

CKJ REVIEW

Management of acute renal replacement therapy in critically ill cirrhotic patients

Jimena Del Risco-Zevallos^{1,*}, Alicia Molina Andújar^{1,*}, Gastón Piñeiro¹, Enric Reverter², Néstor David Toapanta², Miquel Sanz², Miquel Blasco¹, Javier Fernández² and Esteban Poch¹

¹Nephrology and Renal Transplantation Department, Hospital Clínic de Barcelona. University of Barcelona, IDIBAPS, Barcelona, Spain and ²Liver and Digestive ICU, Liver Unit, Hospital Clínic de Barcelona, University of Barcelona, IDIBAPS, Barcelona, Spain

*These authors contributed equally to this work.

Correspondence to: Esteban Poch; E-mail: epoch@clinic.cat

ABSTRACT

Renal replacement therapy (RRT) in cirrhotic patients encompasses a number of issues related to the particular characteristics of this population, especially in the intensive care unit (ICU) setting. The short-term prognosis of cirrhotic patients with acute kidney injury is poor, with a mortality rate higher than 65% in patients with RRT requirement, raising questions about the futility of its initiation. Regarding the management of the RRT itself, there is still no consensus with respect to the modality (continuous versus intermittent) or the anticoagulation required to improve the circuit life, which is shorter than similar at-risk populations, despite the altered haemostasis in traditional coagulation tests frequently found in these patients. Furthermore, volume management is one of the most complex issues in this cohort, where tools used for ambulatory dialysis have not yet been successfully reproducible in the ICU setting. This review attempts to shed light on the management of acute RRT in the critically ill cirrhotic population based on the current evidence and the newly available tools. We will discuss the timing of RRT initiation and cessation, the modality, anticoagulation and fluid management, as well as the outcomes of the RRT in this population, and provide a brief review of the albumin extracorporeal dialysis from the point of view of a nephrologist.

Keywords: AKI, cirrhosis, critical care, dialysis, epidemiology

INTRODUCTION AND SCOPE OF THE PROBLEM

Renal replacement therapy (RRT) in cirrhotic (also known as chronic liver disease) patients encompasses several issues related to the particular characteristics of this population, especially in the intensive care unit (ICU) setting. Despite the increasing literature regarding this topic, currently there is no consensus about when to initiate RRT or how to deal with dialysis

in terms of modality, anticoagulation and volume management. Furthermore, the short-term prognosis of cirrhotic patients who develop multiple organ failure is poor, raising doubts regarding futility.

This review attempts to shed light on the management of acute RRT in this complex population based on the current evidence and new tools available.

Received: 27.10.2021; Editorial decision: 5.1.2022

© The Author(s) 2022. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Epidemiology and definition of acute kidney injury in liver cirrhosis

Acute kidney injury (AKI) occurs in about 20% of hospitalized cirrhotic patients [1] and in about 40% of those admitted to the ICU [2, 3]. Ascites, elevated bilirubin, spontaneous bacterial peritonitis (SBP) and use of aminoglycoside antibiotics have previously been identified as significant risk factors for renal failure in cirrhotic patients [1].

The patient with liver cirrhosis is prone to requiring ICU admission due to their elevated risk of acute decompensation and extra-hepatic organ failure [4]. The prevalence of cirrhotic patients in ICUs is less than 5% in the reported series [4], of which up to 20–30% require RRT [4, 5].

Although one of the most known cause of AKI is hepatorenal syndrome (HRS), it actually is not the most common cause of AKI requiring RRT in the ICU, with acute tubular necrosis (ATN) in the context of sepsis, followed by hypovolemic shock the most common ones [2]. HRS is a specific type of AKI seen in patients with advanced cirrhosis characterized by impairment of kidney function because of vasoconstriction of the renal arteries due to marked splanchnic arterial vasodilation in the absence of substantial abnormalities in kidney histology, with a potential reversibility. It remains a diagnosis of exclusion, but the criteria of cirrhosis and ascites plus no response after 2 days of diuretic withdrawal and volume expansion with albumin are needed for the diagnosis. Biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) are recommended in current European Association for the Study of Liver (EASL) disease guidelines to distinguish between ATN and HRS [6].

Martin-Llahí *et al.* [7] investigated the predictive value of the cause of AKI in hospitalized patients with cirrhosis. Causes were classified into four groups: associated with bacterial infections, hypovolemia, HRS and parenchymatous AKI, being the most frequent cause. Three-month probability of survival ranged from 73% in patients with parenchymatous AKI to 15% for HRS.

In 2015, the International Club of Ascites (ICA) published a new definition of AKI in patients with cirrhosis, based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria but without considering urinary output (Table 1). Thus, based on baseline serum creatinine (sCr) (a value obtained within the previous 3 months), AKI is defined by an absolute increase of sCr ≥ 0.3 mg/dL within 48 h or a percentage increase of sCr $\geq 50\%$ from baseline. Three stages are defined: stage 1 when the previous criteria are met (a relative increase of sCr 1.5- to 2-fold from baseline), stage 2 when the increase in sCr is >2 -fold to 3-fold from baseline and stage 3 when there is an increase of sCr >3 -fold from baseline or sCr is ≥ 4.0 mg/dL with an acute increase of ≥ 0.3 mg/dL or initiation of RRT [8].

More recently, stage 1 has been subdivided into two subgroups based on serum levels of sCr: stage 1A (sCr <1.5 mg/dL) and stage 1B (sCr ≥ 1.5 mg/dL). This sub-classification is supported by the difference in survival and AKI progression or resolution rates between both groups. Also, the aetiology of AKI differs between AKI 1A and 1B, with HRS and ATN being uncommon in AKI 1A, but accounting for 48% of AKI 1B [9].

Outcomes of cirrhotic patients with need of acute RRT

The low prevalence of cirrhotic patients in the ICU is related to the frequent exclusion for admission based on the high ICU mortality rate ($>50\%$) [10, 11], especially in patients with certain characteristics such as AKI, infection at admission or the need of vasopressor therapy, although a slight improvement has been achieved in recent years [4, 12] (Figure 1). This improvement may be explained by a reduction in the organ failure scores at admission due to earlier referral to ICU and/or organizational improvements such as access to tertiary liver centres with access to liver transplant [4].

Several predictive scoring systems for mortality have been developed in general ICU populations to evaluate the severity of illness and prognosis, but they are not specific for cirrhotic

Table 1. International Club of Ascites (ICA-AKI) classification of AKI in patients with cirrhosis, with AKI 1 sub-classification (adapted from reference number [8])

Subject	Definition
Baseline sCr	A value of sCr obtained in the previous 3 months when available can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, the sCr on admission should be used as baseline.
Definition of AKI	<ul style="list-style-type: none"> • Increase in sCr ≥ 0.3 mg/dL (26.5 $\mu\text{mol/L}$) within 48 h or, • A percentage increase in sCr $\geq 50\%$ from baseline, which is known, or presumed, to have occurred within the prior 7 days
Staging of AKI	<p>Stage 1: Increase in sCr ≥ 0.3 mg/dL (26.5 $\mu\text{mol/L}$) or an increase in sCr ≥ 1.5-fold to 2-fold from baseline</p> <p>- 1A: sCr <1.5 mg/dL - 1B: sCr ≥ 1.5 mg/dL</p> <p>Stage 2: Increase in sCr >2-fold to 3-fold from baseline Stage 3: Increase of sCr >3-fold from baseline or sCr ≥ 4 mg/dL (353 $\mu\text{mol/L}$) with an acute increase ≥ 0.3 mg/dL (26.5 $\mu\text{mol/L}$) or initiation of renal replacement therapy</p>
Progression of AKI	<p>Progression: progression of AKI to a higher stage and/or need for RRT</p> <p>Regression: regression of AKI to a lower stage</p>
Response to treatment	<p>No response: no regression of AKI</p> <p>Partial response: regression of AKI stage with a reduction to a value of sCr ≥ 0.3 mg/dL (26.5 $\mu\text{mol/L}$)</p> <p>Full response: return of sCr to a value within 0.3 mg/dL (26.5 $\mu\text{mol/L}$) of the baseline value</p>

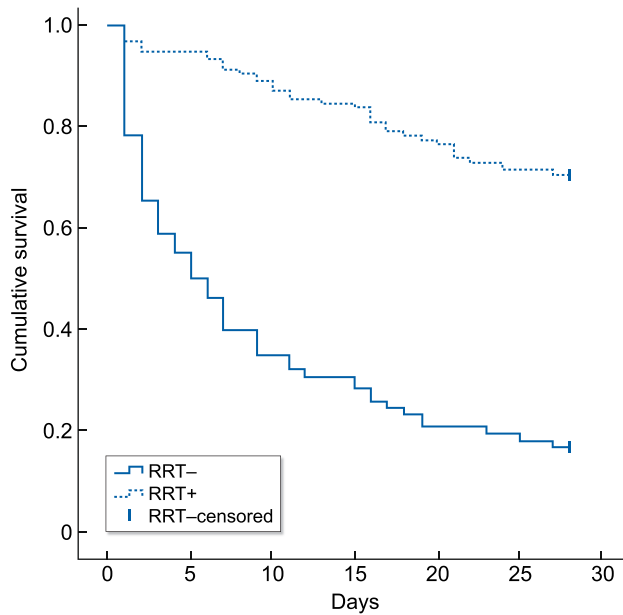


FIGURE 1: Kaplan-Meier curve for 28-day mortality in critically ill cirrhotic patients requiring RRT compared with patients without RRT. Source: Reproduction of Figure of Staufer et al. [5]. Used with permission of the publisher.

patients. Cholongitas et al. described that organ system failure (OSF) and Sequential Organ Failure Assessment (SOFA) had the best predictive ability in this population compared to Acute Physiology and Chronic Health Disease Classification System II score (APACHE) II [13, 14]. For the subgroup of patients with AKI, the SOFA score had the best discriminative accuracy [3]. Regarding specific cirrhosis scores, the model for end-stage liver disease (MELD) is currently used to predict short-term survival in cirrhotic patients and to prioritize recipients for transplantation [15]. In a single study evaluating MELD score in critically ill cirrhotic patients, this model had almost the same discriminative capacity as the SOFA score [area under the curve (AUC): 0.81 versus 0.83] and was better than APACHE II [14].

More recently, Moreau et al. [16] used for the first time a modified SOFA score called Chronic Liver Failure Consortium-SOFA (CLIF-SOFA), which was designed specifically for the Consortium Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) Study Investigators of the European Association for the Study of the Liver (EASL)-CLIF Consortium. This score was as accurate as MELD in the prediction 28-day mortality and based on it, acute-on chronic liver failure was divided in several stages. This score is based on the number of organ failures, but, interestingly, kidney failure is counted separately, increasing the score itself. Later, two independent predictors of mortality (age and white blood cell count) were added to CLIF-SOFA score to create the Chronic Liver Failure-Sequential Organ Failure Assessment Consortium acute-on-chronic liver failure (CLIF-C-ACLF) score [17]. The reader can find an online calculator following this link <https://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf> and the manual formula in Supplementary data, Table S1.

Regarding RRT, the largest retrospective study including cirrhotic patients requiring acute RRT was performed by Allegritti et al. [18]. It included 472 patients between 2005 and 2015 in a network of five acute care hospitals (Partners Healthcare, Massachusetts). The reasons for RRT were HRS or ATN, and

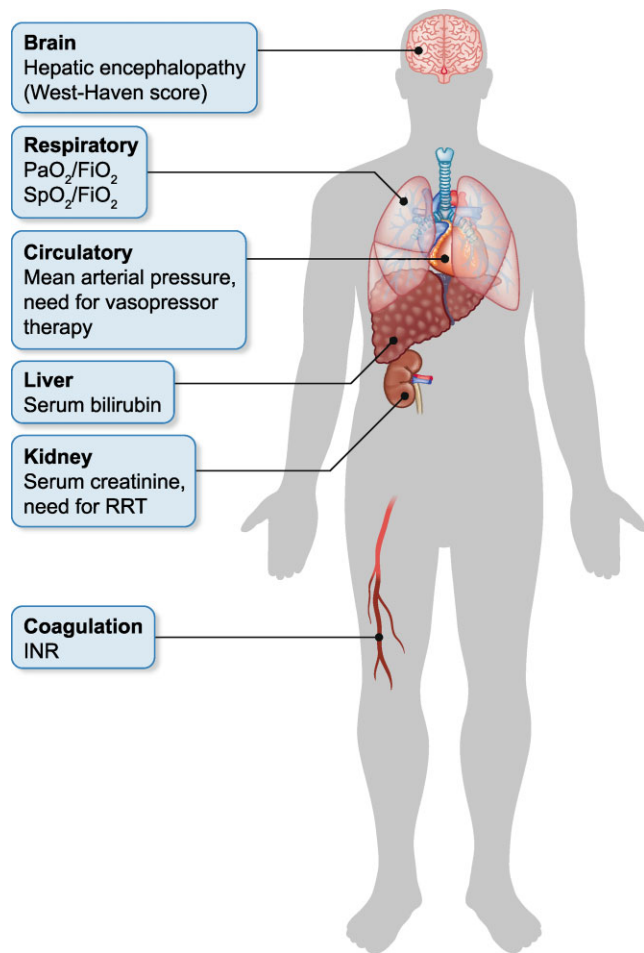


FIGURE 2: Components of CLIF-C-ACLF score, adjusted by age and white-cell count. Forty-eight hours after admission, a CLIF-C-ACLF score of ≥ 59.5 can predict ICU mortality with a sensitivity of 83.3% and a specificity of 85.7% [5] INR: international normalized ratio.

patients were stratified by liver transplant listing status. The authors found that the cause of AKI (HRS versus ATN) was not significantly associated with mortality in patients with cirrhosis who required RRT within listed and non-listed groups. On the contrary, liver transplantation waiting list status or MELD score was associated with mortality and therefore may be emphasized in the decision to initiate RRT. Among those not listed for liver transplantation, mortality rates were extremely high compared with the listed ones (85% versus 46%), but the authors suggest that there may be a selected group of non-listed patients where a time-limited trial of RRT may be appropriate, particularly those who have fewer signs of critical illness.

Another contemporary study conducted by Staufer et al. [5] tried to identify the selected group of patients in which RRT would not be futile, based on calculation of CLIF-C-ACLF, CLIF-SOFA, SOFA and MELD scores on admission, 24 h prior to RRT and 24–48 h after start of RRT. The study included 78 cirrhotic patients requiring acute RRT in ICU and showed that the critical illness score CLIF-C-ACLF calculated 48 h after starting RRT was the best predictor of ICU mortality in RRT patients regardless of liver transplant options (AUC: 0.866). Interestingly, scores calculated on admission had low accuracy for the prediction of ICU mortality, except in patients with five or more organ failures assessed by CLIF-SOFA score (100% mortality), but after

Table 2. Specific challenges of acute haemodialysis in cirrhotic patients

Characteristics	Problems
Decreased effective circulation volume secondary to splanchnic arterial vasodilatation and hypoalbuminemia	Problems with volume management can lead to intradialytic hypotension and cardiac events
Altered haemodynamic and haemostatic pathways	Increased haemorrhagic and/or prothrombotic risk
Hyponatremia and hyperammonemia	Lower circuit lifespan Risk of central pontine myelinolysis Risk of cerebral oedema in acute liver failure patients

48 h, a CLIF-C-ACLF score of ≥ 59.5 could predict ICU mortality with a sensitivity of 83.3% and a specificity of 85.7%, and could help to identify futility (Figure 2) [5]. To our knowledge, this has been the first study to assess CLIF-C-ACLF and CLIF-SOFA score in patients with AKI and need of RRT.

The described studies encourage clinicians not to discard acute RRT in the non-listed cirrhotic population despite the poor prognosis in this group. There may be a selected subgroup of patients with less signs of critical illness where a time-limited trial of RRT may be appropriate.

MANAGEMENT

Those who require RRT represent the most morbid subgroup of the cirrhotic population [5, 19], with specific characteristics compared with patients without liver disease (Table 2). There is an added difficulty in the volume management due to the decreased effective circulating volume because of splanchnic arterial vasodilatation and hypoalbuminemia [20] frequent in these patients. The problems with volume management can lead to intradialytic hypotension and cardiac events. In addition, the haemorrhagic risk in these patients is high and must be carefully assessed to prioritize systemic anticoagulation, regional citrate anticoagulation (RCA) or non-anticoagulation in the RRT prescription. Hyponatremia is frequent in this population. Sodium represents 95% of ionic osmolality and so the main determinant of plasma conductivity. Central pontine myelinolysis is a rare neurologic condition most frequently caused by the rapid correction of hyponatremia, thus in order to avoid it, dialysate conductivity should be adapted. Since ammonia is similar to urea in terms of diffusive clearance, both modalities of continuous renal replacement therapy (CRRT) and intermittent haemodialysis (IHD) should be effective in clearing ammonia, differing only by the rate of removal and the rebound after IHD attributed to delayed ammonia shifts from secondary compartments. IHD removes ammonia and urea more slowly from the cerebrospinal fluid than from plasma, creating an osmotic gradient that could result in cerebral oedema. In patients with acute liver failure, the dialysis can worsen the cerebral oedema secondary to hyperammonemia and thus CRRT should be considered in these situations; the cirrhotic patients are less labile to these changes and its impact is minor but not negligible. It should be pointed out that to date there is not consistent evidence that supports the use of RRT in isolated hepatic encephalopathy [21].

In this section, we will discuss the key points for RRT management in the critically ill cirrhotic patient, summarized in Figure 3.

Timing of RRT initiation

In the critically ill population, the timing of RRT initiation in the absence of life-threatening complications (e.g. hyperkalemia,

pulmonary oedema or severe metabolic acidosis) used to generate a dilemma between clinicians because of conflicting evidence regarding clinical outcomes and survival in an early versus delayed RRT initiation [22]. Nowadays, several clinical trials have shown no benefit of an early start of RRT and are summarized below.

The Artificial Kidney Initiation in Kidney Injury (AKIKI) Study Group has recently published two randomized controlled trials where they studied the differences between outcomes in an early, delayed and more-delayed initiation of RRT. In the first one, they compared the early versus delayed initiation of RRT in patients with AKI stage 3 who were receiving mechanical ventilation and/or catecholamine infusion that who not have an urgent indication of RRT [23]. Early strategy consisted of RRT initiation immediately after randomization. They defined the delayed strategy group as initiation of RRT with the onset of blood urea nitrogen (BUN) level higher than 112 mg/dL, a serum potassium concentration greater than 6 mmol/L, metabolic acidosis with pH < 7.15 or acute pulmonary oedema responsible for severe hypoxemia despite diuretic therapy. One interesting finding was that the need for RRT could be obviated in almost 50% of cases in the delayed-strategy group, resulting in 17 RRT-free days at Day 28. In addition, the recovery of renal function assessed by diuresis was faster in the delayed-strategy group, with no difference in mortality between both groups.

In the second study [22], they focused on two different strategies for a delayed-RRT initiation: in the first (delayed), RRT was initiated immediately after randomization (defined as oliguria for more than 72 h or a BUN concentration higher than 112 mg/dL) and in the second one (more-delayed), it was initiated if BUN concentration was higher than 140 mg/dL or mandatory indication. This resulted in no difference in RRT-free days between groups, and in a multivariable analysis, the 60-day mortality was higher in the more-delayed strategy. However, it is important to highlight that in these two trials, patients with diagnosis of Child C liver cirrhosis were excluded.

Similar results were found in the Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial which did include patients with liver disease [24], where the patients received an accelerated strategy for RRT (defined as initiation of RRT within 12 h after reaching AKIN2 or AKIN3 stage) in contrast to a standard strategy (defined as avoiding RRT until the development of a serum potassium level ≥ 6.0 mmol, a pH ≤ 7.20 , a serum bicarbonate level ≤ 12 mmol/L, clinical perception of volume overload, evidence of severe respiratory failure [ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaFi) of 200 or less], or persistent AKI for at least 72 h after randomization). This study included a total of 337 patients who had liver disease as a pre-existing condition, 172 in the accelerated strategy and 165 in the standard strategy. The aetiology of the liver disease was not specified. They found that

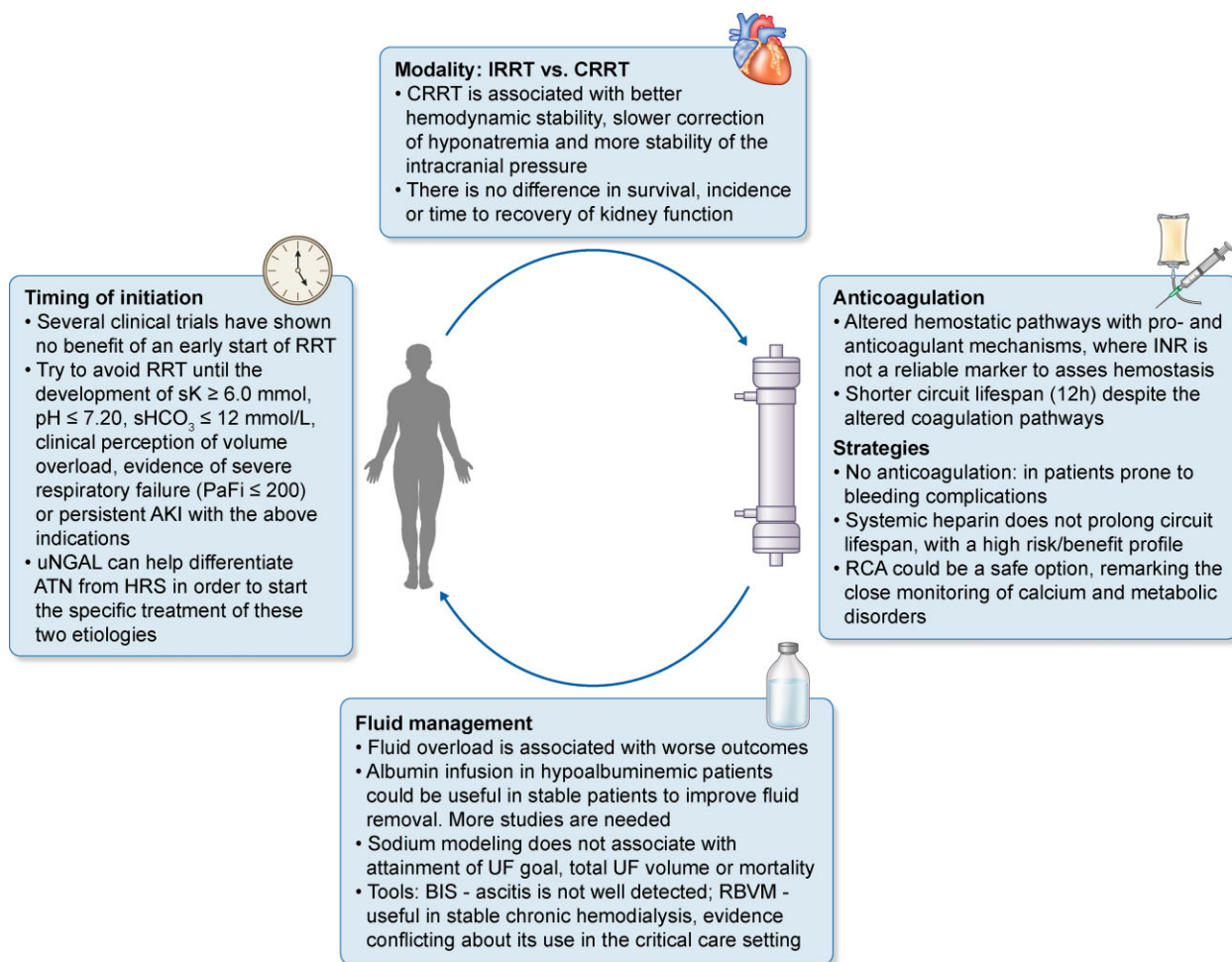


FIGURE 3: Summary of RRT management in the critically ill cirrhotic patient. RRT: renal replacement therapy, sK: serum potassium, $sHCO_3$: serum bicarbonate, AKI: acute kidney injury, uNGAL: urinary neutrophil gelatinase-associated lipocalin, PaFi: ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, HRS: hepatorenal syndrome, BIS: bioimpedance spectroscopy, RBVM: relative blood volume monitoring, IRRT: intermittent renal replacement therapy, CRRT: continuous renal replacement therapy, INR: international normalized ratio, RCA: regional citrate anticoagulation.

an accelerated strategy for the initiation of RRT did not have a lower risk of death at 90 days, with a mortality of 43.9% and 43.7%, respectively. Among the patients who were alive at 90 days, dependence on RRT was greater in the accelerated strategy group [10.4% versus 6.0%, risk ratio (RR) 1.74 [95% confidence interval (CI) 1.24–2.43]], suggesting that greater exposure to RRT or mediated by iatrogenic factors may compromise kidney function recovery. It is also important to note that in the standard strategy group, the RRT was initiated only in 61.8% patients, with a median of 31.1 h. Of note, there was no sub-analysis to assess the outcome of the patients with liver disease.

Nevertheless, there is no consensus about the ideal timing for initiation of RRT in the critically ill cirrhotic population [22, 24, 25]. Although the accepted definition of AKI in cirrhosis is based on sCr levels [26], it is important to take into account the limitations of this biomarker in this particular population. Creatinine production depends on muscle mass and physical activity, often reduced in the cirrhotic patient. Furthermore, the tubular secretion of creatinine is increased in these patients. All this, added to the fact that the sCr value may be affected by volume overload, leads to a potential underestimation of the real sCr [27].

In this scenario, some studies have begun to use different biomarkers to help define established kidney injury. The Early Versus Late Initiation of Renal Replacement Therapy In Critically Ill Patients With Acute Kidney Injury (ELAIN) clinical trial proved that the use of the KDIGO classification together with the use of plasma NGAL can reliably detect patients with progressively deteriorating AKI [25].

NGAL is one of the most studied biomarkers associated with AKI. NGAL is a low molecular weight protein produced by the thick ascending loop and collecting duct cells, and is a marker of kidney injury. Both serum and urine NGAL have performed well in detecting AKI across a variety of ICU populations [28, 29]. However, NGAL and other similar biomarkers, the description of which is beyond the scope of this review, may not be specific for kidney disease and should accordingly be subjected to interpretation depending on the clinical condition [27, 30, 31].

In recent studies, NGAL has been proposed to correctly assess the difference between ATN and other causes of AKI in the cirrhotic population [28, 32, 33]. The clinical significance of establishing this difference lies in the completely different management of these two conditions: treatment of ATN is supportive, i.e. to remove risk factors, treatment of possible infections, haemodynamic and volume monitoring and correction if

impaired and RRT if needed; on the contrary, treatment of HRS is based on volume expansion with albumin and administration of vasoconstrictors, specifically terlipressin, and evaluation for liver transplantation [23].

Huelin *et al.* [28] conducted a prospective study of consecutive patients with cirrhosis admitted to a Liver Unit of a tertiary hospital for acute decompensation of the disease who either had AKI at admission or developed it during hospitalization. The primary objective was to investigate the accuracy of three urinary biomarkers [NGAL, monomeric NGAL (mNGAL) and IL-18] in the prediction of ATN versus other causes of AKI. They found that at enrollment, patients with ATN had NGAL between 153 and 2114 $\mu\text{g/g}$ (mean 799 $\mu\text{g/g}$), mNGAL between 108 and 1838 $\mu\text{g/g}$ (mean 543 $\mu\text{g/g}$) and IL-8 between 11 and 107 pg/g (mean 33 pg/g), while hypovolemia-induced AKI and HRS-AKI had lower values, with a mean NGAL of 48 and 76 $\mu\text{g/g}$, respectively. They concluded that in this cohort, the urinary NGAL has a high accuracy in the differential diagnosis between ATN and other types of AKI, including HRS and hypovolemia-induced AKI. In addition, urine NGAL was also associated with progression of AKI during hospitalization, need for RRT and 28-day mortality [28]. These findings are in concordance with another study of Allegretti *et al.* [32] which found that the urinary NGAL correctly identified ATN from other types of AKI in cirrhosis: at enrollment, urinary NGAL levels were lowest in prerenal AKI [(45 [0, 154] $\mu\text{g/g}$)], higher in HRS [(110 [50, 393] $\mu\text{g/g}$)], and highest in ATN [(344 [132, 1429] $\mu\text{g/g}$)]. They defined that the optimal NGAL cut point to discriminate ATN from non-ATN kidney injury could be of 244 $\mu\text{g/g}$. This biomarker also held value in improving prediction of short-term mortality and AKI stage progression.

More recently, a novel biomarker, urinary C-C motif chemokine ligand 14 (CCL14), has been identified as a predictor of persistent AKI [34], a clinical situation more likely to require RRT. It would be interesting to test the efficacy of this biomarker in the specific population of patients with liver cirrhosis.

In conclusion, there is still no consensus on the ideal timing for initiation of RRT in the critically ill cirrhotic patients. Clinical judgment with careful evaluation of a patient's clinical situation and prognosis continues to be the main determinant as to whether and when to initiate RRT [35]. Novel biomarkers seem to help differentiate acute tubular necrosis (ATN) from other causes of AKI in the cirrhotic population, as well as to predict the need of RRT initiation, and could be a useful tool for clinical practice.

Modality

There are two well-known modalities of acute RRT: intermittent (IRRT) and continuous (CRRT), each with their own benefits and drawbacks. The IRRT is provided generally every 2 days and each treatment typically lasts between 3 and 5 h, achieving a fast removal of small molecules and volume, this last one adjusted to the patient's haemodynamic tolerance. On the other hand, CRRT is intended to last 24 h or longer, providing a slower removal of fluids and solutes. Hybrid haemodialysis modalities [e.g. sustained low efficiency dialysis (SLED) or slow extended daily dialysis (SLEDD)] generally last between 8 and 12 h, with intermediate rates of ultrafiltration and clearance [26, 36, 37].

The initial modality remains the subject of debate. There are several controlled trials and meta-analysis that compare the benefits of CRRT and IRRT in the general critically ill population [38–42]. Vinsonneau *et al.* [42] conducted a multicentre randomized clinical trial comparing IRRT and CRRT, finding no differ-

ences between both techniques in survival rates, renal function recovery or adverse events.

A meta-analysis conducted by Bagshaw *et al.* [38] studied the clinical outcomes of patients in the ICU with AKI that underwent CRRT and IRRT. They found that CRRT was associated with fewer episodes of haemodynamic instability and arrhythmias. However, there were no differences in mortality or recovery of renal function at hospital discharge [38]. Another meta-analysis conducted by The Cochrane Group, also found a higher mean arterial pressure in CRRT versus IRRT, but with similar number of hypotension episodes [39]. Vanholder *et al.* [41] concluded that if there is a haemodynamic benefit for CRRT, this does not translate into differences in survival.

In the critically ill cirrhotic patients there have been no controlled trials to demonstrate superiority of one modality over the other. CRRT may be better tolerated not only because of its alleged haemodynamic benefit, but also because of the slower correction of hyponatremia [43]. Wong *et al.* [44] studied the survival of liver transplant candidates with acute kidney failure and requirement of RRT. She found an overall survival of 33%, with an increased mortality in the patients who received CRRT compared to IHD ($P = 0.02$). However, the patients who were placed on CRRT were more severely ill and with greater haemodynamic instability, with a higher APACHE II score and lower mean arterial pressure, and were more likely intubated or on vasopressors. This difference in mortality is more likely to be related to the patient's characteristics in each group rather than the modality itself, as has been observed in previous studies of the general population [45].

Given the lack of evidence, it is accepted that the choice of RRT modality is determined by the patient's haemodynamic stability and severity of illness [43]. CRRT is preferred in haemodynamically unstable patients, in multi-organ failure, in severe hyponatremia, probably in patients with severe sepsis and hyperammonemia, and in patients with acute liver failure.

Anticoagulation

Patients with cirrhosis have profoundly altered haemodynamic and haemostatic pathways (i.e. reduction in specific coagulation factor V, FVII, FIX, FX, FXI, prothrombin, protein C and protein S, and increase of FVIII and von Willebrand factor activity, thrombocytopenia, etc.), resulting in a procoagulant, anticoagulant or mixed phenotype [46]. In addition, the INR is not a reliable marker to assess haemostasis, as it depends on some procoagulant factors (I, II, V, VII and X), but does not reflect the deficiencies of the anticoagulation system (low C protein), leading to a hypercoagulable state despite the prolonged INR [47, 48]. To delve into the pathophysiology of haemostasis in patients with liver disease, we recommend the article of Zermatten *et al.* [49].

CRRT benefits are compromised with premature interruption of the technique due to inadequate anticoagulation [50]. Also, in the cirrhotic population, the CRRT circuits seem to have a shorter life span compared with other ICU populations, with a median circuit life span of 12 h without anticoagulation [51–53]. Premature filter loss secondary to clotting can reduce the clearance and ultrafiltration rate and contribute to blood loss [50]. There are conflicting data regarding the characteristics that associate with circuit survival times. It has been described that higher activated partial thromboplastin time (APTT), serum bilirubin levels on ICU admission and thrombocytopenia (especially with platelet count $<50 \times 10^9/\text{mm}^3$) are associated with longer circuit lifespan [52]. However, other studies show no relationship between laboratory clotting times or

peripheral platelet count with the duration of the circuit lifespan [53].

Systemic heparin and RCA remain as the two main anticoagulation strategies used in CRRT. According to the KDIGO Guidelines [54], citrate is preferred over heparin for anticoagulation in CRRT in patients with an increased bleeding risk or impaired coagulation and not already receiving effective systemic anticoagulation, but with a low level of evidence (2B).

Regarding anticoagulation with heparin, it has been described that systemic or regional anticoagulation for CRRT in patients with liver disease did not prolong circuit life span, despite the significantly elevated systemic APTT with systemic heparinization, higher intravenous heparin dose with regional heparinization and greater proportion of circuits performed using haemodiafiltration versus haemofiltration. Given these results and the possible complications related to the use of heparin (e.g. thrombocytopenia), heparinization for CRRT in this cohort may not be justifiable [52].

In patients like the cirrhotic population in whom bleeding risk is high, regional anticoagulation with citrate (RCA) may be indicated. This technique consists of citrate infusion to the blood before the extracorporeal circuit that chelates ionized calcium, a mandatory cofactor of many enzymes of the coagulation cascade, thus avoiding coagulation of the circuit. Afterwards the calcium-citrate complexes (CCC) are mainly removed by the dialysis itself (up to 60%) [55, 56] and systemic serum calcium is restored by a post-filter calcium infusion. The remaining CCC is metabolized to bicarbonate by the liver and to a lesser extent by the skeletal muscle and kidney, and a potentially altered metabolism in patients with hepatic impairment has been the matter of concern in past years [57]. When citrate catabolism is normal, RCA administration leads to plasma alkalization. However, if the citrate administration exceeds the body's capacity to metabolize it, the CCC accumulates in the peripheral blood, leading to metabolic acidosis, an increased total blood calcium to ionized calcium (Ca_{tot}/Ca_i) ratio (>2.5) and severe ionized hypocalcemia. The Ca_{tot}/Ca_i ratio reflects on plasma citrate concentrations since total calcium is the sum of albumin and citrate-complexed calcium and ionized calcium is reduced by its union to citrate. This could cause decreased myocardial contractility and vasoplegia, and could be potentially lethal [56]. This constitutes the main reason why historically RCA has been contraindicated in patients with altered liver function.

Current knowledge about the safety profile of citrate in critically ill patients with altered hepatic function is improving. Klingele et al. [58] carried a retrospective study where 69 patients of these characteristics underwent CRRT with RCA. Contrary to what was expected, incidence of metabolic alkalosis and accumulation of citrate was less than expected (24.6% and 23.2%, respectively) (Figure 4). These alterations were corrected with changes of the dialysate and blood flows. No RCA had to be stopped because of hypercalcemia or accumulation of citrate [58]. Furthermore, Zhang et al. [59] conducted a meta-analysis regarding the safety profile of RCA for CRRT in liver failure patients, finding no increased risk of citrate accumulation and no difference in pH, serum lactate level and Ca_{tot}/Ca_i ratio between liver and non-liver failure patients; also, the circuit life was longer. When comparing circuit life span between RCA-CRRT and systemic heparin anticoagulation, the first one is better than the latter (circuit life span 47 h versus 27 h) [50].

To help predict which patients are at risk of citrate accumulation, a prospective observational study was conducted in 28 critically ill patients with decompensated liver cirrhosis or acute liver failure, performing 43 CRRT runs using RCA [60].

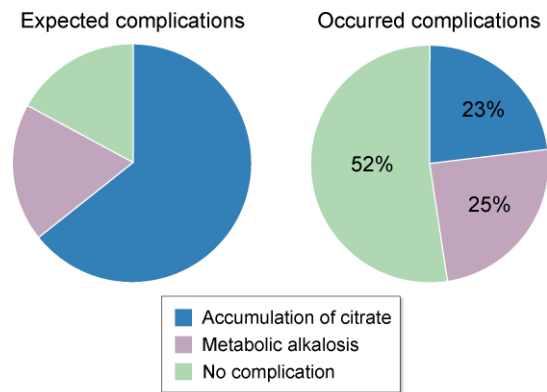


FIGURE 4: Differences between expected and occurred complications in patients with impaired liver function undergoing RRT with regional citrate anticoagulation. The incidence of the expected complication was based on the current knowledge of the metabolism of citrate, and was not estimated. Source: Adaptation of Figure of Klingele et al. [58].

They identified that serum lactate ≥ 3.4 mmol/L and prothrombin time $\leq 26\%$, measured before the onset of the RRT, can predict an increase in the Ca_{tot}/Ca_i ratio ≥ 2.5 with high sensitivity and specificity. On the contrary, liver function showed poor predictive capabilities.

Another strategy to address the circuit life span in patients with liver impairment is to start without any anticoagulation whatsoever [52]. In patients prone to bleeding complications, we recommend to start the CRRT without anticoagulation and if the circuit clots faster than anticipated, RCA-CRRT constitutes a safe alternative to systemic heparin, remarking the need of caution and close monitoring of calcium and metabolic disorders measuring the Ca_{tot}/Ca_i ratio at least twice a day for the first 48 h.

Fluid management

Fluid overload is associated with worse outcomes in critically ill patients and in cirrhotic cohorts as well [61, 62]. These patients have a haemodynamic pattern of hyperdynamia and vasoplegia in the setting of relative hypovolemia. These characteristics worsen with cirrhosis progression, making it difficult to maintain the necessary negative hydric balance in critically ill patients.

Volume assessment requires an integration of different clinical, analytical and technological data [63]. Although physical exam including ultrasound is mandatory, it is usually not precise enough, so new tools such as bioimpedance spectroscopy (BIS) and the relative blood volume monitoring (RBVM) may provide useful information for management.

BIS provides an estimation of intracellular water (ICW) and extracellular water (ECW), which can help to identify the total fluid overload of the patient [64]. One disadvantage is that volumes that are surrounded by a tissue layer such as peritoneum are not well detected, so it is recommended to evacuate the ascitic fluid before using BIS.

The RBVM tool is based on sensors placed in the intermittent dialysis machine [65]. The volume of plasma water is reduced during ultrafiltration, but the intravascular protein mass remains constant even when there are changes in blood volume due to ultrafiltration and refilling. The result is a change in the concentration of proteins and thus in the density of the blood. The initial relative blood volume (RBV) of 100% is reduced to approximately 80% on completion of a dialysis session. The

results of continuous measurement of RBV can be used to ensure that the reduction of blood volume is restricted to a level that is tolerable for the patient. While it has proved to be a useful tool in stable chronic haemodialysis patients [66], evidence is still conflicting regarding whether it can predict intradialytic hypotension in the critical care setting [67].

Another possible tool used to avoid hypotension during dialysis treatment is albumin infusion during the therapy. In a recent study, Macedo *et al.* [68] demonstrated that in hypoalbuminemic patients (defined as serum albumin level < 3 g/dL at the initiation of dialysis), albumin administration results in fewer episodes of hypotension and improved fluid removal, in comparison with sodium chloride 0.9% administration. However, the population was not critically ill and there is a possible confounding factor because the albumin infusion used also contains sodium. Moreover, the study did not specify if cirrhotic patients were included, or the cause of hypoalbuminemia.

Sodium modelling has also been described as a tool for mitigation of intradialytic hypotension in the setting of routine ambulatory dialysis for end-stage renal disease. However existing data suggest that this is not reproducible in a critically ill patient. Lynch *et al.* [69] studied 191 patients with AKI who underwent IHD in the ICU, finding no association between the use of sodium modelling, attainment of ultrafiltration goal, total ultrafiltration volume or the composite outcome of all-cause mortality and dialysis dependence at the time of discharge.

For patients with indication of liver transplantation, CRRT has been used not only before and after the surgery, but also as part of the intraoperative management, especially due to high portal venous pressures and hypervolemia itself, to help in fluid management. It has been also considered a helpful tool in patients at high risk of cerebral oedema. The use of intraoperative CRRT may help sicker patients tolerate the surgery and achieve short-term clinical outcomes comparable to less ill patients without intraoperative RRT, but with no impact on the short- or long-term mortality rate, hospital length of stay and post-liver transplant complications [70].

Cessation of RRT

It is equally important to correctly identify not only the adequate timing to initiate the RRT, but also when to discontinue it. However, there is a lack of evidence on the RRT weaning. SCr decreases because of the RRT and not because of the recovery of kidney function for itself, and therefore it is not a reliable factor for RRT discontinuation. The urine output could be used as a marker with several limitations, such as the potential preservation of urine output during AKI, the occurrence of urine output before renal recovery, and the negative impact of diuretic use on its predictive ability. Anort *et al.* [71] measured the daily urinary urea excretion in ICU patients with AKI undergoing IHD weaning. The inclusion criteria were patients older than 18 years treated with IHD for at least 7 days and four IHD sessions. The exclusion criteria were patients with a decision to forgo life-sustaining treatment, patients who had undergone renal transplantation, patients treated with continuous RRT at the time of weaning, chronic dialysis patients, and patients with urine output less than 100 mL/24 h before the last dialysis session in the ICU. Liver failure was not an exclusion criterion, but it is not specified. They found that values greater than 1.35 mmol/kg/24 h could have a better predictive value than urine output or urinary urea concentration alone.

The BEST study [72] focused on patients discontinuing CRRT in an ICU setting, which included patients with HRS. They found

that urine output at the time of cessation of CRRT was the most important predictor of successful weaning and that diuretic usage negatively affected the predictive ability of urine output. In terms of survival, patients whose CRRT was discontinued successfully had better outcome with an intrahospital mortality of 28.5%, while patients who needed to be retreated with RRT had a mortality of 42.7%.

Another study that focused on CRRT weaning that also included patients with history of liver disease and acute liver failure [73] measured 2-hourly creatinine clearances within the 12-h time period preceding CRRT cessation, finding that a level of 23 mL/min was shown to have optimal sensitivity and specificity, and was better predictor than the sCr and urine output alone.

Regarding the factors associated with failure of discontinuation of RRT, Wu *et al.* [74] found that the independent factors for restarting RRT within 30 days were longer duration of RRT, higher SOFA score, oliguria and age above 65 years. This study included 12 patients with liver failure, of which 10 remained free of dialysis for at least 30 days. Therefore, liver failure on its own does not appear to associate with failure of discontinuation of RRT.

Once the cessation of the CRRT is decided, SLED constitutes an attractive alternative to the regular IHD. It is a hybrid technique that has advantages compared with both CRRT and IHD, and is able to provide satisfactory metabolic control with few episodes of hypotension [75]. Therefore, in the critically ill patients, it could be a useful bridge technique between CRRT and IHD.

ALBUMIN EXTRACORPOREAL DIALYSIS—WHAT THE NEPHROLOGIST NEEDS TO KNOW

In the last decades, extracorporeal systems that clear hepatic toxins have been investigated in order to create a window of opportunity for liver transplantation in acute liver failure or acute-on-chronic liver failure. However, since there are not robust randomized studies, it is difficult to develop evidence-based clinical and biochemical criteria to define the need to initiate therapy and the optimal duration of therapy.

Currently, there are mainly two systems that are used in this context: Molecular Adsorbent Recirculating System (MARS®) (Gambro, Lund, Sweden) and PROMETHEUS® (Fresenius AG, Hamburg, Germany). The main difference remains on the mechanism of albumin-bound toxin removal [76, 77].

In MARS®, blood is dialysed across an albumin-impregnated high-flux dialysis membrane with a cutoff of 50 kDa [78]. The dialysate consists of 20% human albumin in which albumin-bound toxins in blood are released to the membrane and picked up by albumin in the dialysate, whereas water-soluble solutes diffuse across the membrane. The albumin dialysate goes to a high-flux dialysis filter that cleans the water-soluble toxins and subsequently goes through two sequential adsorbent columns containing activated charcoal and anion exchange resin that remove the albumin-bound toxins. In the PROMETHEUS® system, patient plasma is fractionated through an albumin-permeable filter with a cutoff of 250 kDa. Albumin and other plasma proteins cross the membrane and pass across two columns in series: one an anion-exchange column and another a neutral resin adsorber. The cleaned albumin/plasma is returned to the standard blood pool circuit where it is then treated with conventional high-flux haemodialysis that cleans water soluble toxins (creatinine, urea, etc.) [79, 80].

From the nephrologist's point of view, both systems can deplete water-soluble toxins and electrolytes such as potassium, but only MARS has specific studies that demonstrate a meaningful degree of urea reduction [81]. If ultrafiltration for volume control is needed during the technique, only PROMETHEUS can be used. On the other hand, RRT can be performed alone once the session is completed using the same machine, which allows volume management since both techniques are used with monitors of continuous RRT.

CONCLUSION

RRT in cirrhotic patients involves a number of controversial issues related to the particular characteristics of this population. Regarding prognosis, ICU mortality rate is high, especially in those patients not listed for liver transplantation, raising questions regarding the futility of its initiation. Scores of critical illness like CLIF-C-ACLF can help to identify a selected group of patients where a time-limited trial of RRT may be appropriate.

Once an RRT is decided, the timing of initiation should be considered according to the current evidence in general cohorts that show no benefit in an early initiation in a clinical scenario where no urgent dialysis criterion is met. EASL guidelines support using biomarkers like NGAL to distinguish ATN from HRS; however, more studies about other novel biomarkers are needed to support its use in prediction of RRT initiation.

The choice of RRT modality remains a subject of debate, where continuous techniques are associated with fewer hypotension episodes and slower correction of hyponatremia, but show no benefit in terms of survival. It is accepted that the modality should be determined by the patient's haemodynamic stability and severity of illness.

The importance of an adequate anticoagulation during CRRT is that the benefits of this therapy are best achieved when there are no interruptions, and in the cirrhotic patient the CRRT circuits seem to have a shorter life span compared with other ICU populations despite the altered coagulation pathways. The decision of the anticoagulation strategy should be individualized for each patient. In patients with severe thrombocytopenia or with bleeding complications, it is reasonable to start without any anticoagulation whatsoever and if the circuit life span is shorter than anticipated, RCA constitutes a safe alternative, remarking the need of close monitoring of calcium and metabolic disorders.

Volume management is one of the most complex issues in this special population and new tools like BIS and RBVM could be of great help, but more studies are needed in the critical care setting. On the other hand, sodium modelling has not proved to reduce the incidence of intradialytic hypotension or better outcomes.

Despite the increasing literature regarding this topic, the majority of studies about the critically ill patient do not consider the cirrhotic population in this clinical setting. More studies and clinical trials are needed, and a multidisciplinary team with nephrologists, intensivists and hepatologists is recommended in order to handle these complex patients.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

ACKNOWLEDGEMENTS

Original images were created by using BioRender.com.

AUTHORS' CONTRIBUTIONS

J.D.R.-Z., A.M.A. and E.P. participated in the conception, design and drafting of the article. G.P., E.R., N.D.T., M.S., M.B. and J.F. provided intellectual content of critical importance to the work and gave their final approval for the version to be published.

CONFLICT OF INTEREST STATEMENT

We declare that the results presented in this article have not been published previously in whole or part, except in abstract format.

REFERENCES

- Hampel H, Bynum GD, Zamora E et al. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. *Am J Gastroenterol* 2001; 96: 2206–2210
- Du Cheyron D, Bouchet B, Parienti JJ et al. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. *Intensive Care Med* 2005; 31: 1693–1699
- Cholongitas E, Senzolo M, Patch D et al. Cirrhotics admitted to intensive care unit: the impact of acute renal failure on mortality. *Eur J Gastroenterol Hepatol* 2009; 21: 744–750
- McPhail MJW, Parrott F, Wendon JA et al. Incidence and outcomes for patients with cirrhosis admitted to the United Kingdom critical care units. *Crit Care Med* 2018; 46: 705–712
- Staufer K, Roedel K, Kivaranovic D et al. Renal replacement therapy in critically ill liver cirrhotic patients—outcome and clinical implications. *Liver Int* 2017; 37: 843–850
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018; 69: 406–460
- Martin-Llahí M, Guevara M, Torre A et al. Prognostic importance of the cause of renal failure in patients with cirrhosis. *Gastroenterology* 2011; 140: 488–496
- Angeli P, Ginès P, Wong F et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol* 2015; 62: 968
- Huelin P, Piano S, Solà E et al. Validation of a staging system for acute kidney injury in patients with cirrhosis and association with acute-on-chronic liver failure. *Clin Gastroenterol Hepatol* 2017; 15: 438–445
- O'Brien AJ, Welch CA, Singer M et al. Prevalence and outcome of cirrhosis patients admitted to UK intensive care: a comparison against dialysis-dependent chronic renal failure patients. *Intensive Care Med* 2012; 38: 991–1000
- Saliba F, Ichai P, Levesque E et al. Cirrhotic patients in the ICU: prognostic markers and outcome. *Curr Opin Crit Care* 2013; 19: 154–160
- Galbois A, Trompette ML, Das V et al. Improvement in the prognosis of cirrhotic patients admitted to an intensive care unit, a retrospective study. *Eur J Gastroenterol Hepatol* 2012; 24: 897–904
- Cholongitas E, Senzolo M, Patch D et al. Review article: scoring systems for assessing prognosis in critically ill adult cirrhotics. *Aliment Pharmacol Ther* 2006; 24: 453–464

14. Cholongitas E, Senzolo M, Patch D et al. Risk factors, Sequential Organ Failure Assessment and Model for End-Stage Liver Disease scores for predicting short term mortality in cirrhotic patients admitted to intensive care unit. *Aliment Pharmacol Ther* 2005; 23: 883–893
15. Kamath PS, Wiesner RH, Malinchoc M et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; 33: 464–470
16. Moreau R, Jalan R, Gines P et al. Acute-on-chronic liver failure is a distinct syndrome developing in patients with acute decompensation in cirrhosis. *Gastroenterology* 2013; 144: 1426–1437
17. Jalan R, Saliba F, Pavesi M et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J Hepatol* 2014; 61: 1038–1047
18. Allegretti AS, Parada XV, Eneanya ND et al. Prognosis of patients with cirrhosis and AKI who initiate RRT. *Clin J Am Soc Nephrol* 2018; 13: 16–25
19. Nadkarni GN, Simoes PK, Patel A et al. National trends of acute kidney injury requiring dialysis in decompensated cirrhosis hospitalizations in the United States. *Hepatol Int* 2016; 10: 525–531
20. Gine's P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009; 361: 1279–1290
21. Gupta S, Fenves AZ, Hootkins R. The role of RRT in hyperammonemic patients. *Clin J Am Soc Nephrol* 2016; 11: 1872–1878
22. Gaudry S, Hajage D, Martin-Lefevre L et al. Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial. *Lancet North Am Ed* 2021; 397: 1293–1300
23. Gaudry S, Hajage D, Schortgen F et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016; 375: 122–133
24. The STARRT-AKI Investigators. Accelerated versus standard initiation of renal-replacement therapy in critically ill patients with acute kidney injury. *N Engl J Med* 2020; 383: 240–251
25. Zarbock A, Kellum JA, Schmidt C et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA* 2016; 315: 2190–2199
26. Valdenebro M, Martín-Rodríguez L, Tarragón B et al. Renal replacement therapy in critically ill patients with acute kidney injury: 2020 nephrologist's perspective. *Nefrologia* 2021; 41: 102–114
27. Davenport A, Sheikh MF, Lamb E et al. Acute kidney injury in acute-on-chronic liver failure: where does hepatorenal syndrome fit? *Kidney Int* 2017; 92: 1058–1070
28. Huelin P, Solà E, Elia C et al. Neutrophil gelatinase-associated lipocalin for assessment of acute kidney injury in cirrhosis: a prospective study. *Hepatology* 2019; 70: 319–333
29. Allegretti AS, Solà E, Ginès P. Clinical application of kidney biomarkers in cirrhosis. *Am J Kidney Dis* 2020; 76: 710–719
30. Ostermann M, Joannidis M. Biomarkers for AKI improve clinical practice: no. *Intensive Care Med* 2015; 41: 618–622
31. Legrand M, Darmon M, Joannidis M. NGAL and AKI: the end of a myth? *Intensive Care Med* 2013; 39: 1861–1863
32. Allegretti AS, Parada XV, Endres P et al. Urinary NGAL as a diagnostic and prognostic marker for acute kidney injury in cirrhosis: a prospective study. *Clin Transl Gastroenterol* 2021; 12: e00359
33. Ginès P, Solà E, Angeli P et al. Hepatorenal syndrome. *Nat Rev Dis Primers* 2018; 4: 23
34. Hoste E, Bihorac A, Al-Khafaji A et al. Identification and validation of biomarkers of persistent acute kidney injury: the RUBY study. *Intensive Care Med* 2020; 46: 943–953
35. Nanchal R, Subramanian R, Karvellas CJ et al. Guidelines for the management of adult acute and acute-on-chronic liver failure in the ICU: cardiovascular, endocrine, hematologic, pulmonary and renal considerations: executive summary. *Crit Care Med* 2020; 48: 415–419
36. Deep A, Bunchman TE. Continuous renal replacement therapy. *Clin Pediatr Nephrol* 2016; 21: 679–701
37. Schoenfelder T, Chen X, Bleß H-H. Effects of continuous and intermittent renal replacement therapies among adult patients with acute kidney injury. *GMS Health Technol Assess* 2017; 13: Doc01. doi: 10.3205/hta000127
38. Bagshaw SM, Berthiaume LR, Delaney A et al. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. *Crit Care Med* 2008; 36: 610–617
39. Rabindranath KS, Adams J, MacLeod AM et al. Intermittent versus continuous renal replacement therapy for acute renal failure in adults. *Cochrane Database Syst Rev* 2007; 3: CD003773. doi: 10.1002/14651858.CD003773.pub3
40. Lins RL, Elseviers MM, Van Der Niepen P et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. *Nephrol Dial Transplant* 2009; 24: 512–518
41. Vanholder R, Van Biesen W, Hoste E et al. Pro/con debate: continuous versus intermittent dialysis for acute kidney injury: a never-ending story yet approaching the finish? *Crit Care* 2010; 15: 1–7
42. Vinsonneau C, Camus C, Combes A et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. *Lancet* 2006; 368: 379–385
43. Gonwa TA, Wadei HM. The challenges of providing renal replacement therapy in decompensated liver cirrhosis. *Blood Purif* 2012; 33: 144–148
44. Wong LP, Blackley MP, Andreoni KA et al. Survival of liver transplant candidates with acute renal failure receiving renal replacement therapy. *Kidney Int* 2005; 68: 362–370
45. Huelin P, Solà E, Elia C et al. Neutrophil gelatinase-associated lipocalin for assessment of acute kidney injury in cirrhosis: a prospective study. *Hepatology* 2019; 70: 319–333
46. Premkumar M, Sarin SK. Current concepts in coagulation profile in cirrhosis and acute-on-chronic liver failure. *Clinical Liver Disease* 2020; 16: 158–167
47. Cho J, Choi SM, Yu SJ et al. Bleeding complications in critically ill patients with liver cirrhosis. *Korean J Intern Med* 2016; 31: 288–295
48. Nadim MK, Durand F, Kellum JA et al. Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. *J Hepatol* 2016; 64: 717–735
49. Zermatten MG, Fraga M, Moradpour D et al. Hemostatic alterations in patients with cirrhosis: from primary hemostasis to fibrinolysis. *Hepatology* 2020; 71: 2135–2148
50. Zarbock A, Küllmar M, Kindgen-Milles D et al. Effect of regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality among critically ill patients with acute kidney injury: a randomized clinical trial. *JAMA* 2020; 324: 1629–1639

51. Rajakumar A, Appusmay E, Kaliamoorthy I et al. Renal dysfunction in cirrhosis: critical care management. *Indian J Crit Care Med* 2021; 25: 207–214
52. Chua HR, Baldwin I, Bailey M et al. Circuit lifespan during continuous renal replacement therapy for combined liver and kidney failure. *J Crit Care* 2012; 27: 744.e7–744.e15. <https://doi.org/10.1016/j.jcrc.2012.08.016>
53. Agarwal B, Shaw S, Hari MS et al. Continuous renal replacement therapy (CRRT) in patients with liver disease: is circuit life different? *J Hepatol* 2009; 51: 504–509
54. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; 120: c179–c184. doi: 10.1159/000339789. Epub 7 August 2012
55. Zarbock A, Küllmar M, Kindgen-Milles D et al. Effect of regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality among critically ill patients with acute kidney injury: a randomized clinical trial. *JAMA* 2020; 324: 1629–1639
56. Schneider AG, Journois D, Rimmelé T. Complications of regional citrate anticoagulation: accumulation or overload? *Crit Care* 2017; 21: 1–7
57. Kramer L, Bauer E, Joukhadar C et al. Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. *Crit Care Med* 2003; 31: 2450–2455
58. Klingele M, Stadler T, Fliser D et al. Long-term continuous renal replacement therapy and anticoagulation with citrate in critically ill patients with severe liver dysfunction. *Crit Care* 2017; 21: 1–9
59. Zhang W, Bai M, Yu Y et al. Safety and efficacy of regional citrate anticoagulation for continuous renal replacement therapy in liver failure patients: a systematic review and meta-analysis. *Crit Care* 2019; 23: 1–11
60. Schultheiß C, Saugel B, Phillip V et al. Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study. *Crit Care* 2012; 16: R162. <https://doi.org/10.1186/cc11485>
61. Messmer AS, Zingg C, Müller M et al. Fluid overload and mortality in adult critical care patients—A systematic review and meta-analysis of observational studies. *Crit Care Med* 2020; 45: 1862–1870
62. Rzouq F, Alahdab F, Olyae M. New insight into volume overload and hepatorenal syndrome in cirrhosis, “the hepatorenal reflex hypothesis”. *Am J Med Sci* 2014; 348: 244–248
63. Covic A, Siroopol D. Assessment and management of volume overload among patients on chronic dialysis. *Curr Vasc Pharmacol* 2021; 19: 34–40
64. Van der Sande FM, van de Wal-Visscher ER, Stuard S et al. Using bioimpedance spectroscopy to assess volume status in dialysis patients. *Blood Purif* 2020; 49: 178–184
65. Dasselaar JJ, Huisman RM, de Jong PE et al. Measurement of relative blood volume changes during haemodialysis: merits and limitations. *Nephrol Dial Transplant* 2005; 20: 2043–2049
66. Andrulli S, Colzani S, Mascia F et al. The role of blood volume reduction in the genesis of intradialytic hypotension. *Am J Kidney Dis* 2002; 40: 1244–1254
67. Kron S, Leimbach T, Wenkel R et al. Relative blood volume monitoring during renal replacement therapy in critically ill patients with septic shock: a preliminary report. *Blood Purif* 2015; 40: 133–138
68. Macedo E, Karl B, Lee E et al. A randomized trial of albumin infusion to prevent intradialytic hypotension in hospitalized hypoalbuminemic patients. *Crit Care* 2021; 25: 18
69. Lynch KE, Ghassemi F, Flythe JE et al. Sodium modelling to reduce intradialytic hypotension during haemodialysis for acute kidney injury in the intensive care unit. *Nephrology (Carlton)* 2016; 21: 870–877
70. Huang HB, Xu Y, Zhou H et al. Intraoperative continuous renal replacement therapy during liver transplantation: a meta-analysis. *Liver Transpl* 2020; 26: 1010–1018
71. Aniot J, Ait Hssain A, Pereira B et al. Daily urinary urea excretion to guide intermittent hemodialysis weaning in critically ill patients. *Crit Care* 2016; 20: 1–8
72. Uchino S, Bellomo R, Morimatsu H et al. Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. *Crit Care Med* 2009; 37: 2576–2582
73. Fröhlich S, Donnelly A, Solymos O et al. Use of 2-hour creatinine clearance to guide cessation of continuous renal replacement therapy. *J Crit Care* 2012; 27: 744.e1–744.e5. <https://doi.org/10.1016/j.jcrc.2012.08.012>
74. Wu VC, Ko WJ, Chang HW et al. Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy. *Intensive Care Med* 2008; 34: 101–108
75. Caires RA, Abdulkader RCRM, Costa e Silva VT et al. Sustained low-efficiency extended dialysis (SLED) with single-pass batch system in critically ill patients with acute kidney injury (AKI). *J Nephrol* 2016; 29: 401–409
76. Karvellas KJ, Gibney N, Kutsogiannis D et al. Bench-to bedside review: current evidence for extracorporeal albumin dialysis systems in liver failure. *Crit Care* 2007; 11: 215
77. Sponholz C, Katja, M, Dina, R et al. Molecular adsorbent recirculating system and single-pass albumin dialysis in liver failure—a prospective, randomised crossover study. *Crit Care* 2016; 20: 2
78. Schaefer B, Schaefer F, Engelmann G et al. Comparison of Molecular Adsorbents Recirculating System (MARS) dialysis with combined plasma exchange and haemodialysis in children with acute liver failure. *Nephrol Dial Transplant* 2011; 26: 3633–3639
79. Anaya F, Anaya F (ed). *Aféresis terapéutica*. Madrid: ediciones norma-capitel, 2005
80. Rifai K, Manns MP. Review article: clinical experience with prometheus. *Ther Apher Dial* 2006; 10: 1327
81. McIntyre CW, Fluck RJ, Freeman JG et al. Characterization of treatment dose delivered by albumin dialysis in the treatment of acute renal failure associated with severe hepatic dysfunction. *Clin Nephrol* 2002; 58: 376–383