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Long-Term Follow-Up of Kidney Function after Acute Liver Failure or Acute Liver Injury: A Cohort Study

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Keywords
Liver failure · Renal insufficiency · Chronic kidney disease

Abstract

Introduction: Acute liver failure (ALF) is a rare disease with high mortality. Acute kidney injury (AKI) following ALF is frequent. We assessed AKI impact on long-term kidney function among ALF survivors. ***Methods:*** Observational cohort study including consecutive adult (age ≥16 years) patients with ALF or acute liver injury (ALI) admitted to a Portuguese tertiary center intensive care unit (ICU) between October 2013 and February 2020. KDIGO criteria were used to define AKI and chronic kidney disease (CKD). Primary outcome was the estimated glomerular filtration rate (eGFR), defined by the Chronic Kidney Disease Epidemiology Collaboration formula, at least 1 year after index ICU admission. ***Results:*** Among 104 patients with ALF (n = 74) or ALI (n = 30), mean (SD) age was 43.7 (18.0) years, and 44 were male. Among all patients (n = 104), following adjustment for age and SOFA score, AKI during the first 7 ICU days (n AKI = 57 and n renal replacement therapy [RRT] = 32) was independently associated with all-cause mortality (adjusted HR [95% CI] 11.61 [1.49–90.34]; p = 0.019). Among hospital survivors with long-term kidney function available (n = 56), median (interquartile range) >1 year eGFR was 95.3 (75.0–107.7) mL/min/1.73 m^2 (mean [SD] follow-up of 3.1 [1.6] years). Among these hospital survivors, following adjustment for baseline eGFR, AKI during the first 7 ICU days (n AKI = 19 and n RRT = 10) was not associated with >1 year eGFR (p = 0.15). At least 1 year after index ICU admission, 5 patients developed CKD, none RRT-dependent. ***Conclusions:*** Among ALF or ALI survivors, AKI was not associated with significant long-term loss of kidney function.

Função renal de seguimento a longo-prazo após falência hepática aguda ou lesão hepática aguda: um estudo coorte

Palavras Chave
Falência hepática · Insuficiência renal · Doença renal crónica

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Resumo

Introdução: A falência hepática aguda (ALF) é uma doença rara com alta mortalidade. A lesão renal aguda (AKI) após ALF é frequente. Avaliamos o impacto da AKI na função renal de longo prazo entre os sobreviventes de ALF. ***Métodos:*** Estudo observacional de coorte incluindo adultos consecutivos (idade ≥16 anos) com FHA ou lesão hepática aguda (ALI) internados numa unidade de cuidados intensivos (UCI) num centro terciário português entre Outubro de 2013 e Fevereiro de 2020. Os critérios KDIGO foram usados para definir AKI e doença renal crónica (CKD). O endpoint primário foi a taxa de filtração glomerular estimada (eGFR), definida pela fórmula da Chronic Kidney Disease Epidemiology Collaboration, pelo menos um ano após a admissão na UCI. ***Resultados:*** Entre 104 pacientes com ALF (n = 74) ou ALI (n = 30), a idade média (DP) foi de 43.7 (18.0) anos e 44 eram do sexo masculino. Entre todos os pacientes (n = 104), após ajuste para idade e score SOFA, AKI durante os primeiros 7 dias de UCI (n AKI = 57 e n terapia de substituição renal (RRT) = 32) foi independentemente associada à mortalidade por todas as causas (HR ajustado [IC 95%] 11.61 [1.49–90.34]; p = 0.019). Entre os sobreviventes no hospital com função renal de longo prazo disponível (n = 56), a eGFR mediana (IQR) >1 ano foi de 95.3 (75.0–107.7) mL/min/1.73 m^2 (média [DP] de acompanhamento de 3.1 [1.6] anos). Entre esses sobreviventes, após ajuste para eGFR basal, AKI durante os primeiros 7 dias de UCI (n AKI = 19 e n RRT = 10) não se associou com a eGFR >1 ano (p = 0.15). Pelo menos 1 ano após admissão na UCI, 5 pacientes desenvolveram DRC, nenhum dependente de RRT. ***Conclusões:*** Entre os sobreviventes de ALF ou ALI, AKI não se associou com perda significativa da função renal a longo prazo.

Introduction

Acute kidney injury (AKI) is a frequent complication among patients with acute liver failure (ALF), occurring in >50% of patients, and has been associated with poorer short- and long-term clinical outcomes [1–3]. Higher serum creatinine (sCr) has been associated with lower transplant-free survival in paracetamol overdose (APAP) patients; therefore, sCr is one of the prognostic criteria used to select patients for emergency orthotopic liver transplant (OLT) [4, 5].

The association between AKI and the development of chronic kidney disease (CKD) has been extensively reported among survivors of critical illness, and a relationship between the severity of AKI and the magnitude of CKD risk has been consistently described [6, 7].

In ALF, AKI or renal replacement therapy (RRT) at that time of OLT has not been associated with increased risk of CKD [3, 8]. However, data about the potential impact of AKI on long-term kidney function among ALF patients remain scarce. Specifically, little is known about the long-term kidney function among ALF survivors not submitted to OLT [9].

Accordingly, we hypothesized that AKI following ALF could have an impact on long-term kidney function. Therefore, the objectives of this study were the following: (1) to assess long-term kidney function in patients admitted to the intensive care unit (ICU) due to ALF or acute liver injury (ALI); (2) to evaluate the modifying impact of AKI or RRT on long-term kidney function in these patients.

Methods

Study Design, Setting, and Participants

We used a cohort from Curry Cabral Hospital (CCH), Central Lisbon University Hospital Center (CLUHC), prospective registry including all consecutive adult (age ≥16 years) patients with ALF or ALI admitted to the ICU between October 2013 and February 2020 (Fig. 1). We excluded patients with cirrhosis, previous OLT, or CKD under chronic RRT prior to ICU admission.

The liver transplant program started in 1992 is currently the largest in Portugal, performing 100–120 liver transplants per year. CCH is the referral center for all liver transplants in the country's south (catchment population of up to 3 million people). The Local Ethics Committee at CCH, CLUHC, has approved the study's protocol, and the need for informed consent was waived due to the observational nature of this study (INV_363).

All research procedures were conducted according to the principles of the Declaration of Helsinki [10]. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [11].

Operational Definitions

ALF was defined using the following criteria: (a) hepatic encephalopathy (HE) of any degree (West Haven criteria), (b) INR ≥1.5, (c) acute illness onset <26 weeks, and (d) no evidence of cirrhosis [1, 12]. ALI was defined as new liver dysfunction expressed as elevated serum transaminases (>3 times from the upper limit of normal) coupled with any degree of impaired liver function (INR or bilirubin) without concomitant HE or cirrhosis [1, 12]. AKI was diagnosed, and its severity was staged according to the sCr criteria of the KDIGO classification [13]. We defined the presence of AKI by an absolute increase in sCr ≥0.3 mg/dL or ≥1.5 fold relative change from baseline sCr in the first 7 days of ICU stay. Severity was classified as: stage 1, increase in sCr ≥0.3 md/dL or 1.5–1.9 times from baseline; stage 2, increase in sCr 2.0–2.9 times from baseline; and stage 3: increase in sCr 3.0 times from baseline, or an increase to

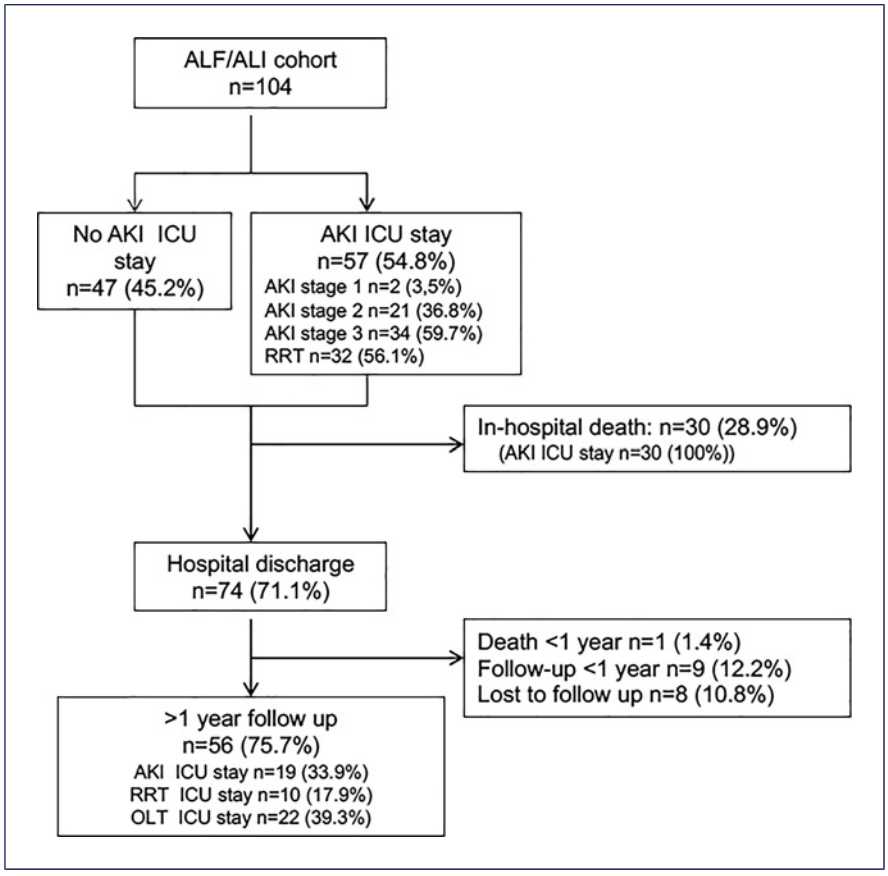

Fig. 1. Flowchart of the entire study cohort.

sCr ≥4.0 mg/dL or RRT initiation. The use of RRT was not standardized; therefore, indications, modality, treatment dose, anticoagulation, and criteria for initiation and suspension of the technique were based on individual clinical judgment. Any patient on RRT was considered to have AKI even if the technique was started for a non-kidney reason (e.g., clearance of ammonia or toxins or temperature control), as sCr loses its diagnostic value under RRT [1]. Urine output data were not consistently available.

Baseline sCr was defined as the lowest sCr value available prior to the day of hospital admission and, if not available, was calculated according to the KDIGO recommendations [14]. Baseline estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula. CKD was defined as eGFR <60 mL/min/1.73 m^2 according to the KDIGO definition [14].

Long-term kidney function was defined as one determination of sCr in steady state >1 year after index ICU admission. The most recent sCr available after >1-year follow-up was considered. Those patients not being followed in CLUHC outpatient clinic were contacted via telephone and asked to provide the most recent laboratory data to investigators.

Exposures and Endpoints

The ALF registry at CCH data captures demographic, clinical, and laboratory data during the first 7 days of ICU stay including: age, sex, and etiology; HE grade (West Haven criteria), invasive mechanical ventilation use, PaO_2/FiO_2 ratio (mm Hg), vasopressor use, mean arterial pressure (mm Hg), RRT use, and Sequential Organ Failure Assessment (SOFA) score; laboratory serum profile including INR, bilirubin (mg/dL), alanine aminotransferase (U/L), ammonia (μmol/L), Factor V (%), creatinine (mg/dL), bicarbonate (mmol/L), pH, lactate (mmol/L), hemoglobin (g/dL), and platelet count (10^3 cells/μL); and immunosuppression regimen [15]. Analysis 1 included all patients with ALF or ALI admitted to the ICU (n = 104) and assessed the impact of AKI or RRT during the first 7 days of index ICU stay (exposures) on all-cause mortality (endpoint) (Fig. 1). Analysis 2 considered only hospital survivors (n = 74) and evaluated the impact of AKI or RRT during the first 7 days of index ICU stay (exposures) on eGFR >1 year after index ICU admission (endpoint).

Statistical Analysis

Descriptive statistics were calculated and expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]) for parametric and non-parametric continuous variables, respectively, and count (%) for categorical variables. Univariable comparisons were performed with χ^2, Fisher's, Student's t, Mann-Whitney, Wilcoxon, or Kruskal-Wallis tests where appropriate. Missing data across all values were 8.4%, and no multiple imputation was performed.

In analysis one, survival analysis with Kaplan-Meier curves (log-rank test) and multivariable Cox proportional hazard model was performed to examine the association of covariables with all-cause

mortality. In analysis 2, multivariable linear regression was used to describe the association of covariables with >1-year eGFR. Covariables initially considered for modeling were those with a p value <0.10 on univariable comparisons. A backward stepwise selection process was performed to select final models' composition based on the best models' performance while avoiding overfitting. Covariables were assessed for multicollinearity and excluded accordingly. Models' performance was assessed by the χ^2 or R^2 statistics.

A p value <0.05 (2-tailed) was considered statistically significant for all comparisons. Statistical analysis was performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' Baseline Characteristics

Among 104 patients included, 74 (71.2%) had ALF, and 30 (28.8%) had ALI. Mean (SD) age was 43.7 (18.0) years, and 44 (42.3%) were males (Fig. 1). The main known causes of ALF/ALI were the following: paracetamol toxicity in 18 patients (17.3%), other drug-induced liver injury in 18 (17.3%), viral hepatitis in 11 (10.6%), and ischemia in 8 (7.7%) (Table 1; online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000536261). Only 3 (2.9%) patients had baseline CKD.

On ICU day one, mean (SD) SOFA score was 7.6 (4.8). Overall, 27 (26.0%) patients had grade 3–4 HE, 21 (20.2%) were mechanically ventilated, 19 (18.3%) were on vasopressors, and 43 (41.3%) had AKI, of which 15 (14.4%) required RRT. At this time point, median (IQR) serum INR, bilirubin, creatinine, and lactate were 2.5 (1.8–3.9), 9.1 (2.7–19.2) mg/dL, 0.86 (0.66–1.55) mg/dL, and 2.0 (1.5–3.4) mmol/L, respectively (Table 1). All baseline characteristics are depicted in Table 1.

Outcomes

Overall, during a mean (SD) follow-up time of 2.4 (1.9) years, 34 (32.7%) patients required OLT and 32 (30.8%) died, 30 (93.8%) of these during the index hospital stay (Table 1; online suppl. Fig. S2). Among the deceased patients, 24 (75%) died without OLT. The main cause of death was ALF-related multiorgan failure in 46.9% (15/32) of cases (online suppl. Fig. S3).

Median (IQR) time to OLT and death were 3 (1–6) and 5 (3–11) days, respectively. Median ICU and hospital length-of-stay were 5 (3–10) and 19 (8–34) days, respectively.

Analysis One: Associations with All-Cause Overall Mortality

Among 104 patients included, during the first 7 days of index ICU stay, 57 (54.8%) had AKI (43 diagnosed on ICU day one and 14 over the following 6 days): stage 1 in 3.5% (n = 2), stage 2 in 36.8% (n = 21), and stage 3 in 59.7% (n = 34). RRT was required in 56.1% of those with AKI (32/57, with 15 started on ICU day one). Continuous RRT (either venovenous hemodiafiltration or hemofiltration) was the modality most frequently used (71.9% [23/32] of all RRT prescriptions).

AKI patients were older (mean age of 47.7 vs. 38.9 years; p = 0.01) and had more often ALF (82.5% vs. 57.4%; p = 0.005) than others. Furthermore, on ICU day one, AKI patients had higher proportion of mechanical ventilation support (31.6% vs. 6.4%; p = 0.001), with lower mean PaO_2/FiO_2 ratio (341.8 vs. 428.7 mm Hg; p < 0.001), higher proportion of vasopressor use (28.1% vs. 6.4%; p = 0.004), higher median lactate (2.9 vs. 1.9 mmol/L; p < 0.001), and higher overall disease severity (mean SOFA score of 10 vs. 5; p < 0.001) than those without AKI. On ICU day one, ALF patients had higher overall disease severity (mean SOFA score of 8 vs. 3; p < 0.001) and were more frequently diagnosed with AKI (63.5% vs. 33.3%; p = 0.005) in comparison to those with ALI.

On univariable analysis, AKI patients or those under RRT had higher all-cause mortality than others (online suppl. Fig. S4). However, among AKI patients, AKI staging proportions (1 or 2 vs. 3) were similar between survivors and non-survivors (46.2% vs. 35.5%; p = 0.47). On multivariable analysis with Cox regression, age {adjusted hazard ratio (aHR) (95% confidence interval [CI]) of 1.03 (1.01–1.05); p = 0.014}, SOFA score on ICU day one (aHR [95% CI] of 1.25 [1.14–1.36]; p < 0.001), and AKI on the first 7 days of ICU stay (aHR [95% CI] of 11.39 [1.46–88.91]; p = 0.019) were independently associated with higher hazard of all-cause mortality (Table 2). A similar effect was observed in a sensitivity analysis following exclusion of ALI patients (online suppl. Table S1).

Analysis 2: Associations with >1-Year eGFR

Among 74 patients discharged alive from the hospital, 27 (36.5%) had AKI during the first 7 days of the index ICU stay, with 13 (17.6%) requiring RRT. Only 56 (75.7%) of these patients had available >1-year kidney function assessment and were considered for this analysis (Fig. 1). Among these 56 hospital survivors, 19 (33.9%) had AKI during the first 7 days of ICU stay, with 10 (17.9%) requiring RRT. AKI and RRT proportions were thus similar between the total number of hospital survivors (n = 74) and the subgroup of those with long-term kidney function assessment available (n = 56) (online suppl. Table S2).

Among these 56 patients, median (IQR) >1-year eGFR was 95.3 (75.0–107.7) mL/min/1.73 m^2 for a mean (SD)

Table 1. Patients' baseline characteristics on ICU day one and outcomes stratified by AKI status on the first 7 days of stay (n = 104)

Characteristics	Overall 104 (100)	AKI 7 days ICU 57 (54.8)	No AKI 7 days ICU 47 (45.2)	p value
Demographic				
Age, years	43.7 (18.0)	47.7 (20.7)	38.9 (12.6)	0.013
Sex (male)	44 (42.3)	28 (49.1)	16 (34.0)	0.12
Etiology (APAP vs. other)	18 (17.3)	9 (15.8)	9 (19.1)	0.65
ALF (vs. ALI)	74 (71.2)	47 (82.5)	27 (57.4)	0.005
Baseline eGFR, mL/min/ 1.73 m^2	79.3 (76.7–80.6)	78.9 (73.8–80.3)	79.6 (78.3–89.1)	0.003
Baseline CKD	3 (2.9%)	3 (5.3%)	0 (0%)	0.25
Organ failures and support				
HE grade 3–4 (vs. other)	27 (26.0)	19 (33.3)	8 (17.0)	0.06
Mechanical ventilation	21 (20.2)	18 (31.6)	3 (6.4)	0.001
PaO_2/FiO_2 ratio, mm Hg	381.1 (126.3)	341.8 (128.9)	428.7 (106.1)	<0.001
Vasopressor use	19 (18.3)	16 (28.1)	3 (6.4)	0.004
MAP, mm Hg	81.9 (69.3–89.8)	79.2 (66.4–90.4)	82.2 (75.2–89.1)	0.19
SOFA score	8 (5)	10 (5)	5 (4)	<0.001
Laboratory parameters				
INR	2.5 (1.8–3.9)	2.4 (2.0–3.9)	2.7 (1.8–4.8)	0.045
Bilirubin, mg/dL	9.1 (2.7–19.2)	5.2 (3.2–18.8)	15.1 (6.1–21.7)	0.24
ALT, U/L, n = 103	1,475 (252–4,086)	2,736 (345–5,800)	1,445 (353–2,431)	0.68
Ammonia, µmol/L, n = 78	133 (83–189)	163 (88–270)	123 (79–189)	0.017
Factor V (%, n = 72)	42.5 (17.3–69.8)	22.0 (14.0–42.0)	65.5 (44.3–82.0)	0.001
Creatinine, mg/dL	0.86 (0.66–1.55)	1.57 (1.10–2.19)	0.61 (0.50–0.72)	<0.001
Urea, mg/dL	28.0 (15.0–65.0)	65.0 (36.0–120.0)	15.0 (11.3–17.8)	<0.001
Lactate, mmol/L, n = 93	2.0 (1.5–3.4)	2.9 (1.8–6.8)	1.9 (1.2–2.3)	<0.001
HCO_{3-}, mmol/L, n = 94	22.0 (18.5–25.0)	20.0 (16.0–23.0)	24.0 (21.3–24.9)	<0.001
pH (n = 94)	7.43 (7.37–7.48)	7.39 (7.32–7.45)	7.47 (7.44–7.49)	<0.001
Hemoglobin, g/L	123 (107–135)	130 (116–143)	126 (115–134)	0.54
Platelets, 10^3 cells/µL	146 (68–239)	108 (58–244)	156 (110–238)	0.027
Outcomes, n (%)				
OLT	34 (32.7)	18 (31.2)	16 (34.0)	0.79
Death	32 (30.8)	31 (54.4)	1 (2.1)	<0.001

Results are presented as n (%), mean (SD), or median (IQR). AKI, acute kidney injury; ICU, intensive care unit; SD, standard deviation; IQR, interquartile range; APAP, paracetamol overdose; HE, hepatic encephalopathy; ALF, acute liver failure; ALI, acute liver injury; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; MAP, mean arterial pressure; SOFA, sequential organ failure assessment; INR, international normalized ratio; ALT, alanine transferase; OLT, orthotopic liver transplant.

Table 2. Cox regression model: multivariable analysis of the association between covariables and overall all-cause mortality among all patients included (n = 104)

Variables	HR	95% CI		p value
		lower	upper	
Age (years)	1.03	1.01	1.05	0.014
SOFA score (ICU day one) (0–24)	1.24	1.14	1.36	<0.001
AKI (7 days of ICU stay)	11.61	1.49	90.34	0.019

Model: n = 104, n events of death = 32; χ^2 statistic = 66, $p < 0.001$. HR, hazard ratio; confidence interval; SOFA, sequential organ failure assessment; AKI, acute kidney injury; ICU, intensive care unit.

follow-up time of 3.1 (1.6) years. Among the 56 hospital survivors, 8.9% (n = 5) developed CKD, none RRT-dependent. CKD prevalence among hospital survivors was similar between those who had AKI or not (10.5% vs. 8.1%, p = 1.0) or those that required RRT or not (10.0% vs. 8.7%; p = 1.0) during the index ICU stay. Among these

56 patients, median (IQR) >1 year eGFR was significantly higher than baseline eGFR (79.3 [76.7–80.6] versus 95.3 [75.0–107.7] mL/min/1.73 m^2; $p = 0.023$).

Among 36 patients transplanted, 21 had available data on calcineurin inhibitor use: 20 were on tacrolimus and 1 was on cyclosporin. For those on tacrolimus, latest single time point within >1 year follow-up mean (SD) through levels was 6.5 (2.2) ng/mL. Among the 56 hospital survivors, median >1 year eGFR was similar between those who had AKI or not (93.0 vs. 96.8 mL/min/1.73 m^2; $p = 0.76$), were treated with RRT or not (102.3 vs. 94.2 mL/min/1.73 m^2; $p = 0.32$), who underwent OLT or not (93.2 vs. 97.1 mL/min/1.73 m^2; $p = 0.21$), or who had ALF versus ALI (93.2 vs. 99.4 mL/min/1.73 m^2; $p = 0.54$) during the index ICU stay (Fig. 2).

On multivariable analysis with liner regression, while higher baseline eGFR was found to be independently associated with higher >1 year eGFR ($p < 0.001$), AKI during the first 7 days of the index ICU stay ($p = 0.75$) was not associated with long-term eGFR (Table 3). The linear regression equation was the following: >1 year eGFR = −398 + 6.22* baseline eGFR + 7.57* AKI (7 days) (baseline eGFR in mL/min/1.73 m^2, AKI [7 days] 0 if no or 1 if yes). A similar effect was observed in a sensitivity analysis following exclusion of ALI survivors (online suppl. Table S3).

Discussion

Key Results and Comparisons with Previous Literature

To the best of our knowledge, we presented a cohort of ALF or ALI patients with one of the longest follow-up evaluation of kidney function. Among all ALF or ALI patients, AKI occurrence was associated with worse all-cause mortality. Among ALF or ALI survivors, long-term kidney function was largely preserved with a median (IQR) >1 year eGFR of 95.3 (75.0–107.7) mL/min/1.73 m^2 irrespective of AKI diagnosis, RRT use, OLT need, or ALF versus ALI occurrence during the index ICU stay.

Contrary to our results, a previous study by Hadem et al. [16], including 134 ALF patients, found that sCr was significantly higher on follow-up after ICU admission. Differences between this study and ours might reflect their shorter follow-up period (median of 226 days following ICU admission) and their use of sCr rather than eGFR as method to quantify kidney function. Interestingly, in the study by Hadem et al. [16], the median follow-up sCr was 0.85 mg/dL, which in fact translates into an eGFR within normal range, considering the median age of their population, thus possibly also in agreement with our findings. Since the accuracy of eGFR as a surrogate for kidney function is poorer at higher levels of actual GFR, both studies suggest that ALF seems to have a modest impact on long-term kidney function. In fact, rates of CKD were close between the 2 cohorts (11.9% in theirs vs. 8.9% in ours). Furthermore, the increase in eGFR from baseline to >1 year we described probably does not translate into a clinically meaningful improvement in kidney function [17].

We also presented conflicting results with respect to the modifying impact of AKI or OLT post-ALF on the long-term kidney function. While Hadem et al. [16] found a significantly higher follow-up sCr among ALF patients that had AKI or OLT, we and others found that neither the occurrence of AKI nor the OLT per se significantly impacted long-term kidney function [3, 9, 16]. We recognize that OLT might lead to a second kidney insult, with new AKI episodes, whether due to surgical complications or organ-related ischemia-reperfusion injury. However, Leithead et al. [18] found that, among patients who underwent OLT due to ALF, AKI or the use of RRT at the time of transplant were not associated with increased risk of CKD [9, 18].

In ALF patients, kidney dysfunction has been described to improve more often than in chronic liver disease patients following OLT [19]. O'Riordan et al. [3] showed that, among patients with APAP and AKI that survived without OLT, 51% of patients returned to normal kidney function at the time of discharge (median follow-up of 38 days), and complete recovery (eGFR >60 mL/min/1.73 m^2) was observed in all of those followed for at least 3 months. The high recovery rates of AKI in the context of APAP may reflect the easily reversible nature of this agents' direct toxicity, both in the liver and in the kidneys [5, 20]. Besides direct toxicity to kidney cells related to specific ALF etiologies, such as mushroom poisoning, acetaminophen, and cotrimoxazole toxicity, or heat stroke-associated rhabdomyolysis, further etiology-independent injury mechanisms may be at play. While hypotension and systemic vasodilatation may contribute to reduction in renal blood flow, the few studies of renal blood flow in ALF are limited to animal models and show conflicting results [3, 18]. Alterations of the circulating concentration of vasoactive compounds, inflammation-associated cytokines, and damage-associated molecular patterns have all been implicated in AKI in ALF [5, 21]. Finally, kidney biopsies in patients with ALF have found focal tubular cell necrosis and focal vascular injury, predominantly of the

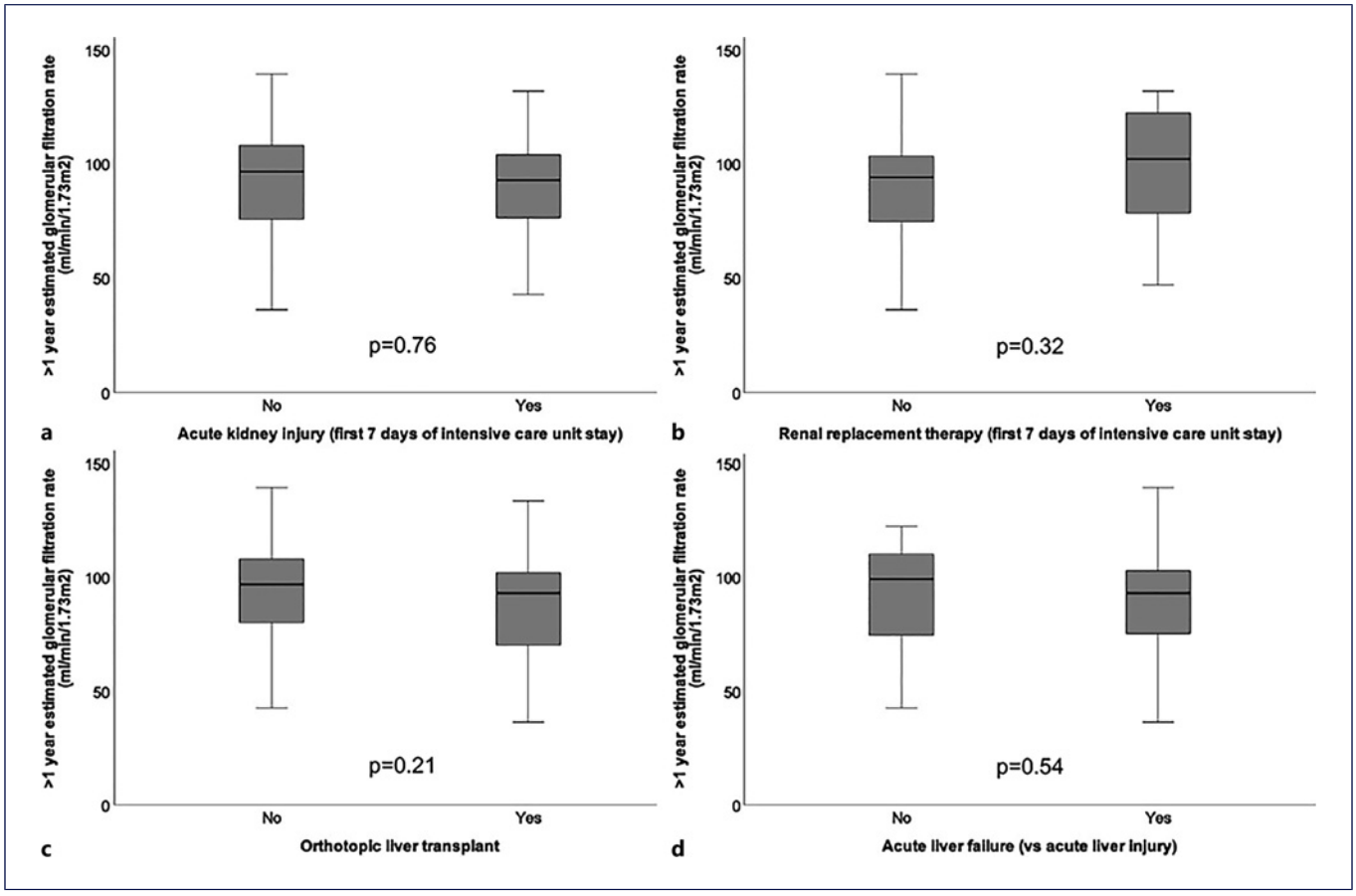

Fig. 2. Long-term eGFR (mL/min/1.73 m^2) stratified by AKI (**a**), RRT (**b**), OLT (**c**), and ALF versus ALI (**d**) status on index ICU stay among hospital survivors (n = 56).

Table 3. Linear regression model: multivariable analysis of the association between covariables and post 1-year eGFR among hospital survivors (n = 56)

Variables	β	95% CI		p value
		lower	upper	
Baseline eGFR, mL/min/1.73 m^2	6.22	3.80	8.64	<0.001
AKI (7 days of ICU stay)	7.57	−4.09	19.23	0.15

SE, standard error; CI, confidence interval; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; ICU, intensive care unit. Model: n included = 56. Regression equation: >1-year eGFR = −398 + 6.22 baseline eGFR +7.57 AKI (7 days) (baseline eGFR in mL/min/1.73 m^2, AKI [7 days] 0 if no or 1 if yes). Performance: R^2 0.34, p < 0.001.

endothelial cells in the glomeruli, peritubular capillaries, and small arterioles [22].

Moreover, the fact that ALF patients tend to be younger (median age <45 years) than the average critically ill patients with AKI, thus with lower number of comorbidities (<3% had baseline CKD), may further contribute to the higher rates of AKI recovery and the lower rates of distant CKD reported among these patients. This may help explain why AKI in ALF seems to have a lower long-term impact on kidney function in comparison to septic or other subgroups of critically ill patients.

Strengths, Limitations, and Implications

Some of the sicker ALF patients develop a severe systemic inflammatory response syndrome within the first few days of their disease course, often leading to distributive shock. Thus, ALF is likely most severe within the first 7 days of its course. The fact that we considered AKI diagnosis and RRT use for the first 7 days of the index ICU stay may have allowed to better capture the degree of kidney dysfunction that may ensue in the context of ALF.

Following ALF, the native liver may take months to regenerate. After OLT, nephrotoxic immunosuppression drugs may also take months to wean or adjust. In this context, the assessment of long-term kidney function >1 year following the index ICU admission (median follow-up time of 3 years) may have helped to better characterize the long-term impact of AKI in ALF or ALI survivors.

However, our results should be interpreted considering the following limitations. First, this was a single-center cohort, therefore prone to selection bias. Nevertheless, the local prospective registry including consecutive patients with standardized definitions and management approach may have mitigated such bias. Second, we did not have data on urine output to further improve the diagnostic evaluation of AKI, as recommended by the guidelines [13]. Nevertheless, sCr has been the most widely used biomarker for the assessment of kidney function in critically ill patients, and previous studies did not find added value of incorporating urinary output data to diagnose AKI in ALF [23, 24]. Finally, the absence of data on urinary sediment or biomarkers may have precluded any analyses considering possible different kidney injury mechanisms associated with diverse ALF etiologies, especially in a setting with a lower prevalence of APAP [25, 26].

Despite these limitations, we think our study adds to the literature by reinforcing that AKI may not negatively impact long-term kidney function in ALF or ALI survivors, a rather unique finding in the critical illness literature. In this context, strategies for kidney function surveillance following an AKI episode in ALF patients may be adapted accordingly. In the future, further studies could address gaps in knowledge about this topic, for example, by extending studies on the different mechanisms of kidney injury associated with diverse ALF etiologies.

Conclusions

Among ALF or ALI survivors, AKI during the first 7 days of ICU stay was not associated with significant loss of kidney function following at least 1 year of follow-up.

Statement of Ethics

This study protocol was reviewed and approved by the Central Lisbon University Hospital Center Ethics Committee (INV_363). The informed consent was waived by the Central Lisbon University Hospital Center Ethics Committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Pedro Fidalgo and Filipe S. Cardoso conceived the idea, collected data, performed analysis, and wrote the manuscript. Pedro Póvoa, Nuno Germano, and Constantine J. Karvellas provided content expertise and approved the final version of the manuscript.

Data Availability Statement

Data may be available upon reasonable request.

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