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Title:

LIVER CIRRHOSIS, CONTRAST-INDUCED ACUTE KIDNEY INJURY AND EARLY KIDNEY TUBULAR DAMAGE BIOMARKERS: A PROSPECTIVE CONTROLLED STUDY.

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SUMMARY

ABSTRACT

Background & Aims: Nephrotoxicity due to intravenous iodinated contrast media (ICM) administration in patients with cirrhosis is still a debated issue, as the available evidence is scarce and based on very heterogeneous studies, often conducted on small and retrospective cohorts with conflicting results. This study aims to evaluate incidence and predisposing factors of acute kidney injury (AKI) in patients with cirrhosis undergoing contrast-enhanced computed tomography (CECT).

Methods: We performed a prospective, multi-center, three-cohort study including 444 inpatients overall: 148 patients with cirrhosis (cohort 1) and 163 without cirrhosis (cohort 3) undergoing CECT, as well as 133 patients with cirrhosis (cohort 2) not exposed to ICM. Kidney function parameters were assessed at T0, 48-72 hours (T1), 5 and 7 days after CECT/enrollment. Urinary neutrophil gelatinase-associated lipocalin (U-NGAL), an early biomarker of tubular damage, was measured in 50 consecutive patients from cohort 1 and 50 consecutive patients from cohort 2.

Results: AKI incidence was not significantly increased in patients with cirrhosis undergoing CECT compared to the other two cohorts (4.8%, 1.5%, 2.5% in cohorts 1, 2, 3 respectively, p=ns). Most AKI cases recorded were mild and transient. The presence of concomitant infections was the only independent predictive factor of CI-AKI (OR 22.18, 95%CI 2.87-171.22, p=0.003). No significant modifications of U-NGAL between T0 and T1 were detected, neither in cohort 1 nor in cohort 2 [median ΔU-NGAL: +0.2 (-7,6 - +5,5) ng/ml and +0.0 (-6,8 - +9,5) ng/ml, respectively (p=0.682)].

Conclusions: Post-CECT AKI risk in cirrhosis is low, not significantly different from that of the general population undergoing CECT and of the cirrhotic population unexposed to ICM. It mostly consists in mild and rapidly resolving episodes of renal

dysfunction and it is not associated with tubular kidney injury. An increased risk of CI-AKI appears to be limited to those patients with cirrhosis and ongoing infections. Therefore, the current recommendations of performing contrast imaging studies cautiously in cirrhosis appear outdated, except for infected patients, who show a significantly higher risk of CI-AKI.

List of Abbreviations:

-CI-AKI: contrast-induced acute kidney injury

-AKI: acute kidney injury

-CM: contrast media

-KDIGO: Kidney Disease Improving Global Outcome

-sCr: serum creatinine

-eGFR: estimated glomerular filtration rate

-ICM: iodinated contrast media

-GFR: glomerular filtration rate

-CKD: chronic kidney disease

-CECT: contrast-enhanced computed tomography

-U-NGAL: urinary neutrophil gelatinase-associated lipocalin

-BMI: body mass index

-MELD: Model for End-stage Liver Disease

-MDRD: Modification of Diet in Renal Disease

-CKD-EPI: Chronic Kidney Disease – Epidemiology Collaboration

-Una: urinary sodium

-U-urea: urinary urea

-uCr: urine creatinine

-CMIA: chemiluminescent microparticle capture two-phase immunological assay

-LoQ: limit of quantification

-CV: coefficient of variation

-IQR: interquartile range

-NAG: N-acetyl-β-D-glucosaminidase

1. INTRODUCTION

1.1 CI-AKI in the general population

Contrast-induced acute kidney injury (CI-AKI) is defined as the development of acute kidney injury (AKI) following administration of intravascular contrast media (CM). The 2012 Kidney Disease Improving Global Outcome (KDIGO) Clinical Practice Guideline for AKI recommends defining and staging CI-AKI according to the same criteria used for the other types of AKI[1], as reported in **Table 1**. Therefore, previous definitions of "contrast induced nephropathy" as a rise in serum creatinine (sCr) of ≥0.5 mg/dl (≥44 μmol/l) or a 25% increase from baseline value, assessed at 48 hours after a radiological procedure, should be abandoned.

Table 1. CI-AKI definition and staging[1].

AKI DEFINITION		
Any of the following: *Increase in sCr by ≥0.3 mg/dl within 48 hours; or *Increase in sCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or *Urine volume <0.5 ml/kg/h for 6 hours		
AKI STAGING		
Stage	sCr	Urine output
1	*1.5–1.9 times baseline, OR *≥0.3 mg/dl increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	*3.0 times baseline, OR *increase in sCr to ≥4.0 mg/dl, OR *initiation of renal replacement therapy, OR *in patients <18 years, decrease in eGFR to <35 ml/min/1.73 m^2	*<0.3 ml/kg/h for ≥24 hours, OR *Anuria for ≥12 hours

sCr, serum creatinine; eGFR, estimated glomerular filtration rate

Reported incidence rates of CI-AKI in the general population greatly vary from around 1% to 25% depending on the definitions used to identify CI-AKI, on the dose, type and administration route (intra-arterial or intra-venous) of CM, and on the pre-existing risk factors in the study population.[2,3,4,5]

Many predisposing factors have been identified (e.g. diabetes mellitus, congestive heart failure, advanced age, anemia, dehydration, concurrent exposition to nephrotoxic drugs), however, the most important one remains pre-existing kidney function impairment.[4,5,6,7] In 2012, KDIGO Guideline[1] agreed that the risk of CI-AKI in the general population becomes clinically relevant when the estimated glomerular filtration rate (eGFR) is <45 ml/min/1.73 m^2, thus recommending the adoption of preventive measures in these patients. However, according to more recent guidelines from the American College of Radiology and National Kidney Foundation, prophylaxis for CI-AKI is indicated for patients with ongoing AKI or eGFR <30 ml/min/1.73 m^2 who are not undergoing maintenance dialysis, whereas in case of eGFR 30–44 ml/min/1.73 m^2 prophylaxis is discretionary in the presence of concomitant additional risk factors for CI-AKI.[8,9]

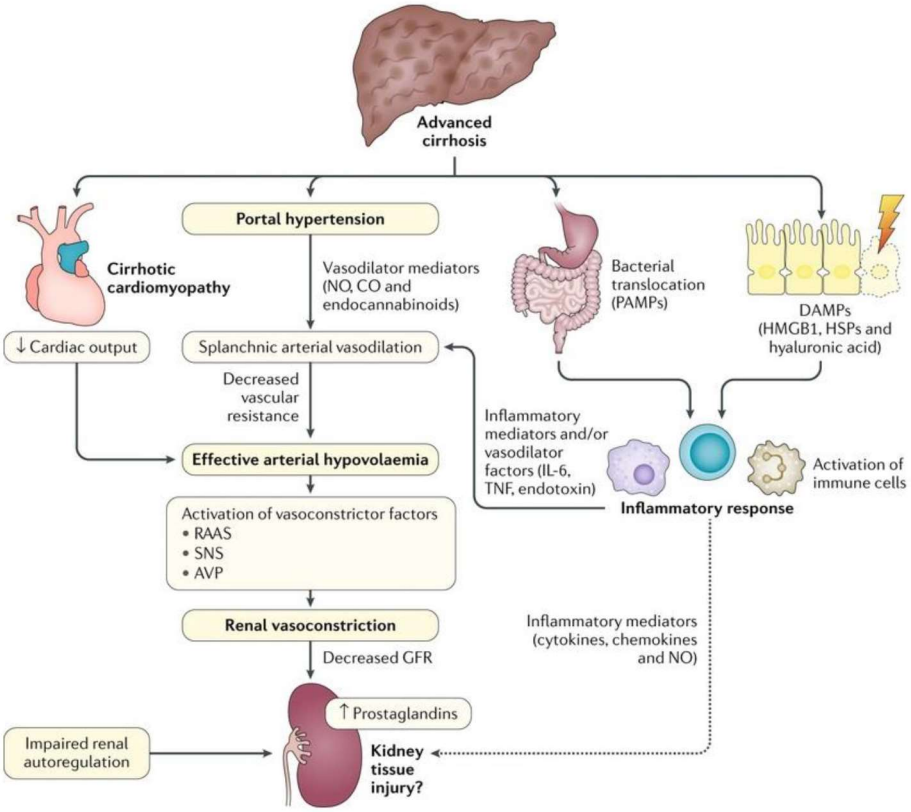
Several mechanisms have been proposed to explain the renal impairment induced by iodinated contrast media (ICM), but ischemia of the outer medulla appears to be the predominant one. The outer medulla is an area with high metabolic requirements at baseline and it is, therefore, more sensitive to the stress induced by the administration of ICM, which increases oxygen demand and decreases oxygen delivery to this area. Following ICM administration, blood osmolality increases and consequently tubular activity is enhanced to excrete the osmotic overload, leading to increased oxygen consumption. On the other hand, ICM causes vasoconstriction of vasa recta through activation of adenosine, endothelin and renin-angiotensin system and inhibition of

nitric oxide and vasodilatory prostaglandins, thus resulting in a reduced oxygen supply to the outer medulla. Furthermore, osmotic natriuresis and diuresis activate tubuloglomerular feedback, leading to vasoconstriction of glomerular afferent arterioles and to decreased GFR.[10,11] Direct tubular cytotoxicity has been suggested as another potential mechanism of CI-AKI, since intense vacuolization of the proximal tubular cells, loss of brush border and even frank tubular necrosis have been shown in CI-AKI cases.[12] Both tissue ischemia and direct tubular toxicity may result in release of reactive oxygen species; hence oxidative stress and consequent inflammation may cause death of tubular cells and thus contribute to kidney injury. Finally, aggregation of Tamm-Horsfall proteins, increased tubular fluid viscosity and increased urate excretion can cause tubular plugging.[7]

1.2 CI-AKI in cirrhosis

Liver cirrhosis, especially if decompensated, is characterized by a well-known susceptibility to kidney dysfunction induced by a variety of precipitating factors, such as infections, gastrointestinal bleeding, large volume paracentesis without adequate volume expansion, excessive diuretic therapy, nephrotoxic drugs, as well as the increase in intra-abdominal pressure associated with tense ascites (through the increase of renal venous pressure). Furthermore, cirrhosis in its advanced stages is also burdened by a deranged autoregulation of renal blood flow. While in healthy subjects renal autoregulation acts to maintain a stable renal blood flow and GFR regardless of systemic arterial pressure variations, this homeostatic system is impaired in cirrhosis, resulting in a more fragile kidney function, particularly in more severely decompensated patients (**Figure 1**).[13]

Figure 1. Pathophysiology of kidney functional impairment in advanced cirrhosis.



1.2.1 Review of previous literature on CI-AKI in cirrhosis

At the present day, the risk of nephrotoxicity due to CM is still debated in patients with cirrhosis.[14] Although they have been empirically considered at higher risk for CI-AKI than the general population, the available evidence is limited and based on very heterogeneous studies, mostly flawed by a retrospective and/or uncontrolled design, often relying on obsolete definitions of CI-AKI and providing conflicting results (**Table 2**).[15-24] At present, European guidelines recommend that contrast imaging should be performed cautiously, particularly in decompensated cirrhosis with ascites, in female patients, in the presence of hyperazotemia or of known chronic kidney disease (CKD).[14]

Table 2. Review of available studies on CI-AKI in cirrhosis.

Author (year)	Study design	CI-AKI definition	Study population	CI-AKI incidence and other main results
Najjar (2002)[15]	Retrospective, controlled	Unspecified	72 patients with vs. 72 patients without cirrhosis undergoing CECT	AKI incidence: 2.8% in patients with cirrhosis vs 1.4% in those without (p=ns)
Guevara (2004)[16]	Prospective, uncontrolled	Two consecutive sCr determinations ≥ 1.5 mg/dL within 24h in patients who received ICM and with no other causes for the development of renal failure GFR measured at baseline and 48h post-CECT	31 patients with cirrhosis with baseline sCr <2 mg/dl exposed to ICM after ≥5 days withdrawal of diuretic therapy	AKI incidence: 0% -No significant differences in measured GFR, UNa and free water excretion -Significant increase in N-acetyl-beta-D-glucosaminidase, a tubular injury marker
Lodhia (2009)[17]	Retrospective, uncontrolled	eGFR decrease ≥ 25% within 7 days from CECT	216 patients with cirrhosis undergoing CECT	AKI incidence: 25% -Ascites: risk factor (3x) for CI-AKI -68% AKI persistence ≥1 week -11% evolution in CKD
Choi (2012)[18]	Retrospective, uncontrolled	sCr increase ≥ 25% or ≥ 0.5 mg/dL within 2-5 days after CECT	81 patients with cirrhosis with eGFR <60 ml/min/1.73m^2 undergoing pre-CECT i.v. prophylaxis of CI-AKI	AKI incidence: 3.7% -Ascites: increased AKI risk
Safi (2015)[19]	Retrospective, controlled	sCr increase ≥ 25% or ≥ 0.5 mg/dL or eGFR decrease ≥ 25% within 72h from contrast exposure	84 patients with cirrhosis undergoing CECT vs 68 undergoing contrast-enhanced MRI	AKI incidence: 17.9% in CECT group vs 5.9% in MRI group (p = 0.026)
Filomia (2016)[20]	Retrospective, controlled	sCr increase ≥ 0.3 mg/dL or ≥ 50% within 48h	249 patients with cirrhosis undergoing CECT vs 203 not undergoing CECT Exclusion criteria: eGFR <30 ml/min/1.73 m^2, active infections, recent intake of nephrotoxic drugs	AKI incidence: 8.8% in CECT group vs 3% in control group (p = 0.01) -90% AKI stage 1 -58.8% AKI persistence at 3 months -Ascites, female sex, high basal BUN: risk factors for CI-AKI
Ul Abideen (2018)[21]	Restrospective, uncontrolled	sCr increase ≥ 0.3 mg/dL within 48h	470 patients with cirrhosis undergoing CECT Exclusion criteria: CKD, SBP, sepsis, chronic heart failure, intake of NSAIDs, diuretics, ACEi or ARBs	AKI incidence: 5.1% -Patients who developed CI-AKI had worse liver function indices (MELD, MELD-Na, bilirubin and INR), lower serum sodium, lower mean eGFR values
Kuo (2018)[22]	Retrospective -Designed to assess a protective effect of silymarine on CI-AKI	Unspecified	6038 patients with cirrhosis undergoing CECT (50% taking silymarine vs 50% not)	AKI incidence: 2.4%
Khan (2020)[23]	Retrospective, controlled	sCr increase ≥0.3 mg/dL within 48h or ≥1.5 times baseline within 7 days, or urine output <0.5 mL/kg/h for at least 6 hours	173 patients with cirrhosis undergoing CECT vs 243 undergoing contrast-enhanced MRI	AKI incidence: 2.9% in CECT group vs 5.8% in MRI group (p=0.25) -68% of AKIs could be attributed to aetiologies other than contrast exposure

Tergast (2022)[24]	Retrospective + prospective, controlled	sCr increase ≥0.3 mg/dL within 48h or ≥1.5 times baseline within 7 days, or urine output <0.5 mL/kg/h for at least 6 hours	Retrospective cohort. Patients with cirrhosis and ascites undergoing paracentesis: 98 undergoing CECT vs. 513 controls Prospective cohort. Patients with cirrhosis and ascites: 13 undergoing CECT vs. 105 controls NGAL analysis: 10 patients undergoing CECT vs 74 controls	Retrospective cohort: - AKI incidence: 8% in CECT group vs 15% in controls (p= 0.08) - no increased risk of CI-AKI in lower eGFR Prospective cohort: - 28-day AKI incidence: 44% in CECT group vs 43% in controls (p=0.85) -28-day severe AKI incidence: 9% in CECT group vs 4% in controls (p=0.54) NGAL analysis: - no significant difference in NGAL levels between the two groups

CI-AKI, contrast induced-acute kidney injury; CECT, contrast-enhanced computerized tomography; sCr, serum creatinine; ICM, iodinated contrast media; GFR, glomerular filtration rate; UNa, urinary sodium; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; MRI, magnetic resonance imaging; BUN, blood urea nitrogen; SBP, spontaneous bacterial peritonitis; NSAIDs, non-steroidal anti-inflammatory drugs; ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensinogen receptor II blockers; MELD, model for end stage liver disease; INR, international normalized ratio; NGAL, neutrophil gelatinase-associated lipocalin.

1.2.2 Aims of the study

This study was designed to evaluate the incidence and predisposing factors of AKI in patients with cirrhosis undergoing contrast-enhanced computed tomography (CECT), in comparison with cirrhotic controls unexposed to ICM and with non-cirrhotic patients submitted to CECT. Furthermore, the development of ICM-induced tubular damage was assessed by measuring urinary neutrophil gelatinase-associated lipocalin (U-NGAL), a well-known early and sensitive marker of tubular injury, in a subset of patients with cirrhosis.

2. PATIENTS AND METHODS

2.1 Study cohorts

This is a prospective controlled observational multicenter cohort study collecting data on a series of consecutive patients with and without cirrhosis hospitalized in the Gastroenterology and Hepatology division of A.O.U. Città della Salute e della Scienza Hospital-University of Turin and of Santa Croce and Carle Hospital of Cuneo, Italy, between 13/03/2019 and 31/07/2021. All the patients with cirrhosis undergoing CECT for clinical purposes (cohort 1) were consecutively enrolled, along with two control cohorts, one composed of patients with cirrhosis unexposed to ICM (cohort 2), and the other one of patients without cirrhosis undergoing CECT (cohort 3).

All the patients hospitalized during the above-mentioned period were considered eligible for the study if they met the following inclusion criteria: age ≥18 years, liver cirrhosis defined by standard clinical or histological criteria (for cohorts 1 and 2), clinical indication to perform CECT (for cohorts 1 and 3).

Exclusion criteria were: concomitant administration of vasoactive drugs (e.g. norepinephrine, terlipressin, somatostatin), administration of intravascular ICM in the 14 days before enrollment, previous solid organ transplantation, long-term dialysis, events potentially perturbating clinical stability and kidney function parameters occurring between the basal sCr determination and the 7 days following CECT in cohorts 1 and 3 or following enrollment in cohort 2 (i.e. new exposition to potential nephrotoxic agents, new-onset infections, gastrointestinal bleeding, large volume paracentesis without adequate volume expansion, massive fluid losses, heart failure, modification of diuretic dosage in patients already under diuretics).

Of note, patients with known concomitant infections were not excluded, provided that the infections were already ongoing at the time of enrollment, that patients were treated with adequate empiric or culture-guided antibiotic therapy[14], and as long as hemodynamic stability was maintained.

Ethical approval for this study was provided by the Ethical Committee of A.O.U. Città della Salute e della Scienza Hospital and A.O. Ordine Mauriziano of Turin on 13 March 2019 (N° 316/2019) and by the Ethical Committee of Santa Croce and Carle Hospital of Cuneo on 3 April 2019 (N° 31/2019). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from each patient enrolled.

The research is being reported in line with the STROBE criteria (Strengthening the reporting of observational studies in epidemiology).[25]

2.2 Analyses

In cohorts 1 and 3 a basal sCr value (T_0) was recorded within 24-48 hours prior to CECT and a second sCr determination was recorded 48-72 hours after CECT (T_1). For patients in cohort 2 a sCr value at the time of enrollment was considered as T_0, with a second determination recorded at 48-72 hours (T_1). Being described the possibility of late increases in sCr up to about 5 days after exposure to contrast media, sCr was also recorded 5 (T_2) and 7 days (T_3) after CECT/enrollment.[8]

Demographic, clinical and biochemical variables were recorded on a specific database, including sex, age, ethnicity, height, weight, BMI, etiology of cirrhosis, mean arterial pressure, heart rate, Child-Pugh, MELD and MELD-Na scores, eGFR (according to MDRD-4, MDRD-6, CKD-EPI and Cockcroft-Gault formulas), known pre-

existing CKD, diabetes, arterial hypertension, congestive heart failure, hepatocellular carcinoma, esophageal varices, presence and grade of ascites, hepatic encephalopathy, concomitant medications (including intravenous fluids and human albumin administration), sCr, serum sodium, potassium, albumin, bilirubin, INR, transaminases, serum urea, white blood cell count, C-reactive protein, urinary sodium (UNa), urinary urea (U-urea), urine creatinine (uCr), amount and type of ICM administered, adoption of preventive measures for CI-AKI[1] in patients with pre-existing CKD or eGFR <45 ml/min/1.73 m^2, need for renal replacement therapy.

Measures for AKI prevention included intravenous volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, together with oral N-acetyl-cysteine, as per international guidelines.[1]

AKI was defined as per KDIGO guidelines as modified in ICA-AKI criteria.[1,26]

As soon as the equipment for laboratory analysis was made available (May 2019), U-NGAL concentrations were assessed at T_0 and T_1 in a subset of 100 consecutive patients with cirrhosis, 50 from cohort 1 and 50 from cohort 2.

Finally, only in those patients who developed CI-AKI, a 3- and 6-month follow-up was scheduled, including clinical examination and laboratory tests, to evaluate the resolution or persistence of kidney dysfunction.

All laboratory tests were carried out in the two participating centers, except for U-NGAL dosage, which was carried out exclusively in the laboratory of the Città della Salute e della Scienza Hospital of Turin. U-NGAL concentrations were measured by chemiluminescent microparticle capture two-phase immunological assay (CMIA) using monoclonal mouse antibodies on Alinity i analyzer (Abbott Laboratories, Abbott Park, Illinois, U.S.A.). U-NGAL levels were normalized for uCr and reported in µg/g

creatinine. All study samples were processed within 4 hours of collection and stored at -80°C. All NGAL measurements were performed in batch at the end of the study. The functional sensitivity (LoQ) of the assay was 3.0 ng/mL; within-run and between-run precision assessment yielded <5% coefficient of variation (CV) and <10% CV, respectively.

2.3 Statistics

Continuous variables were reported as median and interquartile range (IQR), while categorical variables as number (n) and frequency (%). Data normality was checked by D'Agostino-Pearson test. P-values for pairwise comparisons correspond to Kolmogorov-Smirnov, Wilcoxon Rank Sum and $\chi 2$ or Fisher's exact tests for numerical, ordinal and nominal data, respectively. Kruskal-Wallis tests were used to compare continuous variables among multiple independent groups, while comparisons between paired measurements were performed by Wilcoxon Signed Rank test.

Propensity score analysis was performed to adjust for the different demographic and clinical characteristics between cohort 1 and 2. Propensity score matching method was applied on the two cohorts of cirrhotic patients using the R package MatchIt[2], which performs pairing, subset selection, and subclassification with the aim of creating patients' groups balanced on included covariates. Specifically, among all the parameters significantly different at baseline between cohorts 1 and 2 and in order to avoid multicollinearity, we considered as covariates sex, BMI, MELD-Na, Child-Pugh and eGFR (MDRD-4). The propensity score estimation was then performed using the default model, which is a logistic regression using R function glm (generalized linear models). 1:1 matching was performed and, considering the estimated propensities,

extreme matched pairs of patients were filtered out in order to preserve a standardized mean difference to assess the balance of variables lower than 0.1.

Logistic regression analysis was used to test the association between one or more variables with the outcome (AKI development); the strength of association was reported as odd ratio (OR) with the corresponding 95% confidence interval (CI). Variables that resulted significantly associated to AKI development at univariate analysis were selected in order to avoid multicollinearity, dichotomized according to their median values, and then tested by multivariate regression analysis.

A sample size calculation was made considering all the manuscripts available at the time of our study protocol submission to Ethics Committee. Considering the summary results from previous studies[15-20], with a two-sided significance of 0.05 and a power of 0.80, a total of 408 patients was required with 1:1:1 ratio among the three cohorts.

Statistical analyses were performed by using R package atable and MedCalc Software v.18.9.1 (MedCalc bvba, Ostend, Belgium). P-values ≤0.05 were considered statistically significant.

3. RESULTS

Overall, 444 patients were included in the analysis. A total of 148, 133 and 163 patients were included in cohorts 1, 2 and 3, respectively. Main patients' characteristics are shown in **Table 3**.

Data on etiology of cirrhosis are presented according to the prevalent cause of liver damage. As regards metabolic-associated steatotic liver disease (MASLD), which can be associated with an increased susceptibility to kidney damage, it was present in 33

(22%) and 32 (24%) patients in cohorts 1 and 2, respectively, either alone or as cofactor of liver injury. Similarly alcoholic liver disease, either pure or as a cofactor, was reported in 75 (51%) and 71 (53%) patients in cohorts 1 and 2, respectively.

Of note, 3 patients in cohort 1 and 2 patients in cohort 2 had pre-renal AKI at admission, which was completely resolved before enrolment in the study.

As regards indications for CECT, the vast majority of cirrhotic patients underwent the examination to diagnose and/or stage hepatocellular carcinoma (HCC) or portal vein thrombosis (57%), 27% of CECTs were requested for purposes of pre-liver transplant evaluation, whereas a minority were aimed to investigate non-HCC cancers (5%) or various acute extra-hepatic diseases (11%). On the contrary, in patients without cirrhosis CECTs were mainly requested to assess for acute extra-hepatic diseases (60%) or non-HCC cancers (38%), in one case (1%) to investigate a portal vein thrombosis (1%), and in one case as a pre-liver transplant assessment for a patient with polycystic liver disease (1%).

All the patients in cohorts 1 and 3 were administered non-ionic, low- or iso-osmolality CM.

Table 3. Patients' characteristics and AKI incidence in the three cohorts.

	COHORT 1 Cirrhosis + CECT	**COHORT 2 Cirrhosis, no CECT**	**COHORT 3 No cirrhosis + CECT**	**p value***	**p value†**
Patients, n	148	133	163		
Age (years), median (IQR)	61 (54–67)	59 (52–68)	66 (54–78)	0.640	**<0.001**
Gender (M/F), n	109/39	81/52	94/69	**0.031**	**0.005**
BMI (Kg/m^2), median (IQR)	26.3 (23.6–29.2)	24.5 (22.0–28.4)	23.7 (21.4–26.6)	**0.015**	**<0.001**
MAP (mmHg), median (IQR)	86.7 (76.7–96.7)	83.3 (76.7–91.8)	91.7 (83.3–98.3)	0.095	**0.007**
Etiology					
Viral, n (%)	68 (45.9%)	45 (33.8%)	-		
Alcohol, n (%)	50 (33.8%)	53 (39.8%)	-	0.130	-
MASLD, n (%)	22 (14.9%)	21 (15.8%)	-		
Other, n (%)	8 (5.4%)	14 (10.5%)	-		
Reasons for hospitalisation, n					
Ascites/hydrotorax	47	44	3	0.898	**<0.001**
GI bleeding/anemia	21	20	18	0.867	0.493
Hepatic encephalopathy	19	21	/	0.499	/
Jaundice	4	3	6	1.000	0.753
AKI	3	2	0	1.000	0.107
ACLF	5	4	/	1.000	/
TIPS placement/revision	3	2	/	1.000	/
HCC treatment	6	2	/	0.288	/
Liver transplant assessment	7	5	1	0.774	**0.030**
Fever/suspected infection	9	8	11	1.000	1.000
Other[#]	24	22	124	1.000	**<0.001**
Indications for CECT, n (%)					
Evaluation of portal vein patency/exclusion or staging of HCC	84 (57%)		1 (1%)		**<0.001**
Liver transplant assessment	40 (27%)	NA	1 (1%)	/	**<0.001**
Investigation of non-HCC cancers	8 (5%)		62 (38%)		**<0.001**
Investigation of acute extra-hepatic diseases	16 (11%)		99 (60%)		**<0.001**
Child-Pugh score					
A, n (%)	42 (28.4%)	11 (8.3%)	-	**<0.001**	-
B, n (%)	70 (47.3%)	70 (52.6%)	-		
C, n (%)	36 (24.3%)	52 (39.1%)	-		
MELD, median (IQR)	14 (11–18)	16 (13–20)	-	**0.028**	-
MELD-Na, median (IQR)	15.4 (11.9–19.5)	17.4 (13.0–21.9)	-	**0.007**	-
sCr (mg/dL), median (IQR)	0.80 (0.66–1.01)	0.91 (0.69–1.15)	0.78 (0.65–0.95)	0.068	0.760
eGFR (MDRD-4), median (IQR)	97.7 (75.0–125.9)	86.4 (61.0–113.6)	94.0 (75.9–118.6)	**0.013**	0.870
eGFR (MDRD-6), median (IQR)	87.6 (62.5–109.5)	76.6 (51.9–105.5)	90.2 (71.7–111.9)	**0.048**	0.160
Known history of CKD, n (%)	12 (8.1%)	18 (13.5%)	10 (6.1%)	0.200	0.516
eGFR (MDRD-4) <60 ml/min/1.73 m^2, n (%)	16 (11%)	32 (24%)	20 (12%)	**0.005**	0.960
Type 2 diabetes, n (%)	40 (27.0%)	36 (27.1%)	25 (15.3%)	1.000	**0.017**
Arterial hypertension, n (%)	43 (29.1%)	35 (26.3%)	78 (47.9%)	0.710	**0.001**
Congestive heart failure, n (%)	3 (2.0%)	2 (1.5%)	2 (1.2%)	1.000	0.910
Concomitant infection, n (%)	14 (9.5%)	17 (12.8%)	24 (15.0%)	0.490	0.190
Active HCC, n (%)	39 (26.4%)	28 (21.1%)	0	0.370	-
Esophageal varices,					
No, n (%)	48 (32.4%)	43 (33.1%)	-		
F1, n (%)	32 (21.6%)	40 (30.8%)	-	0.360	-
F2, n (%)	39 (26.4%)	29 (22.3%)	-		
F3, n (%)	5 (3.4%)	2 (1.5%)	-		
Eradicated, n (%)	24 (16.2%)	16 (12.3%)	-		
Previous ascites, n (%)	73 (49.3%)	81 (60.9%)	-	0.068	-
Ascites grade					
0, n (%)	61 (41.2%)	42 (31.6%)		0.190	-

1, n (%) 2, n (%) 3, n (%)	29 (19.6%) 44 (29.7%) 14 (9.5%)	25 (18.8%) 44 (33.1%) 22 (16.5%)	- - - -		
Patients submitted to paracentesis between T0-T3, n	8	7	NA	1.000	/
Volume of ascites drained (L), median (IQR)	5.0 (3.0-7.0)	5.5 (4.0-7.0)	NA	0.598	/
Previous hepatic encephalopathy, n (%)	45 (30.8%)	48 (36.4%)	-	0.390	-
Previous variceal bleeding, n (%)	37 (25.7%)	28 (21.1%)	-	0.440	-
Concomitant potentially nephrotoxic therapy, n (%)	34 (23.0%)	32 (24.1%)	75 (46.0%)	0.940	**<0.001**
Albumin infusion < 14 days, n (%)	51 (34.5%)	45 (34.1%)	-	1.000	-
Loop diuretics, n (%)	104 (70.7%)	104 (78.2%)	14 (8.6%)	0.200	**<0.001**
Loop diuretics dose (mg/day), median (IQR)	50 (25–75)	50 (25–80)	25 (20–50)	0.260	0.079
Antialdosteronic drugs, n (%)	102 (69.4%)	98 (73.7%)	6 (3.7%)	0.510	**<0.001**
Antialdosteronic dose (mg/day), median (IQR)	200 (200–300)	200 (100–400)	100 (50–200)	0.650	0.260
Beta-blockers, n (%)	71 (48.0%)	61 (45.9%)	33 (20.4%)	0.820	**<0.001**
Other antihypertensive drugs, n (%)	18 (12.2%)	10 (7.5%)	61 (37.4%)	0.270	**<0.001**
Proton pump inhibitors, n (%)	73 (49%)	68 (51%)	73 (45%)	0.738	0.481
s-Na (mmol/L), median (IQR)	137 (135–140)	136 (133–139)	140 (137–142)	0.300	**<0.001**
s-K (mmol/L), median (IQR)	4.0 (3.7–4.3)	3.9 (3.6–4.2)	3.9 (3.6–4.2)	0.084	0.720
Total bilirubin (mg/dL), median (IQR)	1.8 (1.1–3.9)	2.8 (1.3–4.7)	0.7 (0.5–1.6)	**0.023**	**<0.001**
INR, median (IQR)	1.50 (1.31–1.72)	1.55 (1.33–1.95)	1.16 (1.06–1.25)	0.150	**<0.001**
AST (IU/L), median (IQR)	41 (29–68)	37 (25–67)	21 (14–61)	0.380	**<0.001**
ALT (IU/L), median (IQR)	26 (20–46)	23 (16–38)	22 (12–82)	0.150	**0.002**
WBC (10^9/L), median (IQR)	5.3 (3.7–8.1)	5.6 (3.9–7.8)	8.3 (6.5–11.7)	0.710	**<0.001**
CRP (mg/L), median (IQR)	10.4 (4.8–28.5)	11.4 (3.8–26.2)	26.5 (5.5–90.0)	0.520	**<0.001**
Albumin (g/dL), median (IQR)	3.1 (2.6–3.7)	2.9 (2.6–3.2)	3.2 (2.9–3.6)	**0.002**	0.380
s-urea (mg/dL), median (IQR)	33 (25–43)	35 (21–52)	25 (16–35)	0.140	**<0.001**
ICM dose (g), median (IQR)	50 (44–56)	-	44 (41–48)	-	**<0.001**
ICM type -Iomeprol -Iopromide -Ioversol -Iobitridol -Iodixanol	 85 (57.4%) 61 (41.2%) 0 (0%) 0 (0%) 2 (1.4%)	-	 58 (35.6%) 99 (60.7%) 4 (2.5%) 1 (0.6%) 1 (0.6%)	-	-
AKI prophylaxis, n (%)	11 (7.4%)	-	11 (6.7%)	-	0.815
Volume of intravenous fluids on CECT day (mL/24h), median (IQR)	250 (0–850)	-	1000 (300–1750)	-	**<0.001**
U-NGAL (ng/mL), median (IQR)	17.70 (11.85-32.53)	19.50 (10.55-30.93)	-	0.069	-
AKI (KDIGO criteria), n (%) -stage 1A -stage 1B -stage 2 -stage 3	7 (4.8%) 4 (57%) 2 (29%) 1 (14%) 0	2 (1.5%) 2 (100%) 0 0 0	4 (2.5%) 3 (75%) 1 (25%) 0 0	0.240	0.430

Data are presented as median (interquartile range), or number (proportion). *p values for the comparison between cohort 1 and 2. †p values for the comparison between cohort 1 and 3. Level of significance: p <0.05 (p-values for pairwise comparisons correspond to Kolmogorov-Smirnov, Wilcoxon Rank Sum and χ2 or Fisher's exact tests for numerical, ordinal and nominal data, respectively).

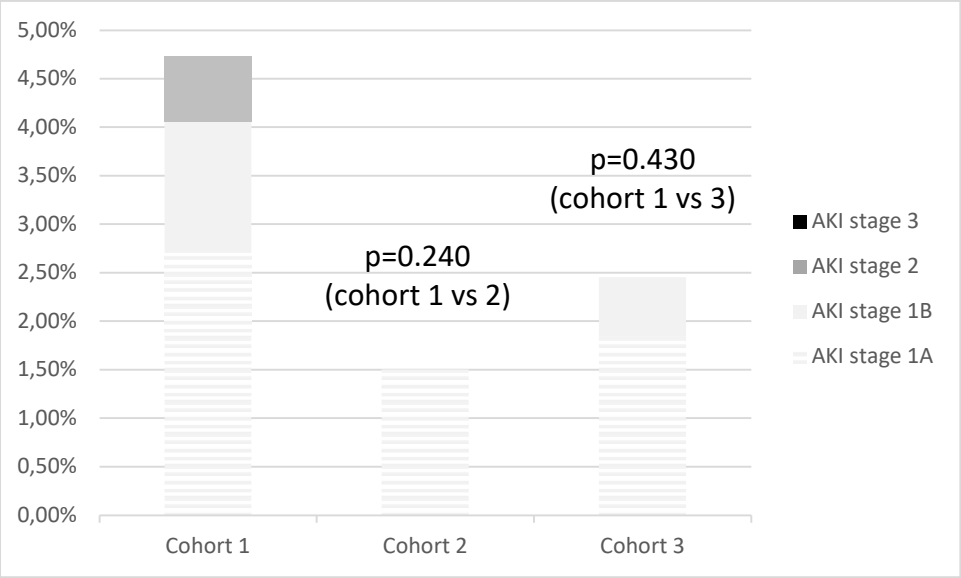
BMI, body mass index; MAP, mean arterial pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; HCC, hepatocellular carcinoma; MELD, model for end stage liver disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CKD, chronic kidney disease; sCr, serum creatinine; s-Na, serum sodium; s-K, serum potassium; INR, international normalized ratio; WBC, white blood cell count; CRP, C-reactive protein; ICM, iodinated contrast media; AKI, acute kidney injury; CECT, contrast-enhanced computerized tomography; U-NGAL, urinary neutrophil gelatinase-associated lipocalin; GI, gastrointestinal; ACLF, acute-on-chronic liver failure; TIPS, transjugular intrahepatic portosystemic shunt; NA, not available.

Other reasons for hospitalization in group 1: 6 hepato-/porto-pulmonary syndrome, 4 biliopancreatic diseases, 4 liver enzymes elevation, 3 abdominal pain, 1 bone fracture, 1 Budd-Chiari syndrome, 1 complicated inguinal hernia, 1 endoscopic elective procedure, 1 post-surgical complications, 1 portal vein thrombosis, 1 weight loss. Other reasons for hospitalization in group 2: 6 biliopancreatic diseases, 6 abdominal pain, 3 cardiac diseases, 2 diarrhea, 2 diabetes decompensation, 1 endoscopic elective procedure, 1 spontaneous hemoperitoneum in HCC, 1 haemoptysis. Other reasons for hospitalization in group 3: 58 biliopancreatic diseases, 13 diarrhea, 13 inflammatory bowel diseases, 10 abdominal pain, 8 gastrointestinal cancer, 4 diverticulitis, 4 weight loss, 4 liver enzyme elevation, 3 dysphagia, 3 endoscopic elective procedure, 2 post-surgical/endoscopic complications, 1 pyloric stenosis, 1 portal vein thrombosis.

3.1 Acute kidney injury

A total of 13 AKI cases were recorded: 7 cases (4.8%) in cohort 1, 2 cases (1.5%) in cohort 2 and 4 cases (2.5%) in cohort 3, with no statistically significant difference between the groups (p=0.240 for comparison between cohort 1 and 2, p=0.430 for comparison between cohort 1 and 3; **Table 3** and **Figure 2**).

Fig. 2. AKI incidence and severity in the three study cohorts.



Bars represent AKI incidences in the three studied cohorts. Bar colors/textures indicate the stage of severity of AKI episodes, as indicated in the legend.

Level of significance: p <0.05 (Wilcoxon Signed Rank test).

A propensity matched analysis was performed to adjust for the observed differences in baseline characteristics between cohorts 1 and 2 (sex, BMI, Child-Pugh and MELD-Na score, eGFR): 104 patients per cohort were kept for the statistical comparison, and

both CI-AKI incidence and all the patients' characteristics showed no significant differences between the two cohorts. Despite the reduction of samples, no AKI cases were filtered out, resulting in observed CI-AKI rates of 6.7% and 1.9% for cohort 1 and 2, respectively (**Table 4**).

Table 4. Patients' characteristics and AKI incidence in the two cohorts of patients with cirrhosis after propensity score matching.

	COHORT 1 Cirrhosis + CECT	**COHORT 2 Cirrhosis, no CECT**	**p value**
Patients, n	104	104	
Age (years), median (IQR)	61 (54–67)	60 (53.8–68.3)	0.720
Sex (M/F), n	75/29	61/43	0.058
BMI (Kg/m2), median (IQR)	26.2 (23.7–29.5)	24.4 (22.4–28)	0.061
MAP (mmHg), median (IQR)	83.3 (76.7–93.3)	83.3 (76.7–90)	0.440
Etiology Viral, n (%) Alcohol, n (%) MASLD, n (%) Other, n (%)	 44 (42%) 38 (37%) 17 (16%) 5 (5%)	 36 (35%) 40 (38%) 19 (18%) 9 (9%)	0.550
Child-Pugh score A, n (%) B, n (%) C, n (%)	 10 (10%) 61 (58%) 33 (32%)	 6 (6%) 51 (49%) 47 (45%)	0.110
MELD, median (IQR)	15.4 (11.9–19.2)	17 (12.7–20.5)	0.120
MELD-Na, median (IQR)	17 (12.8–21.6)	18.3 (13.9–22.8)	0.300
sCr (mg/dL), median (IQR)	0.8 (0.65–1.04)	0.88 (0.69–1.09)	0.390
eGFR (MDRD-4), median (IQR)	96.4 (73.3–127.4)	88 (64.1–110.2)	0.230
eGFR (MDRD-6), median (IQR)	82.4 (60.6–109.3)	78.4 (55.2–102.5)	0.500
Known history of CKD, n (%)	12 (12%)	12 (12%)	1.000
eGFR (MDRD-4) <60 ml/min/1.73 m^2, n (%)	14 (13%)	21 (20%)	0.270
Type 2 diabetes, n (%)	26 (25%)	28 (27%)	0.870
Arterial hypertension, n (%)	29 (28%)	27 (26%)	0.880
Congestive heart failure, n (%)	3 (3%)	2 (2%)	1.000
Concomitant infection, n (%)	12 (12%)	13 (12%)	1.000
Active HCC, n (%)	25 (24%)	22 (21%)	0.740
Esophageal varices, No, n (%) F1, n (%) F2, n (%) F3, n (%) Eradicated, n (%)	 32 (31%) 24 (23%) 30 (29%) 1 (1%) 17 (16%)	 33 (32%) 35 (34%) 21 (20%) 2 (2%) 11 (11%)	0.210
Previous ascites, n (%)	60 (58%)	64 (62%)	0.670

Ascites grade 0, n (%) 1, n (%) 2, n (%) 3, n (%)	 31 (30%) 25 (24%) 36 (35%) 12 (11%)	 34 (33%) 18 (17%) 35 (34%) 17 (16%)	0.540
Previous hepatic encephalopathy, n (%)	37 (36%)	38 (37%)	1.000
Previous variceal bleeding, n (%)	24 (23%)	22 (21%)	0.750
Concomitant potentially nephrotoxic therapy, n (%)	24 (23%)	24 (23%)	1.000
Albumin infusion <14 days, n (%)	43 (41%)	34 (33%)	0.250
Loop diuretics, n (%)	82 (79%)	84 (81%)	0.970
Loop diuretics dose (mg/day), median (IQR)	50 (25–75)	50 (25–80)	0.310
Antialdosteronic drugs, n (%)	81 (78%)	77 (74%)	0.540
Antialdosteronic dose (mg/day), median (IQR)	200 (200–300)	200 (100–300)	0.300
Beta-blockers, n (%)	51 (49%)	45 (43%)	0.490
Other antihypertensive drugs, n (%)	10 (10%)	5 (5%)	0.280
s-Na (mmol/L), median (IQR)	137 (133–140)	136.5 (132.8–139)	0.720
s-K (mmol/L), median (IQR)	3.9 (3.7–4.3)	3.9 (3.6–4.2)	0.900
Total bilirubin (mg/dL), median (IQR)	2.55 (1.4–4.5)	2.9 (1.3–6)	0.720
INR, median (IQR)	1.5 (1.36–1.79)	1.63 (1.36–1.99)	0.120
AST (IU/L), median (IQR)	42 (32–78)	37 (25.5–67)	0.120
ALT (IU/L), median (IQR)	26 (19–44)	23 (16–35.5)	0.300
WBC (10^9/L), median (IQR)	5.7 (3.8–8.1)	5.7 (3.9–7.3)	0.990
CRP (mg/L), median (IQR)	11.2 (5.1–31)	11.4 (3.9–26.1)	0.560
Albumin (g/dL), median (IQR)	3 (2.6–3.4)	2.9 (2.6–3.2)	0.095
s-urea (mg/dL), median (IQR)	34.5 (25–44.8)	35.5 (20–50.3)	0.240
ICM dose (g), median (IQR)	48.1 (44.4–56)	-	-
ICM type -Iomeprol -Iopromide -Ioversol -Iobitridol -Iodixanol	 61 (58.7%) 35 (33.7%) 0 (0%) 0 (0%) 2 (1.9%)	-	-
AKI prophylaxis, n (%)	8 (7.6)	-	-
Volume of intravenous fluids on CECT day (mL/24h), median (IQR)	500 (0–1000)	-	-
U-NGAL (ng/mL), median (IQR)	19.8 (12.9-37.1)	19.5 (12.7-31.5)	0.910
AKI (KDIGO criteria), n (%) -stage 1A -stage 1B -stage 2 -stage 3	7 (6.7%) 4 (57.1%) 2 (28.6%) 1 (14.3%) 0	2 (1.9%) 2 (100%) 0 0 0	0.170

Data are presented as median (interquartile range), or number (proportion). Level of significance: $p < 0.05$ (p-values for pairwise comparisons correspond to Kolmogorov-Smirnov, Wilcoxon Rank Sum and $\chi 2$ or Fisher's exact tests for numerical, ordinal and nominal data, respectively).

BMI, body mass index; MAP, mean arterial pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; HCC, hepatocellular carcinoma; MELD, model for end stage liver disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CKD, chronic kidney disease; sCr, serum creatinine; s-Na, serum sodium; s-K, serum potassium; INR, international

normalized ratio; WBC, white blood cell count; CRP, C-reactive protein; ICM, iodinated contrast media; AKI, acute kidney injury; CECT, contrast-enhanced computerized tomography; U-NGAL, urinary neutrophil gelatinase-associated lipocalin.

The baseline characteristics of those patients who developed AKI in the three cohorts are summarised in **Table 5**.

Table 5. Baseline characteristics, liver and kidney function parameters, T0 and T1 U-NGAL levels of patients who developed AKI.

Cohort	AKI stage	Sex	Age (years)	Child-Pugh score	MELD	MELD-Na	Total bilirubin (mg/dl)	INR	T0 s-Cr (mg/dl)	MDRD-4 (ml/min/ 1.73 m^2)	Ascites grade	Presence of infections	U-NGAL T0 (ng/mL)	U-NGAL T1 (ng/mL)
1	1A	M	79	C10	15	22	3,1	1,5	0,51	167	2	Yes	-	-
	2	M	43	A6	10	18	0,6	1,32	0,76	119	2	Yes	-	-
	1A	F	60	B8	16	16	0,8	2,44	0,61	107	0	No	12	21
	1A	M	63	B9	19	22	8,7	1,48	0,68	125	0	Yes	37.7	44.8
	1B	M	56	C12	30	30	22,2	2,41	1,18	68	2	Yes	172.7	58.5
	1B	M	67	C11	34	34	35,2	2,49	1,51	49	2	Yes	13.9	41.1
	1A	M	65	A6	12	12	1,1	1,65	0,65	131	2	No	10	14
2	1A	F	68	C10	15	15	2,7	1,55	0,51	128	3	No	-	-
	1A	M	57	B9	12	13	1,4	1,48	0,94	88	3	No	10	10
3	1A	F	57	-	-	-	0,6	1,04	0,49	139	-	No	-	-
	1A	F	68	-	-	-	0,2	1,31	0,44	151	-	No	-	-
	1A	M	75	-	-	-	15,8	1,33	1,02	76	-	No	-	-
	1B	M	67	-	-	-	4,0	1,12	1,18	66	-	No	-	-

Most cases of AKI were mild and transient. Among the 7 AKI cases in cohort 1, 2 cases were lost at follow-up, 4 cases resolved completely within 1-3 months, whereas 1 patient was then diagnosed with hepatorenal syndrome and started terlipressin treatment 5 days after CT because of progressive kidney function deterioration and finally underwent orthotopic liver transplantation 9 days after CT (of note, baseline sCr values were restored after liver transplantation). As regards cohort 2, both cases of AKI resolved completely before discharge from the hospital. Among the 4 AKI cases in cohort 3, 3 cases resolved completely before discharge or within 3-month follow-up, whereas the remaining patient was lost at follow-up. No patient needed dialysis.

The comparison of kidney function parameters at T0 and T1 showed statistically significant but clinically irrelevant increases in sCr, UNa and U-urea after CM administration in cohort 1 (**Table 6**). No significant changes in kidney function parameters were detected in cohort 2.

Table 6. Comparison of kidney function at T0, T1, T2 and T3 in patients with cirrhosis exposed (cohort 1) or not (cohort 2) to contrast media.

	Parameters	T0	T1	P for comparison between T0 and T1	T2	P for comparison between T0 and T2	T3	P for comparison between T0 and T3
COHORT 1	sCr (mg/dl)	0.80 (0.66–1.01)	0.82 (0.68-1.01)	**0.031**	0.81 (0.60-1.04)	0.132	0.81 (0.64-1.01)	0.140
	s-Urea (mg/dl)	33 (25-43)	34 (25-50)	0.122	-	-	-	-
	UNa (mmol/L)	72.0 (51.5-106.5)	85.5 (56.0-118.0)	**0.032**	-	-	-	-
	U-K (mmol/L)	28.0 (17.0-35.0)	23.0 (17.0-33.0)	0.652	-	-	-	-
	UCr (g/L)	0.59 (0.36-0.97)	0.71 (0.42-1.21)	0.063	-	-	-	-
	U-urea (g/L)	9.85 (7.35-17.9)	12.66 (8.30-18.50)	**0.047**	-	-	-	-
	eGFR, MDRD-4 (ml/min/1.73 m^2)	97.7 (75.0–125.9)	95.7 (75.5-118.6)	0.058	96.7 (76.7-122.2)	0.170	95.9 (81.5-118.1)	0.146
	U-NGAL (ng/ml) – 50 pts	17.70 (11.85-32.53)	17.50 (11.28-31.43)	0.889	-	-	-	-
	U-NGAL/UCr (µg/g) - 50 pts	22.89 (10.64-83.65)	26.55 (16.39-49.76)	0.912	-	-	-	-
COHORT 2	sCr (mg/dl)	0.91 (0.69–1.15)	0.88 (0.68-1.11)	0.292	0.90 (0.71-1.07)	0.759	0.88 (0.69-1.09)	0.601
	s-Urea (mg/dl)	35 (21-52)	33 (22-52)	0.951	-	-	-	-
	UNa (mmol/L)	67.0 (43.0-104.0)	67.6 (53.0-92.0)	0.772	-	-	-	-
	U-K (mmol/L)	23.0 (17.3-28.0)	23.0 (14.6-31.0)	0.788	-	-	-	-
	UCr (g/L)	0.50 (0.31-0.90)	0.51 (0.32-0.72)	0.833	-	-	-	-
	U-urea (g/L)	7.50 (5.35-10.70)	7.50 (4.40-11.25)	0.796	-	-	-	-
	eGFR, MDRD-4 (ml/min/1.73 m^2)	86.4 (61.0–113.6)	87.1 (60.3-116.9)	0.375	85.7 (66.5-115.5)	0.661	84.3 (65.9-114.0)	0.322
	U-NGAL (ng/ml) – 50 pts	19.50 (10.55-30.93)	20.90 (12.50-31.90)	0.681	-	-	-	-
	U-NGAL/UCr (µg/g) - 50 pts	34.31 (18.75-60.67)	43.70 (25.89-76.24)	0.701	-	-	-	-

Level of significance: $p < 0.05$ (Wilcoxon Signed Rank test).

sCr, serum creatinine; s-Urea, serum urea; Una, urinary sodium; U-K, urinary potassium; UCr, urinary creatinine; U-urea, urinary urea; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; U-NGAL, urinary neutrophil gelatinase-associated lipocalin.

Variations (Δ) of kidney function parameters and U-NGAL between T0 and T1 were also calculated and compared between cohort 1 and the other two cohorts (**Table 7**).

Table 7. Delta changes of kidney function parameters and U-NGAL between T0 and T1 in the three cohorts.

Delta T1-T0	Cohort 1	Cohort 2	Cohort 3	p value*	p value†
ΔsCr (mg/dL), median (IQR)	+0.02 (-0.05 to +0.10)	-0.01 (-0.09 to +0.07)	-0.03 (-0.12 to +0.05)	**0.029**	**0.001**
Δs-Urea (mg/dL), median (IQR)	+1 (-5 to +8)	+1 (-6 to +5)	0 (-4 to +4)	0.389	0.300
ΔU-Na (mmol/L), median (IQR)	+6.0 (-12.0 to +34)	-3.5 (-22.0 to +23.0)	+28.5 (-17.0 to +59.5)	0.093	0.508
ΔU-K (mmol/L), median (IQR)	-0.9 (-7.8 to +6.5)	0 (-7.8 to +9.0)	+6.0 (-12.5 to +11.0)	0.659	0.510
ΔU-Cr (g/L), median (IQR)	+0.05 (-0.12 to +0.31)	+0.01 (-0.21 to +0.21)	+0.02 (-0.53 to +0.14)	0.202	0.452
ΔU-Urea (g/L), median (IQR)	+0.80 (-2.28 to +5.96)	-0.10 (-2.58 to +2.61)	+4.25 (-9.60 to +6.55)	0.375	0.784
ΔeGFR (MDRD-4, mL/min/1.73 m^2)	-2.30 (-13.50 to +7.75)	+2.20 (-8.58 to +13.50)	+5.00 (-8.53 to +17.53)	**0.031**	**0.001**
ΔU-NGAL (µg/g)	+0.20 (-7.58 to +5.50)	0.00 (-6.80 to +9.50)	NA	0.682	NA

*p values for the comparison between cohort 1 and cohort 2. †p values for the comparison between cohort 1 and cohort 3. Level of significance: p <0.05 (Wilcoxon Rank Sum Test).

ΔsCr, delta of serum creatinine; Δs-Urea, delta of serum urea; ΔU-Na, delta of urinary sodium; ΔU-K, delta of urinary potassium; ΔU-Cr, delta of urine creatinine; ΔU-Urea, delta of urinary urea; ΔeGFR, delta of glomerular filtration rate estimated by MDRD-4 formula; ΔU-NGAL, delta of urinary NGAL.

Logistic regression analysis identified the following variables as significantly associated with AKI development in patients with cirrhosis exposed to CM: MELD score, MELD-Na score, presence of concomitant infections, total serum bilirubin, C-reactive protein and total volume of fluids infused on the day of CT scan examination (**Table 8**).

At multivariate logistic regression analysis, only the presence of concomitant infections resulted significantly and independently associated with AKI development (OR 22.18, 95%CI 2.87-171.22, p=0.003), whereas no significant association was observed for MELD-Na, CRP and amount of liquid infusion at CT (**Table 8**).

Table 8. Regression analysis for variables associated with AKI development (cohort 1).

Variables	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Age	1.02 (0.94–1.11)	0.569		
Gender (male)	2.16 (0.25–18.51)	0.484		
BMI	0.94 (0.83–1.07)	0.327		
MAP	0.99 (0.92–1.06)	0.672		
Viral etiology	1.58 (0.34–7.34)	0.557		
Child-Pugh score A	1.00 (0.19-5.37)	1.000		
MELD	1.12 (1.00-1.26)	**0.048**		
MELD-Na	1.14 (1.02–1.28)	**0.022**	3.06 (0.27–34.85)	0.367
eGFR (MDRD4)	1.01 (0.99–1.03)	0.616		
eGFR (MDRD6)	1.00 (0.98–1.03)	0.873		
CKD-EPI	1.00 (0.97-1.04)	0.993		
CKD	0.75 (0.04-14.00)	0.848		
Type 2 diabetes	1.11 (0.21–5.99)	0.900		
Arterial hypertension	0.15 (0.01–2.77)	0.205		
Congestive heart failure	nc			
Concomitant infections	36.39 (6.18–214.38)	**0.0001**	**22.18 (2.87-171.22)**	**0.003**
Esophageal varices (presence)	1.18 (0.22–6.34)	0.843		
Ascites	1.82 (0.34–9.71)	0.483		
Concomitant hepatic encephalopathy	3.10 (0.55-17.32)	0.197		
Potential nephrotoxic therapy	1.35 (0.25-7.29)	0.727		

Albumin infusion < 14 days	5.28 (0.99-28.26)	0.052		
Dose of albumin infused < 14 days	1.01 (1.00-1.02)	0.210		
Loop diuretics	5.80 (0.32-105.26)	0.235		
Loop diuretics dose	1.00 (0.98–1.02)	0.878		
Antialdosteronic drugs therapy	6.19 (0.34-112.35)	0.217		
Antialdosteronic drugs dose	1.00 (0.99-1.01)	0.809		
Beta blockers	0.17 (0.02-1.42)	0.101		
Other antihypertensives	0.44 (0.02-8.06)	0.581		
sCr	0.86 (0.07- 10.81)	0.905		
s-Na	0.88 (0.75- 1.02)	0.091		
Total bilirubin	1.13 (1.03-1.23)	**0.007**		
INR	3.03 (0.86-10.69)	0.084		
AST	1.00 (1.00-1.01)	0.884		
WBC	1.00 (1.00–1.00)	0.853		
CRP	1.02 (1.00-1.03)	**0.011**	2.21 (0.20-24.66)	0.520
Albumin	1.65 (0.51-5.28)	0.403		
s-urea	1.01 (0.98-1.05)	0.505		
ICM dose	0.95 (0.86-1.05)	0.292		
Nephroprophylaxis	0.75 (0.04-14.00)	0.848		
Volume of intravenous fluids on CECT day	1.00 (1.00-1.00)	**0.005**	0.49 (0.06-3.95)	0.507

Level of significance: p <0.05 (Logistic regression analysis).

BMI, body mass index; MAP, mean arterial pressure; MELD, model for end stage liver disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; CKD, chronic kidney disease; sCr, serum creatinine; s-Na, serum sodium; INR, international normalized ratio; WBC, white blood cell count; CRP, C-reactive protein; ICM, iodinated contrast media; CECT, contrast-enhanced computerized tomography.

3.2 NGAL

No significant modifications of U-NGAL values between T0 and T1 could be detected in the series of consecutive patients tested for this marker, neither in cohort 1 nor in cohort 2 (**Table 6**). Median U-NGAL variations were +0.2 (-7,6 - +5,5) ng/ml and +0.0 (-6,8 - +9,5) ng/ml in cohorts 1 and 2, respectively (p=0.682, **Table 7**).

T1 NGAL values were not significantly different in cohort 1 compared to cohort 2 [17.50 (11.28-31.43) vs 20.90 (12.50-31.90), p=0.445]. Considering cohort 1, post-CECT (T1) NGAL values were not significantly different in patients who developed AKI compared to non-AKI patients (35.88 ± 18.16 vs 25.92 ± 29.03 respectively, p=0.459).

4. DISCUSSION

Although cirrhosis has been traditionally considered as a predisposing factor for CI-AKI, only few studies have explored the safety of ICM administration in this peculiar group of patients. As shown in **Table 2**, most of those studies were retrospective, uncontrolled and based on different selection criteria as well as on old and diverse definitions of CI-AKI, which altogether led to very heterogeneous and uncertain incidence data, often not consistent with the perceived risk of this complication in common clinical practice.

To our knowledge, this is the first controlled study on CI-AKI prospectively enrolling a large cohort of patients with cirrhosis. Our results show that CI-AKI risk in cirrhosis is limited (4.8%), lower than that reported by several previous studies[17,19,20], and not significantly different from the risk observed in the general population. Furthermore, AKI incidence appears to be non-significantly increased in patients with cirrhosis exposed to ICM compared to the unexposed ones, thus suggesting that at least a proportion of the AKI episodes recorded after CECT can be unrelated to CM itself. Indeed, it is well-known that spontaneous increases in sCr can be frequently observed and, when occurring after ICM administration, they can be mistaken for CI-AKI, thus leading to an overestimation of the risk of this complication.[27,28] Therefore, there should be caution in attributing a worsening of kidney function to CM.

Notably, most AKI cases in our cohorts were mild (stage 1), with only minor elevations in sCr, asymptomatic and uncomplicated, with no need for therapeutic intervention, undergoing rapid and spontaneous resolution in few days before discharge from the hospital or otherwise completely resolved at 3-month follow-up. This is in contrast with previous reports by Lodhia et al.[17] and Filomia et al.[20] who described AKI persistence

longer than 7 days in 68% of cases and longer than 3 months in 59% of cases, respectively.

These conflicting results cannot be explained by the use of different types of ICM, because intravenous low-osmolality ICM were administered both in the previously published papers on CI-AKI in cirrhosis and in our cohorts.

The use of different definitions of CI-AKI might partly explain the lower overall rate of events in our population compared to previous studies. Until introduction of KDIGO criteria in 2012, CI-AKI was variously defined, often with criteria more inclusive than the current ones. For instance, if we adopted the definition (eGFR decrease ≥25% within 7 days from CECT) used by Lodhia et al.[17], the manuscript that reported the highest CI-AKI incidence, we would have recorded AKI incidence rates of 12.2%, 9% and 6.7% in cohorts 1, 2 and 3, respectively. Furthermore, we adopted exclusion criteria aimed at minimizing the risk of labelling as “contrast-induced” a number of AKI episodes due to other etiologies (e.g. volume depletion, use of nephrotoxic agents, etc). This risk appears indeed very likely in the previous studies as almost all had a retrospective design, even more so when they were uncontrolled.

A broader analysis of various kidney function parameters aiming to search for even minimal changes induced by ICM revealed no clinically significant modifications after ICM administration in patients undergoing CECT. Only minor but statistically significant increases in sCr, UNa and U-urea were detected in cohort 1 after CM administration, although their clinical meaning appears negligible. As regards the increase in UNa excretion, it could be explained by the known natriuretic effect of ICM.[29] Similarly, differences in Δ-sCr and Δ-eGFR among the cohorts were statistically but not clinically significant.

In 2004 Guevara et al. suggested the existence of a subclinical grade of kidney tubular damage induced by ICM, not detectable by sCr modifications or GFR measurement, but proven by the increase in urinary levels of a sensitive marker of tubular damage, N-acetyl-β-D-glucosaminidase (NAG).[16] Aiming to verify this result and to detect even subclinical degrees of kidney impairment, we assessed the modifications of the urinary concentrations of NGAL, a widely studied and promising marker of tubular damage, in a subgroup of consecutive patients with cirrhosis. No significant modifications of median U-NGAL values between T0 and T1 could be detected in the series of patients tested for this marker, neither in cohort 1 nor in cohort 2.

NGAL has been suggested to be an earlier and more sensitive marker of CI-AKI compared to sCr in the general non-cirrhotic population undergoing CECT, although the literature is not univocal.[30-34] Nevertheless, only one previous study evaluated NGAL after CECT in a small sample of 10 patients with cirrhosis, reporting no difference in their post-CECT plasma NGAL values compared to 74 control subjects.[24] Our study confirms this finding in a larger number of patients with cirrhosis, with no statistically significant difference in T1 U-NGAL values between those who developed AKI after CECT and those who did not.

Provided that multiple reports proved the capacity of U-NGAL to predict the development of AKI in cirrhosis by detecting early occurrence of kidney tubular damage[35-38], our results indicate that ICM administration is seldom the cause of significant tubular damage.

Considering the results of the present study, it seems reasonable to conclude that the vast majority of the events classified as CI-AKI on the basis of KDIGO criteria are indeed independent from ICM administration and more likely attributable to spontaneous sCr fluctuations.

At logistic regression analysis total serum bilirubin, MELD and MELD-Na score, the presence of concomitant infections, C-reactive protein and total volume of fluids infused on the day of CECT resulted to be significantly associated with AKI development in patients with cirrhosis exposed to ICM. The counterintuitive association between higher volume of fluids infused and AKI development could be explained by the tendency to administer more intravenous hydration in those patients considered at higher AKI risk on the basis of pre-existing risk factors and/or clinical judgment. Of note, other variables classically recognized as risk factors for CI-AKI, such as age, female gender, baseline eGFR, pre-existing CKD, diabetes, arterial hypertension, presence of ascites, concomitant diuretic therapy and ICM dose were not significantly associated with AKI. Finally, at multivariate logistic regression analysis only the presence of concomitant infections resulted to be significantly and independently associated with AKI development in patients with cirrhosis exposed to ICM. Although the results obtained by multivariate logistic regression analysis are limited by the low number of AKI events, they are consistent with the well-known role of infections and of systemic inflammation in the development of kidney impairment in cirrhosis, notwithstanding the exclusion from the study of patients with severe infections associated to hemodynamic instability and septic shock.[39]

The strengths of the present study are the prospective design, the comparison with two control cohorts, the use of an approved definition of (CI-)AKI according to KDIGO criteria, the use of well-defined selection criteria leading to the enrolment of “real life” patients, including those with ongoing diuretic therapy (74%) or with already ongoing infections (9.5%), provided that the diuretic dose was unchanged between T0 and T3 and that haemodynamic stability was maintained. The retrospective and/or uncontrolled design of previous studies could be responsible for relevant bias in data

collection and analysis, leading to the classification as CI-AKI even of cases where the availability of complete data would have led to a different diagnosis (e.g. AKI induced by dehydration, hypovolemia, shock). The availability of a control group of patients with cirrhosis not exposed to ICM allows us to account for spontaneous sCr fluctuations which otherwise would be hard to differentiate from CI-AKI episodes. On the other hand, the comparison with a cohort of non-cirrhotic patients allows us to assess if cirrhosis per se increases the risk of CI-AKI compared to the general population.

One further strength of our work is the assessment of U-NGAL that, as a more sensitive and earlier marker of tubular damage than sCr, confirms the negative results of the study.

We acknowledge some limitations. First, this was an observational, non-randomized study and a patients' selection bias cannot be excluded. One could argue that patients in cohort 2 were not prescribed a CECT due to worse basal kidney function and increased *a priori* risk of CI-AKI. Indeed, cohort 2 displays higher median sCr and lower median eGFR. However, these differences appear negligible on a clinical ground, not sufficient to justify a more precautional behavior of the clinician avoiding CECT in this cohort. Indeed, CECT was not performed in these patients because of lack of clinical indication and not for other reasons. Furthermore, a randomized approach in this context would not be ethically feasible. Also liver function, as expressed by Child-Pugh, MELD and MELD-Na score, is significantly, although slightly if considered from a clinical point of view, worse in cohort 2 compared to cohort 1 and this could represent another limitation of the study, as previous evidence showed that worse liver function can be associated with an increased risk of CI-AKI in cirrhosis.[21] However, as shown in Table 4, the two patients who developed AKI in cohort 2 were

not characterized by exceedingly worse kidney or liver function parameters at baseline compared to median cohort 1 values, which, together with the clinical considerations expressed above, makes the two groups convincingly comparable. Moreover, a propensity matched analysis was performed to adjust for those significant differences observed in baseline characteristics between cohorts 1 and 2, confirming the absence of any statistically significant difference in AKI incidence between the two cohorts. Second, our population of patients with cirrhosis, due to the relatively high prevalence of virus-related liver disease, may not be fully representative of other countries, in particular those with higher burden of metabolic-associated steatotic liver disease and alcohol-related cirrhosis, which could entail a higher risk of kidney dysfunction. Finally, it has to be acknowledged that the results of the present study cannot be extrapolated to CI-AKI risk after intra-arterial ICM administration, which is known to be associated with a greater risk of CI-AKI in the general population.[1] Further studies should be specifically designed to assess CI-AKI risk following intra-arterial route of ICM administration in cirrhosis.

5. CONCLUSIONS

In conclusion, this observational prospective controlled study shows that CI-AKI risk after intravenous ICM administration in cirrhosis has been previously overestimated and appears to be not significantly different from that of the general population. AKI episodes recorded in patients with cirrhosis undergoing CECT are sporadic, mostly mild, spontaneously resolving and not evolving, not associated to tubular kidney injury, with non-statistically different incidence compared to controls with cirrhosis unexposed

to ICM and therefore more likely attributable to spontaneous sCr fluctuations unrelated to CM. The recommendation of performing contrast imaging studies cautiously in cirrhosis does not seem reasonable anymore, with the exception of infected patients, which have a significantly higher risk of CI-AKI.

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