	1.15
	PaO2/FiO2 ratio	0.005	1.01	1.00	1.01
ICU day 7 (n=92) [b]	PaO2/FiO2 ratio	0.048	1.01	1.00	1.01
	IMV	0.02	0.20	0.06	0.74
	White blood cell count	0.004	1.14	1.04	1.25

Multivariate analysis for intra-abdominal hypertension (≥ 12 mmHg) risk factors in intensive care. Stepwise backward logistic regressions are shown. a Variables included: PaO2/FiO2 ratio, West-Haven score and platelets (step 1), CLIF-C score (step 2), and paracentesis (step 3). b Variables included: white blood cell count, PaO2/FiO2 ratio and IMV (step 1), SAPS II score (step 2), and paracentesis (step 3). Abdominal hypoperfusion corresponds to abdominal perfusion pressure < 60 mmHg.
Abbreviations: C.I., confidence interval; ICU, intensive care unit; PaO2, partial arterial oxygen pressure; FiO2, inspired oxygen fraction; SAPS, simplified acute physiologic score; MAP, mean arterial pressure; ACLF, acute-on-chronic liver failure.

4.4. Discussion

4.4.1. Overall

This is the largest study to address the impact of APP on clinical outcomes in critically ill patients with cirrhosis (279,280,292). The typical patient in our cohort was under 60 years-old, male, with alcoholic liver disease and ascites, admitted in intensive care with ACLF grade 3.

The main findings of this study were: (i) a high prevalence of AhP, in approximately half of the population at baseline and in two thirds of patients during the first week of ICU stay, (ii)

AhP was independently associated with higher clinical severity, (iii) these patients were five times more likely to be submitted to paracentesis at baseline, and (iv) 28-day mortality risk factors included higher clinical severity, total bilirubin and HE at ICU admission.

Chronically increased IAP is present in the physiological state of pregnancy (293-296) and in pathological states such as morbid obesity (297, 298), decompensated heart failure (299-301) and liver cirrhosis (302, 303).

Specific clinical thresholds for IAP and APP in the patient with cirrhosis are yet to be defined, particularly, since advanced cirrhosis with PH leads to multiple compensatory mechanisms. These include a hyperdynamic state (due to splanchnic and systemic arterial vasodilation resulting in reduced effective blood volume) with compensatory vasoconstriction and reduced organ perfusion, cardiomyopathy, microvascular and endothelial dysfunction. Furthermore, systemic inflammation, mitochondrial dysfunction, oxidative stress and metabolic changes can lead to tissue injury and extrahepatic OF (304). Such mechanisms potentially modify pathophysiologic responses to acute critical illness comparatively to other types of patients and illnesses (i.e., acute pancreatitis, major burns and abdominal surgery).

In our cohort of critically ill liver cirrhosis patients the mean APP baseline value was low when compared to other populations of intensive care patients (305,306). In a mixed population of 100 intensive care patients, where 42% of patients had IAH, the overall mean APP value was 74 (± 17) mmHg (305). In another study, 50 patients with severe acute pancreatitis had a mean APP of 80 (± 5) mmHg (306). Comparatively, our cohort presented lower APP with respective differences of minus 11 and minus 17 mmHg.

4.4.2. Abdominal hypoperfusion

Nearly two thirds of our patients had AhP during the ICU stay. Two studies in critically ill patients with cirrhosis reported a high prevalence of AhP (279,280). In the first study, Al-Dorzi et al. analyzed 61 septic shock patients, reporting a prevalence of AhP of 70% at ICU admission. Interestingly, an APP of 55 mmHg was identified as the best cut-off value to discriminate survivors from non-survivors, and AhP was not significantly associated with any of the studied outcomes in multivariate analysis. This study concluded that IAH was associated with increased ICU morbidity and mortality, although no independent risk factors for IAH were found (279). In the second study, Mayr et al. reported a prevalence of AhP between 25 and 50% of cases (inferred from a median APP value of 63 [57, 70] mmHg, n = 22). They were able to quantify hepatosplanchnic blood flow impairment due to IAH (280). Our study confirms a high prevalence of AhP among critically ill patients with cirrhosis.

Acute-on-chronic liver failure severity score was predictive of AhP at baseline and during the first week of ICU stay. This reflected the severity of our typical ACLF grade 3 patient with septic shock and multiorgan failure, frequently treated with noradrenaline and terlipressine perfusions combined. Whereas, for less severe upper gastrointestinal bleeding and hepato-renal syndrome, terlipressine was the preferred vasoactive agent. Three quarters of our cohort received vasopressor therapy, nonetheless, arterial hypotension persisted in one fifth of patients at baseline. In our view, higher clinical severity with the presence of hypotension combined with increased IAP was the main reason for the association between higher ACLF grade and AhP.

Patients with AhP were five times more likely to be submitted to paracentesis at admission. We considered these results signaled an increased clinical awareness for diagnostic

screening of SBP and the treatment and prevention of IAH in these high-risk patients. We did not considered paracentesis as a cause of AhP, particularly, since PPCD preventive measures were standard-of-care, and a higher fluid balance at ICU admission was observed in the AhP patient group. Despite not observing an association between LVP and AhP, an increase in APP and an improvement in hepatosplanchnic blood flow has been described after LVP. This was corroborated by ultrasound hepatic artery resistance index, hepatic vein maximum flow velocity, and indocyanine green plasma disappearance rate (positively correlated to APP and inversely correlated to IAP), considered a dynamic surrogate marker of hepatic perfusion and hepatocellular function (280,281,307,308). Fundamentally, patients not submitted to paracentesis were clinically justified, inasmuch as the use of paracentesis has been suggested as a key inpatient quality of care measure in patients with cirrhosis (309, 310).

4.4.3. Mortality

Baseline APP was lower in non-survivors than in survivors at 28 days, although it presented an inadequate predictive ability. Abdominal hypoperfusion was not a risk factor for mortality in our cohort, probably due to the small sample size and the multifactorial nature of critical illness. Unambiguously, mortality was associated with baseline clinical severity and total bilirubin, reflecting the dual character of the “acute” critical illness and the “chronic” liver disease in this population in intensive care. Additionally, HE WH score was the only independent risk factor for 28-day mortality in the subset of patients with baseline APP data. This highlights the vital importance of acute neurologic disfunction in critically ill patient with cirrhosis, as previously reported (292,310,311).

Furthermore, patients with AhP had longer ICU LOS, indicating greater patient comorbidity and higher associated healthcare costs.

Our findings support the rationale for considering APP as a critical vital sign that may further assist the clinician in titrating MAP and optimizing IAP, thus preventing deleterious effects of persistent critical pressures (282,283,287,312,313). The treatment and prevention of AhP in high-risk patients with cirrhosis is prudential.

4.4.4. Limitations

Limitations in this study include a relatively small sample size, due to slow recruitment aggravated by the COVID-19 pandemic onset, and missing baseline APP data due to workload and delayed patient enrolment into the study protocol. Additionally, the lack of longitudinal data on organ dysfunction and the impact of therapies aimed at optimizing APP precluded further results and outcome analysis. The impact of AhP on specific OFs should be specifically addressed in the future.

Strengths of this study include the fact that it is the largest prospective study addressing APP in consecutive critically ill patients with cirrhosis, minimizing selection bias provides data on the impact of baseline paracentesis in the critically ill patient with cirrhosis, and opens the field for further research (314). Future studies on AhP, IAH and ACS should focus on the first week of ICU admission (314, 315).

4.5. Conclusion

This study confirms a high prevalence of AhP in critically ill patients with cirrhosis. Abdominal hypoperfusion was independently associated with higher ACLF grade and paracentesis performed at ICU admission.

Mortality at 28 days was higher among patients with AhP and independent risk factors were higher clinical severity, total bilirubin and HE.

Abdominal perfusion pressure can be considered a critical vital sign and prevention and treatment of AhP in the high-risk patient with cirrhosis is prudential.

Chapter 5

Acute Kidney Injury

5.1. Introduction

Acute kidney injury in the patient with cirrhosis includes a wide spectrum of pathophysiological mechanisms. It can be divided into hepatorenal syndrome (HRS-AKI), a functional syndrome in advanced PH and non-HRS-AKI due to other precipitant events (316). Particularly, AKI is one of the main clinical features of the ACLF syndrome, characterized by systemic inflammation, dysregulated immune response and high mortality (317,97). Hence, AKI therapies are based on treating the precipitant events, preventing hypovolemia and treating hemodynamic disorders with albumin administration and vasoconstrictors (318,86).

Intra-abdominal hypertension and AhP are often overlooked as potential concomitant mechanisms for AKI in the critically ill patient with cirrhosis with ascites (319). Especially, since paracentesis is a safe therapeutic option to treat IAH due to ascites, thus optimizing APP and improving organ perfusion (319,176).

This study aimed to analyze the impact of AhP on AKI in critically ill patient with cirrhosis.

5.2. Methods

5.2.1. Design and settings

This was a post-hoc analysis from a prospective, observational study of critically ill patients with cirrhosis set in a 22-bed general ICU specialized in liver disease in a tertiary university hospital with a regional liver transplant program (320).

Patients were recruited between October 2016 and December 2021 and followed-up to hospital discharge.

5.2.2. Patient selection

Patient selection used the following inclusion criteria: 1) age ≥18 years, 2) first ICU admission during the index hospital stay and 3) a medical condition for admission. The exclusion criteria considered: 1) any type of surgery in the 4 weeks preceding the index ICU admission, 2) contra-indication for intravesical IAP measurements, 3) patients with ICU stay duration inferior to 24 hours, 4) patients with previous liver transplant (LT), and 5) absence of IAP and APP measurements at ICU admission.

5.2.3. Definitions

The definition of arterial hypotension (AhT) corresponded to a MAP < 65 mmHg, regardless of vasopressor support. All reported pressure values correspond to daily means, unless otherwise stated.

For this study, acute renal failure (ARF) was defined by stage 3 International Club of Ascites (ICA) AKI criteria in patients with cirrhosis, determined by 1) an increase of serum creatinine >3-fold from baseline, or 2) serum creatinine ≥4.0 mg/dl (353.6 μmol/L) with an acute increase ≥0.3 mg/dl (26.5 μmol/L), 3) or initiation of renal replacement therapy (RRT) (86). The lowest value of creatinine measured at ICU admission was considered as the reference for the “3-fold increase of serum creatinine” to determine the presence of ARF during the study period.

The temporal definition of the term "baseline" correlates to ICU admission calendar day (D0) plus the following calendar day of ICU stay (D1). The baseline pressure values were calculated using the mean of all aggregated values during D0 plus D1. Additionally, the term

"persisting" refers to the time period from D1 up to D7, specifically, with regard to mean pressure values (i.e., "persisting APP" refers to the 7-day mean APP pressure value).

Outcome assessment was performed at D7, unless otherwise stated.

5.2.4. Outcomes

The primary outcome was the prevalence of ARF. The secondary outcomes included daily urine output, number of renal replacement free days and survival rate at 28 days, and ICU length-of-stay.

Whenever ICU discharge or liver transplant occurred before D7, the available data prior to these events was used.

To calculate RRT-free days within a 28-day time frame from ICU admission we considered, inclusively, not only the days between the start and the end of RRT (censoring the end date at D28 if it was surpassed), but also subtracted this number of days from 28. If death occurred before D28 in patients receiving RRT, the number of RRT-free days considered was zero to penalize the event of death (323).

5.2.5. Statistical analysis

Outcome variables were compared between groups of patients with or without baseline AhP and with or without persisting AhP during the study period.

Continuous variables are reported as mean and standard deviation or as median and interquartile range as appropriate, and categorical variables reported as frequencies and proportions. Mann-Whitney U test was used to compare non-normal distribution continuous variables or, otherwise, T-test for normal distribution variables, between two independent

groups was applied. Chi-square and Fisher's exact tests were used to compare the frequencies of categorical variables between independent groups. Significant statistical difference was defined as a two-sided p value ≤0.05. Multivariate analysis was performed, after assessing for statistical assumptions, using backward stepwise logistic regression, and included variables based on clinical importance and statistical significance with p value ≤0.10 in univariate analysis. Statistical software IBM SPSS Statistics for Windows, version 27.0. Armonk, NY was used for analysis.

5.2.6. Ethics

The study protocol was approved by the Ethics Committee at Centro Hospitalar Universitário Lisboa Central (CES nº397/2017), and waived the need for individual informed consent for this observational study. All study procedures followed the principles of the Declaration of Helsinki (256).

5.3. Results

5.3.1. Patient characteristics

For this study 720 patients were screened, 116 were found eligible and the final analysis included 58 patients, as detailed in the patient flowchart (Figure 20).

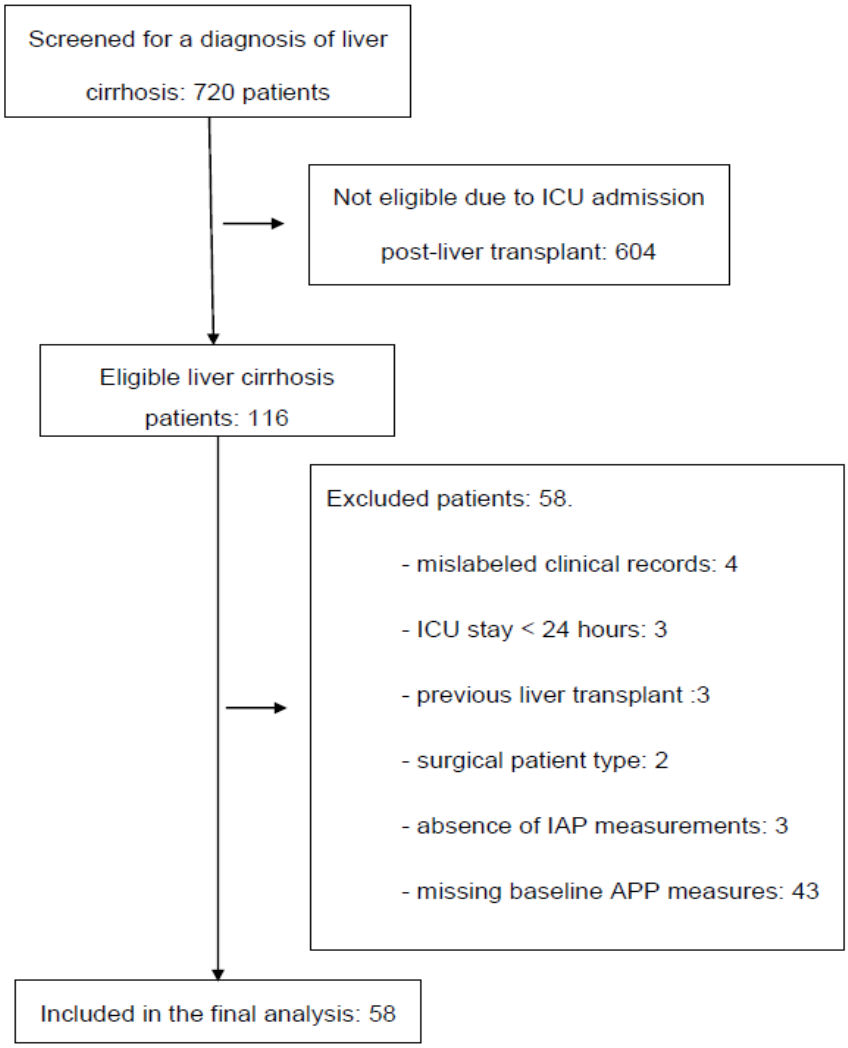


Figure 20. Study patient flowchart. Abbreviations: ICU, intensive care unit; IAP, intra-abdominal pressure; APP, abdominal perfusion pressure.

Patients in this study had a mean age of 57 (±8.4) years and 79.3% were male. The most frequent liver disease etiologies were single alcohol (50%), combined HCV and alcohol (14%), non-alcoholic steato-hepatitis (7%), single HCV (5%) and non-C viral hepatitis (5%). Ascites was present in 93% of patients and neoplasm in 22% of cases. The most frequent precipitant events leading to ICU admission were infection (38%), bleeding (17%) and AKI (10%). The median ACLF grade was 3 [2, 3] and MELDNA score was 31 [23, 37], the mean SAPS II score was 49 (±16) and CLIF-C score was 53 (±11). In total, there were 54 (93%) patients with ACLF criteria and the grade distribution was: 1 - 12%; 2 - 26%; and 3 - 55% (Table 27).

Table 27. Baseline characteristics of critically ill liver cirrhosis patients.

Baseline variables	Overall (n=58)
Age (years)	57 (8.4)
Male gender (%)	46 (79)
Liver disease etiology (%)	
Alcohol	29 (50.0)
Alcohol + HCV	8 (13.8)
Precipitant (%)	
Infection	22 (37.9)
Bleeding	10 (17.2)
Encephalopathy	5 (8.6)
AKI	6 (10.3)
West-Haven score	2 [0, 3]
Hematocrit (%)	24 (6.4)
Leucocytes (cel/µL)	13.5 (8.6)
Platelets (cel/µL)	65 [42, 115]
INR	2.45 (1.01)
Creatinine (mg/dL) [a]	1.8 [0.9, 2.9]
Urea (mg/dL)	91 [56, 136]
Bilirubin (mg/dL)	6.5 [2.8, 15]
Albumin (g/dL)	27.0 (11.1)
Ammonia (µg/dL)	240 [164, 306]
C-reactive protein (mg/L)	46 [17, 79]
PaO2/FiO2	268 (129)
pH	7.34 (0.12)
Lactate (mmol/L)	2.6 [1.5, 4.3]
Urine output (mL/24h)	1230 [483, 2006]
Fluid balance (mL/24h)	796 [-384, 2340]
Paracentesis (%) [b]	22 (37.9)
Drained ascites (mL)	1700 [50, 4375]
IMV (%)	30 (52)
Vasopressors (%)	42 (72)
RRT (%)	13 (22)
SAPS II	49 (16)
MELDNA	31 [23, 37]
ACLF grade	3 [2, 3]
CLIF-C	53 (11)
IAP	12 (4.9)
MAP	77 (13)
APP	63 [56, 71]

Values are presented in count (%), mean (SD) or median [P25, P75]. IAP, MAP and APP values correspond to those calculated from ICU admission day (D0) plus the following day (D1).
[a] Highest creatinine value during the initial 24 hour of ICU admission.
[b] Paracentesis of any type, including diagnostic and large-volume paracentesis.
Abbreviations: HCV, hepatitis C virus; AKI, acute kidney injury; INR, international normalization ratio; PaO2, oxygen arterial partial pressure; FiO2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; RRT, renal replacement therapy; SAPS, simplified acute physiology score, MELDNA, model for end-stage liver disease sodium; ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; IAP, intra-abdominal pressure; MAP, mean arterial pressure; APP, abdominal perfusion pressure; SD, standard deviation; P, percentile.

During the first 24 hours of admission, vital organ support was provided using renal replacement therapy in 22%, invasive mechanical ventilation in 52% and vasopressors in 72% of patients (Table 27).

Overall, 28-day mortality was 60%, and ICU LOS (days) was 6.5 [2.3, 10.8]. Hospital mortality was 69% and there was a liver transplant rate of 17.2%.

5.3.2. Abdominal hypoperfusion

The total number of measurements of APP was 527, corresponding to approximately 9 per patient during the study period.

Comparison between groups of patients with and without baseline AhP are detailed in Table 28.

Table 28. Comparison of patients with and without baseline abdominal hypoperfusion.

Baseline variables	APP ≥ 60 mmHg (n=33)	APP < 60 mmHg (n=25)	p value
Age (years)	57 (8.7)	56 (8.1)	0.8
Male gender (%)	27 (82)	19 (76)	0.8
Liver disease etiology (%)			0.6
Alcohol	17 (52)	12 (48)	
Alcohol + HCV	4 (12)	4 (16)	
Precipitant (%)			0.8
Infection	13 (43.3)	9 (36)	
Bleeding	5 (16.7)	5 (20)	
Encephalopathy	2 (6.7)	3 (12)	

AKI	4 (13)	2 (8.0)	
West-Haven score	1 [0, 3]	2 [0, 3]	0.6
Hematocrit (%)	24 (6.9)	25 (5.8)	0.5
Leucocytes (cel/μL)	12 (7.0)	16 (10)	0.1
Platelets (cel/μL)	54 [42, 93]	70 [47, 120]	0.3
INR	2.4 (0.9)	2.5 (1.1)	0.6
Creatinine (mg/dL) *	1.5 [0.8, 2.9]	2.3 [1.4, 2.9]	0.2
Urea (mg/dL)	73 [44, 108]	121 [72, 197]	0.02
Bilirubin (mg/dL)	6.7 [3.6, 23]	5.7 [2.2, 10]	0.1
Albumin (g/dL)	29 (9.7)	24 (13)	0.2
Ammonia (μg/dL)	254 [175, 307]	221 [164, 267]	0.6
C-reactive protein (mg/L)	34 [15, 67]	50 [23, 93]	0.3
PaO2/FiO2	287 (131)	244 (124)	0.2
pH	7.38 (0.09)	7.30 (0.14)	0.01
Lactate (mmol/L)	2.1 [1.3, 3.6]	3.4 [1.9, 9.9]	0.04
Urine output (mL/24h)	1290 [880, 1935]	975 [405, 2030]	0.3
Fluid balance (mL/24h)	468 [60, 1423]	1310 [-778, 3174]	0.3
Paracentesis (%)	10 (30)	12 (48)	0.3
Drained ascites (mL)	2110 [375, 4375]	1560 [50, 4375]	0.6
IMV (%)	12 (36)	18 (72)	0.02
Vasopressors (%)	21 (64)	21 (84)	0.2
RRT (%)	8 (24)	5 (20)	0.9
SAPS II	43 (14)	56 (17)	0.003
MELDNA	31 [22, 39]	31 [26, 36]	0.9
ACLF grade	3 [1, 3]	3 [2, 3]	0.2
CLIF-C	52 (12)	55 (8.6)	0.3
IAP	10 (4.1)	13 (5.6)	0.051
MAP	84 (11)	68 (7.3)	<0.001
APP	70 [65, 82]	55 [52, 59]	<0.001

Values are presented in count (%), mean (SD) or median [P_{25}, P_{75}]. IAP, MAP and APP values correspond to the mean calculated from ICU admission day (D0) plus the following day (D1).
* Highest creatinine value during the initial 24 hour of ICU admission.
Abbreviations: HCV, hepatitis C virus; AKI, acute kidney injury; INR, international normalization ratio; PaO2, oxygen arterial partial pressure; FiO2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; RRT, renal replacement therapy; SAPS, simplified acute physiology score, MELDNA, model for end-stage liver disease sodium; ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; IAP, intra-abdominal pressure; MAP, mean arterial pressure; APP, abdominal perfusion pressure; SD, standard deviation; P, percentile.

Patients with baseline AhP presented higher serum urea concentration, lower arterial blood pH, higher arterial blood lactate, higher rate of IMV support and higher clinical severity as assessed by SAPS II score when compared to those without AhP (Table 28).

Critical pressures at baseline presented overlapping distribution as illustrated in Figure 21.

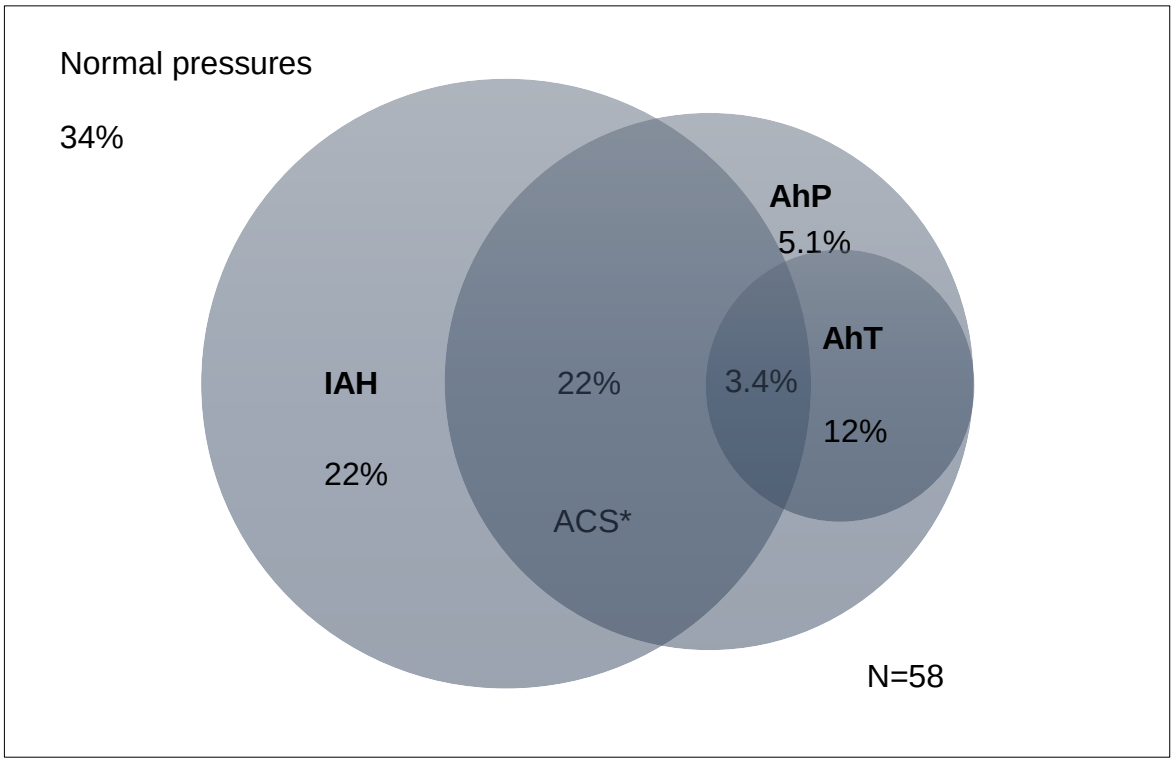


Figure 21. Venn diagram illustrating the overlap of baseline critical pressures' distribution. *ACS accounted for 5.1% of patients in the corresponding area. Abbreviations: IAH, intra-abdominal hypertension (>12 mmHg); AhP, abdominal hypoperfusion (abdominal perfusion pressure <60 mmHg); AhT, arterial hypotension (mean arterial blood pressure <65 mmHg); ACS, abdominal compartment syndrome.

The overall baseline frequency of AhP was 43.1%, IAH was 48.3%, *Ah*T was 15.5% and ACS accounted for 5.1% of patients (Figure 21). The prevalence of AhP during the first seven days in the ICU was 75.3%.

Considering the persistence of critical pressures during the first week of ICU stay, the frequency of persisting AhT, persisting IAH and persisting AhP were, respectively, 13.8%, 46.6% and 29.3%.

5.3.3. Acute kidney injury

During the first week of ICU stay 48.3% of patients presented ARF, including 5.2% of patients with a 3-fold increase from baseline serum creatinine, 19.0% with an increase to over 4 mg/dL of serum creatinine with an acute increase of at least 0.3 mg/dL, and 43.1% initiating RRT. Additionally, 62.1% presented a urinary output less than 0.3mg/kg/24 hour.

The comparison of baseline characteristics for patients with and without ARF during the period are detailed in Table 29.

Table 29. Comparison of patients with and without acute renal failure during the first week in ICU.

N=58	Without acute renal failure (n=30)	With acute renal failure (n=28)	p value
Age (years)	57 (7.1)	57 (9.7)	1.0
Male gender (%)	26 (87)	20 (71)	0.3
Liver disease etiology (%)			0.6
Alcohol	16 (53)	13 (46)	
Alcohol + HCV	4 (13)	4 (14)	
Precipitant (%)			0.1
Infection	8 (27)	14 (54)	
Bleeding	6 (21)	4 (15)	
Encephalopathy	3 (10)	2 (7.7)	
AKI	3 (10)	3 (12)	
West-Haven score	1 [0, 3]	2 [0, 3]	0.8
Hematocrit (%)	24 (7.5)	24 (5.1)	1.0
Leucocytes (cel/μL)	11 (7.2)	16 (9.1)	0.01
Platelets (cel/μL)	67 [38, 115]	63 [46, 106]	0.6
INR	2.3 (1.0)	2.7 (1.0)	0.1
Creatinine (mg/dL) [a]	1.1 [0.8, 1.8]	2.9 [2.0, 4.6]	<0.001
Urea (mg/dL)	76 [45, 96]	127 [72, 193]	0.01
Bilirubin (mg/dL)	5.8 [2.9, 12]	9.6 [2.9, 20]	0.5
Albumin (g/dL)	26 (13)	28 (8.8)	0.8
Ammonia (μg/dL)	210 [156, 299]	253 [181, 306]	0.6
C-reactive protein (mg/L)	35 [12, 65]	55 [18, 87]	0.3
PaO2/FiO2	279 (139)	257 (118)	0.5
pH	7.39 (0.10)	7.30 (0.12)	0.004
Lactate (mmol/L)	2.2 [1.3, 3.6]	3.6 [1.6, 10]	0.04
Urine output (mL/24h)	1495 [1096, 2240]	603 [344, 1413]	0.004
Fluid balance (mL/24h)	326 [-493, 1227]	1367 [327, 2797]	0.054

Paracentesis (%) [b]	10 (33)	12 (43)	0.6
Drained ascites (mL)	1435 [238, 4000]	1900 [50, 5538]	0.5
IMV (%)	14 (47)	16 (57)	0.6
Vasopressors (%)	19 (63)	23 (82)	0.2
RRT (%)	0 (0)	13 (46)	<0.001
SAPS II	43 (14)	55 (17)	0.004
MELDNA	26 [18, 31]	36 [31, 40]	<0.001
ACLF grade	2 [1, 3]	3 [2, 3]	0.01
CLIF-C	48 (10)	59 (9.3)	<0.001
IAP	11 (4.2)	12 (5.6)	0.3
MAP	79 (14)	75 (10)	0.3
APP	64 [57, 80]	62 [56, 69]	0.4

The term “acute renal failure” is defined as stage 3 International Club of Ascites Acute Kidney Injury.
Values are presented in count (%), mean (SD) or median [P25, P75]. IAP, MAP and APP values correspond to the mean calculated from ICU admission day (D0) plus the following day (D1).
[a] Highest creatinine value during the initial 24 hour of ICU admission.
[b] Paracentesis of any type, including diagnostic and large-volume paracentesis.
Abbreviations: HCV, hepatitis C virus; AKI, acute kidney injury; INR, international normalization ratio; PaO2, oxygen arterial partial pressure; FiO2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; RRT, renal replacement therapy; SAPS, simplified acute physiology score, MELDNA, model for end-stage liver disease sodium; ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; IAP, intra-abdominal pressure; MAP, mean arterial pressure; APP, abdominal perfusion pressure; SD, standard deviation; P, percentile.

Patients who developed ARF during the first week presented differences in baseline variables, including: lower pH, and higher WBC count, serum urea concentration, arterial blood lactate and clinical severity scores, as well as a trend for higher fluid balance, when compared to those how did not develop ARF. Additionally, AKI-related variables serum creatinine, urine output and RRT were higher in ARF patients.

The daily APP values during the first seven days of ICU were divided by groups of patients with and without ARF, as illustrated in Figure 22.

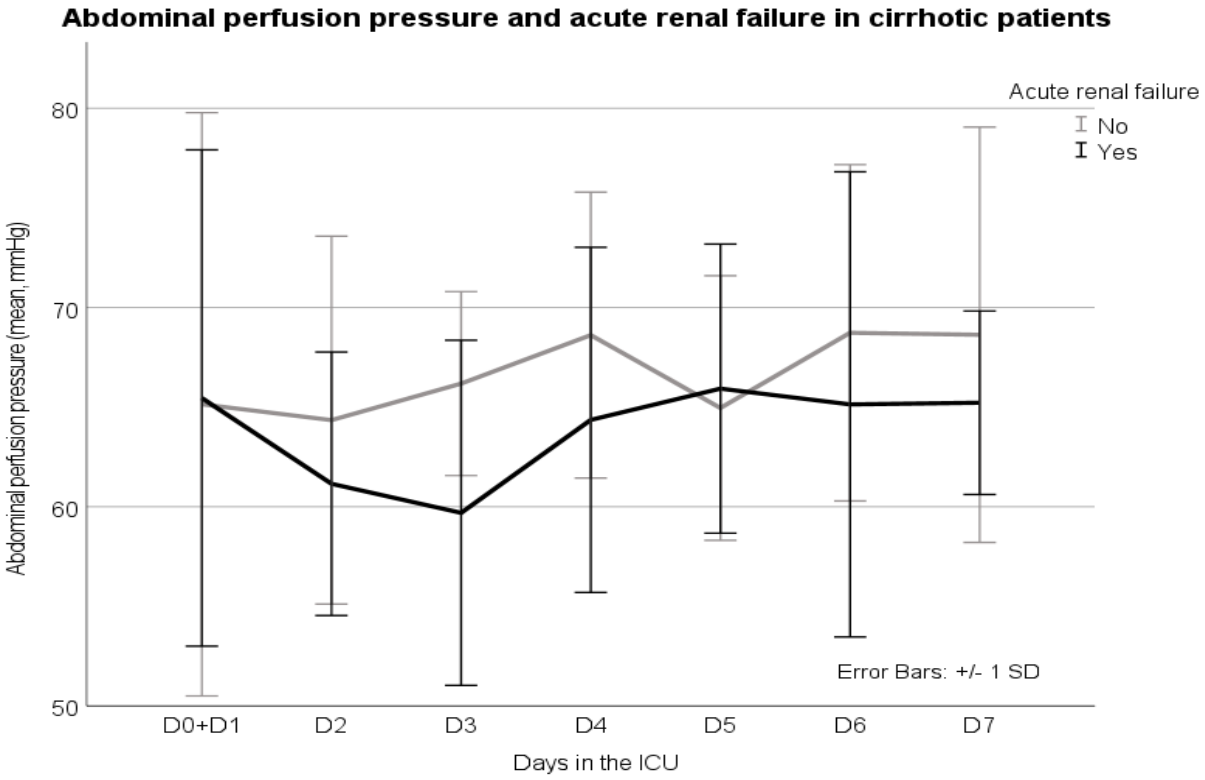


Figure 22. Abdominal perfusion pressure and acute renal failure in patients with cirrhosis.

There were no significant intra-day differences in daily APP between patients with and without ARF during the first seven days in the ICU (Figure 22).

We compared AKI variables and outcomes between patients with or without baseline AhP and with or without persisting AhP (Table 30).

Table 30. Renal function and outcomes in patients with cirrhosis and abdominal hypoperfusion.

	Baseline			Persisting [a]		
n=58	APP <60 mmHg (n=25)	APP ≥60 mmHg (n=33)	p	APP <60 mmHg (n=17)	APP ≥60 mmHg (n=41)	p
Baseline creatinine (mg/dL)[b]	1.4 [1.1, 2.1]	1.2 [0.8, 2.4]	0.4	1.6 [1.1, 2.4]	1.2 [0.8, 2.1]	0.2
Max. creatinine (mg/dL)[a]	2.3 [1.5, 3.6]	2.1 [1.1, 3.6]	0.7	2.3 [1.6, 3.8]	2.1 [1.0, 3.2]	0.2
Urine output (mL/day)[a]	1022 [130, 1574]	1056 [474, 1656]	0.3	205 [87, 804]	1095 [759, 1701]	0.003
Anuria (%)[a]	17 (68.0)	19 (57.6)	0.6	14 (82.4)	22 (53.7)	0.07
RRT (%)[a]	10 (40.0)	15 (45.5)	0.8	10 (58.8)	15 (36.6)	0.2
RRT-free days at 28 days	28 [0, 28]	28 [0, 28]	0.8	0 [0, 28]	28 [0, 28]	0.07
ICA-AKI stages (%)			0.8			0.048
No AKI	6 (24.0)	10 (30.3)		1 (5.9)	15 (36.6)	
Stage 1	7 (28.0)	6 (18.2)		4 (23.5)	9 (22.0)	
Stage 2	0 (0)	1 (3.0)		0 (0.0)	1 (2.4)	
Stage 3	12 (48.0)	16 (48.5)	1.0[c]	12 (70.6)	16 (39.0)	0.04[d]
Mortality at 28 days (%)	19 (76.0)	16 (48.5)	0.03	12 (70.6)	23 (56.1)	0.3
ICU LOS (days)	6 [2, 12]	7 [4, 10]	0.2	2 [1, 4]	8 [5, 12]	<0.001

Abdominal hypoperfusion corresponds to an APP < 60 mmHg. Variables are presented using median [interquartile range] and count (%).

[a] Considering the first 7-day (D1 to D7) in the intensive care.

[b] Lowest creatinine value during the initial 24 hours of ICU admission, used for acute kidney injury criteria.

[c] p value of 1.0, when comparing stage 3 ICA-AKI versus non-stage 3 combined categories

[d] p value of 0.04, when comparing stage 3 versus non-stage 3 combined categories

Abbreviations: APP, abdominal perfusion pressure; AhP, abdominal hypoperfusion; mmHg, millimeters of mercury; RRT, renal replacement therapy; ICA, International Club of Ascites; AKI, acute kidney injury; RIFLE, risk, injury, failure, loss of renal function and end-stage renal disease; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease Improving Global Outcome; ICU. intensive care unit; LOS, length-of-stay.

The rate of ARF was comparable between patients with and without baseline AhP (respectively, 48.0% vs. 48.5%, p=1.0) and was significantly higher among those with persisting AhP (respectively, 70.6% vs. 39.0%, p=0.04), compared to those without persisting AhP (Table 30).

We conducted a risk factor multivariable analysis for the development of ARF, including persisting APP, and excluding urinary output due to correlation with serum urea (Table 31).

Table 31. Risk factors for the presence of acute renal failure in the ICU.

			95% C.I.	
n=58	**p**	**aOR**	**Lower**	**Upper**
Urea (mg/dL)	0.04	1.01	1.001	1.02
WBC (cel 10^9/mL)	0.03	1.10	1.01	1.19
Persisting APP (mmHg)	0.04	0.93	0.86	0.996

Acute renal failure is defined as stage 3 International Club of Ascites acute kidney injury and "Persisting" corresponds to the daily mean value during the period from day 1 up to day 7 of ICU stay.
Stepwise backward logistic regression including: baseline serum urea, minimum pH, maximum lactate, WBC, fluid balance, and persisting (7-day mean) APP. The inclusion of persisting MAP and IAP in a secondary step produced the same results.
Abbreviations: ICU, intensive care unit; C.I., confidence interval; aOR, adjusted odds ratio; WBC, white blood cell count; APP, abdominal perfusion pressure, MAP, mean arterial pressure; IAP, intra-abdominal pressure.

The results showed an independent association between ARF and higher serum concentration, higher WBC and lower persisting APP (Table 31). When we adjusted these associations for persisting IAP and MAP, the results were unchanged.

We performed a ROC curve to determine the ability of persisting APP to discriminate those patients that develop ARF during the first seven days (Figure 23).

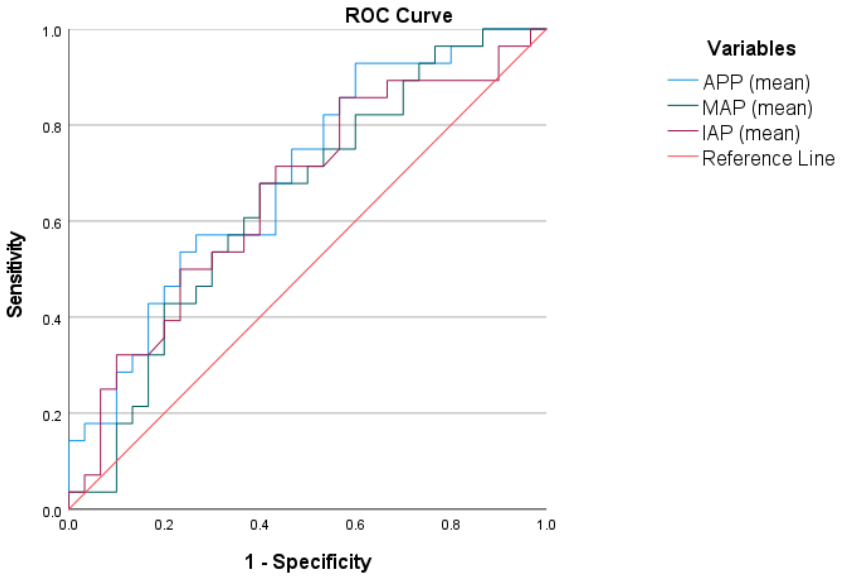


Figure 4 caption

Figure 23. Receiver operator characteristic curves for the ability of persisting APP, IAP and MAP to predict ARF. Area under the curve for APP:0.69 ±0.07, 95% CI0.56-0.83, p=0.01; IAP: 0.66±0.07, 95% CI 0.51-0.80, p=0.04; and MAP 0.64±0.07, 95% CI 0.50-0.79, p=0.06.

Persisting APP had a good ability to discriminate ARF during the first week of ICU stay, comparable to both persisting IAH and hypotension (Figure 23). The optimal ARF predicting APP cut-off value was ≤ 69 mmHg (sensitivity of 0.93, specificity of 0.40 and Youden index of 0.33) (324).

5.3.4. Other results

The number of RRT-free days was comparable within groups of baseline APP and persisting APP.

Mortality at 28 days was significantly higher in patients with baseline AhP (respectively, 76.0% vs. 48.5%, p=0.03), and similar within groups of persisting APP.

Intensive care unit length-of-stay (LOS) (days) was similar within group of baseline APP and was significantly lower among those with persisting AhP (Table 3). Furthermore, ICU LOS was significantly lower among 28-day non-survivors when compared to survivors (respectively, 5 [2, 9] vs. 9 [4, 16], p=0.047).

5.4. Discussion

5.4.1. Main findings

This is the first study to demonstrate a temporal relation between low APP and ARF in patients with cirrhosis. Our main findings revealed that higher baseline serum urea and WBC, as well as lower persisting APP were independent risks factors for ARF in critical patient with cirrhosis with acute medical illness.

5.4.2. Abdominal hypoperfusion

The prevalence of baseline AhP in our cohort was high and comparable with previous studies with reported prevalence values between 47-70% in similar populations (320,215).

The majority of patients with AhP had concomitant IAH. On the other hand, all patients with hypotension had AhP. Nearly two thirds of cases presented with any abnormal critical pressure at baseline, whether it was AhT, IAH or AhP alone or combined.

5.4.3 Acute kidney injury

Acute kidney injury is frequent in mixed populations of intensive care patients, with reported incidence between, approximately, 20-50%, including 50% in patients with liver cirrhosis (325-328).

Our results suggest the importance of maintaining an adequate APP to prevent ARF in the critical patient with cirrhosis.

The temporal relation between the onset of IAH and the development of AKI in different types of patients has been reported (243,329). More than two decades ago, Sugrue et al. described, in surgical patients, the gradual effect of IAH on renal function, with a mean lag period of 2.7 (±6.5) days between the onset of IAH and renal impairment, assessed by the rise of serum creatinine concentration(328). Regueira et al. found that serum creatinine levels were directly proportional to higher degrees of IAH and inversely related to APP, in a surgical-medical mixed population of septic shock (SS) patients. Both these studies used a modified Kron technique for IAP measure (330). More recently, Dalfino et al., using current standard methodology for IAP measure (174), reported a mean lag period between IAH and ARF onset of 1 (±1.8) day, in a medical-surgical mixed population of critically ill patients (329).

This study focused specifically on APP using current methods for measurement of IAP. We observed that lower persisting APP was an independent risk factor for ARF. However, the same association with ARF was not found for low baseline APP, nor was there any intra-day difference in any single daily APP values between groups of patients with and without ARF. We consider that persisting APP captured the deleterious cumulative effect of lower APP values on renal function during a seven day period. This is similar to the impact of the duration of IAH on clinical outcomes, such as mortality and RRT as described by Kyoung et al in surgical patients with severe sepsis (243). Additionally, persisting APP remained an independent risk factor for ARF after adjusting for persisting IAP and MAP, both fundamental variables are critical in the APP equation.

Furthermore, we determined an optimal APP cut-off value (persisting APP < 70 mmHg), predictive of ARF in our cohort of critically ill patients with cirrhosis, and this may be useful in clinical practice. Reports of similar APP cut-off values that predict clinical outcomes have been described and may add to the generalizability of our results. In their study, Fethi Gül et al. described a mean baseline APP threshold of ≤ 72 mmHg associated with an increase in Doppler-based renal resistive index, suggested to predict worsening renal perfusion in 38 mechanically ventilated patients (331). Bieda et al. reported a mean APP cut-off value of 70 mmHg during the initial 72 hours to discriminate between survivors and non-survivors in a sample of 40 patients with ruptured aortic aneurism (332). In another study, Vidal et al. observed that baseline APP (unspecified if calculated with maximum or mean IAP) was independently associated with hospital survival, with a best cut-off value ≥ 75 mmHg in a medical-surgical mixed population of 83 critically ill patients (333). These two studies used a modified Kron technique for IAP measure, possibly overestimating IAP and, therefore,

underestimating APP values. Two additional studies in a mixed and in a surgical cohort of patients, found APP cut-off values of 52 and 50 mmHg predicted ARF and survival, respectively, although they used the worst single APP values (not mean daily values) or did not consider current IAP measure methods (329,334). Few studies address the issue of IAP and APP, particularly regarding renal function. Furthermore, there is a wide variety of differences in patient populations and methodology of IAP measure and APP reporting standards, and specific APP cut-off thresholds should be carefully interpreted. Our study in patients with cirrhosis suggest that maintaining an APP target of ≥70 mmHg may be useful as a therapeutic end-point to optimize renal perfusion and prevent OF in patients with cirrhosis, although this requires confirmatory studies.

White blood cell count at baseline was also an independent risk factor for the development of ARF in our cohort, but not infection as precipitant event. The WBC count can be considered as a surrogate marker for systemic inflammation. The ACLF syndrome is an inflammatory paradigm with mainstay AKI, multi-organ failure and increased mortality in patients with cirrhosis, and WBC count is acknowledged in the CLIF-C prognostic score (97,335).

Systemic inflammation is a common feature shared between the two subtypes of AKI, namely, HRS-AKI and HRS-NAKI, described in liver disease patients (316). The pathophysiologic mechanism of HRS-AKI is traditionally ascribed to splanchnic vasodilation, cardiac dysfunction, adrenal insufficiency and inflammation, while, HRS-NAKI is mainly characterized by the role of inflammation and bacterial translocation, bile acids toxicity, worsening PH, cardiac disfunction and renal hypoperfusion.

In an animal model of cirrhosis and HRS, Chang et al. were able to demonstrate causality between increases in IAP and *de novo* interstitial inflammatory infiltrates in renal histopathology after merely 24 hours of induced IAP of 5 mmHg, as well as significant increases in serum urea and creatinine after 10 mmHg of induced IAP (319). Although they provided no data regarding APP, IAH as a pathophysiologic mechanism for inflammation and AKI was established, and this was a shared characteristic in most patient in our cohort

Urea is one of the oldest biomarkers in nephrology, however, blood urea nitrogen (BUN) is suboptimal for estimation of renal function (336). Most BUN is generated in the liver as a product of protein metabolism and an important proportion of urea filtered by the glomerular capillaries is reabsorbed from the tubules. Whereas, virtually all filtered creatinine is excreted in the urine making it a most practical marker. Blood urea nitrogen´s clearance falls markedly, even though glomerular filtration rate remains normal at low urinary flow (337). In our study serum urea was inversely correlated with urinary output and behaved as an early AKI marker at baseline. Blood urea nitrogen concentration also depends on nonrenal factors independent of kidney function (i.e., protein intake, catabolic state, upper gastrointestinal bleeding, volume status, and therapy with high-dose steroids) and many of these factors are found in patients with cirrhosis (336).

Unsurprisingly, urine output was reduced among those with persisting AhP and with ARF, acting as an early marker of impaired hemodynamics, renal hypoperfusion and AKI. This is a relevant point that would lead to consider additional AKI clinical scores that include urine output (RIFLE(71), AKIN(338) and KDIGO(339)) and their ability to stratify the severity of AKI in the critically ill patient with cirrhosis, although this discussion is beyond the scope of this study.

The pathophysiologic complexity of the typical ACLF patient in this cohort is clear, with multiple AKI mechanisms frequently coexisting. This sustains the evolving nature of definitions and classifications of AKI, particularly in the patient with cirrhosis (86).

Furthermore, mortality at 28 days was increased among those patients with baseline AhP, and ICU length-of-stay was lower among those with persisting AhP and non-survivors, indicating a real impact of APP on outcomes.

Finally, an important proportion of patients during the study period presented persisting critical pressures, AhT and IAH, indicating a potential for improvement in the clinical management of APP. Despite the high prevalence of AhP in high-risk patients with cirrhosis, APP is still frequently overlooked. We advocate for clinical awareness and a structured approach for APP to assist the physician's decision to further optimize management of IAP and MAP in the critically ill patient with cirrhosis.

5.4.4. Limitations

We acknowledged some limitations: 1) the use of D0 lowest creatinine value for baseline calculation of AKI criteria may have excluded some diagnosis of ARF already established at baseline 2) the frequency of contrast-enhanced computed tomography, although uncommonly performed in these patients, was not asserted, nor the subsequent risk for contrast-induced AKI; 3) the relatively small sample size may have been underpowered to detect significant differences in outcomes such as RRT-free days, 4) possible selection bias at ICU admission, since some patients were excluded for not having baseline calculation of APP, and 5) the use of serum creatinine may underestimate AKI in the patient with cirrhosis, whereas cystatin-C may be a better marker, although this corresponds to the current clinical practice.

5.5. Conclusion

Critically ill patients with cirrhosis presented a high prevalence of AhP during the first week of ICU stay, and those with baseline AhP had a higher 28-day mortality.

Nearly half of the cohort presented ARF and risk factors were higher serum urea and WBC, as well as low persisting APP.

A temporal relation between AKI and APP was observed, given that low persisting APP was predictive of ARF, with an optimal cut-off value of <70 mmHg.

We advocate for a structured clinical APP approach to assist the physician in the optimization of IAP and MAP in high-risk patients with cirrhosis.

Chapter 6

Clinical Trial Protocol

6.1. Introduction

6.1.1. Background and rationale

Chronic liver disease patients with cirrhosis and ascites are at high risk for increased IAP, and both the presence and the duration of IAH are known independent risk factors for mortality in the critically ill patient (176,243).

The prevalence of IAH and ACS is very high among critically ill patients with liver cirrhosis when compared to other mixed populations of intensive care patients (244–340). In the setting of IAH, paracentesis reduces abdominal wall tension and improves overall intra-abdominal hemodynamics by minimizing IAP and optimizing abdominal perfusion pressure (APP) of intra-abdominal organs (176).

Clinical practice guidelines for the critically ill patient with IAH/ACS, based on expert opinion, recognize liver dysfunction/cirrhosis with ascites as a risk factor. Hence, it suggests the evacuation of obvious intra-peritoneal fluid with the use of percutaneous catheter drainage as part of a stepwise medical management algorithm to reduce and maintain IAP < 16 mmHg (176). Nonetheless, IAH develops in more than three quarters of critically ill patients with cirrhosis during their first week of ICU stay (215,340).

Therefore, a strategy for the prevention and treatment of IAH/ACS could improve patient outcomes in the critically ill patient with cirrhosis by minimizing IAP and optimizing APP and potentially leading to improved multi-organic function.

In fact, some studies in intensive care have shown that LVP is safe and associated with short-term improvement of renal, pulmonary, and hepatic dysfunction, although follow-up and clinical outcomes in the ICU were not assessed (213-215,341, 342). Furthermore, therapeutic

LVP is the standard-of-care in the treatment of tense ascites and HRS in acutely decompensated liver cirrhosis patients (343,70). An experimental study has demonstrated causality between small increases of IAP (5–10 mmHg), after 24 hours, and the development of AKI in HRS (319). However, the recommendation for paracentesis in the treatment of IAH/ACS is based on low-quality evidence considering the lack of studies comparing different therapeutic paracentesis strategies in the critically ill patient with cirrhosis with IAH (176).

6.1.2. Objectives

The general aim of this trial is to assess the impact of IAH on organ disfunction and clinical outcomes in the critically ill patient with cirrhosis with ascites.

The specific objective of this trial is to compare the outcomes of two different methods of therapeutic paracentesis used in our clinical practice in the prevention and treatment of IAH, specifically, regarding the impact on renal function, as well as respiratory, neurological, cardiovascular, hematological, and hepatic functions, in addition to 28-day mortality and ICU length-of-stay (LOS).

6.1.3. Trial hypothesis

The trial hypothesis states that a continuous passive paracentesis (CPP) strategy in the treatment of IAH improves organ dysfunction and clinical outcomes when compared to standard LVP in the critically ill cirrhotic with ascites.

6.2. Methods

6.2.1. Trial design, settings and participants

This is an investigator-initiated, single-site, open label, randomized clinical trial with parallel group allocation ratio of 1:1 to assess for efficacy and safety.

This trial is set in a general intensive care unit (ICU) specialized in liver disease at Hospital de Curry Cabral, Centro Hospitalar Universitário Lisboa Central (CHULC), located in Lisboa, Portugal, a tertiary university hospital, with an expected duration of 36 months.

The population of interest is the critically ill patient, which present a life-threatening condition that requires pharmacological and/or mechanical support of vital organ functions, with liver cirrhosis and ascites admitted in the ICU due to and acute decompensation.

All patients with liver cirrhosis admitted in the ICU stay are eligible for this trial.

Inclusion criteria are defined by the following:

1. Adult patient (≥ 18 years old),
2. Diagnosis of liver cirrhosis and
3. Presence of ascites grade ≥ 2 (56).

Exclusion criteria are defined by the following:

1. Extreme age (≥ over 75 years old),
2. Acute surgical condition or laparotomy in the preceding 4 weeks,
3. Previous liver transplant,
4. Hemorrhagic ascites (red blood cells count > 10,000/mL)(334),
5. Extreme clinical severity (APACHE II ≥ 34),

6. Any of the following conditions present 24 hour after admission:
    a. Hemorrhagic shock with active uncontrolled bleeding,
    b. Refractory shock (mean arterial pressure < 65 mmHg) despite multiple vasopressor support,
7. Predictably short (< 72 h) ICU stay and
8. Therapeutic futility determined by the medical staff.

Notes:

a) These criteria are applied independently of any previous treatments of ascites, including recent LVP (i.e., in the emergency department before ICU admission), and
b) Examples of "predictably short (< 72 hour) ICU stay, precluding patient enrolment, may be, i.e., the reversal of clinical instability after initial therapy and adequate resuscitation in the ICU, such as < 6 hour of vasopressor support; variceal bleeding controlled in the ICU without developing OF; or prompt reversal of oliguria/AKI.

6.2.2. Informed consent

The informed consent will be obtained by the attending physician from the proposed trial participant or authorized surrogate. In the particular case where the patient is not clinically able to decide (i.e., sedation or encephalopathy), and an authorized surrogate is not available, the Ethics Committee allowed for a presumed form of patient consent to participate in the clinical trial, based on public interest in the results of this study. The Principal Investigator (P.I.) and another ICU professional will endeavor any reasonable means to contact the authorized surrogate and provide written proof. Additionally, if at any time the patient, or it is authorized

surrogate, is able to decide, then he/she may choose to withdraw consent to participate and be removed from the trial.

6.2.3. Interventions

This trial compares two methods of therapeutic paracentesis, namely, CPP versus standard-of-care LVP in the prevention and treatment of IAH. The CPP is expected to optimize ascitic fluid drainage, therefore, providing better prevention and treatment of IAH, rather than intermittent LVP, that allows for the periodical accumulation the potential deleterious effects of intermittent increases of IAP.

The measurements of IAP will be performed every 6 to 8 hours according to our center's monitoring protocol and our clinical practice regarding the management of specific thresholds of IAP follows the current clinical guidelines to titrate therapy to maintain IAP less than 16 mmHg (176).

6.2.3.1. Control group—large-volume paracentesis

1. Ultrasound-guided (Ultrasound GE Vivid T8®) placement of an intra-abdominal catheter, 14 Gauge Optiva8®), or similar, as indicated by the attending physician in accordance with international clinical guidelines (176,56).

2. Collection of ascitic fluid for laboratorial and microbiological analyses with every new paracentesis.

3. Large-volume paracentesis will be performed as needed throughout the ICU stay with a maximal duration of 8 hours for each session.

4. The volume of drained ascites through LVP is determined by the attending physician, according to the usual clinical practice, without specified maximum volume limit.

6.2.3.2. Intervention group—continuous passive paracentesis

1. Ultrasound-guided (Ultrasound GE Vivid T8®) placement of an intra-abdominal double lumen catheter, Kit Certofix® Duo720, or similar, for paracentesis.

2. Aseptic Seldinger technique, with an acute angle of percutaneous needle insertion with the abdominal surface.

3. Adhesive, suture-free, abdominal wall catheter fixation.

4. Continuous passive ascitic fluid drainage, preferentially through the proximal lumen (lateral opening) to minimize obstruction.

5. Collection of ascitic fluid every 48 hour for laboratorial and microbiological analyses.

6. The trial intervention catheter will be in place for a maximum duration of 7 days.

7. The catheter should be removed after 7 days of intervention or prior to ICU discharge, whatever occurs first.

8. After the 7th day of intervention, paracentesis should be performed using the standard LVP approach as needed.

The 7-day duration of the intervention was determined based on previous studies revealing that the cumulative prevalence of IAH reaches a relative steady-state 5 days after ICU admission, with a median ICU stay of between 5 and 8 days in the studied populations (246,345). Furthermore, the impact of IAH on renal disfunction, assessed by the rise in serum creatinine, may lag up to approximately 3 days (346). Therefore, we considered reasonable a

period of 7 day for the trial intervention, while minimizing the risk of paracentesis catheter-associated infection, albeit considered safe (347-349).

6.2.4. Safety procedures and assessment

The attending physician's judgment is definitive regarding all clinical decisions, including protocol modification, interruption, or discontinuation, and these should be clearly stated in the patient's clinical record.

Clinical management will comply with current guidelines, including strict prevention, detection, and treatment of paracentesis-related complications, including paracentesis associated circulatory dysfunction, hypovolemia, intra-abdominal organ perforation and bleeding, catheter-related abdominal wall infection, and secondary peritonitis and abdominal wall fistula or bleeding (56). Paracentesis-related complications and harm will be actively screened and reported by clinicians.

In case of signs of catheter-related complication, particularly in the intervention group, appropriate therapeutic measures should be taken and the paracentesis catheter should be replaced when feasible at a different site for continued protocol intervention.

Paracentesis associated circulatory dysfunction is prevented with standard-of-care intravenous 20% albumin infusion (8 g for each 1 l of drained ascitic fluid) administered to all patients and, additionally, crystalloid infusion may be indicated by the attending physician to strictly avoid hypovolemia (56).

Intra-abdominal organ perforation and bleeding are prevented with (a) ultrasound guided paracentesis and (b) coagulopathy treatment, mandatory in case of severe thrombocytopenia

(platelet count < 50,000/mL) or hypofibrinogenemia (< 0.7 g/L), as clinically indicated by the attending physician or the Blood Transfusion department (350-354).

Catheter-related abdominal wall infection and secondary peritonitis are to be prevented with aseptic paracentesis technique and standard catheter point of insertion surveillance for signs of inflammation or infection, similar to central venous catheter procedures (355).

We do not use prophylactic antibiotics along with the indwelling abdominal paracentesis catheter in the CPP intervention group nor in the control group.

The definition of secondary peritonitis includes the following: (1) polymorphonuclear cell count elevation > 50% in 48 hour after the initial paracentesis or (2) microbiologic "de novo" isolation of bacteria after 48 hour after paracentesis.

In case of isolated bacterial culture of suspected skin contaminants, without signs of infection, a new direct ascitic tap at a different site should be performed to confirm or exclude a diagnosis of secondary peritonitis. Whenever a clinical diagnosis of secondary peritonitis is considered, antibiotic treatment should be immediately started according to standard clinical practice.

In case of paracentesis catheter-associated infection in the intervention group, similar to catheter-related bloodstream infection diagnosis and treatment, the catheter must be removed and, when clinically feasible, replaced via a new direct ascitic tap at a different site (355). This will allow for ascitic fluid analysis after 48 hour to monitor for treatment response, according to clinical guidelines, and to complete the 7-day period of the trial intervention (56).

If abdominal wall fistula or bleeding occurs, the insertion point should be sutured for closure and hemostasis.

6.2.5. Outcomes

The primary outcome is serum creatinine concentration. The secondary outcomes are IAP, measured creatinine clearance, daily urine output, CLIF-SOFA and the incidence of stage 3 KDIGO AKI score, as well as 28-day RRT-free days, 28-day survival rate, and ICU LOS. The outcomes variables will be assessed at day seven (D7) after randomization (D0), unless otherwise stated. Additionally, IAP, serum creatinine concentration, measured creatinine clearance, daily urine output, and CLIF-SOFA will be analyzed using their maximum or minimum and daily mean values between D1 and D7.

Whenever ICU discharge or liver transplant occurs before D7, the last available data prior to these events will be used for outcome assessment. Additionally, stage 3 AKI will be considered when RRT or death occurs and, in these circumstances, a serum creatinine concentration value of 4 mg/dL and creatinine clearance value of 10 mL/min will be used for outcome assessment as mentioned in the literature (86,73,71).

6.2.6. Sample size

The sample size was calculated using the statistical noncentral t function, with a one-sided alpha level of 0.05 (356). The calculations were based on the expected renal function and IAP variation between groups, since we assume the former to be dependent of the latter.

To support the trial rationale of an expected clinically significant IAP decrease of 3 mmHg in the intervention group, a total of 44 patients are considered necessary to detect a statistically significant difference, with 1:1 allocation ratio, 80% statistical power, and 95% confidence level. This estimate is based in a post-hoc analysis of 61 patients with cirrhosis from a multicentric randomized controlled trial in shock patients where a mean difference in

IAP of 3 mmHg was found between survivors and non-survivors (13.7 ± 3.9 and 16.7 ± 3.9 mmHg, respectively) (215).

Regarding the primary outcome, to detect a clinically and statistically significant decrease in serum creatinine of 0,4 mg/dL in the intervention group, a total of 60 patients is estimated, with a 1:1 allocation ratio, 95% statistical power, and 95% confidence. This estimation is based on a multicentric observational study of acutely decompensated patients with cirrhosis. In this study, ACLF patients with at least one OF had a mean creatinine difference of 0,4 mg/ dL between survivors and non-survivor groups (0.9 ± 0.45 and 1.3 ± 0.48 mg/dL) (97).

We arbitrarily estimate that protocol non-adherence/attrition or violation after randomization may affect approximately 15% of cases and, therefore, to ensure that the number of patients that complete the protocol is reached for the primary outcome, the total sample size is set at 70 patients with a 1:1 group allocation ratio.

6.2.7. Participant timeline

The participants' timeline begins with the screening for eligibility at ICU admission, obtainment of informed consent, enrolment, and randomized trial group allocation during the initial 24 h of stay. The calendar day in which group allocation takes place is considered trial "day zero" (D0).

The placement of the abdominal double-lumen catheter is intended to be performed as soon as possible after the allocation in the intervention group in order to optimize IAP and prevent and treat IAH. This procedure does not require special training beyond standard ultrasound-guided Seldinger technique.

Unforeseen catheter placement delay of more than 24 h after group allocation without clinical justification will lead to patient exclusion from the trial.

Protocol interventions and measurements will be maintained up to D7, after which post-trial care and follow-up will ensue until hospital discharge. This trial is expected to complete recruitment and follow-up of 70 patients in 36 months, until July 2025.

6.2.8. Patient recruitment, retention and follow-up

To optimize patient enrollment, nursing and medical staff will screen all admissions for patients with cirrhosis into the ICU and signal them to the P.I. for timely recruitment.

The PI will promote participant retention and complete follow-up by daily checking with the clinical staff for new eligible patients, assuring protocol adherence, complete monitoring during the ICU and hospital stays of enrolled patients.

Strategies to improve adherence to the trial protocol include regular sessions and briefings with the nursing and medical staff throughout the duration of the trial addressing patient recruitment and enhanced protocol compliance, focusing on IAP and APP monitoring, 8 hour urine sample collection procedures, and trial-related interventions.

The proposed interventions are to be, exclusively, implemented in the intensive care setting, although both post-trial care and patient follow-up will continue up to hospital discharge.

Patients enrolled in this study are covered from negligence or harm by the clinical trial insurance contracted by the study sponsor (CHULC, reference no. 706/22).

6.2.9. Assignment of interventions: allocation sequence generation

The patient allocation method consists of stratified randomization with blocks within each subgroup. This method is particularly useful with randomizing small samples due to the ability to create balanced groups regarding predetermined variables or characteristics at the beginning of the trial, reducing differences in baseline trial group characteristics that could harm later result analysis and conclusions.

In this small sample size trial, patients will be stratified according to maximum serum creatinine and maximum IAP, expected to be the two most important variables to balance between trial groups at baseline. Stratified randomization will homogenize trial groups *ad initio* to reduce the probability of unbalanced baseline group characteristics and biased results.

The stratification process will use two strata, namely, maximum IAP and maximum serum creatinine, thus creating four subgroups (I–IV): (I) IAP < 16 mmHg + serum creatinine < 1.5 mg/dL, (II) IAP < 16 mmHg + serum creatinine ≥ 1.5 mg/dL, (III) IAP ≥ 16 mmHg + serum creatinine < 1.5 mg/dL, and (IV) IAP ≥ 16 mmHg + serum creatinine ≥ 1.5 mg/dL (215,86). Each subgroup (I–IV) contains sequential blocks of randomized trial group allocation (A) control and (B) intervention, with a 1:1 ratio (i.e., AABB, ABAB, BABA, BBAA), as exemplified in Table 32.

Table 32. Example of randomized controlled trial stratification subgroups.

Stratification subgroups (I–IV)	**Creatinine < 1.5 mg/dL**	**Creatinine ≥ 1.5 mg/dL**
IAP < 16 mmHg	I) ABAB, ABBA, …	III) BABA, BBAA, …
IAP ≥ 16 mmHg	II) BABA, AABB, …	IV) BBAA, BAAB, …

Stratification subgroups (I-IV) created using maximum intra-abdominal pressure (IAP) and serum creatinine as strata. Example of stratified randomization with blocks within each subgroup (A, B).

6.2.10. Concealment mechanism and implementation

The adopted concealment mechanism of the allocation sequence will use sequentially numbered (#), opaque, sealed envelopes and the random sequence for trial group allocation in blocks will be generated by the P.I. using an online tool (357).

To prevent biased selection of patients, the PI will remotely screen for new patient admissions and alert the ICU staff for possible candidates. The patient's attending physicians are responsible for applying the protocol, deciding patient eligibility, and checking for inclusion/exclusion criteria and obtaining the informed consent.

Once patient enrollment has been established, the attending physicians, who are blinded for the allocation blocks, will determine the corresponding stratification subgroup by using IAP and creatinine values, and open the respective sealed envelope containing the group allocation. The PI will provide any required assistance and be informed of the patient allocation.

The allocation mechanism will be implemented by the patient's attending physician, after determining the stratification group (I–IV) by opening the corresponding envelope with the lowest available number (#).

Given the open nature of the trial, the assigned interventions will be unblinded for the clinical staff and patient. Outcome assessment and data analysts will also be unblinded for patient's group allocation given the objective character of the outcomes and the open trial intervention.

6.2.11. Data collection

The assessment and collection of trial data will start at patient enrollment (D0) including vital signs, specific therapies (i.e., albumin, transfusions), vital organ support, blood, urine, and ascitic fluid tests, repeatedly up to D7.

The trial protocol includes the daily collection of an 8 hour (480 min) urine volume, at blocked nocturnal interval from 23 to 7 o´clock, for measurement of creatinine clearance, based on the following formula: creatinine clearance (mL/min) = (urinary creatinine [mg/mL] × urine volume [mL])/(serum creatinine [mg/mL] × urine collection time [480 min]) (358).

Daily blood analysis includes complete hemogram, coagulation, biochemistry and arterial blood gas. Ascitic fluid will be collected with every new paracentesis and repeated every 48 hour in the intervention group for screening of infectious complications.

Collected trial variables are mainly included in clinical severity scores APACHE II, SAPS II, CLIF-C ACLF, CLIF-SOFA, SOFA, RIFLE, KDIGO, ICA-AKI, MELD, and MELDNA, and incorporate liver disease etiology, precipitant event for critical illness, urine output, serum creatinine, estimated and measured creatinine clearance, and number of days on RRT, Glasgow coma score and WH scale, number of days under vasopressor support and dosage, PaO2/ FiO2 ratio, positive end-expiratory pressure and number of days under mechanical ventilation, total bilirubin, coagulation international normalized ratio, platelet count, arterial blood lactate and prescribed albumin dosage. Intermediate effect variables IAP and APP will be measured throughout ICU stay to test the trial rationale.

6.2.12 Data management and confidentiality

Patient identification will be coded and pseudo-anonymized in a list kept confidential by the PI up to 1 year after publication of trial results, which it will be destroyed afterwards.

Data will be collected into a database (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp), located in a secure institutional space, accessible only through specific ID and passwords, restricted to the PI and associated investigators.

The PI will be responsible for collected data quality and the database safeguard for a period of 10 years after patient enrollment is complete.

The coded list will be used for patient confidentiality and pseudo-anonymization, to allow for quality control while managing and analyzing the database. It will be kept in a secure institutional space, accessible only through specific ID and passwords.

6.3. Results

6.3.1. Statistical analysis

For the descriptive analysis, quantitative variables will be reported as means and standard deviations or as medians and interquartile ranges (P25-P75), as appropriate and categorical variables reported as frequencies and percentages.

Quantitative variables will be analyzed using the assessment day value (D7), the daily mean value and their maximum or minimum values. Mann–Whitney U test will be used to compare study groups, assuming a non-normal distribution, or two independent sample t-test, in case of normal distribution. Dichotomous categorical variables will be analyzed using chi-

square or Fisher's exact tests. Using daily values, mixed effects regression models will be used to consider the autocorrelation structure between the longitudinal measurements.

Regarding stage 3 AKI as secondary outcome, odds ratios and corresponding 95% confidence intervals will be estimated using logistic regression models. For the study of RRT-free days, competing risks survival models will be applied considering death as the competing risk. Regarding time until death, joint survival regression models will be used to take into consideration the association of longitudinal markers with time until death. For LOS, linear regression models will be applied. For all regression studies, univariable and multivariable analyses will be performed to account for potential confounders. The absolute risk of paracentesis-related complications will be reported for both trial groups. A level of significance $\alpha = 0.05$ will be considered and data will be analyzed using the R Statistical Software (360).

Data will be analyzed according to intention-to-treat (ITT). Protocol adherence, with intervention initiation and completeness, will be reported. Missing data will not be imputated and will be described.

6.3.2. Interim analyses

An interim analysis will be performed when the trial completes the follow-up of 30 patients to assess for safety and outcomes. The trial will be terminated in case of significant harm or if significant statistical difference on the primary outcome is achieved.

6.3.3. Methods for additional analyses

Subgroup analysis are planned to compare the outcomes of groups of patients with or without serum maximum creatinine ≥ 1.5 mg/dL, maximum or mean IAP value ≥ 16 mmHg before randomization and baseline or mean APP value < 60 mmHg up to D7.

6.3.4. Oversight and monitoring

The trial coordination will be in charge of the PI and a steering committee will include two additional collaborators.

A data monitoring committee (DMC) composed by three independent external collaborators, including a statistician, will report to the PI and the Research Center on aspects of trial conduct, such as recruitment, identify the need to make adjustments, and analyze for significant outcomes or harm.

6.3.5. Adverse event reporting and harms

Should any adverse events, unintended effects, or harm be detected, it is the attending physician's responsibility to report to the PI and the Research Centre of CHULC.

The DMC is expected to perform trial conduct audits once 20 and 40 randomized patients have completed 28-day follow-up and at trial conclusion.

6.3.6. Dissemination plans

The dissemination of the trial results will take place in the form of public presentations and publications in the appropriate scientific media.

6.4. Discussion

This is the first RCT to compare the impact of different therapeutic paracentesis strategies on organ dysfunction and clinical outcomes in the prevention and treatment of IAH in critically ill patients with cirrhosis and ascites. Ultimately, we expect to discuss these strategies and improve clinical practice.

Our center has experience in treating critically ill patients with cirrhosis, ascites and IAH and we use both LVP and CPP strategies empirically. The CPP has the potential to minimize IAP, optimize APP, and reduce the number of required abdominal punctures, as well as the risk of perforation and bleeding. However, it may entail higher risk of infection and abdominal wall fistula, when compared to intermittent LVP. The need to better understand the impact of these interventions set the grounds for this trial.

The use of a double lumen catheter for continuous ascitic fluid drainage presents important advantages over a single lumen catheter because: (1) it is more resistant to obstruction by "kinking" due to its internal section pillar and (2) the proximal (lateral) opening is less prone to obstruction by viscera or clotting than the distal (pointing) one. Furthermore, the use of the Seldinger technique to insert the abdominal paracentesis catheter, using an acute angle of percutaneous insertion (ideally, less than 45°), avoiding a perpendicular approach, (1) reduces catheter kinking and (2) may prevent insertion site fistula, given the oblique multiplane closure trajectory. These details are even more important given the duration of the CPP strategy.

The use of intra-abdominal percutaneous catheters in patients with cirrhosis and ascites has been demonstrated to be safe and effective outside of the ICU setting (347,349). We do not use prophylactic antibiotics associated with paracentesis in this trial nor in our usual clinical practice. Similarly, in the prevention of catheter-related bloodstream infections, the use of prophylactic antibiotics is not recommended in the clinical management of non-tunneled central venous catheters (350). Additionally, the use of prophylactic antibiotics in the intervention arm would create an important therapeutic differences between study groups and hinder the comparison of results.

Possible limitations in our trial protocol include the following: (1) underpowered sample size to identify significant differences for some secondary outcomes and paracentesis-related complications or harm; (2) reduced generalizability of results due to the single-center, specialized liver disease ICU setting; (3) selection bias due to the fixed block size randomization; for this reason, the group allocation will be revealed by the attending physician, rather than the PI; (4) clinical reasons may induce protocol non-adherence or violation, although this may reflect real-world conditions and improve generalizability of results.

Finally, we selected serum creatinine as the primary outcome variable to compare trial groups since it remains the most practical biomarker of renal function in patients with AKI (86). Even though serum creatinine has some limitations, particularly regarding interpretation in the individual patient with cirrhosis, the randomization process should homogenize patient characteristics at baseline and allow for the comparison of results between groups.

This research trial conforms with the ethical norms and standards in the Declaration of Helsinki, including local Ethics Committee (reference no. 632/2018, 11/02/2022) and registration (ClinicalTrials.gov NCT04322201). This trial has received internal funding granted from the Research Center (reference FFI 06/2019), exclusively for specific laboratory analysis described in the trial protocol.

The present trial protocol corresponds to version 10.4, January 2022, and has been implemented in August 2022. The recruitment process began with the enrolment of the first patient in September 2022 and is expected to be complete in 36 months, by July 2025.

Trial registration: ClinicalTrials.gov NCT04322201. Registered 20/12/2019, https://trialsearch.who.int/Trial2.aspx?TrialID=NCT04322201.

This protocol was structured and published according to the SPIRIT checklist template as provided by *Trials* journal (361,362).

Chapter 7

Discussion

7.1. Critically ill Patients with liver Cirrhosis

7.1.1. The majority of patients were male with alcohol-related liver cirrhosis.

The European region has the highest levels of reported per capita consumption of any other region (363). Overall, this region has seen increases in cirrhosis, liver cancer and mortality in recent decades as a result of changes in the underlying risk factors. However, in a cluster of European countries, in which Portugal is included, mortality from cirrhosis and other chronic liver diseases has seen a decreasing trend, with a respective decrease in alcohol consumption, since the 1970s up to 2015 (6).

Cirrhosis and chronic liver diseases, excluding liver cancer, accounted for 0.9% (1127/125223) of all deaths occurring in Portugal, during 2021 (364). This set of diseases represented 497 DALY, half of which were alcohol-related, and were 3.4 times higher among males than females (respectively, 790 vs. 232 DALY per 100000 individuals), during 2019 (365). A significant reduction in the overall burden of liver cirrhosis, assessed by a decrease in hospital admissions, mortality and potential years of life lost was observed in the Portuguese population between 2010 and 2017. The number of hospitalized patients with cirrhosis remained stable during this period, mostly were male (82.2%), the most frequent etiology was isolated alcoholic liver disease (71%), and a noteworthy decrease of hepatitis C-related admissions after the wide availability of direct-acting antivirals in 2015 (9,366).

7.1.2. Infection was the most frequent precipitant event for clinical decompensation.

Infection was, consistently, the most frequent precipitant event for acute clinical decompensation in our cohort of critically ill patients with liver cirrhosis. Up to half of our patients were admitted in intensive care due to severe infection with septic shock. The most

frequently observed infectious precipitant event of ACLF was pneumonia, followed by SBP and urinary tract infections. This confirmed other reports of infectious precipitant events in ACLF patients. These infectious events were significantly more frequent in severe ACLF grade 3 patients, particularly, pneumonia and SBP, when compared to acutely decompensated cirrhosis patients without ACLF (97,103).

7.1.3. The clinical severity of patients was high with multiorgan failure.

Circa half of our ACLF patients presented multiorgan failure with ACLF grade 3 at ICU admission. Vital organ support at ICU admission was provided to the vast majority of patients, approximately, vasopressor support in 2/3, IMV in 2/5 and RRT in 1/5 of cases.

These results likely reflect the clinical setting in which they are drawn from. Empirically, an ICU adjacent to an Emergency Department with immediate access to Gastroenterology and endoscopic treatment is more prone to receive patients with variceal bleeding. Patients with their first episode of variceal bleeding have a reported average 6-week mortality rate up to 20% and outcomes have steadily improved over time with access to intensive care (367,369). Whereas, the additional hospital transfer of a critically ill patient to an ICU in a liver transplant center, such as in our center, may induce a selection bias towards more severe patients, such as those with septic shock and/or multiorgan failure with higher mortality rates (369).

The reference study CANONIC described a cohort of patients with similar demography, liver disease etiology and frequent infectious precipitant event, however with different settings (hospital ward and ICU), and less severe ACLF grade 1 and lower mortality (97). Furthermore, in a large meta-analysis with 1904 patients, exclusively in intensive care, demography and liver disease etiology were also similar to ours, however the primary reason for admission was

variceal bleeding. The patients in this meta-analysis were less severe, more than half (53.3%) presented OF ≤1 and only 19.4% ACLF. The mortality rate was also lower in the ICU (42.4%) and in-hospital (54.1%). Additionally, infection with septic shock was associated with worse outcome, and centers with a liver transplantation program (such as ours) were associated with higher in-ICU mortality (225).

7.1.4. Short term mortality was high.

A high overall 28-day mortality rate was observed in the pooled cohorts (97/172, 56.4%) of patients from our center. There is a broad range of worldwide reported short term mortality rates (between 16% in-ICU up to 74% in-hospital) among population-based cohorts and meta-analysis of patients with cirrhosis in intensive care (370-374). The etiology of chronic liver disease, the type of precipitant event, the clinical severity and the ICU settings are fundamental factors to take into consideration *a priori*, and preclude direct comparisons, particularly with such a discrepant range of values. The results at our center results show consistent 28-day mortality rates in the 2 studied periods (56.3% [40/71] between March 2013 – December 2016 and 56.4% [57/101] between October 2016 – December 2021).

7.1.5. Risk factors for short term mortality were related to OF, systemic inflammation and metabolic dysfunction.

The independent risk factors for 28-day mortality included the total number of OFs, HE WH score, total bilirubin, oxygenation PaO2/FiO2 ratio, WBC count, arterial blood lactate, as well as clinical severity scores SAPS II and MELD at ICU admission. Additionally, arterial blood lactate and INR at day 3 of ICU stay were also found to predict 28-day mortality. These

are all well known risk factors, although the number of OFs and lactate deserve further consideration.

The number of OF is the basis of the ACLF grading system, with particular emphasis on renal and brain dysfunction in less severe ACLF grade 1 (97). The ACLF grade 3 category represents, by definition, a group of patients with 3 or more (maximum of 6) OFs. Hence, the exact total number of OFs is able to further discriminate between these severe ACLF grade 3 patients with multiorgan failure and provide improved prognostic prediction.

The production of lactic acid mostly occurs in the muscle and is increased during anaerobic stress conditions such as fasting, sepsis and shock. The liver is responsible for blood lactate clearance, converting it to glucose through gluconeogenesis, known as the lactic acid cycle, or the Cory cycle (375). Conceptually, the lactic acid cycle is disrupted in ACLF patients, both from increased production due to the anaerobic stress of critical illness and due to the reduced clearance resulting from cirrhosis and liver injury. From the clinical perspective, the dynamic trend of arterial lactate concentration is a valuable prognosis biomarker in critical illness, and integrates multiple prognostic scores for liver disease patients. (376-380)

7.1.6. Liver transplant improves survival in selected ACLF patients.

Liver transplant in critically ill patients with cirrhosis was performed within 28 days of ICU admission in an important proportion of cases (26/172, 15.1%) in our aggregate cohorts. Half of these patients survived to hospital discharge home. Liver transplant is an effective treatment for selected ACLF patients, conferring improved vital outcomes as reported in the recent literature on LT in ACLF. In a multicentric study in 73 severe ACLF grade 3 the 1-year LT survival rate was 84%, with more complications and longer hospital stay (381). In a

European multicentric study in 234 ACLF patients, 1-year LT survival was 81%, with wide variation in patient characteristics (382). Furthermore, in a North-American study, 4806 ACLF grade 3 patients had an overall 1-year LT survival rate of 86.2%. Additionally, those who had early LT (≤ 7 days from listing) had improved outcome when compared to those with late LT (days 8-28 from listing) (383). Therefore, LT is an effective treatment option with improved outcomes, reaching over 80% 1-year survival rate, in selected, optimized ACLF patients within optimal timing (384). However, if severe ACLF patients should receive higher LT priority is still a matter of debate (385).

7.2. Intra-Abdominal Hypertension

7.2.1. The prevalence of IAH and ACS was high.

There was a high prevalence of IAH and ACS, respectively, circa 4/5 and 1/4 of the cohort, in critically ill patients with cirrhosis in the ICU.

Patients in mixed medical-surgical intensive care have reported lower prevalence of IAH between 32-51%, and of ACS between 4.2-8.2% of ACS (244,246). The IROI study was the first and largest prospective multicenter cohort study of IAP an included 491 consecutive mixed ICU patients. The reported prevalence of IAH, assessed as daily mean values, on the day of ICU admission was 34%, and 49% during a 12 day period. Likewise, the prevalence of ACS was 3.9% at admission and 6.3% during the same period. In our cohort of patients with cirrhosis, using a comparable daily mean value of IAP, there was a higher prevalence of IAH at ICU admission day (56%) and during the ICU stay (77%). Additionally, there was a higher prevalence of ACS (17%) during the intensive care stay. The prevalence of IAH and ACS

during the ICU stay was even higher in septic shock patients with cirrhosis, as reported by Al-Dorzi et al., where 97% of patients had IAH, and 39% had ACS during the first 7 days of ICU stay (215). Our data confirms a high prevalence of IAH and ACS in patients with cirrhosis and acute medical illness in intensive care.

7.2.2. Higher IAP was associated with higher short-term mortality

At 28 days of ICU admission, non-surviving patients presented a higher maximum IAP and a higher overall mean IAP when compared to survivors. Importantly, maximum IAP was a risk factor for 28-day mortality when adjusted for general clinical severity SAPS II score.

The IROI study showed that the presence of IAH, and the maximum IAH grade during the first 12 days of ICU stay were independent predictors of 28-day mortality. Furthermore, AL-Dorzi et al., reported that IAH during the first week of ICU stay as an independent risk factor for increased in-ICU mortality. However, the mere presence of IAH was not an independent risk factor for 28-day mortality in our cohort of patients with cirrhosis.

Abdominal compartment syndrome was associated with higher 28-day mortality, when compared to those with lower grade I-II IAH, and the short mortality rate in these patients was comparable with the reported in the IROI study.

7.2.3. Risk factors for IAH and ACS

Alcoholic cirrhosis neurologic failure and higher oxygenation ratio at admission were risk factors for IAH during the ICU stay.

The etiology of CLD was a risk factor for the development of IAH. Alcohol is the main etiology for CLD in European countries and is an important co-factor for fibrosis progression in other etiologies, negatively affecting outcomes. Despite a number of histological similarities,

cases of alcoholic liver disease can be differentiated from other causes (267). Our data, however did not allow to draw further considerations.

Regarding neurologic failure, a few studies have reported a correlation between IAH and ICP (255,259,264). According to the Monro-Kellie hypothesis, IAP could be transmitted to the central nervous system (265) due to backflow in the venous plexus of the spinal canal and the intracranial veins, and due to cranial excursion of the diaphragm causing elevated intrathoracic pressure and augmented central venous pressure reducing venous drainage from the central nervous system (259,265,266). Such mechanism could represent an additional pathophysiologic rationale for HE in liver disease patients with increased IAP (259,266).

A higher arterial blood oxygenation PaO2/FiO2 ratio at admission, reflecting improved oxygenation, was independently associated with a higher likelihood of IAH during the ICU stay. This was a surprising finding since IAH is transmitted to the thorax causing reduced pulmonary compliance and respiratory volumes. Additionally, those patients submitted to IMV at admission had less IAH. In other words, patients with IAH had better arterial blood oxygenation and required less IMV. We speculate this could be attributed to a set of reasons: 1) the use of non-invasive ventilation, 2) IMV for airway protection, with reduced PEEP, thus improving oxygenation without off-setting IAH (PEEP ≥8 cm H20 is a known risk factor for IAH)(246); 3) higher intensity of anti-IAH measures (i.e. deeper sedation and analgesia, neuromuscular blockade, gastric decompression, LVP) in IMV patients. Unfortunately, our data did not provide additional reasoning for these associations and further studies are warranted to confirm these findings.

The only risk factor for ACS was “infection” as a precipitant event of acute decompensation among patients with IAH. Patients with ACS had higher MELD and

MELDNA scores and WBC count, reflecting higher severity of cirrhosis and higher systemic inflammation. This leads to consider that infection (i.e., spontaneous bacterial peritonitis) may result in increased systemic inflammation and ascites formation resulting in higher grades of IAH. This relationship between infection and the development of ACS deserves future study as well.

7.3. Abdominal Hypoperfusion

7.3.1. Abdominal perfusion pressure was low in critical patients with cirrhosis.

Our cohort presented a low mean APP value on ICU admission day when compared to other populations of intensive care patients (386,387). Specifically, APP was nearly 15% lower than in populations of patients with severe acute pancreatitis and other mixed intensive care patients (386,387). The prevalence baseline AhP was high, affecting approximately half of our cohort. It was, nonetheless, lower than Al-Dorzi et al. reported in septic shock patients with cirrhosis, with a prevalence of AhP of 70% at ICU admission (215).

During the first week of ICU stay, AhP affected approximately two thirds of our cohort of patients with cirrhosis. Specifically, no other studies were found to, address the issue in this manner. However, Mayr et al. measured APP immediately before and after LVP and reported a prevalence of AhP between 25 and 50% of cases in the ICU (273). Our study confirms that patients with cirrhosis have lower APP than other types of critical patients and present a high prevalence of AhP.

7.3.2. Acute-on-chronic liver failure severity was a risk factors for AhP.

A higher ACLF grade at ICU admission was predictive of AhP both at baseline and during the first week of ICU stay. This reflected the severity of our typical ACLF grade 3 patient with septic shock and multiorgan failure. Thus, a higher clinical severity with low MAP combined with increased IAP due to ascites, presented as was the logic reason for the association between higher ACLF grade and AhP.

7.3.3. Patients with AhP were more frequently submitted to paracentesis at intensive care admission.

Patients with baseline AhP were five times more likely to be submitted to paracentesis on ICU admission day. This may indicate an increased clinical awareness for the treatment and prevention of IAH, as well as for the diagnostic screening of SBP in these high-risk patients. On the other hand, LVP performed at admission was not associated with a lasting effect on IAP during the following days. We speculate this was probably due to anti-IAH measures applied throughout the ICU stay, including LVP after admission day. The absence of data regarding paracentesis and other anti-IAH measures throughout the entire ICU stay were a limitation, although it sets the ground for additional research.

7.3.4. Lower APP was associated with worst vital outcome.

Baseline APP was significantly lower in non-survivors than in survivors at day 28. Abdominal hypoperfusion, however, was not a risk factor for 28-day mortality in our cohort. Comparatively, Al-Dorzi et al. also reported AhP to be not significantly associated with outcome, although an APP cut-off value of 55 mmHg was described as the best discriminator between survivors and non-survivors (215). Abdominal hypoperfusion was not a risk factor in

our cohort, probably due to relatively small sample size, the observed time frames and the multifactorial nature of critical illness in patients with cirrhosis.

7.4. Acute Kidney Injury

7.4.1. The prevalence of AKI and ARF was high in critical patients with cirrhosis.

Our cohort of critically ill patients with cirrhosis in intensive care presented a high incidence of AKI (388,389). Nearly 3/4 of our cohort had any stage of AKI during the first seven days of ICU stay. This prevalence of AKI was higher than reported in the literature, with up to half of the patients with cirrhosis requiring ICU admission having any stage of AKI (389). In a meta-analysis of AKI in patients with cirrhosis, three studies in intensive care pooled together a prevalence of 47.7% (353/740) cases of AKI (388-392). Furthermore, in post LT patients with cirrhosis the overall incidence of AKI ranged widely between 12-70% (389).

The prevalence of ARF was very high in our cohort. Circa half of our population presented stage 3 ICA-AKI criteria, which is very high when compared to the previously referenced studies. While these studies reported AKI prevalence in up to half of the population, instead, we observed a similar rate for merely stage 3 ICA-AKI. This emphasizes the importance and severity of AKI, with known deleterious consequences in ACLF patients.

7.4.2. Low persisting APP was a risk factor for ARF.

Independent risk factors for ARF during the study period included higher serum urea concentration and WBC count at admission, as well as lower persisting APP

Persisting APP captured the cumulative deleterious effect of low APP on renal function, even though there were no intra-day APP differences between groups of patients with and

without ARF. This observation was 1) comparable to the temporal relationship between the duration of increased IAP and increased mortality, as described in critical surgical patients, and 2) sensible to the known lag (1-3 days) between the onset of increased IAP and the development of AKI (243,346,393).

Furthermore, a persisting APP cut-off value <70 mmHg was optimal to predict the event of ARF, with a good ability to discriminate these patients. Therefore, APP may prove to be a clinically valuable sign to assist the physician's decision to further optimize the management of IAP and MAP in the critically ill patient with cirrhosis.

7.5. Randomized Controlled Trial Protocol

7.5.1. Strategies for the prevention and treatment of IAH in patients with cirrhosis.

Has we have seen, patients with cirrhosis and ascites are at high risk for IAP, higher IAP was associated with higher short-term mortality and low persisting APP was associated with ARF. Both the presence and the duration of IAH are known independent risk factors for mortality in the critically ill patient (176, 243). In the setting of IAH, paracentesis reduces abdominal wall tension and improves overall intra-abdominal hemodynamics by minimizing IAP and optimizing APP of intra-abdominal organs (176). Clinical practice guidelines for the critically ill patient with IAH/ACS and for ACLF, recognize this rationale and suggest the evacuation of obvious intra-peritoneal fluid with the use of percutaneous catheter drainage to reduce IAP (176,394). Nonetheless, IAH develops in more than three quarters of critically ill patients with cirrhosis during their first week of ICU stay (215,340).

Therefore, a strategy for the prevention and treatment of IAH/ACS could improve patient outcomes in the critically ill patient with cirrhosis by minimizing IAP and optimizing APP, potentially leading to improved outcomes. In fact, some studies in intensive care have shown that LVP is safe and associated with short-term improvement of renal, pulmonary, and hepatic dysfunction, although follow-up and clinical outcomes in the ICU were not assessed (213-215,273,342). Therapeutic LVP is the standard-of-care in the treatment of tense ascites and HRS in acutely decompensated liver cirrhosis patients (70,343). Furthermore, an experimental study has shown causality between small increases of IAP (5–10 mmHg), after merely 24 hours, and the development of acute renal injury in HRS (319). However, the recommendation for paracentesis in the treatment of IAH/ACS is based on low-quality evidence and, to the best of our knowledge, there are no studies comparing different therapeutic paracentesis strategies in the critically ill patient with cirrhosis with IAH (176,394).

7.5.2. A randomized controlled trial protocol.

With the aim of assessing the impact of prevention and treatment of IAH on organ disfunction and clinical outcomes, a RCT was designed and implemented in intensive care. The specific aim of this RCT was to compare the outcomes of two different methods of therapeutic paracentesis used in the prevention and treatment of IAH.

The trial hypothesis states that a sustained CPP strategy in the treatment of IAH improves organ dysfunction and clinical outcomes when compared to standard intermittent LVP in the critically ill cirrhotic with ascites. Thus, using the duration of the paracentesis, time as a therapeutic variable.

The primary outcome of this RCT is serum creatinine concentration, since it remains the most practical biomarker of renal function in patients with AKI (86). The secondary outcomes include IAP variation, CLIF-SOFA score and organ subscores assessed at D7, in addition to 28-day mortality and ICU length-of-stay (LOS).

This RCT is expected to confirm previous findings, shed light on unanswered questions, strengthen the body of evidence in the literature on IAH in the critically ill patient with cirrhosis and improve patient care.

7.6. Conclusion

In conclusion, a series of studies with different methodologies were conducted to study IAH in critically ill patient with cirrhosis. The typical patient in our cohorts was under 60 years-old, male, with alcohol-related cirrhosis, admitted in intensive care due to septic shock and multiorgan failure ACLF grade 3. The short-term mortality was high and risk factors were related to OF, systemic inflammation and metabolic dysfunction. Liver transplant in selected patients was a vital therapeutic option. There was a high prevalence of IAH and ACS, and risk factors included alcoholic cirrhosis, higher HE and oxygenation ratio, and infection as precipitant event. Increased IAP was a risk factor for short-term mortality when adjusted for clinical severity at admission. Our cohort presented low APP and the severity of ACLF was a risk factor for AhP. Patients with AhP were more likely to be submitted to paracentesis at admission, suggesting increased clinical awareness. There was a very high prevalence of AKI and ARF in critically ill patients with cirrhosis, and low persisting APP was a risk factor. A

RCT has been designed and implemented to compare two therapeutic paracentesis strategies in the prevention and treatment of IAH and improve patient care.

The presented results and conclusions raised questions that may provide guidance for future research:

1. Important subsets of ACLF patients with specific diagnosis of precipitant events of clinical decompensation deserve larger studies, such as those with SBP, pneumonia or variceal bleeding, thus reducing the heterogeneity seen within the syndrome;
2. The particular finding that IAH was associated with higher oxygenation PaO2/FiO2 ratio requires additional confirmation, since our data could not provide a reasonable pathophysiological explanation, and it contrasts with studies in other populations of patients with IAH;
3. The study of clinical marker cystatin-C may improve the diagnostic accuracy and prognostic of AKI in ACLF patients;
4. The hypothesis that a clinical management strategy based on maintaining an APP >70 mmHg during the ICU stay reduces AKI and improve clinical outcomes in the critically ill patient with liver cirrhosis should be tested in a RCT.
5. External validation of our results and conclusions is warranted in larger, preferably multicentric studies.

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