

# Abdominal Hypoperfusion and Acute Kidney Injury in the Critically Ill Patient with Liver Cirrhosis: A Prospective Cohort Study

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## Learning Points

- Acute kidney injury (AKI) has a high prevalence in critically ill patients, especially in patients with liver cirrhosis, ascites, and increased intra-abdominal pressure. Abdominal hypoperfusion is an often underdiagnosed pathophysiological mechanism.
- In critical patients with liver cirrhosis in intensive care, higher serum urea concentration and increased white blood cell count at baseline, and low persisting abdominal perfusion pressure (APP) were independent risk factors for developing AKI
- It is fundamental to maintain an adequate APP, and a target of  $\geq 70$  mm Hg may be useful as a therapeutic endpoint to optimize renal perfusion and prevent AKI

## Keywords

Acute kidney injury · Liver cirrhosis · Acute-on-chronic liver failure · Abdominal compartment syndrome

## Abstract

**Background:** Reduced abdominal perfusion pressure (APP) is an underdiagnosed potential pathophysiological mechanism for acute kidney injury (AKI) in the patient

with liver cirrhosis and ascites. This study aimed to analyze the prevalence of abdominal hypoperfusion (AhP) (APP <60 mm Hg) and the impact of APP on AKI in critically ill patients with liver cirrhosis. **Methods:** This was a post hoc analysis from a prospective cohort study set in a general ICU at a tertiary university hospital. Patients were recruited between October 2016 and December 2021. Acute renal failure (ARF) was defined by stage 3 AKI according to the International Club of Ascites. **Results:**

Fifty-eight patients were included, with a mean age of 57 ( $\pm 8.4$ ) years, 79% were male, and 93% had acute-on-chronic liver failure at admission. The prevalence of AhP reached 75%, and 29% of cases had persisting AhP during the first week of ICU stay. Patients with baseline AhP had a higher 28-day mortality compared to those without AhP (respectively, 76% vs. 49%,  $p = 0.03$ ). Acute renal failure developed in 48% of patients. Higher serum urea (aOR: 1.01, 95% CI: 1.00–1.02,  $p = 0.04$ ) and white blood cell count (aOR: 1.1, 95% CI: 1.01–1.2,  $p = 0.02$ ) at ICU admission, as well as low persisting APP (aOR: 0.9, 95% CI: 0.86–0.98,  $p = 0.02$ ) were independent risk factors for ARF. **Conclusion:** Critically ill patients with liver cirrhosis presented a high prevalence of ARF, independently associated with higher baseline serum urea and WBC, and lower persisting APP. A structured clinical approach to optimize APP may reduce renal dysfunction in high-risk patients with cirrhosis.

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## Hipoperfusão abdominal e lesão renal aguda no doente crítico com cirrose hepática – estudo de coorte prospectivo

### Palavras Chave

Lesão renal aguda · Cirrose hepática · Doença hepática crônica agudizada · Síndrome de compartimento abdominal

### Resumo

**Introdução:** A pressão de perfusão abdominal (PPA) é um possível mecanismo fisiopatológico para a lesão renal aguda (LRA) frequentemente sub-diagnosticado no paciente cirrótico com ascite. Este estudo teve como objetivo analisar a prevalência de hipoperfusão abdominal (hPA) (PPA <60 mm Hg) e o impacto da PPA na lesão renal aguda em doentes com cirrose e doença crítica. **Métodos:** Esta foi uma análise pós-hoc de um estudo de coorte prospectivo de doentes críticos com cirrose hepática realizado numa unidade de cuidados intensivos (UCI) polivalente de um hospital universitário terciário. Os doentes foram recrutados entre outubro de 2016 e dezembro de 2021. A falência renal aguda (FRA) foi definida de acordo com o estágio 3 de LRA do International Club of Ascites. **Resultados:** Cinquenta e oito doentes foram incluídos, com uma média de idade de 57 ( $\pm 8.4$ ) anos, 79.3% eram do sexo masculino e 93.1% apresentavam a síndrome *acute-on-chronic liver failure*. A prevalência de

hPA foi de 75.3%, e 29.3% dos casos apresentaram hPA persistente durante a primeira semana na UCI. Os doentes com hPA basal apresentaram um aumento de mortalidade aos 28 dias em comparação com aqueles sem hPA (76.0% vs. 48.5%,  $p = 0.03$ ). Verificou-se FRA na admissão em 48.3% dos pacientes. O aumento da concentração da ureia sérica (aOR 1.01, IC95% 1.001–1.02,  $p = 0.04$ ) e da contagem de leucócitos (CL) (aOR 1.1, 95% IC: 1.01–1.2,  $p = 0.02$ ) na admissão à UCI, bem como a redução persistente da PPA (aOR 0.9, 95% IC: 0.86–0.98,  $p = 0.02$ ) foram fatores de risco independentes para o desenvolvimento de FRA. **Conclusão:** Os doentes críticos com cirrose hepática apresentaram uma alta prevalência de FRA, cujos fatores de risco independentes incluíram o aumento da ureia sérica e da CL basais, e a redução persistente da PPA. Uma abordagem clínica estruturada para otimizar a PPA poderá reduzir a lesão renal aguda nos doentes cirróticos de alto risco.

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## Introduction

Acute kidney injury (AKI) in the patient with liver cirrhosis presents a wide spectrum of pathophysiological mechanisms. It can be divided into hepatorenal syndrome (HRS-AKI), a functional syndrome in advanced portal hypertension, and non-HRS-AKI due to other precipitant events [1]. Particularly, AKI is one of the main clinical features of the acute-on-chronic liver failure (ACLF) syndrome, as described by the CANONIC study, characterized by systemic inflammation, dysregulated immune response, and high short-term mortality [2, 3]. Current AKI therapies are based on treating the precipitant events, preventing hypovolemia, and treating hemodynamic disorders with albumin administration and vasoconstrictors [4, 5].

In the critically ill patient with cirrhosis, ascites and increased intra-abdominal pressure (IAP) are related to portal hypertension. Abdominal perfusion pressure (APP) is the difference between mean arterial pressure (MAP) and IAP. Abdominal hypoperfusion (AhP) (APP <60 mm Hg) is often overlooked as a potential concomitant mechanism for AKI in the critically ill patient with liver cirrhosis, especially if ascites is present [6]. Even more, paracentesis is a safe therapeutic option to treat intra-abdominal hypertension (IAH), thus

optimizing APP and improving organ perfusion [6–10]. This study aimed to analyze the impact of APP on AKI in critically ill patients with liver cirrhosis.

## Methods

### *Design and Settings*

This was a post hoc analysis from a prospective observational study of critically ill patients with liver cirrhosis set in a 22-bed general ICU specialized in liver disease in a tertiary university hospital with a regional liver transplant program [11]. Patients were recruited between October 2016 and December 2021 and followed up to hospital discharge.

Data were collected at admission and throughout the ICU stay and included demographic and clinical variables for the calculation of general and liver specific severity scores, as well as liver cirrhosis etiology, acute illness precipitating event, arterial blood lactate concentration and vital organ support with vasopressors, invasive mechanical ventilation (IMV), and renal replacement therapy (RRT). Patient data were retrieved on site or from medical records and collected in an anonymous and protected database. IAP was a routine measurement in our clinical practice.

The study protocol was approved by the Ethics Committee at Centro Hospitalar Universitário Lisboa Central (CES No. 397/2017), and the need for individual informed consent for this observational study was waived. All study procedures followed the principles of the Declaration of Helsinki [12].

### *Patient Selection*

All patients with liver cirrhosis admitted to the ICU were consecutively screened for eligibility for this study. 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 [13].

Patient selection used the following inclusion criteria: (1) age  $\geq 18$  years, (2) first ICU admission during the index hospital stay, and (3) presence of a bladder catheter. The exclusion criteria were (1) surgical patient or any type of surgery in the 4 weeks preceding the index ICU admission, (2) contraindication for intravesical IAP measurements, (3) patients with ICU stay duration inferior to 24 h, (4) patients with previous liver transplant (LT), and (5) absence of IAP and APP measurements at ICU admission.

### *Definitions*

IAH and abdominal compartment syndrome (ACS) definitions, IAP measurement methodology, and clinical management of these patients followed the updated guidelines by the World Society of Abdominal Compartment Syndrome (WSACS) [7, 14, 15]. Accordingly, IAH was classified into grade I–IV (respectively, 12–15, 16–20, 21–25, and  $>25$  mm Hg), and ACS was defined as IAP  $>20$  mm Hg with an acute organ dysfunction. The definition of hypotension corresponded to a MAP  $<65$  mm Hg, regardless of vasopressor support, and AhP was defined by mean APP lower than 60 mm Hg. Reported pressure values correspond to daily means, unless otherwise stated.

IAP monitoring was prescribed every 6–8 h from the moment of ICU admission and was performed via trans-bladder measurement technique with a maximum of 25 mL of saline solution

and zero-pressure reference point set at the phlebostatic axis in the midaxillary line [7]. APP was, thereafter, calculated using the difference between the corresponding MAP and IAP ( $APP = MAP - IAP$ ).

ACLF and organ failure were defined as described in the CANONIC study [3]. Clinical management of patients with cirrhosis during the study period adhered to updated guidelines [5, 16]. This included withdrawal of all diuretic therapy, nephrotoxic drugs, vasodilators, and nonsteroidal anti-inflammatory drugs in patients with a diagnosis of AKI at admission and/or during the ICU stay.

For this study, acute renal failure (ARF) was defined by stage 3 International Club of Ascites (ICA) AKI criteria in patients with liver cirrhosis, determined by (1) an increase of serum creatinine  $>3$ -fold from baseline, (2) serum creatinine  $\geq 4.0$  mg/dL ( $353.6 \mu\text{mol/L}$ ) with an acute increase  $\geq 0.3$  mg/dL ( $26.5 \mu\text{mol/L}$ ), or (3) initiation of RRT [5]. The lowest value of creatinine measured at ICU admission was considered as the reference for the “3-fold increase of serum creatinine,” as well as the presence of any day of RRT, for ARF assessment during the study period.

The temporal definition of the term “baseline” corresponds to ICU admission calendar day (D0) plus the following calendar day of ICU stay (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. The rationale for choosing a study period of 7 days relied upon the observation that the cumulative prevalence of IAH and AhP become relatively stable between days 5–7, and that there is a mean lag of up to 3 days for an increase in creatinine to become apparent after the onset of IAH [11, 17]. Therefore, less than 7 days could exclude patients that developed AhP and subsequent ARF, and more than 7 days could include more cases of ARF or death, potentially unrelated to APP.

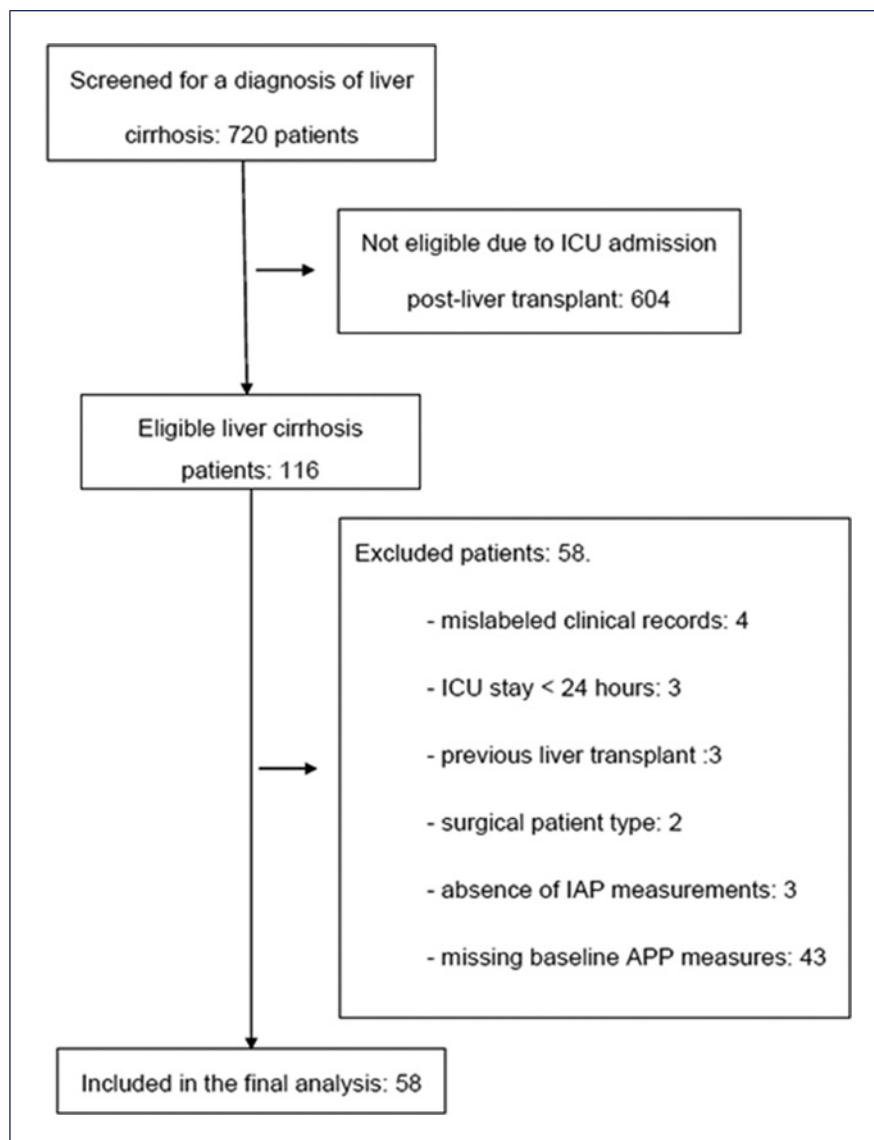
### *Outcomes*

The primary outcomes were the prevalence of AhP and 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 (LOS). Whenever ICU discharge or LT occurred before D7, the available data prior to these events was used.

To calculate RRT-free days within a 28-day period from ICU admission, we considered, inclusively, the days between the start and the end of RRT (censoring the end date at D28 if it was surpassed) and 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 [18].

### *Statistical Analysis*

Outcome variables were compared between groups of patients with and without baseline AhP and persisting AhP during the study period. Continuous variables were 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.  $\chi^2$  and Fisher’s exact tests were used to compare the frequencies of categorical variables between independent groups. Significant



**Fig. 1.** Study patient flowchart. ICU, intensive care unit; IAP, intra-abdominal pressure; APP, abdominal perfusion pressure.

statistical difference was defined as a two-sided  $p$  value  $\leq 0.05$ . 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  $\leq 0.10$  in univariate analysis. Statistical software IBM SPSS Statistics for Windows, version 27.0, Armonk, NY, USA, was used for analysis.

## Results

### *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 (Fig. 1). None of the

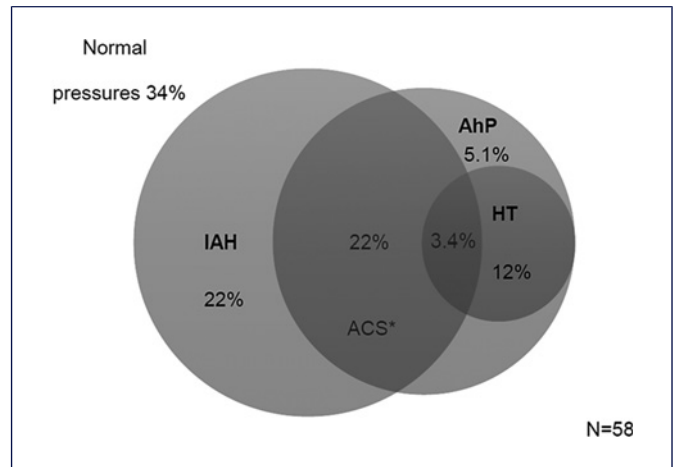
patients had previous ICU admissions nor contraindication for intravesical IAP measures. The total number of measurements of APP was 527, corresponding to approximately 9 per patient during the study period.

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 alcohol-related (50%), alcohol and hepatitis C virus (14%), nonalcoholic steato-hepatitis (7%), hepatitis C virus-related (5%), and hepatitis B virus-related (5%). Ascites was present at baseline in 93% of patients. Liver neoplasm was present in 22% of cases with 11 confirmed or suspected hepatocellular carcinoma (including 9 patients with three or less lesions and 2 multinodular), 1 lymphoma, and 1 unknown neoplastic

**Table 1.** Baseline characteristics of critically ill patients with liver cirrhosis at ICU admission

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 event, %	
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, cells/ $\mu$ L	13.5 (8.6)
Platelets, cells/ $\mu$ L	65 [42, 115]
INR	2.45 (1.01)
Creatinine, mg/dL <sup>a</sup>	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, $\mu$ g/dL	240 [164, 306]
C-reactive protein, mg/L	46 [17, 79]
PaO <sub>2</sub> /FiO <sub>2</sub>	268 (129)
pH	7.34 (0.12)
Lactate, mmol/L	2.6 [1.5, 4.3]
Urine output, mL/24 h	1,230 [483, 2,006]
Fluid balance, mL/24 h	796 [-384, 2,340]
Ascites, %	54 (93)
Paracentesis, % <sup>b</sup>	22 (37.9)
Drained ascites, mL	1,700 [50, 4,375]
IMV, %	30 (52)
Vasopressors, %	42 (72)
RRT, %	13 (22)
SAPS II	49 (16)
MELD-Na	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 [P<sub>25</sub>, P<sub>75</sub>]. IAP, MAP, and APP values correspond to those calculated from ICU admission day (D0) plus the following day (D1). HCV, hepatitis C virus; AKI, acute kidney injury; INR, international normalization ratio; PaO<sub>2</sub>, oxygen arterial partial pressure; FiO<sub>2</sub>, fraction of inspired oxygen; IMV, invasive mechanical ventilation; RRT, renal replacement therapy; SAPS, simplified acute physiology score, MELD-Na, 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. <sup>a</sup>Highest creatinine value during the initial 24 h of ICU admission. <sup>b</sup>Paracentesis of any type, including diagnostic and large-volume paracentesis.



**Fig. 2.** Venn diagram illustrating baseline critical pressures' distribution in patients with cirrhosis. Illustration of the overlapping distribution (%) of baseline critical pressures in patients with cirrhosis (N = 58) admitted to intensive care. The overall frequency of AhP was 43.1%, IAH was 48.3%, HT was 15.5%, and (\*) ACS accounted for 5.1% of patients in the corresponding area. IAH, intra-abdominal hypertension (>12 mm Hg); AhP, abdominal hypoperfusion (APP <60 mm Hg); HT, hypotension (mean arterial blood pressure <65 mm Hg); ACS, abdominal compartment syndrome.

infiltration. The prevalence of chronic kidney disease was 21% (including 12.1% mild, 5.2% moderate, and 3.4% severe), with no patients receiving chronic dialysis. No previous ACLF episodes were documented within the index hospital stay, and 19 patients (33%) had past hospitalization within the previous 12 months. The most frequent precipitant events leading to ICU admission were infection (38%), portal hypertension-related bleeding (17%), AKI (10%), and encephalopathy (8.6%).

At ICU admission, median MELD-Na score was 31 [19, 20], and mean SAPS II score was 49 ( $\pm$ 16) and chronic liver failure consortium (CLIF-C) score was 53 ( $\pm$ 11). In total, there were 54 (93%) patients with ACLF criteria at baseline, and the clinical severity distribution was grade 1 in 12%; grade 2 in 26%; and grade 3 (with three or more organ failures) in 55% of cases. During the first 24 h of admission, vital organ support was provided using RRT in 22%, IMV in 52%, and vasopressors in 72% of patients (Table 1).

Overall, 28-day mortality was 60%, hospital mortality was 69%, and ICU LOS (days) was 6.5 (2.3, 10.8) with a LT rate of 17.2%. No patients were submitted to transjugular intrahepatic portosystemic shunt. The highest classification of IAH during the first week of ICU was grade 1 in 41.1%, 2 in 24.1%, 3 in 10.3%, and 4 in 3.4%.

### Abdominal Hypoperfusion

The prevalence of baseline AhP was 43.1%, with a cumulative prevalence of 75.3% in any given day during the first week of ICU stay. Patients with baseline AhP had higher clinical severity as assessed by SAPS II score, lower pH, and higher lactate concentration and needed IMV more frequently at admission. Comparison between groups of patients with and without baseline AhP is detailed in online supplementary Table 1 (for all online suppl. material, see <https://doi.org/10.1159/000538939>).

Critical pressures (hypotension, IAH, and AhP) at baseline overlapped as illustrated in Figure 2. The frequency of persisting hypotension, IAH, and AhP were, respectively, 8 (13.8%), 27 (46.6%), and 17 (29.3%).

### Acute Kidney Injury

The prevalence of AKI was 65.5%, as assessed by the APACHE score at ICU admission and did not include 2 CKD patients. At baseline, serum creatinine was above the normal threshold of 1.2 mg/dL in 40 (69.0%) patients, including all CKD patients. Acute kidney failure was accounted in 25.0% of patients starting RRT at admission, in 27.8% (15/54) patients with urinary output of less than 0.3 mL/kg/h in 24 h during the first calendar day of ICU stay, and in 37.0% (20/54) of patients combining both criteria.

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% 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 0.3 mg/kg/24 h.

Comparison of baseline characteristics of patient with and without ARF during the period is detailed in Table 2. In univariate analysis, baseline variables associated with ARF included lower pH and higher white blood cell (WBC) count, serum urea, arterial blood lactate, and SAPS II score, as well as a trend for higher fluid balance. There were no significant differences in daily APP between patients with and without ARF during the first 7 days in the ICU, as illustrated in Figure 3.

The rate of ARF was similar 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 when compared to those without it (respectively, 70.6% vs. 39.0%,  $p = 0.04$ ) (Table 3).

Multivariable analysis for the development of ARF, including persisting APP as a continuous variable, and excluding urinary output due to correlation with serum urea, revealed independent association with higher serum

urea (aOR: 1.01, 95% CI: 1.001–1.02,  $p = 0.04$ ), WBC (aOR: 1.10, 95% CI: 1.01–1.19,  $p = 0.03$ ), and lower persisting APP (aOR: 0.93, 95% CI: 0.86–0.996,  $p = 0.04$ ) (online suppl. Table 2).

Furthermore, persisting AhP had a good ability to discriminate ARF (ROC AUC: 0.69, SD: 0.07, 95% CI: 0.56–0.83,  $p = 0.01$ ) (online suppl. Fig. 1), comparable to both persisting IAH and hypotension. Additionally, the optimal persisting APP cutoff value that predicted ARF was  $\leq 69$  mm Hg (sensitivity of 0.93, specificity of 0.40, and Youden index of 0.33) [21].

We performed further analysis to assess how the presence of persisting MAP would influence the results. When we included persisting MAP and persisting IAP in the multivariate analysis ( $n = 58$ ), independent risk factors for ARF were unchanged with persisting APP as a continuous variable (aOR: 0.93,  $p = 0.04$ , 95% CI: 0.86–0.996) and baseline WBC (aOR: 1.10,  $p = 0.03$ , 95% CI: 1.01–1.19) and urea (aOR: 1.01,  $p = 0.04$ , 95% CI: 1.00–1.02). Similar results were observed when we used persisting AhP, persisting hypotension, and persisting IAH as categorical variables, instead of the corresponding continuous values. When we excluded patients with persisting hypotension (all with concomitant persisting AhP) from the multivariate analysis, in a smaller sample ( $n = 50$ ), independent risk factors for ARF were baseline arterial blood lactate (aOR: 1.75,  $p = 0.04$ , 95% CI: 1.03–2.97) and urea (aOR: 1.02,  $p = 0.005$ , 95% CI: 1.01–1.03).

### 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. Finally, ICU 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, 7],  $p = 0.047$ ).

## Discussion

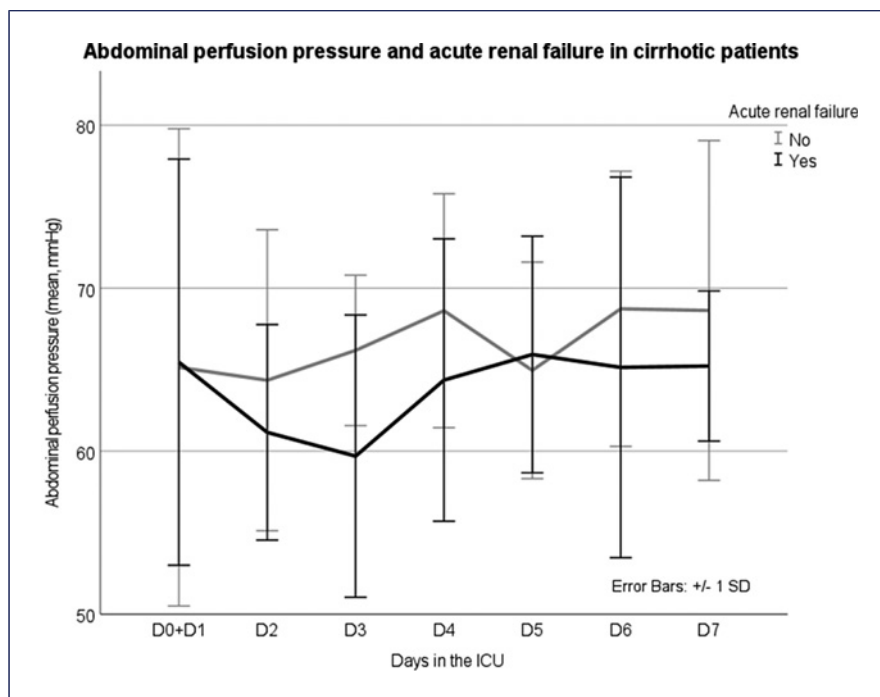
### Main Findings

This is the first study to demonstrate a temporal relation between reduced APP and ARF in critical patients with liver cirrhosis. Our main findings revealed that higher serum urea and WBC at baseline, as well as lower persisting APP were independent risk factors for ARF in critical patients with liver cirrhosis.

**Table 2.** Comparison of baseline characteristics of patients with and without ARF during the first 7 days in the ICU

	Without ARF	With ARF	<i>p</i> value
<i>N</i> = 58	30	28	
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, cells/ $\mu$ L	11 (7.2)	16 (9.1)	0.01
Platelets, cells/ $\mu$ L	67 [38, 115]	63 [46, 106]	0.6
INR	2.3 (1.0)	2.7 (1.0)	0.1
Creatinine, mg/dL*	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, $\mu$ g/dL	210 [156, 299]	253 [181, 306]	0.6
C-reactive protein, mg/L	35 [12, 65]	55 [18, 87]	0.3
PaO <sub>2</sub> /FiO <sub>2</sub>	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/24 h	1,495 [1,096, 2,240]	603 [344, 1,413]	0.004
Fluid balance, mL/24 h	326 [-493, 1,227]	1,367 [327, 2,797]	0.054
Ascites, %	26 (90)	27 (96)	0.4
Paracentesis, %	10 (33)	12 (43)	0.6
Drained ascites, mL	1,435 [238, 4,000]	1,900 [50, 5,538]	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
MELD-Na	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)	0.32
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 [P<sub>25</sub>, P<sub>75</sub>]. IAP, MAP, and APP values correspond to the mean calculated from ICU admission day (D0) plus the following day (D1). HCV, hepatitis C virus; AKI, acute kidney injury; INR, international normalization ratio; PaO<sub>2</sub>, oxygen arterial partial pressure; FiO<sub>2</sub>, fraction of inspired oxygen; IMV, invasive mechanical ventilation; RRT, renal replacement therapy; SAPS, simplified acute physiology score, MELD-Na, 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. \*Highest creatinine value during the initial 24 h of ICU admission.



**Fig. 3.** APP and ARF in patients with cirrhosis. ARF is defined as stage 3 International Club of Ascites acute kidney injury (ICA-AKI).

**Table 3.** Renal function and outcomes in cirrhotic patients with baseline and persistent AhP in intensive care

	Baseline			Persisting <sup>a</sup>		
	APP <60 mm Hg	APP ≥60 mm Hg	<i>p</i> value	APP <60 mm Hg	APP ≥60 mm Hg	<i>p</i> value
<i>n</i> = 58	25	33		17	41	
Baseline creatinine, mg/dL <sup>b</sup>	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
Maximum creatinine, mg/dL <sup>a</sup>	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 <sup>a</sup>	1,022 [130, 1,574]	1,056 [474, 1,656]	0.3	205 [87, 804]	1,095 [759, 1,701]	0.003
Anuria, % <sup>a</sup>	17 (68.0)	19 (57.6)	0.6	14 (82.4)	22 (53.7)	0.07
RRT, % <sup>a</sup>	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, % <sup>a</sup>			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)	<sup>c</sup>	12 (70.6)	16 (39.0)	<sup>d</sup>
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 mm Hg. Overall APP reflects the mean of the daily APP values. Variables are presented using median [interquartile range] and count (%). APP, abdominal perfusion pressure; AhP, abdominal hypoperfusion; mm Hg, 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. <sup>a</sup>Considering the first 7 days (D1 to D7) in the intensive care. <sup>b</sup>Lowest creatinine value during the initial 24 h of ICU admission, used for acute kidney injury criteria. <sup>c</sup>*p* value of 1.0, when comparing stage 3 ICA-AKI versus non-stage 3 combined categories. <sup>d</sup>*p* value of 0.04, when comparing stage 3 versus non-stage 3 combined categories.

### *Abdominal Hypoperfusion*

The prevalence of baseline AhP in our cohort was high and comparable with other studies (47–70%) [11, 22]. Nearly two-thirds of cases presented critical pressures with either hypotension, IAH, and/or AhP at baseline, and, on one hand, the majority of patients with AhP had concomitant IAH and, on the other hand, all patients with hypotension had AhP.

### *Acute Kidney Injury*

The prevalence of AKI at baseline was higher than expected in our study, affecting approximately two-thirds of patients, and nearly half of the cohort developed ARF during the 7-day study period, with high RRT requirement. Comparatively, the overall incidence of AKI in mixed populations of intensive care patients has been reported between 20 and 50%, including 50% in patients with liver cirrhosis [19, 23, 24]. Our results may be due to the high severity of patients admitted at our ICU (i.e., septic shock (SS) and multiorgan failure) since our center serves as a reference for LT and emergent transplant is a therapeutic option in selected patients.

We demonstrated that reduced persisting APP was predictive of ARF. Few studies reported a temporal relation between the onset of IAH and the development of AKI [17, 25, 26]. More than 2 decades ago, Sugrue et al. [17] described, in surgical patients, the gradual effect of IAH on renal function, with a mean lag period of 2.7 ( $\pm 6.5$ ) days between the onset of IAH and renal impairment, assessed by the rise of serum creatinine concentration. Regueira et al. [27] 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 SS patients. Both these studies used a modified Kron technique for IAP measure [28]. More recently, Dalfino et al. [26], using current standard methodology for IAP measure [7], reported a mean lag period between IAH and ARF onset of 1 ( $\pm 1.8$ ) day in a medical-surgical mixed population of critically ill patients. Furthermore, Al-Dorzi et al. [22] in their study with 61 patients with liver cirrhosis and SS described IAH as a risk factor for increased RRT requirement [18]. In our study in patients with liver cirrhosis, low persisting APP was an independent risk factor for ARF, even though there were no significant differences in baseline APP (Table 2), nor in discrete daily APP values between groups of patients with and without ARF (Fig. 3). We considered that persisting APP mean value captured the deleterious 7-day cumulative effect of lower APP values on renal function, signaling the impact of the prolonged duration of low APP rather than short-term at baseline.

This is in-line with the impact of the duration of IAH on mortality as described by Kyoung et al. [25] in surgical patients with severe sepsis. This is even more relevant since persisting APP remained an independent risk factor for ARF after adjusting for the corresponding persisting IAP and MAP both fundamental variables in the APP equation.

Additionally, we determined an optimal APP cutoff value (persisting APP  $< 70$  mm Hg) to predict ARF in our cohort of critically ill patients with liver cirrhosis, and this may be useful in clinical practice. Reports of similar APP cutoff values that predict clinical outcomes have been described, and these add to the generalizability of our results. In their study, Gül et al. [29] described a mean APP threshold of  $\leq 72$  mm Hg associated with an increase in Doppler-based renal resistive index, suggested to predict worsening renal perfusion in mechanically ventilated patients. In another study, Bieda et al. [30] reported, in patients with ruptured aortic aneurism, a mean APP cutoff value of 70 mm Hg to discriminate between survivors and non-survivors. Furthermore, Vidal et al. [31] observed, in a medical-surgical mixed population of critically ill patients, that APP was independently associated with hospital survival, with a best cutoff value  $\geq 75$  mm Hg, using the modified Kron technique. In two other studies, APP cutoff values of 52 and 50 mm Hg predicted ARF and survival, respectively, although they used the worst APP values (not mean daily values) or did not use current IAP measure methods [26, 32]. Our study in patients with liver cirrhosis suggests that maintaining an APP target of  $\geq 70$  mm Hg may be useful as a therapeutic endpoint to optimize renal perfusion and prevent organ failure during the ICU stay, although this requires confirmatory studies.

White blood cell count at baseline was an independent risk factor for the development of ARF in our cohort, but not infection as precipitant event, and this can be interpreted as a surrogate marker for systemic inflammation. The ACLF syndrome is an inflammatory paradigm with mainstay AKI, multiorgan failure, and increased mortality in patients with liver cirrhosis, and WBC count is well acknowledged in the CLIF-C prognostic score [3, 33].

Systemic inflammation is a common feature shared between the two subtypes of AKI, hepatorenal syndrome (HRS)-AKI and non-HRS-AKI, described in liver disease patients [1]. The pathophysiologic mechanism of HRS-AKI is traditionally ascribed to splanchnic vasodilation, cardiac dysfunction, adrenal insufficiency, and inflammation, while non-HRS-AKI is mainly characterized by the role of inflammation and bacterial translocation, bile

acid toxicity, worsening portal hypertension, cardiac dysfunction, and renal hypoperfusion [6].

In an animal model of cirrhosis and HRS, Chang et al. [6] were able to demonstrate causality between increases in IAP and de novo interstitial inflammatory infiltrates in renal histopathology, after merely 24 h of induced IAP of 5 mm Hg, as well as significant increases in serum urea and creatinine at 10 mm Hg of IAP. Most of our patients had IAH and, although there were no data regarding APP, a pathophysiologic mechanism for inflammation and AKI was established.

Urea is one of the oldest biomarkers in nephrology; however, blood urea nitrogen (BUN) is suboptimal for estimation of renal function [34]. 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. BUN's clearance falls markedly, even though glomerular filtration rate remains normal, at low urinary flow [35]. In our study, serum urea was inversely correlated with urinary output and behaved as early AKI markers at baseline. BUN 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 liver cirrhosis [34]. Without surprise, 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 scores that include urine output (RIFLE [20], AKIN [36], and KDIGO [37]) and their ability to stratify the severity of AKI in the critically ill cirrhotic patient, although this is outside of the scope of this study. The pathophysiologic complexity of the typical ACLF patient in this cohort is clear, and multiple injury mechanisms coexist, thus justifying the evolving nature of definitions and classifications of AKI [5].

ACLF syndrome is characterized by increased short-term mortality, and our results are comparable with similar cohorts described in the literature [3, 11, 38]. Patients with baseline AhP had higher 28-day mortality, with higher clinical severity SAPS II score and lactate concentration, worst pH, and more IMV at admission. Furthermore, we consider clinically relevant the 28-day mortality rate in patients with persisting AhP when compared with normal persisting APP (respectively, 70.6% vs. 56.1%), although it did not reach statistical significance likely due to a small sample size. The ICU

LOS was lower among those with persisting AhP and the deceased, highlighting the link between of APP and outcomes.

Finally, an important proportion of patients during the study period presented persisting critical pressures, particularly IAH, despite paracentesis and vasopressor use, indicating a potential for improved clinical management of AhP. Although our study did not focus on vasopressors, we did confirm that noradrenaline and/or terlipressine used at baseline did not significantly affect APP or ARF up to day 7.

Given the high prevalence of AhP in high-risk patients with liver cirrhosis, APP must not be overlooked. A structured clinical approach for a target APP >70 mm Hg, including the optimization of IAP and MAP (above 75 mm Hg if necessary) may reduce AKI and ARF in critical patients with liver cirrhosis.

### Limitations

We acknowledge some limitations: (1) the use of D0 lowest creatinine value as reference for the calculation of AKI criteria may have excluded diagnosis of AKI and 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) serum creatinine may have underestimated AKI in these patients with liver cirrhosis, whereas cystatin-C may be a better marker; and finally (6) no specific urinary biomarkers were used to differentiate the etiologies of AKI, including acute tubular necrosis, HRS-AKI, and others since we did not use these in our clinical practice.

### Conclusion

Critical patients with liver cirrhosis and ACLF presented a very 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 independent risk factors were high serum urea and WBC at baseline, as well as low persisting APP.

A temporal relation between APP and AKI was observed, with a persisting APP cutoff value predictive of ARF in the ICU. We advocate for a structured clinical

APP approach to assist the physician in the optimization of IAP and MAP for improved outcomes in high-risk patients with liver cirrhosis.

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## Statement of Ethics

This study complies with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. The Ethics Committee at Centro Hospitalar Universitário Lisboa Central (CES No. 397/2017) approved this study. Informed patient consent to participate was waived by the Local Ethics Committee given the observational nature of this study.

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## Conflict of Interest Statement

The authors of this study have no conflicts of interest to declare.

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## Author Contributions

Rui Pereira designed the study, collected data, performed the analysis, and wrote the manuscript. All authors reviewed and approved the final manuscript.

## Data Availability Statement

The dataset used during the current study is available from the corresponding author on reasonable request.

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