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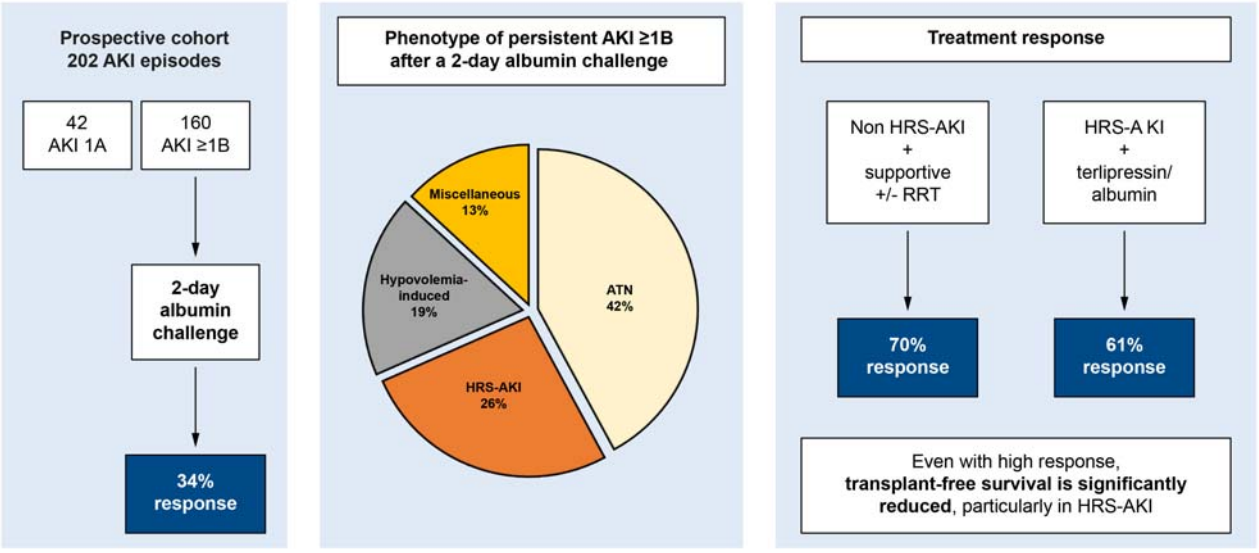
Authors

Ann Thu Ma, Cristina Solé, Adrià Juanola, …, Isabel Graupera, Elisa Pose, Pere Ginès

Correspondence

pgines@clinic.cat (P. Ginès).

Graphical abstract



Highlights

- In 2018, EASL published an algorithm for the diagnosis/management of acute kidney injury in patients with cirrhosis.
- This algorithm had not been validated in real-world practice.
- In this prospective study, this algorithm was associated with high renal response rates, both overall and in different phenotypes.
- The use of the algorithm resulted in the swift diagnosis and treatment of hepatorenal syndrome.
- These results support the use of this algorithm in clinical practice.

Impact and implications

The occurrence of acute kidney injury (AKI) in patients with cirrhosis is associated with poor short-term mortality. Improving its rapid identification and prompt management was the focus of the recently proposed EASL AKI algorithm. This is the first prospective study demonstrating that high AKI response rates are achieved with the use of this algorithm, which includes identification of AKI, treatment of precipitating factors, a 2-day albumin challenge in patients with AKI ≥1B, and supportive therapy in patients with persistent AKI not meeting HRS-AKI criteria or terlipressin with albumin in those with HRS-AKI. These findings support the use of this algorithm in clinical practice.

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Prospective validation of the EASL management algorithm for acute kidney injury in cirrhosis

Ann Thu Ma[1,2,3,4,5], Cristina Solé[6], Adrià Juanola[1,2,3], Laia Escudé[1,2,3], Laura Napoleone[1,2,3], Emma Avitabile[1,2,3], Martina Pérez-Guasch[1,2,3,4], Marta Carol[1,2,3,4], Enrico Pompili[1,2,3], Jordi Gratacós-Ginés[1,2,3], Anna Soria[1,2,3], Ana Belén Rubio[1,2,3,4], Marta Cervera[1,2,3,4], Maria José Moreta[1,2,3], Manuel Morales-Ruiz[4,7], Elsa Solà[8], Esteban Poch[4,9], Núria Fabrellas[2,3,4], Isabel Graupera[1,2,3,4], Elisa Pose[1,2,3,4], Pere Ginès[1,2,3,4,*]

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Background & Aims: The management of acute kidney injury (AKI) in cirrhosis is challenging. The EASL guidelines proposed an algorithm for the management of AKI, but this has never been validated. We aimed to prospectively evaluate this algorithm in clinical practice.

Methods: We performed a prospective cohort study in consecutive hospitalized patients with cirrhosis and AKI. The EASL management algorithm includes identification/treatment of precipitating factors, 2-day albumin infusion in patients with AKI ≥stage 1B, and treatment with terlipressin in patients with hepatorenal syndrome (HRS-AKI). The primary outcome was treatment response, which included both full and partial response. Secondary outcomes were survival and adverse events associated with terlipressin therapy.

Results: A total of 202 AKI episodes in 139 patients were included. Overall treatment response was 80%, while renal replacement therapy was required in only 8%. Response to albumin infusion was achieved in one-third of episodes. Of patients not responding to albumin, most (74%) did not meet the diagnostic criteria of HRS-AKI, with acute tubular necrosis (ATN) being the most common phenotype. The response rate in patients not meeting the criteria for HRS-AKI was 70%. Only 30 patients met the diagnostic criteria for HRS-AKI, and their response rate to terlipressin was 61%. Median time from AKI diagnosis to terlipressin initiation was only 2.5 days. While uNGAL (urinary neutrophil gelatinase-associated lipocalin) could differentiate ATN from other phenotypes (AUROC 0.78), it did not predict response to therapy in HRS-AKI. Ninety-day transplant-free survival was negatively associated with MELD-Na, ATN and HRS-AKI as well as uNGAL. Three patients treated with terlipressin developed pulmonary edema.

Conclusions: The application of the EASL AKI algorithm is associated with very good response rates and does not significantly delay initiation of terlipressin therapy.

Introduction

Acute kidney injury (AKI) occurs in 20 to 50% of patients admitted to hospital for acute decompensation of cirrhosis and is associated with poor short-term prognosis.[1–7] Prompt identification of AKI and intervention are key to achieve rapid recovery of kidney function and to improve patient survival. In patients with cirrhosis, the management of AKI is more challenging than in patients without liver disease because of the existence of hepatorenal syndrome (HRS-AKI), which only occurs in the setting of cirrhosis. HRS-AKI is characterized by high mortality rates but has a specific pharmacological treatment, which consists of vasoconstrictors and albumin.[1,8–10] Therefore, any management strategy for AKI in cirrhosis should aim at early identification and management of all types of AKI, particularly of HRS-AKI.

In 2018, the European Association for the Study of the Liver (EASL) proposed an algorithm for the diagnosis and management of AKI in cirrhosis[9] that is based on a former algorithm of the International Club of Ascites (ICA).[8] The EASL-AKI algorithm consists of the following steps: i) classification of patients according to severity of AKI into two groups, AKI stage 1A and AKI stage 1B or greater; ii) identification and treatment of potential triggering factors, which include bacterial infections (common in patients with cirrhosis), hypovolemia (particularly related to gastrointestinal bleeding or renal fluid losses due to overdiuresis), nephrotoxic drugs (particularly non-steroidal anti-inflammatory drugs), and management of shock, if present; iii) a 2-day albumin infusion test in patients with AKI stage 1B or greater without gastrointestinal or renal fluid losses – this step is based on the current diagnostic criteria of HRS-AKI and is

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* Corresponding author. Address: Liver Unit, Hospital Clinic de Barcelona, Barcelona, Spain.
E-mail address: pgines@clinic.cat (P. Ginès).
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intended to treat any subtle hypovolemia that could have been missed from a clinical standpoint; and iv) application of diagnostic criteria of HRS-AKI to patients with persistent AKI after the administration of albumin, to categorize patients into those with HRS-AKI and those without. The goal of this algorithm is to perform a rapid and stepwise assessment of patients so that the different types of AKI that occur in cirrhosis, including hypovolemia-induced, acute tubular necrosis (ATN) and HRS-AKI, can be identified and treated accordingly. This algorithm was built on current diagnostic criteria of HRS-AKI and expert opinion, and to our knowledge has not been validated in clinical practice.

On this background, the current study was aimed at prospectively validating the EASL-AKI management algorithm in a large consecutive series of patients with cirrhosis and AKI. The main objectives were to evaluate the outcomes of kidney function and patient survival overall and at the different steps of the management algorithm.

Patients and methods

Patient population

This was a prospective cohort study that included consecutive patients admitted to the Liver Unit (both intensive care unit [ICU] and conventional hepatology ward) at the Hospital Clinic, Barcelona, from June 2019 to June 2021. Patients aged ≥18 years with a diagnosis of cirrhosis (based on liver histology or combination of clinical, biochemical and imaging criteria) who were admitted for complications of their cirrhosis and were diagnosed with AKI either at admission or during hospitalization were included. Patients could be included more than once if the AKI fully responded between episodes. Exclusion criteria were: hepatocellular carcinoma outside the Milan criteria, extra-hepatic cancer, significant extra-hepatic disease (chronic obstructive pulmonary disease with a Global Initiative for Chronic Obstructive Disease ≥3, congestive heart failure with a New York Heart Association classification ≥3), terminal disease being palliated, chronic kidney disease (CKD) already on renal replacement therapy (RRT), HIV infection, prior kidney or liver transplant, elective admission or lack of informed consent. Signed informed consent was obtained from the patient or their legal representative. This study was approved by the research and ethics board of the Hospital Clinic de Barcelona (HCB/2018/0863), in concordance with the 1975 Declaration of Helsinki.

Study protocol and patient assessment

AKI management was performed according to the EASL AKI algorithm (Fig. S1[9]). In brief, in this algorithm, patients with AKI are classified according to four stages by order of severity: 1A, 1B, 2 and 3 (see Definitions below). The subdivision of AKI 1 into AKI 1A and 1B depends on whether serum creatinine is <1.5 mg/dl or ≥1.5 mg/dl, respectively, at the time of AKI diagnosis. Indeed, a recent study demonstrated that patients with AKI 1B had significantly worse prognosis than those with AKI 1A, arguing for differential management.[2] In the EASL algorithm, patients with an initial AKI stage 1A are treated by removal of risk factors including diuretics, non-selective beta-blockers (NSBBs) and nephrotoxic drugs, as well as treatment of infection, if present. Patients with progression of AKI to stage ≥1B are managed similarly to patients with an initial AKI stage ≥1B. Patients with an initial AKI stage ≥1B are additionally provided with volume expanders. Patients with clear dehydration or gastrointestinal bleeding are treated with crystalloid fluids or blood products, respectively, as specified in the 2018 EASL guidelines.[9] Patients with typical features of fluid overload, including elevated jugular venous pressure, presence of crackles on examination or signs of pulmonary edema on chest X-ray, are not provided any further fluid. In all other patients, albumin 1 g/kg for 2 days is administered. Patients with AKI stage ≥1B who receive albumin and who improve to an AKI stage 1A or who have a full response of AKI after 2 days are considered albumin-responders. The remaining patients, considered albumin non-responders, are assessed for whether they meet HRS-AKI criteria or not. In those who meet criteria, treatment with terlipressin and albumin is initiated. In our centre, terlipressin is administered as a continuous infusion at a starting dose of 2 mg daily and increased by 2 mg daily every 72 h if there is no response indicated by a decrease in serum creatinine (see Definitions below for response). For patients not meeting HRS-AKI criteria, tailored treatment based on AKI phenotype is performed, which may include the use of RRT. In the current protocol, in addition to routine blood and urine analysis, urinary neutrophil gelatinase-associated lipocalin (uNGAL) was measured after the administration of albumin or other fluids in those with persistent AKI ≥1B, as previously described.[11] Data on AKI management, including albumin and terlipressin timing and dosage, were also collected. Patients were followed until 90 days following discharge, liver transplant or death, whichever occurred first.

Study outcomes

The primary outcome of this study was AKI response to treatment (see Definitions below). Secondary outcomes included: 90-day transplant-free survival and adverse events associated with albumin and terlipressin use.

Definitions

AKI was defined as per ICA criteria, which do not include urinary sodium nor urinary osmolarity,[8] and AKI staging was defined as per EASL criteria, which includes the subdivision of AKI 1 into stages 1A and 1B, as mentioned above.[9] AKI was considered community-acquired if AKI was present at admission, and hospital-acquired if AKI developed during hospitalization. For community-acquired AKI, baseline serum creatinine was defined as the value closest to admission within 3 months, and if not available, within 12 months. For hospital-acquired AKI, the baseline creatinine was defined as creatinine at admission or during admission. Hypovolemia-induced AKI was diagnosed when patients presented with hypovolemia with fluid loss from gastrointestinal bleeding, diarrhea or treatment with diuretics.[12] HRS-AKI was defined as per ICA criteria.[8] In patients who did not meet the criteria of HRS-AKI, ATN was diagnosed when at least two out of four of the following criteria were met: fractional excretion of sodium (FeNa) >2%, urinary osmolality <400 mOsm/L, urinary sodium >40 mEq/L and presence of shock or use of nephrotoxic drugs.[13,14] Miscellaneous AKI included AKI that was not classifiable by the above criteria or was considered multifactorial. Only the miscellaneous AKI phenotypes were reviewed by an independent

nephrologist (EP) for adjudication of etiology. Full response of AKI was defined as serum creatinine decreasing back to within 0.3 mg/dl of the baseline value.[8] Partial response was defined as a decrease in at least one AKI stage without reaching <0.3 mg/dl of baseline serum creatinine,[8] except for albumin-treated AKI, where partial response was defined as returning to AKI stage 1A.[9] We defined treatment response as either full or partial response occurring during hospitalization. Patients were followed through hospitalization to assess for AKI response.

Comparison with a control group of patients with cirrhosis and AKI not managed with the EASL management algorithm

To gain further insight into the efficacy of the EASL algorithm on kidney outcomes and survival, we compared the results obtained in the current cohort with those of a historical cohort from our Unit.[12] The main similarities between the two cohorts are: i) patients were evaluated prospectively; ii) patients were hospitalized with decompensated cirrhosis and AKI and were admitted to either the regular ward or the liver ICU; iii) the acute impairment of kidney function was defined using AKI criteria; iv) the study methodology was very similar; and v) terlipressin was already available. Differences are mainly related to the fact that in the historical cohort, patients with HRS were treated following the recommendations of the 2007 ICA algorithm for type 1 HRS,[15] while the current EASL-AKI algorithm allows for an earlier identification of AKI phenotypes and earlier use of specific therapies, particularly albumin in AKI stage 1B and terlipressin for patients meeting HRS-AKI criteria, compared to previous AKI algorithms.

Statistical analyses

Categorical variables were reported as proportions and compared with the Fisher's exact test, and continuous variables were reported as median and interquartile range (IQR) and compared with Mann-Whitney *U* test or Kruskal Wallis test, as appropriate. Significance was set at two-tailed 0.05 for all analyses. The 90-day survival was estimated by the Kaplan-Meier method and compared by means of the log-rank test. For survival analysis, patients who underwent a liver transplant were censored at the time of transplant. Cox proportional hazard regression analysis, with backward stepwise approach, was used to identify predictors of 90-day mortality, which were then expressed as hazard ratios (HRs). Statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL).

Results

Study population

The flow diagram of patient inclusion is presented in Fig. 1. A total of 202 episodes of AKI in 139 patients were studied: 94 patients had one episode, 33 had two episodes, and 12 had three episodes or more. In 21 of 45 patients with recurrent AKI (47%), the subsequent episode of AKI occurred during the same hospitalization after full response of an initial episode. The baseline characteristics of patients at the time of diagnosis of AKI in the 202 episodes are shown in Table S1. Median age was 62 years, most patients were male, and the most common

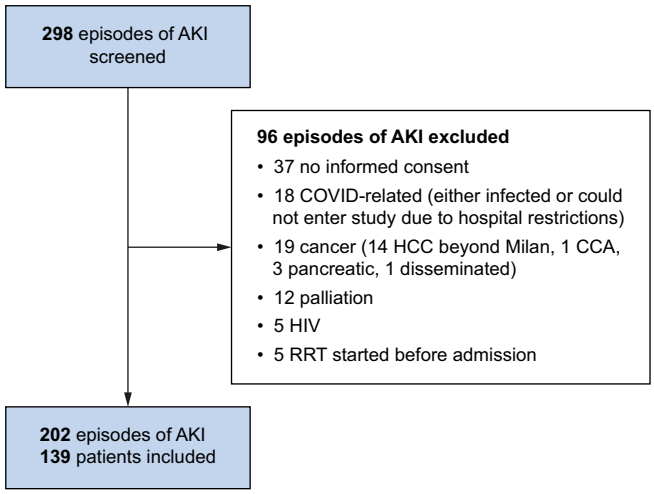

Fig. 1. Flowchart of included AKI episodes. AKI, acute kidney injuru; CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; RRT, renal replacement therapy.

etiology was alcohol-related cirrhosis. CKD was present in 19% of cases. As expected for a cohort of patients with AKI, patients had advanced cirrhosis with high model for end-stage liver disease (MELD) scores. More than half of the AKI episodes had infection as a potential precipitant factor, while gastrointestinal bleeding was much less common. At diagnosis, most patients had AKI stage 1B or greater (160/202, 79%), while a smaller number had AKI stage 1A (42/202, 21%).

Kidney-related outcomes

Of the 202 AKI episodes, overall response was achieved in 162 (80%), composed of 140 full and 22 partial responses. In the whole population, RRT was required in only 17/202 episodes (8%). Patients with CKD had similar rates of AKI response compared to those without CKD, regardless of AKI phenotype (74% *vs.* 82%, respectively, $p = 0.27$). The flow of patients through the EASL AKI algorithm and the respective response rates of the different patient categories are shown in Fig. 2 and Table 1. Of the 42 AKI episodes diagnosed at stage 1A, 20 had full response (48%), 6 persisted (14%), while 16 progressed (38%) to a stage greater than AKI 1A. The presence of shock was more frequent in AKI 1A episodes that progressed to higher stages compared to those that did not (31% *vs.* 4%, respectively, $p = 0.02$), and the median baseline MELD-Na was higher (27 *vs.* 22, $p = 0.02$, respectively). There were no differences in the use of diuretics or NSBBs, nor in the rate of nosocomial AKI.

Patients with AKI stage ≥1B

A total of 176 AKI episodes had AKI ≥1B, including 160 diagnosed at stage ≥1B and 16 more diagnosed at stage 1A but that progressed. One-hundred and thirty-nine of the 176 (78%) were treated with albumin within the first 48 h after AKI diagnosis, and the remaining 37 patients were treated with other intravenous fluids as per the EASL algorithm or had signs of fluid overload that prevented the use of albumin. After albumin therapy, a third of AKI episodes (47 of 139, 34%) showed either full response of AKI or downstaging to stage 1A (36 and 11,

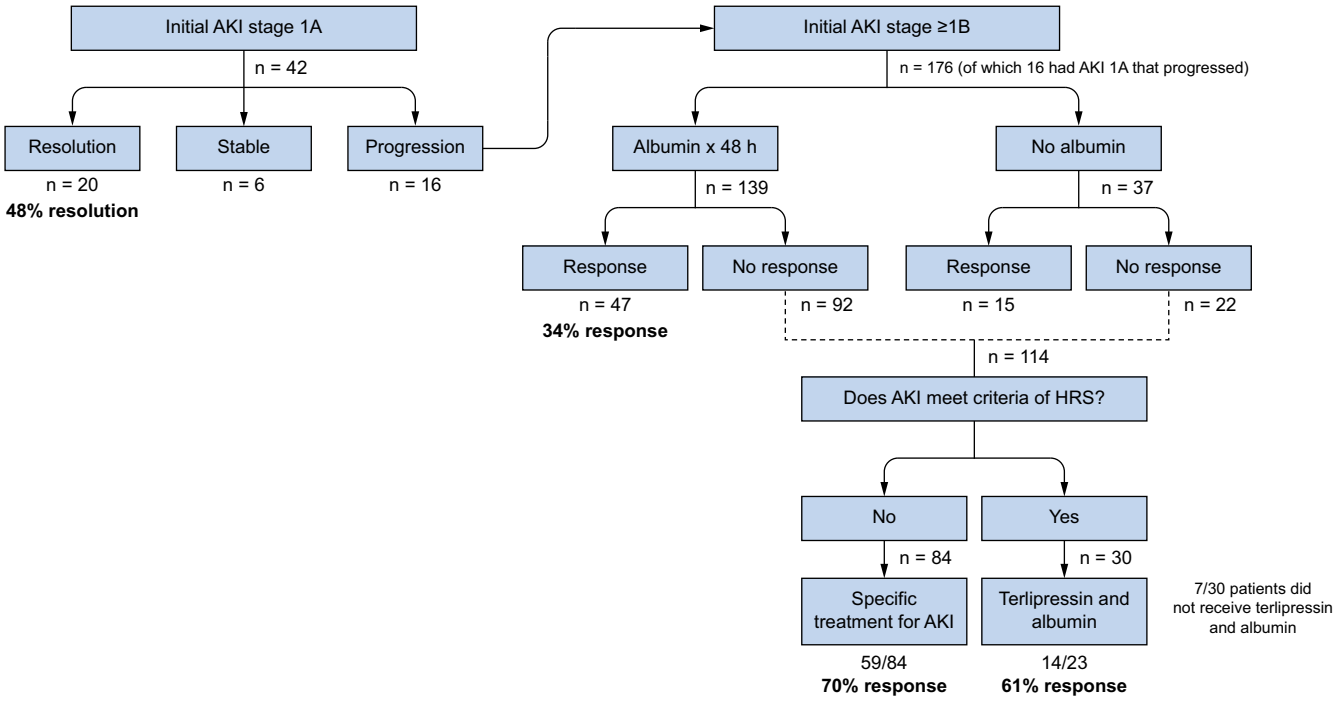

Fig. 2. Flow diagram of included AKI episodes, adapted from the EASL AKI algorithm. Patients with HRS-AKI who are responders have a 58% transplant-free survival at 90 days, which is higher than that reported in Table 1B (38%), since patients who underwent liver transplantation (n = 4) were censored at time of liver transplantation in this KM analysis rather than excluded. AKI, acute kidney injury; HRS, hepatorenal syndrome; KM, Kaplan-Meier.

respectively). In comparison to non-responders, albumin-responders had less severe AKI and lower serum creatinine levels, MELD-Na score, and C-reactive protein levels (Table 2). The total amount of albumin received in the first 48 h was higher in non-responders compared to that of responders (0.8 [0.5-1.2] g/kg/day vs. 0.6 [0.4-0.8] g/kg/day respectively, p = 0.01). Albumin treatment was discontinued due to respiratory failure caused by pulmonary edema in two patients. The first of these patients had a single kidney due to remote history of nephrectomy due to cancer, CKD with an eGFR of 43 mL/min/1.73 m^2, as well as arterial hypertension, and had received albumin 20 g for two consecutive days in addition to a single pool of platelets. The second patient had arterial hypertension at baseline and presented with pneumonia, and had received albumin 60 g for two consecutive days. Neither of these patients had known underlying cardiac disease.

Of the 176 AKI ≥1B episodes, diuretics, NSBBs and NSAIDS were in use in 51, 31 and 12 cases, respectively, on the day of AKI diagnosis. These medications were discontinued in most patients, with only 17%, 15% and 0% of all AKI cases still on diuretics, NSBBs and NSAIDS, respectively, by day 3 of AKI. Most patients who were still on diuretics or NSBBs had AKI stage 1B rather than higher stages. Interestingly, AKI response by day 3 was not significantly different based on whether diuretics or NSBBs were discontinued (data not shown).

Patients with AKI stage ≥1B not meeting criteria for HRS-AKI

Of the 114 AKI episodes not responding to albumin (or other fluids), most (84, 74%) did not meet the diagnostic criteria for HRS-AKI. The most common AKI phenotype in this group was ATN in 48 (57%) patients, followed by hypovolemia-induced in 21 (25%), and miscellaneous in 15 (18%). Causes of AKI in the

Table 1. Kidney- and patient-related outcomes by study group, in patients with persistent AKI after 48 h.

	AKI meeting HRS-AKI criteria	AKI not meeting HRS-AKI criteria
Kidney outcomes[a]	**n = 23**[b]	**n = 84**
Overall response	61%	70%
Full response	48%	50%
Partial response	13%	20%
Patient outcomes[c]	**n = 13**[b]	**n = 60**
Overall 90-day transplant-free survival	23%	60%
By AKI response		
AKI response	29%	74%
AKI no response	17%	24%

AKI, acute kidney injury; HRS, hepatorenal syndrome.
[a]For kidney outcomes, all AKI episodes were considered.
[b]23 of the 30 HRS-AKI patients were treated with terlipressin and albumin and were included in this analysis.
[c]For patient outcomes, only the first episode of AKI was considered. Patients who received a liver transplant or were lost to follow-up within 90 days were excluded from this analysis, corresponding to 4 and 0 in AKI-HRS and 2 and 1 in non-HRS-AKI, respectively.

Table 2. Characteristics of patients by response to albumin.

	Albumin-responders	Albumin non-responders	*p* value
	n = 47	n = 92	
Age, years	63 [57-68]	61 [54-67]	0.41
Male gender	38 (81)	75 (82)	1
Cirrhosis etiology			
Alcohol	26 (55)	62 (67)	0.29
MASLD	6 (13)	7 (8)	
HCV	5 (11)	4 (4)	
Type 2 diabetes	18 (38)	28 (30)	0.47
Chronic kidney disease	7 (15)	20 (22)	0.37
Ascites	36 (77)	81 (88)	0.09
Child-Pugh score, A/B/C	3/23/21 (6/49/45)	2/36/54 (2/39/59)	0.16
Infection	27 (57)	59 (64)	0.47
Gastrointestinal bleeding	3 (6)	9 (10)	0.75
Hospital-acquired AKI	17 (36)	34 (37)	1
AKI stage at diagnosis, 1A/1B/2/3	1/35/8/3 (2/75/17/6)	12/34/22/24 (13/37/24/26)	**<0.001**
MELD	21 [17-24]	27 [21-32]	**<0.001**
MELD-Na	26 [21-29)	30 [24-33]	**<0.001**
Creatinine (mg/dl)	1.7 [1.6-2.0]	2.1 [1.7-3.0]	**<0.001**
Sodium (mEq/L)	134 [128-136]	132 [129-137]	0.88
Bilirubin (mg/dl)	2.6 [1.6-3.9]	4.1 [1.6-11.5]	0.06
Albumin (g/L)	31 [27-34]	28 [25-33]	0.15
CRP (mg/dl)	2.7 [0.5-5.1]	4.0 [2.1-8.4]	**0.01**
WBC ($\times 10^9$/L)	6.6 [4.0-10.6]	7.8 [4.5-12.0]	0.20
Platelets ($\times 10^9$/L)	84 [51-122]	92 [56-147]	0.53
INR	1.5 [1.3-1.8]	1.7 [1.4-2.2]	0.09
Daily amount of albumin received in the first 48 h (g/kg), weight-based	0.6 [0.4-0.8]	0.8 [0.5-1.2]	**0.01**

Continuous variables are presented as median [IQR], categorical as n (%). *P* value in bold designates statistical significance of <0.05.
Statistical significance using Fisher's exact test, Mann-Whitney *U* test or Kruskal Wallis test, as appropriate.
AKI, acute kidney injury; CRP, C-reactive protein; INR, international normalized ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; WBC, white blood count.

15 patients in the miscellaneous group were: cardiorenal syndrome in 3, obstructive nephropathy in 2, glomerulonephritis in 1, interstitial nephritis in 1, and mixed or unclassifiable in 8. Comparison of baseline characteristics of these different phenotypes is shown in Table S2.

Fifty-nine of the 84 (70%) AKI episodes responded to treatment of specific precipitating factors, in combination with RRT in 16 cases. The response rate was higher in patients with hypovolemia-induced AKI compared to ATN or miscellaneous causes, yet differences were not statistically significant (86% *vs.* 65% and 67%, respectively, $p = 0.20$). Urinary NGAL was not associated with response, neither in the overall group of patients not meeting HRS-AKI criteria, nor in the subgroup of patients with ATN (210 *vs.* 351 μg/g creatinine in response *vs.* non-response, respectively, in the whole group, $p = 0.10$; and 319 *vs.* 503 μg/g creatinine in response *vs.* non-response, respectively, in the ATN subgroup, $p = 0.15$). Of note, 6 AKI episodes considered to be miscellaneous AKI were thought to have a functional component to the AKI, whilst not meeting strict HRS-AKI criteria due to mild hematuria or proteinuria. Five of these six patients were treated with terlipressin and albumin, and two of them had response to therapy.

Patients with HRS-AKI

Only 30 of the 114 (26%) AKI episodes not responding to albumin met criteria for HRS-AKI. Baseline characteristics of these patients are shown in Table S2. Of the 30 AKI episodes, 23 were treated with terlipressin and albumin, while the remaining seven were not because of comorbidities that could increase the risk of ischemic events or therapeutic limitations due to advanced age and/or contraindications to liver transplantation. Urinary NGAL levels in patients with HRS-AKI were significantly lower than those of patients with ATN (98 [53-198] *vs.* 446 [134-1,654] μg/g creatinine, $p < 0.001$), but not significantly different from those of patients with other AKI phenotypes (86 [53-450] and 85 [69-153] μg/g creatinine for hypovolemia-induced and miscellaneous AKI, respectively; Fig. S2). The AUROC for uNGAL to differentiate ATN *vs.* non-ATN was 0.783 (95% CI 0.691-0.874, $p < 0.001$). The best cut-off for uNGAL that maximized the Youden index was 307 μg/g creatinine. Of note, 15/41 (37%) patients with ATN had a uNGAL below this cut-off, while 3/30 patients with HRS-AKI had a uNGAL above this cut-off.

Terlipressin was administered as a continuous infusion, at a maximum median daily dose of 4 mg [2-6], for a median duration of 6 days [3-11]. The median time from AKI diagnosis to terlipressin administration was only 2.5 days [1-6]. At the time of terlipressin initiation, the median serum creatinine was 2.4 mg/dl [1.9-2.8], while the AKI stage was 1B in 13 patients, stage 2 in 6 and stage 3 in only 4. The response rate in the group of patients with HRS-AKI receiving terlipressin and albumin was 61%. Median serum creatinine at initiation of terlipressin was not significantly different in terlipressin responders *vs.* non-responders (2.2 [1.9-2.8] mg/dl *vs.* 2.5 [2.0-2.7] mg/dl, $p = 0.64$). In addition, response to terlipressin was numerically higher in patients with serum creatinine <2.5 mg/dl *vs.* ≥2.5 mg/dl at the time of terlipressin initiation, though the difference did not reach statistical significance (9/12 [75%] *vs.* 5/11 [46%], respectively, $p = 0.21$). Similarly, there was no significant difference in response in patients with AKI-HRS stage 1B compared to those with stage 2 or 3 (8/13 [62%] *vs.* 6/10 [60%], respectively, $p = 1$). One patient who did not respond to

terlipressin received RRT. Urinary NGAL levels were not significantly different in terlipressin responders compared to non-responders (87 *vs.* 79 μg/g creatinine, respectively, p = 0.67). Twelve patients (52%) treated with terlipressin for HRS-AKI had clinically significant adverse events that required a reduction of terlipressin dose (n = 1) or discontinuation of treatment (n = 11), including four who experienced diarrhea, two with pulmonary edema, one with cardiac ischemia with pulmonary edema, and two with peripheral ischemia (Table 3). One of the three patients who developed pulmonary edema had underlying congestive heart failure (New York Heart Association <3) secondary to severe mitral regurgitation. Pulmonary edema in this case occurred on day 11 of terlipressin use, at a dose of 8 mg/24 h, after having received a total of 380 g of albumin, and having achieved partial response of AKI, with a serum creatinine of 4.0 mg/dl decreasing to 1.9 mg/dl (baseline serum creatinine of 1.2 mg/dl). All patients recovered following terlipressin discontinuation, and there was no death attributable to the use of terlipressin. Response to terlipressin was lower in patients with such adverse events compared to those without (42% *vs*. 82, respectively), though this did not reach statistical significance (p = 0.09).

Survival

At 90 days and considering only the first episode of AKI, out of the 139 individual patients included, 82 (59%) were alive, 45 (32%) had died, 10 (7%) had undergone liver transplantation, and 2 (1%) were lost to follow-up. Survival of patients according to AKI response is shown in Table 1B and Fig. 3A,B. Similarly, probability of survival by AKI phenotype is presented in Fig. S3. In HRS-AKI, 90-day transplant-free survival was low, even in patients who responded to terlipressin. Only one patient with HRS-AKI and without response to terlipressin survived without liver transplantation.

In the whole cohort, patients who died by 90 days had more advanced liver disease with higher Child-Pugh and MELD-Na scores, as well as higher rates of infection and of ATN and HRS-AKI phenotypes, than those that were still alive by 90 days (Table 4). In the subgroup of patients with uNGAL available (n = 75, of whom 42 were alive and 33 had died by 90 days), uNGAL was higher in patients who died than in those who survived (157 [80-442] *vs.* 83 [53-397] μg/g creatinine, respectively, p = 0.046). There was no significant difference in 90-day mortality in those with or without CKD (30% *vs*. 33%, respectively, p = 0.83).

In the first Cox regression model adjusting for age and MELD-Na, ATN and HRS-AKI were, respectively, associated with HRs of 3.09 (95% CI 1.37-6.97, p = 0.006) and 4.19 (95% CI 1.79-9.83, p = 0.001) for death at 90 days, using hypovolemia-induced AKI as baseline. In the second model adjusting for age, MELD-Na, urinary NGAL was significantly associated with 90-day mortality (HR 1.0002; 95% CI 1.00006-1.0003; p = 0.03) (Table S3).

Table 3. Clinically significant adverse events associated with terlipressin and albumin in the 23 patients with HRS-AKI.

Adverse events	n = 12
Diarrhea/gastrointestinal symptoms	4
Pulmonary edema	2
Pulmonary edema with cardiac ischemia	1
Peripheral ischemia	2
Atrial fibrillation	1
Bradycardia	1
Hyponatremia	1

AKI, acute kidney injury; HRS, hepatorenal syndrome.

Comparison with a control group of patients with cirrhosis and AKI not managed with the EASL management algorithm

There were no major differences between the study group and the control group in patient characteristics except for a slightly higher frequency of stage 2 and 3 AKI in the study group compared to the control group (Table 5). The frequency of AKI recovery was higher and the 90-day mortality lower in the group treated with the EASL algorithm compared to the control group.

Discussion

The management algorithm for AKI in cirrhosis that was evaluated in this study is based on three principles: identification and treatment of potential triggering factors (mainly infections and hypovolemia), an albumin challenge for 2 days in patients with severe AKI (stage ≥1B) without clinical evidence of volume depletion (no albumin challenge for hypovolemic patients who are treated with saline, blood or other fluids as needed), and treatment with terlipressin in non-responders to the albumin test who meet diagnostic criteria for HRS-AKI. The main findings of this prospective study are: i) the response rate was high and similar across AKI phenotypes: 85%, 65% and 61% for hypovolemia-induced, ATN and HRS-AKI, respectively; ii) only 17/202 episodes (8%) required treatment with RRT; iii) the 2-day albumin infusion test was associated with a positive response in approximately one-third of patients; and iv) the algorithm allowed for rapid identification of patients with HRS-AKI, so that patients were treated with terlipressin after a very short period following the diagnosis of AKI, with an associated high response rate achieved. The current results, therefore, indicate that the EASL management algorithm for AKI is a very useful tool in clinical practice due to its simplicity, easy applicability, and high effectiveness. It is important to emphasize that the EASL AKI management algorithm is simple and straightforward, so that it can easily be applied to most settings and countries and does not require special tools or training. The exceptions may be access to albumin, which may not be available everywhere, as well as to terlipressin, which may not be available and/or may be too expensive. The latter can however be substituted by norepinephrine.

This study provides interesting information about the usefulness of an albumin infusion test as part of the diagnostic criteria for HRS-AKI in cirrhosis. The use of this albumin challenge has been controversial because it is only based on expert opinion and may delay the initiation of therapy with terlipressin in patients with HRS-AKI, thus potentially reducing the likelihood of response to therapy. Our findings strongly support the use of the albumin test in the diagnosis of HRS-AKI because it was associated with response to therapy in 34% of patients. This is an important finding because it reduced the need for terlipressin therapy in a significant proportion of patients. The downside of it was that 1% of patients treated developed pulmonary edema. Therefore, patients treated should be carefully monitored for the development of respiratory

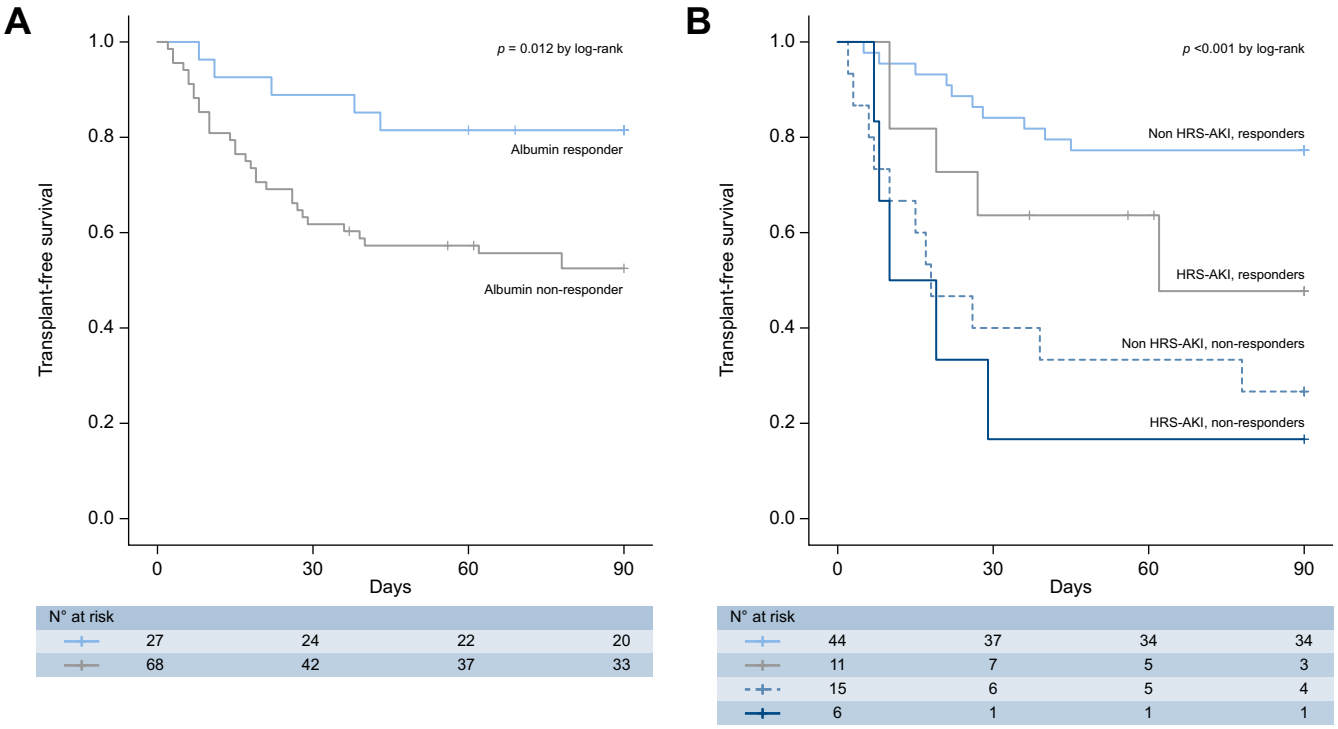

Fig. 3. 90-day transplant-free survival by response to albumin and by HRS-AKI criteria and response. (A) Patients who were not treated with albumin have been excluded from this analysis. Level of significance: $p = 0.012$ (log-rank). (B) Level of significance: $p < 0.001$ (log-rank). AKI, acute kidney injury; HRS, hepatorenal syndrome.

complications even when albumin is only given for 2 days. Of note, the use of albumin should be considered as an integral part of the EASL AKI algorithm rather than a standalone treatment, alongside other important measures such as holding diuretics, providing antibiotics in the presence of infection, etc. Regarding the use of fluids other than albumin, the 2018 EASL guidelines in fact recommend that patients with hypovolemia due to fluid losses or gastrointestinal bleeding be treated with saline or packed red blood cells, respectively, and not with albumin.[9]

The application of the management algorithm resulted in a rapid diagnosis of HRS-AKI, which allowed for a rapid initiation of therapy with terlipressin. Current evidence indicates that early initiation of terlipressin at lower levels of serum creatinine is associated with higher likelihood of response.[16,17] In the current cohort, the median serum creatinine at the start of terlipressin therapy was of only 2.4 mg/dl, which is lower than the pretreatment serum creatinine values in most of the randomized-controlled trials (RCTs), including a mean of 3.5 mg/dl in patients included in the CONFIRM trial, a study comparing terlipressin *vs.* placebo in patients with type 1 HRS published recently.[18] As such, using the AKI management algorithm results in earlier initiation of terlipressin, at a median serum creatinine that is lower than the prior cut-off for type 1 HRS. Moreover, the median time from diagnosis of AKI to start of terlipressin therapy was of only 2.5 days, which confirms that diagnosis of HRS-AKI was done very quickly and was rapidly followed by specific therapy. Notably, with this approach, the response rate to terlipressin was 61%, an efficacy rate similar or higher than that reported in most RCTs.[1,18–20] This high response rate is likely due to the effectiveness of the algorithm in ruling out causes of AKI other than HRS-AKI (that would not have responded to terlipressin) and ruling in true-positive cases, together with a rapid initiation of specific therapy. While we used the predetermined ICA's definition of AKI response, supported by the EASL guidelines, *ad hoc* analyses using an older definition of response of serum creatinine ≤1.5 mg/dl at least 2 days apart yielded a lower rate of 10/23 (41%) response to terlipressin. Of the four patients who were no longer considered to have responded according to this older definition: two patients had partial response, with serum creatinine decreasing from 2.8 mg/dl to 1.8 mg/dl and from 4.0 mg/dl to 2.0 mg/dl, respectively; one patient had responded fully with the serum creatinine back to within 0.3 mg/dl of baseline, but had a new episode of AKI 24 h later with a rise in serum creatinine; and one patient with a baseline serum creatinine of 1.2 mg/dl responded, with serum creatinine decreasing from 1.7 mg/dl down to 1.4 mg/dl on two measurements 48 h apart, but with one reading of serum creatinine of 1.5 mg/dl in between. On the other hand, it should also be emphasized that the number of patients who were diagnosed with HRS-AKI was low compared to the total number of cases with AKI included, only 30 of 202 (15% of all cases), with 23 being eligible for terlipressin therapy. These values indicate that among patients with cirrhosis and impaired kidney function, HRS-AKI is the exception rather than the rule, a message that should be kept in mind when caring for hospitalized patients with decompensated cirrhosis. These findings are supported by a recent large multicentric retrospective study.[21] Our results therefore suggest that terlipressin should truly be given to a relatively small proportion of all patients with AKI.

Table 4. Characteristics of patients by survival status at 90 days.

	Alive	Dead	*p* value
	n = 82	n = 45	
Age	63 [54-68]	63 (56-68)	0.91
Male gender	63 (77)	34 (76)	1
Cirrhosis etiology			
Alcohol	41 (50)	30 (67)	0.17
HCV	8 (10)	3 (7)	
MASLD	13 (16)	1 (2)	
DM	33 (40)	14 (31)	0.34
CKD	18 (22)	8 (18)	0.65
Ascites	56 (68)	43 (96)	**0.001**
Infection	38 (46)	33 (73)	**0.005**
Gastrointestinal bleeding	10 (12)	5 (11)	1
Child-Pugh score, A/B/C	11/42/29 (13/51/35)	0/11/34 (0/24/76)	**<0.001**
Hospital-acquired AKI	24 (29)	18 (40)	0.24
AKI stage at diagnosis, 1A/1B/2/3	16/38/12/16 (20/46/15/20)	15/16/4/10 (33/36/9/22)	0.32
AKI phenotype			
Hypovolemia	45 (55)	9 (20)	**0.009**
ATN	15 (18)	17 (38)	
HRS-AKI	4 (5)	14 (31)	
Miscellaneous	18 (22)	5 (11)	
MELD	21 [17-26]	28 [21-32]	**<0.001**
MELD-Na	25 [20-29]	31[25-35]	**<0.001**
Creatinine (mg/dl)	1.9 [1.5-2.6]	1.9 [1.5-2.5]	0.91
Sodium (mEq/L)	135 [130-138]	130 [125-135]	**<0.001**
Bilirubin (mg/dl)	2.5 [1.1-4.6]	5.4 [2.7-18]	**<0.001**
Albumin (g/L)	30 [26-35]	26 [23-31]	**0.003**
CRP (mg/dl)	2.9 [0.8-5.4]	3.5 [2.1-6.6]	0.10
WBC ($\times 10^9$/L)	6.6 [4.2-10.2]	9.1 [5.1-12.0]	0.053
Platelets ($\times 10^9$/L)	106 [60-167]	90 [52-134]	0.09
INR	1.4 [1.3-1.7]	1.7 [1.4-2.4]	**0.002**
uNGAL on day 3 (μg/g creat)[1]	83 [53-397]	157 [80-442]	**0.046**

Patients who underwent LT (n = 10) or were lost to follow-up (n = 2) were excluded from this analysis. *P* value in bold designates statistical significance of <0.05.
Continuous variables are presented as median (IQR), categorical as n (%).
Statistical significance using Fisher's exact test, Mann-Whitney *U* test or Kruskal Wallis test, as appropriate.
AKI, acute kidney injury; CKD, chronic kidney disease; CRP, C-reactive protein; DM, diabetes mellitus; INR, international normalized ratio; MASLD, metabolic-associated steatotic liver disease; MELD, model for end-stage liver disease; uNGAL, urinary neutrophil gelatinase-associated lipocalin; WBC, white blood count.
[1]Available in 75/139 patients.

Despite the high response rate overall and in all phenotypes, AKI remains a severe complication with a 90-day transplant-free survival rate of only 59%. These numbers are much worse in patients with HRS-AKI. Indeed, in the absence of liver transplantation, patients with HRS-AKI have poor prognosis, even for those who respond to terlipressin, with a 90-day survival rate of 29%. These results call for MELD exception points in patients with HRS-AKI being treated with terlipressin who are transplant candidates.[22]

RCTs on terlipressin have shown that some patients treated with terlipressin for HRS-AKI develop respiratory failure due to pulmonary edema.[18,23,24] This important side effect has been reported mainly in patients with severe liver failure, particularly those with acute-on-chronic liver failure grade 3.[18] The

Table 5. Comparison of characteristics and outcomes of the control group and study group.

	Control group[12]	Study group (current study)
Recruitment years	2009-2011	2019-2021
Number of AKI episodes	177	202
Age, years	60 ± 12	61 ± 10
Etiology of cirrhosis, alcohol/HCV (%)	79/68 (45/39)	123/16 (61/8)
Serum creatinine at AKI diagnosis, mg/dl	1.8 ± 1.0	2.2 ± 1.1
Bilirubin, mg/dl	6.1 ± 7.9	6.7 ± 9.3
Albumin, g/L	25 ± 5	29 ± 6
INR	1.6 ± 0.5	1.7 ± 0.6
Child-Pugh score, A/B/C (%)	12/71/94 (7/40/53)	14/83/105 (7/41/52)
MELD at AKI diagnosis	21 ± 7	24 ± 7
AKI stage at diagnosis, 1/2/3 (%)	136/20/21 (77/11/12)	132/36/34 (66/18/17)
AKI recovery[1]	107/177 (60)	158/202 (78)
Mortality at 90 days[2]	93/166 (56)	45/127 (35)

AKI, acute kidney injury; INR, international normalized ratio; MELD, model for end-stage liver disease. Values are presented in mean ± SD or n (%).
[1]AKI recovery, defined as AKI stage 2-3 to stage 1 or no AKI, or AKI stage 1 to no AKI, during hospitalization.
[2]Excluding lost to follow-up and liver transplant.

pathogenic mechanisms are not completely understood but may be related, at least in part, to excessive albumin administration causing circulatory overload, together with increased systemic vascular resistance causing increased cardiac afterload and decreased cardiac output.[25] The results of our study provide evidence of the frequency of this complication in a real-life scenario. Notably, this complication was observed in 3 of the 23 (13%) patients, a rate similar to that observed in the CONFIRM trial.[18] This occurred even though terlipressin was given as a continuous infusion rather than in bolus, a form of administration that reduces ischemic adverse events,[26] and that care was taken not to give too much albumin the days before starting treatment with terlipressin. Thus, it seems that this complication may occur despite the application of some preventive measures. Therefore, more research is needed to explore the pathophysiology of this complication and improve methods to prevent it.

We have confirmed the utility of urinary NGAL to differentiate ATN and non-ATN AKI in a real-life scenario. We found a cut-off of 307 μg/g creatinine, which differs slightly from previous studies reporting a cut-off of 220-244 μg/g creatinine and 220 ng/ml (non-normalized uNGAL),[4,11,27] but was similar to that found in another study where the cut-off was 365 ng/ml.[28] With an AUROC of 0.78, uNGAL should not be used in isolation to differentiate AKI phenotype, as this approach may lead to misclassification of certain patients. Contrary to a recent cohort study,[27] we did not identify uNGAL as a predictor of terlipressin response in HRS-AKI. Our data are in line with a previous study from our group.[11] Moreover, uNGAL was an independent predictive factor for 90-day transplant-free survival. As such, at this time, it seems that uNGAL may be most useful in the differential diagnosis and prognosis of AKI in cirrhosis.

Our study has several limitations. As mentioned previously, given that this is a non-randomized trial, the true beneficial effect of the different interventions in the EASL AKI algorithm cannot be ascertained. To circumvent this issue, we compared the outcomes in our study group with those of a prospectively collected historical control group.[12] Although these findings should be interpreted with caution, the comparison shows that the current algorithm is associated with higher AKI recovery and lower 90-day mortality. This may be due to early management of AKI and earlier use of terlipressin therapy for HRS-AKI in the current study. Moreover, tools such as point-of-care ultrasound may be used to guide albumin administration in the future, but were not used in the current study. Second, we had a relatively small number of patients with HRS-AKI, therefore the study could be underpowered for the analysis of predictors of response to terlipressin. Finally, the study was performed in a single unit with a long-standing experience in the diagnosis and management of renal complications of cirrhosis, and findings may not be generalizable to all settings. However, the EASL algorithm is straightforward, simple, and clear, so that it can be easily followed, without significant obstacles to its application in clinical practice. Important work from the Global AKI collaboration, an international prospective study on AKI in cirrhosis, will provide much needed data on differing practices and outcomes.[29]

In conclusion, our prospective study provides important evidence supporting the effectiveness of the EASL AKI management algorithm in clinical practice, with high response rates throughout the different AKI stages and phenotypes, thus providing validation of this algorithm in real clinical practice. Furthermore, our findings indicate that survival in subgroups of patients, particularly those with HRS-AKI, is poor in the absence of liver transplantation, even with treatment response.

Affiliations

[1]*Liver Unit, Hospital Clinic de Barcelona, Barcelona, Spain;* [2]*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain;* [3]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEReHD), Madrid, Spain;* [4]*Faculty of Medicine and Health Sciences, University of Barcelona, Spain;* [5]*Toronto Centre for Liver Disease, University Health Network, Toronto, Canada;* [6]*Hepatology Unit, Digestive Service, Parc Taulí University Hospital, Institut d'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Sabadell, Spain;* [7]*Biochemistry and Molecular Genetics department, Hospital Clinic, Barcelona, Spain;* [8]*Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, California, USA;* [9]*Nephrology and Kidney Transplant department, Hospital Clinic, Barcelona, Spain*

Abbreviations

AKI, acute kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease; EASL, European Association for the Study of Liver; HRS, hepatorenal syndrome; MELD, model for end-stage liver disease; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

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Conflict of interest

PG consults for and received grants from Gilead, Grifols, and Mallinckrodt, and consults for Novartis, Martin, and Ferring. The other authors have declared no conflict of interest.

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

Authors' contributions

ATM designed the study, recruited patients, collected data, performed statistical analyses, and drafted the manuscript. CS designed the study, recruited patients, collected data, and contributed to manuscript writing. AJ and LE recruited patients, collected data and contributed to manuscript writing. LN, EA, MPG, MC, EP, JGG, AS, ABR, MC, MJM recruited patients, collected data, and contributed to writing the manuscript. MM provided expertise on urinary NGAL measurement and reviewed the manuscript. ES contributed to study design, patient recruitment, data collection and manuscript drafting. EP provided expertise for diagnosis ascertainment of recruited patients and contributed to manuscript writing. NF, IG and EP contributed to manuscript writing. PG oversaw the study design and manuscript drafting. All authors approved the final manuscript.

Data availability statement

The data sets of this study are available from the corresponding author upon reasonable request.

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Supplementary data

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