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Nephrologist Interventions to Avoid Kidney Replacement Therapy in Acute Kidney Injury

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Keywords
Acute kidney injury · Hemodialysis · Mortality

Abstract
Background: Based on the pathophysiology of acute kidney injury (AKI), it is plausible that certain early interventions by the nephrologist could influence its trajectory. In this study, we investigated the impact of 5 early nephrology interventions on starting kidney replacement therapy (KRT), AKI progression, and death. ***Methods:*** In a prospective cohort at the Hospital Civil of Guadalajara, we followed up for 10 days AKI patients in whom a nephrology consultation was requested. We analyzed 5 early interventions of the nephrology team (fluid adjustment, nephrotoxic withdrawal, antibiotic dose adjustment, nutritional adjustment, and removal of hyperchloremic solutions) after the propensity score and multivariate analysis for the risk of starting KRT (primary objective), AKI progression to stage 3, and death (secondary objectives). ***Results:*** From 2017 to 2020, we analyzed 288 AKI patients. The mean age was 55.3 years, 60.7% were male, AKI KDIGO stage 3 was present in 50.5% of them, sepsis was the main etiology 50.3%, and 72 (25%) patients started KRT. The overall survival was 84.4%. Fluid adjustment was the only intervention associated with a decreased risk for starting KRT (odds ratio [OR]: 0.58, 95% confidence interval [CI]: 0.48–0.70, and $p \leq 0.001$) and AKI progression to stage 3 (OR: 0.59, 95% CI: 0.49–0.71, and $p \leq 0.001$). Receiving vasopressors and KRT were associated with mortality. None of the interventions studied was associated with reducing the risk of death. ***Conclusions:*** In this prospective cohort study of AKI patients, we found for the first time that early nephrologist intervention and fluid prescription adjustment were associated with lower risk of starting KRT and progression to AKI stage 3.

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Introduction

The pathophysiology of acute kidney injury (AKI) is complex and associated with substantial morbidity and mortality [1, 2]. AKI remains one of the largest risk factors for the development of chronic kidney disease (CKD) with possible progression into kidney replacement therapy (KRT) dependence and also mortality in patients admitted to intensive care units (ICUs) [3]. Despite great advances in the understanding of risk factors, diagnosis, and management of AKI, the risk of mortality remains high [4, 5]. Early diagnosis and referral to specialized care by nephrologists have been shown to result in earlier adequate treatment of AKI. Delayed consultation of nephrologists associates with higher mortality [6–10], with statistics that reinforce the unarguable importance of early intervention. These interventions include optimization of fluid management, antibiotic dose and nutritional adjustments, nephrotoxic withdrawal, removal of hyperchloremic solutions, and others [11], all of which attempt to treat or ameliorate the various complications of AKI. Each of these has the potential to affect the course of AKI and the resulting outcomes. Despite the above being well-established facts, there is still a remarkable lack of data on the efficacy of each of the possible interventions. We aimed to identify the potential of each respective nephrology intervention to reduce the necessity to start KRT, the progression of AKI, and mortality.

Materials and Methods

Study Design and Patient Population

A prospective, observational cohort study was conducted at the Hospital Civil de Guadalajara Fray Antonio Alcalde, Mexico, between August 2017 and March 2020. The hospital is a tertiary referral academic center with 1,709 beds. Studied patients were in the attention of the nephrology staff by consult request of the primary medical or surgical team. Only hospitalized patients in the ICU and wards with suspected AKI and under consult by the nephrology staff by request of the attending physician were included; due to the limited number of beds in the ICU, many patients who deserve to be in the ICU are managed in wards.

The initial request and the following treatment were fully at the discretion of the medical team and influenced by the study team. The responsible attending nephrologist ran daily rounds and was available 24 h/day. AKI was diagnosed based on the serum creatinine KDIGO criteria [11]. The inclusion criterion was early nephrology consultation, defined as consultation that occurred before 48 h after the AKI diagnosis. The exclusion criteria were CKD grade 5, defined as a calculated glomerular filtration rate <15 mL/min/1.73 m^2 by the 4-variable Modification of Diet in Renal Disease Study-4 (MDRD-4) equation, chronic dialysis, hospitalization stay shorter than 48 h, transplant patients, AKI diagnosis over 24 h after nephrology consultation, and missing data (unable to complete the analysis). A 10-day intramural follow-up period after AKI diagnosis was chosen retrospectively because all patients that started KRT did so within the first 10 days of follow-up [12]. The study was approved by the Hospital Civil de Guadalajara Fray Antonio Alcalde Institutional Review Board (HCG 146/18) and was conducted in adherence with the Declaration of Helsinki. Informed consent was obtained from all the subjects. The protocol followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [13].

Data Collection

Demographic and clinical variables were collected as age, diabetes, hypertension, hypothyroidism, CKD stage (CKD was diagnosed as per the estimated glomerular filtration rate [eGFR]of <60 mL/min/1.73 m^2, using the MDRD-4 equation) [11], smoking, cerebrovascular disease, and ischemic heart disease; cardiovascular, surgical, or medical hospital admission; drugs such as analgesics, antibiotics, antihypertensive medication, diuretics, vasopressors, statins, and aspirin during the course of hospitalization; the baseline serum creatinine level was defined as the most frequent value within a year before admission; contributing factors of AKI such as sepsis (Sepsis-3 criteria) [14], clinically assessed hypovolemia, cardiorenal syndrome [15], nephrotoxic drugs and shock; prespecified biochemical data such as hemoglobin, platelets, leukocytes, glucose, urea, creatinine, sodium, potassium, chloride, phosphate, calcium, arterial pH, PCO_2, PO_2, bicarbonate, and lactate levels.

Nephrology Interventions

Early nephrology interventions were performed following the KDIGO guidelines [11] and expert panel recommendations [10]; we focused on 5 prespecified interventions as follows: (1) fluid adjustment, (2) nephrotoxic withdrawal, (3) antibiotic dose adjustment according to eGFR by MDRD-4, (4) nutritional adjustment, and (5) removal of hyperchloremic solutions. Fluid adjustment was defined as the use of fluids according to the clinical scenario and/or with point of care ultrasound evaluation of the inferior caval vein (diameter and collapsibility index or the pulse pressure variability) and lungs for the presence of pleural B lines, in the cases where the device was available. In those with suspected clinical hypovolemia, isotonic crystalloids were used; in those where there was no need for intravenous fluids or there was a risk of fluid overload, fluids, starches, and dextrans were reduced or suspended, respectively. Following or concomitant with fluid resuscitation, hypotensive patients were given vasoconstrictor, most commonly norepinephrine, titrated to a target mean arterial pressure greater than 65 mm Hg. Nephrotoxic withdrawal was defined as the cessation of those drugs known to be nephrotoxic according to KDIGO AKI guidelines and expert panel recommendations [11, 16, 17]. Antibiotic dose adjustment was defined as the dose adjustment by the eGFR according to the MDRD-4 equation [14, 18]. Nutritional adjustment was defined as nutritional adjustment according to the KDIGO AKI guidelines, and the recommendation was 25–30 kcal/kg/day with protein requirements of at least 1.0 up to 1.7 g/kg/day [11]. Removal of hyperchloremic solutions was defined as the removal or replacement of hyperchloremic fluid, such as changing 0.9% saline to Ringer lactate or glucose 5% (in patients with hypernatremia or serum sodium >145 mmol/L).

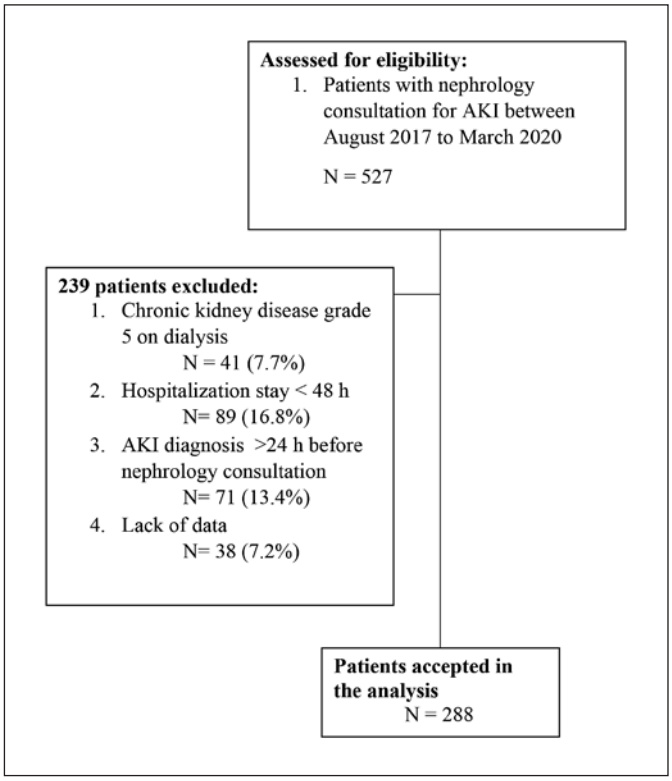

Fig. 1. Flowchart of study population. AKI, acute kidney injury; CKD, chronic kidney disease.

Classic indications for KRT were fluid overload-resistant to diuretics, severe hyperkalemia, severe metabolic acidosis, and uremic manifestations, including encephalopathy, pericarditis, and convulsion [11, 19, 20]. Data were collected by 2 observers who were not involved in patient care.

Study Outcomes

The primary outcome was to determine which of the predefined early nephrology interventions reduces the necessity to start KRT. The secondary outcomes were to determine whether variables were associated with AKI progression (defined as worsening stage of AKI) and mortality, as well as if there was an association between early nephrology intervention and these outcomes. As an exploratory analysis, we wanted to identify which of the classic KRT indications in AKI patients (fluid overload, hyperkalemia, acid-base disorders, and uremia) were independently associated with starting KRT and mortality.

Statistical Analysis

Categorical descriptive data are presented as frequencies and continuous variables as the means ± SDs and percentages (%). The Shapiro-Wilk test was used to determine the distribution of the variables that presented an abnormal distribution, so it was decided to use the Wilcoxon signed-rank test to determine the differences between the variables. Survival probabilities for the tested groups were assessed using the construction of Kaplan-Meier survival curves and comparison by the log-rank test. To assemble comparable groups, we employed the nearest neighbor propensity score matching in a 1:1 fashion for the comparison was applied to compare AKI outcomes with early nephrology interventions. A univariate and multivariate binary logistic regression model was used to determine the variables associated with KRT, AKI progression, and mortality during the first 10-day follow-up, adjusted for age, sex, diabetes, hypertension, smoking, hypothyroidism, CKD, cerebrovascular and ischemic heart diseases, analgesics, antibiotics, antihypertensives, diuretics, vasopressors, body mass index, sepsis, hypovolemia, cardiorenal syndrome, nephrotoxic drugs, shock, liquid, antibiotic dose and nutritional adjustment, nephrotoxic withdrawal, removal of hyperchloremic solutions, and AKI grade. The results are reported as odds ratios (ORs) and the corresponding confidence intervals (CIs). ORs that do not cross unit and $p < 0.05$ were considered statistically significant. R Studio program® (version 1.1.38, 2017) was used for data analyses.

Results

Baseline Characteristics Associated with KRT

Between August 2017 and March 2020, a total of 527 patients were referred to nephrology consultation for suspected AKI during their hospitalization. We excluded 41 (7.7%) patients with CKD grade 5 on dialysis, 89 (16.8%) with a hospitalization stay shorter than 48 h, 71 (13.4%) with AKI diagnosis more than 24 h before nephrology consultation, and 38 (7.2%) patients with lack of data, resulting in 288 patients included in the final analysis as shown in Figure 1. Baseline characteristics of patients according to KRT groups are shown in Table 1. Sixty (60%) were males, with a mean age of 55.3 ± 18.3 years. A total of 116 (40.2%) patients had diabetes; 16 (5.5%) had hypothyroidism; 147 (51.2%) had a medical noncardiovascular or surgical hospital admission cause; 165 (57.2%) were receiving analgesics, 221 (76.7%) antibiotics, and 117 (40.6%) received diuretics during hospitalization. AKI KDIGO 3 was present in 145 (50.5%) patients, and the main contributors to AKI were sepsis (50.3%) and hypovolemia (45.8%). Fluid adjustment was the principal nephrologist nondialytic intervention in 238 (82.6%) patients. A total of 72 (25%) patients needed KRT, and 45 (15.6%) patients died during the follow-up. AKI patients requiring KRT presented more often with hypothyroidism, presented less frequently with cardiovascular and surgical hospital admission, had an increased use of vasopressors, had more severe AKI KDIGO grades, and had fluid adjustment and nephrotoxic withdrawal less often and had a higher mortality than patients who did not need KRT as shown in Table 1. The overall survival for the 10-day follow-up was 84.4% (95% CI: 0.80–0.88) is shown in online suppl. Figure 1; for all online suppl. material, see www.karger.com/doi/10.1159/000517615.

Table 1. Baseline demographic, clinical, and laboratory characteristics of patients according to KRT groups

Variable	Total	KRT	Non-KRT	*p* value
N (%)	288	72 (25)	216 (75)	
Age, years, mean (SD)	55.3 (18.3)	51.8 (18.3)	56.4 (18.1)	0.07
Gender, *N* (%)				
Male	175 (60.7)	40 (55.5)	135 (62.5)	0.29
Female	113 (39.3)	32 (44.5)	81 (37.5)	
BMI, kg/m^2, mean (SD)	26.3 (6.3)	26.7 (7.0)	26.1 (6.1)	0.49
Comorbidities, *N* (%)				
Diabetes	116 (40.2)	27 (37.5)	89 (41.2)	0.58
Hypertension	126 (43.7)	29 (40.2)	97 (44.9)	0.49
Smoker	55 (19.0)	11 (15.2)	44 (20.3)	0.34
Hypothyroidism	16 (5.5)	8 (11.1)	8 (3.7)	0.01
CKD grade 1–4	98 (34.0)	22 (30.5)	76 (35.1)	0.47
Cerebrovascular disease	12 (4.1)	3 (4.1)	9 (4.1)	1.00
Ischemic heart disease	10 (3.4)	1 (1.3)	9 (4.1)	0.26
Hospital admission, *N* (%)				
Cardiovascular	46 (15.9)	10 (13.8)	36 (16.6)	0.57
Surgical	95 (32.9)	17 (23.6)	78 (36.1)	0.06
Other medical	147 (51.2)	45 (62.6)	102 (47.3)	0.02
Hospitalization drugs, *N* (%)				
Analgesics	165 (57.2)	44 (61.1)	121 (56.0)	0.45
Antibiotics	221 (76.7)	58 (80.5)	163 (75.4)	0.37
Antihypertensive	82 (28.4)	19 (26.3)	63 (29.1)	0.65
Diuretics	117 (40.6)	34 (47.2)	83 (38.4)	0.18
Vasopressors	79 (27.4)	29 (40.2)	50 (23.1)	0.004
Statins	49 (17.0)	9 (12.5)	40 (18.5)	0.24
Aspirin	49 (17.0)	9 (12.5)	40 (18.5)	0.24
AKI grade, *N* (%)				
KDIGO-1	65 (22.5)	6 (8.3)	59 (27.3)	<0.001
KDIGO-2	78 (27.0)	8 (11.1)	70 (32.4)	<0.001
KDIGO-3	145 (50.5)	58 (80.6)	87 (40.3)	<0.001
Contributing factors to AKI, *N* (%)				
Sepsis	145 (50.3)	44 (61.1)	101 (46.7)	0.03
Hypovolemia	132 (45.8)	28 (38.8)	104 (48.1)	0.17
Cardiorenal syndrome	34 (11.8)	5 (6.9)	29 (13.4)	0.14
Nephrotoxic drugs	52 (18.0)	13 (18.0)	39 (18.0)	1.00
Shock	92 (31.9)	31 (43.0)	61 (28.2)	0.01
Biochemical data, mean (SD)				
Serum hemoglobin, g/dL	10.2 (2.3)	9.9 (1.9)	10.3 (2.5)	0.33
Serum platelets, 10^9/L	207.5 (134.8)	175.3 (92.2)	218.2 (155.1)	0.02
Serum leukocytes, 10^9/L	12.6 (6.7)	14.4 (7.5)	12.0 (7.2)	0.03
Serum glucose, mg/dL	129.6 (56.6)	122.3 (58.5)	132.0 (76.5)	0.19
Serum urea, mg/dL	151.6 (80.9)	184.5 (91.1)	140.7 (87.3)	<0.001
SCr, mg/dL	3.9 (2.8)	5.4 (2.9)	3.4 (2.5)	<0.001
Serum sodium, mEq/L	136.6 (7.1)	135.3 (8.8)	137.1 (9.7)	0.07
Serum potassium, mEq/L	4.5 (0.8)	4.8 (2.1)	4.4 (2.0)	0.001
Serum chloride, mEq/L	102.7 (13.5)	99.5 (12.1)	103.8 (14.3)	0.09
Serum phosphate, mg/dL	5.4 (2.3)	6.8 (3.2)	4.9 (2.7)	0.51
Serum calcium, mg/dL	8.0 (6.1)	9.0 (7.1)	7.7 (3.5)	0.93
Arterial pH	7.34 (0.09)	7.33 (0.06)	7.35 (0.10)	0.12
PCO_2, mm Hg	34.5 (16.5)	35.7 (14.4)	34.1 (18.1)	0.98
PO_2, mm Hg	72.0 (42.6)	79.7 (33.8)	69.6 (43.2)	0.55
Serum bicarbonate, mEq/L	19.4 (9.4)	18.5 (7.4)	19.3 (10.5)	0.20
Serum lactate, mmol/L	3.1 (3.2)	2.5 (1.3)	3.3 (2.1)	0.54

Table 1 (continued)

Variable	Total	KRT	Non-KRT	*p* value
Nephrologist nondialysis intervention, *N* (%)				
Fluid adjustment	238 (82.6)	33 (45.8)	205 (94.9)	<0.001
Nephrotoxic withdrawal	73 (25.3)	8 (11.1)	65 (30.0)	0.001
Antibiotic dose adjustment	46 (15.9)	9 (12.5)	37 (17.1)	0.35
Nutritional adjustment	8 (2.7)	0 (0.0)	8 (3.7)	0.09
Remove hyperchloremic solutions	13 (4.5)	1 (1.3)	12 (5.5)	0.14
KRT, *N* (%)				
Hemodialysis	66 (22.9)	66 (91.6)	–	–
Peritoneal dialysis	6 (2.1)	6 (8.4)	–	–
Cause of KRT, *N* (%)				
Hyperkalemia	21 (7.2)	21 (29.1)	–	–
Acid-base disorders	24 (8.3)	24 (33.3)	–	–
Fluid overload	44 (15.2)	44 (61.1)	–	–
Uremia	26 (9.0)	26 (36.1)	–	–
Mortality, *N* (%)	45 (15.6)	20 (27.7)	25 (11.5)	0.001

AKI, acute kidney injury; CKD, chronic kidney disease; KDIGO; Kidney Disease Initiative Global Outcomes; KRT, kidney replacement therapy; BMI, body mass index; SCr, serum creatinine.

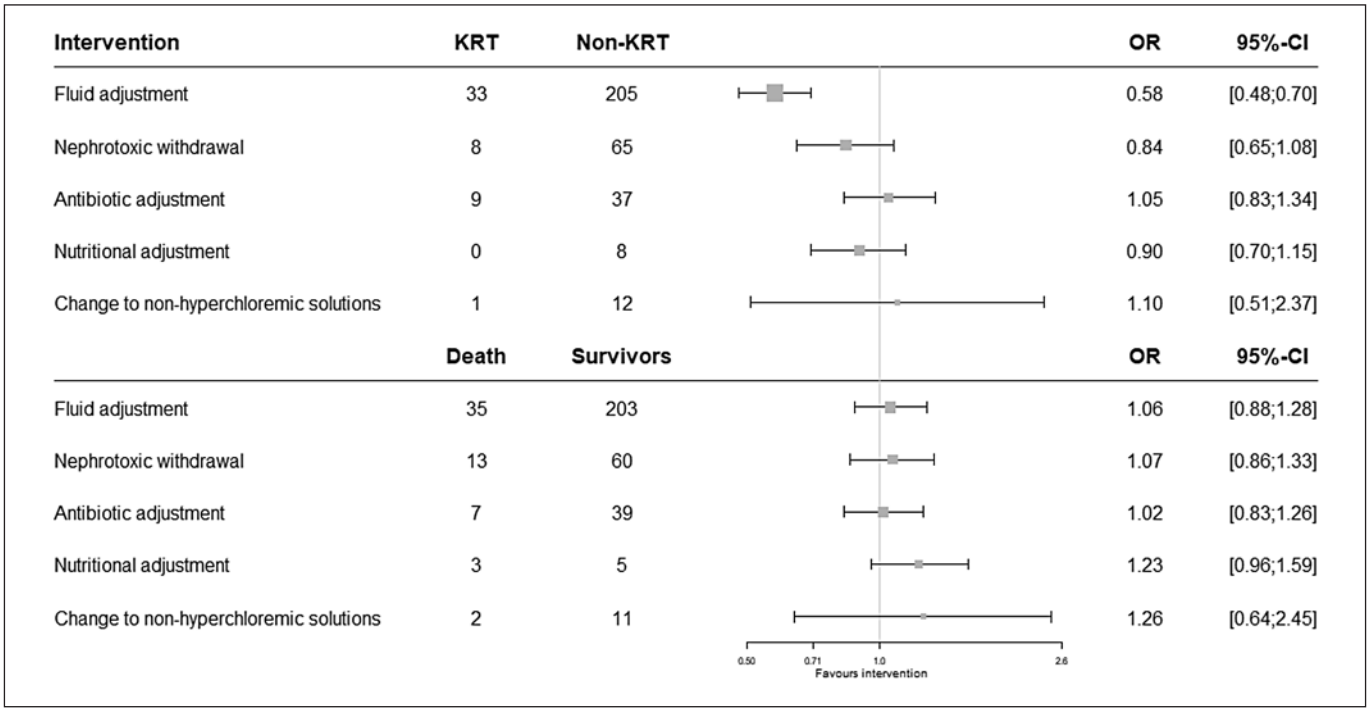

Fig. 2. Forest plot of early nephrologist intervention associated with KRT and death. KRT, kidney replacement therapy; OR, odds ratio; CI, confidence interval.

Primary Outcome, Nephrologist Interventions, and Their Impact on the Initiation of KRT

A multivariate analysis showed that variables associated with an increased risk for KRT were hypothyroidism (OR: 1.19, 95% CI: 1.00–1.42, and $p = 0.04$), diuretics (OR: 1.18, 95% CI: 1.08–1.30, and $p = 0.001$), and AKI KDIGO 3 (OR: 1.25, 95% CI: 1.13–1.37, and $p \leq 0.001$). In an attempt to identify variables and nephrologist inter-

Table 2. Univariable-multivariable logistic regression model to determine the variables associated with start KRT in AKI patients before propensity score analysis

	Univariate (95% CI)	*p* value	Multivariate (95% CI)	*p* value
Age	0.99 (0.99–1.00)	0.64	0.99 (0.99–1.00)	0.06
Female	0.98 (0.83–1.16)	0.86	1.09 (0.88–1.33)	0.40
Type 2 diabetes mellitus	0.97 (0.87–1.07)	0.58	1.07 (0.97–1.19)	0.14
Hypertension	1.01 (0.85–1.20)	0.86	1.02 (0.82–1.26)	0.85
Smoker	0.95 (0.76–1.18)	0.65	0.99 (0.79–1.24)	0.95
Hypothyroidism	1.03 (0.79–1.35)	0.78	1.11 (0.85–1.46)	0.43
CKD grade 1–4	1.01 (0.84–1.21)	0.85	0.91 (0.75–1.11)	0.37
Cerebrovascular disease	1.10 (0.70–1.73)	0.65	1.25 (0.78–2.02)	0.34
Ischemic heart disease	0.84 (0.47–1.49)	0.56	0.75 (0.40–1.41)	0.38
BMI	0.99 (0.98–1.01)	0.90	0.99 (0.98–1.01)	0.59
Sepsis	1.10 (0.93–1.30)	0.24	1.03 (0.86–1.24)	0.69
Hypovolemia	1.01 (0.85–1.20)	0.86	0.97 (0.80–1.17)	0.77
Cardiorenal syndrome	0.77 (0.60–0.99)	0.04	0.83 (0.61–1.13)	0.24
Nephrotoxic drugs	1.00 (0.80–1.23)	1.00	1.02 (0.81–1.29)	0.81
Shock	1.13 (1.02–1.26)	0.01	1.03 (0.92–1.15)	0.58
Vasoactive drugs	1.07 (0.90–1.27)	0.39	1.14 (0.94–1.38)	0.16
AKI KDIGO 1	0.76 (0.61–0.95)	0.02	1.01 (0.74–1.37)	0.94
AKI KDIGO 2	0.96 (0.74–1.24)	0.79	1.00	1.00
AKI KDIGO 3	1.21 (1.01–1.45)	0.03	1.28 (0.99–1.66)	0.053
NSAIDs	1.04 (0.88–1.23)	0.61	1.06 (0.88–1.27)	0.51
Antibiotics	1.06 (0.87–1.29)	0.54	1.01 (0.80–1.27)	0.90
Antihypertensive	0.98 (0.81–1.18)	0.85	1.04 (0.85–1.28)	0.67
Diuretics	1.07 (0.79–0.96)	0.01	1.23 (1.00–1.50)	0.04
Fluid adjustment	0.61 (0.52–0.71)	<0.001	0.58 (0.48–0.70)	<0.001
Nephrotoxic withdrawal	0.83 (0.66–1.04)	0.11	0.84 (0.65–1.08)	0.19
Antibiotic adjustment	0.89 (0.71–1.12)	0.35	1.05 (0.83–1.34)	0.64
Nutritional adjustment	0.77 (0.57–1.04)	0.09	0.90 (0.70–1.15)	0.41
Remove hyperchloremic solutions	1.00 (0.49–2.01)	1.00	1.10 (0.51–2.37)	0.80

AKI, acute kidney injury; KDIGO; Kidney Disease Initiative Global Outcomes; NSAIDs, nonsteroidal analgesic anti-inflammatory drugs; CKD, chronic kidney disease; BMI, body mass index; CI, confidence interval; KRT, kidney replacement therapy.

ventions associated with the initiation of KRT in AKI patients at the 10-day follow-up, a decreased risk was fluid adjustment (OR: 0.57, 95% CI: 0.51–0.64, and $p \leq 0.001$) and nephrotoxic withdrawal (OR: 0.87, 95% CI: 0.79–0.96, and $p = 0.01$) as shown in online suppl. Table 1.

Propensity Score-Matching Analysis

A propensity score-matching analysis on sex and age was further applied to analyze the potential impact of nephrologist interventions on outcomes in AKI patients; it would be enough to match the groups sufficiently well based on the existing evidence that the 2 variables carry different risks for the development and evolution of AKI. After this analysis, 72 patients with fluid adjustment were compared with 72 patients treated with other interventions. The main prognostic covariables were properly balanced between subgroups after propensity score-matching analysis, and no significant differences were observed (online suppl. Fig. 2, 3). Consistent with the results for the entire cohort, diuretics increased the risk of KRT (OR: 1.23, 95% CI: 1.00–1.50, and $p < 0.004$), and fluid adjustment decreased the risk (OR: 0.58, 95% CI: 0.48–0.70, and $p < 0.001$), even after adjusting for potential confounders as shown in Table 2 and Figure 2. Similar results were observed with secondary outcomes.

Secondary Outcomes, Variables Associated with AKI Progression, and Mortality according to Nephrologist Intervention

Nephrologist fluid adjustment (OR: 0.59, 95% CI: 0.49–0.71, and $p \leq 0.001$) was the only variable associated with a reduction in AKI progression to KDIGO stage 3

Table 3. Univariable-Multivariable logistic regression model to determine the variables associated with AKI progression to stage 3 at 10-day follow-up before propensity score analysis

	Univariate (95% CI)	*p* value	Multivariate (95% CI)	*p* value
Age	0.99 (0.99–1.00)	0.64	0.99 (0.99–1.00)	0.14
Female	0.94 (0.83–1.06)	0.34	0.90 (0.79–1.02)	0.10
Type 2 diabetes mellitus	0.98 (0.83–1.16)	0.86	1.05 (0.85–1.29)	0.61
Hypertension	1.01 (0.85–1.20)	0.86	1.06 (0.86–1.32)	0.54
Smoker	0.95 (0.76–1.18)	0.65	1.00 (0.79–1.25)	0.99
Hypothyroidism	1.03 (0.79–1.35)	0.78	1.03 (0.79–1.36)	0.78
CKD grade 1–4	1.01 (0.84–1.21)	0.85	0.93 (0.76–1.13)	0.51
Cerebrovascular disease	1.10 (0.70–1.73)	0.65	1.38 (0.85–2.24)	0.18
Ischemic heart disease	0.84 (0.47–1.49)	0.56	0.76 (0.40–1.45)	0.41
BMI	0.99 (0.98–1.01)	0.90	0.99 (0.98–1.01)	0.56
Sepsis	1.10 (0.93–1.30)	0.24	1.04 (0.86–1.26)	0.64
Hypovolemia	1.01 (0.85–1.20)	0.86	0.99 (0.81–1.20)	0.93
Cardiorenal syndrome	0.77 (0.60–0.99)	0.04	0.82 (0.60–1.12)	0.21
Nephrotoxic drugs	1.00 (0.80–1.23)	1.00	1.04 (0.83–1.32)	0.52
Shock	0.96 (0.85–1.09)	0.55	0.86 (0.72–1.02)	0.09
Vasoactive drugs	1.07 (0.90–1.27)	0.39	1.11 (0.91–1.34)	0.27
NSAIDs	1.04 (0.88–1.23)	0.61	1.05 (0.87–1.27)	0.56
Antibiotics	1.06 (0.87–1.29)	0.54	1.02 (0.81–1.29)	0.82
Antihypertensive	0.98 (0.81–1.18)	0.85	1.03 (0.84–1.28)	0.71
Diuretics	0.95 (0.81–1.13)	0.62	1.15 (0.94–1.41)	0.15
Fluid adjustment	0.61 (0.52–0.71)	<0.001	0.59 (0.49–0.71)	<0.001
Nephrotoxic withdrawal	0.83 (0.66–1.04)	0.11	0.88 (0.68–1.13)	0.33
Antibiotic adjustment	0.89 (0.71–1.12)	0.35	1.04 (0.81–1.32)	0.74
Nutritional adjustment	0.77 (0.54–1.09)	0.14	0.75 (0.52–1.07)	0.12
Remove hyperchloremic solutions	1.00 (0.49–2.01)	1.00	1.28 (0.59–2.78)	0.52

NSAIDs, nonsteroidal analgesic anti-inflammatory drugs; AKI, acute kidney injury; CKD, chronic kidney disease; BMI, body mass index; CI, confidence interval.

after the score matching and multivariable analysis is shown in Table 3. Vasopressors (OR: 1.25, 95% CI: 1.06–1.47, and $p = 0.008$) and the need for KRT (OR: 1.15, 95% CI: 1.01–1.35, and $p = 0.04$) increased the mortality risk at the 10-day follow-up as shown in Table 4, after the score matching and multivariable analysis.

Exploratory Analysis, Identification of Variables Associated with the Classic Indication to Initiate KRT, and Mortality

Among the classic indications to initiate KRT in AKI patients as having fluid overload, hyperkalemia, acid-base disorders, and uremia, we found that fluid overload was the main cause that led to starting KRT (1.91, 95% CI: 1.75–2.08, and $p < 0.001$), followed by uremia (1.46, 95% CI: 1.31–1.63, and $p < 0.001$) in multivariable analysis as shown in online suppl. Table 2. We also found that fluid overload was the only factor significantly associated with mortality (1.13, 95% CI: 1.00–1.27, and $p = 0.04$).

Discussion

In this single-center prospective cohort study in AKI patients, we showed that fluid adjustment was an early nephrologist intervention that could reduce the risk of starting KRT and reduce AKI progression to KDIGO grade 3. We found that fluid adjustment was associated with a 42% reduction in the probability of starting KRT. Fluid adjustment may be one of the most relevant strategies in AKI patients [21, 22]. It is a spectrum of interventions that have different positive effects on the injured kidney. For example, in patients with hypovolemia, a frequent etiology of AKI [23], timely fluid administration may be a preventive measure against AKI and should be effective both through restoring the circulating volume, improving the impaired renal perfusion, and promoting the recovery of kidney functions [24]. In AKI, the rationale of fluid therapy is to restore the mean arterial pressure (which determines renal perfusion pressure) and

Table 4. Univariable-Multivariable logistic regression model to determine the variables associated with mortality at 10-day follow-up in AKI patients before propensity score analysis

	Univariate (95% CI)	*p* value	Multivariate (95% CI)	*p* value
Age	1.00 (0.99–1.00)	0.29	1.00 (0.99–1.00)	0.20
Female	0.96 (0.88–1.04)	0.37	0.93 (0.85–1.01)	0.28
Type 2 diabetes mellitus	0.91 (0.80–1.05)	0.23	0.94 (0.79–1.12)	0.53
Hypertension	0.90 (0.79–1.04)	0.17	0.96 (0.80–1.16)	0.71
Smoker	1.04 (0.86–1.24)	0.65	1.04 (0.86–1.27)	0.64
Hypothyroidism	1.05 (0.84–1.32)	0.61	1.02 (0.81–1.30)	0.82
CKD grade 1–4	0.92 (0.80–1.07)	0.32	0.99 (0.83–1.17)	0.94
Cerebrovascular disease	0.98 (0.68–1.42)	0.93	1.14 (0.75–1.72)	0.53
Ischemic heart disease	0.80 (0.50–1.28)	0.36	0.76 (0.44–1.31)	0.33
BMI	0.99 (0.98–1.00)	0.41	0.99 (0.98–1.01)	0.77
Sepsis	1.01 (0.88–1.16)	0.81	0.91 (0.78–1.07)	0.30
Hypovolemia	0.94 (0.82–1.08)	0.44	0.98 (0.83–1.16)	0.87
Cardiorenal syndrome	0.88 (0.72–1.08)	0.25	0.95 (0.73–1.25)	0.75
Nephrotoxic drugs	1.17 (0.98–1.39)	0.07	1.09 (0.89–1.33)	0.37
Vasoactiver drugs	1.37 (1.20–1.56)	<0.001	1.25 (1.06–1.47)	0.008
AKI KDIGO 1	0.91 (0.75–1.09)	0.33	1.00 (0.76–1.31)	0.97
AKI KDIGO 2	1.02 (0.82–1.26)	0.83	1.00	1.00
AKI KDIGO 3	1.05 (0.90–1.22)	0.52	1.00 (0.80–1.26)	0.95
NSAIDs	0.88 (0.77–1.01)	0.07	0.87 (0.74–1.02)	0.10
Antibiotics	1.21 (1.03–1.42)	0.02	1.12 (0.91–1.36)	0.26
Antihypertensive	0.85 (0.73–0.99)	0.04	0.92 (0.77–1.10)	0.40
Diuretics	0.93 (0.82–1.07)	0.35	0.97 (0.81–1.16)	0.79
KRT	1.13 (1.00–1.29)	0.05	1.15 (1.01–1.35)	0.04
Fluid adjustment	1.00 (0.86–1.15)	0.95	1.06 (0.88–1.28)	0.49
Nephrotoxic withdrawal	1.11 (0.92–1.33)	0.26	1.07 (0.86–1.33)	0.51
Antibiotic adjustment	1.07 (0.88–1.29)	0.48	1.02 (0.83–1.26)	0.81
Nutritional adjustment			1.23 (0.96–1.59)	0.10
Remove hyperchloremic solutions	1.33 (0.75–2.37)	0.32	1.26 (0.64–2.45)	0.49

AKI, acute kidney injury; CKD, chronic kidney disease; KDIGO, Kidney Disease Initiative Global Outcomes; NSAIDs, nonsteroidal analgesic anti-inflammatory drugs; BMI, body mass index; CI, confidence interval; KRT, kidney replacement therapy.

cardiovascular output (required for adequate renal blood flow). There is a fine line between achieving proper fluid resuscitation and fluid overload; unfortunately, the kidney is particularly affected by fluid overload, which can lead to increased renal subcapsular pressure and lowered renal blood flow and glomerular filtration rate [25]. Cautious fluid administration guided by markers of fluid responsiveness can be considered [26] because excessive fluid administration should be avoided to prevent harmful fluid overload [27, 28]. Regarding this issue, our results showed that the main cause of starting KRT was fluid overload, with a significant 1.91-fold increase risk (online suppl. Table 2) and a 13% increased risk of mortality in those patients, which is similar to those found in other cohort studies [21, 29]. In patients with established AKI, further fluid overloading has been linked with lower survival and less renal recovery [30, 31]; limiting and resolving fluid overload might prompt earlier use of KRT. Our results reaffirm the importance of how the nephrologist's early intervention with fluid adjustment could positively change the trajectory of patients with AKI.

As we observed in our study, the use of diuretics was associated with a significant 1.23-fold increase in the risk of starting KRT (Table 2). The use of diuretics in AKI has been controversial, and some benefits have been described; higher post-AKI furosemide doses had a protective effect against mortality [32]. In addition, starting diuretics at the cessation of CRRT contributed to the successful discontinuation of CRRT by reducing the volume overload risk in critically ill patients with AKI [33]. In contrast to a meta-analysis of 28 randomized trials, furosemide in patients with AKI or at risk for starting AKI did

not have a lower mortality, reduced incidence of AKI, worsening of AKI, or decreased utilization of RRT [34]. We could explain the higher risk of KRT utilization in our study because patients with AKI were prescribed diuretics due to complications such as oliguria, anuria, or fluid overload.

Based on our results, none of the early nephrologist interventions reduced the risk of death in AKI patients. The multifactorial nature of AKI in hospitalized patients demands a multidisciplinary approach [35], where nephrologists can help in identifying early risk factors, adopting strategies to prevent the progression to more severe forms, and offering support renal therapy, not just KRT, when indicated. Ronco and Bellomo [36] in 1998 described the formal development of the specialty area called critical care nephrology, and the first aim was to recognize that the management of AKI in the ICU demands a multidisciplinary approach. Improving the quality of care provided to AKI patients, plausibly mitigating the cost of care, and improving short- and long-term outcomes are goals that have not been universally achieved. Therefore, understanding how the management of AKI may be amenable to quality improvement programs is needed.

In our study, we found that the use of vasopressors was associated with an increase of 25% in the probability of mortality. It is possible that this event is a reflection of the severity of the patients since it would represent a state of shock and hemodynamic instability that compromises perfusion of the tissues and is associated with a higher inhospital mortality [37] but may also be associated with decreased kidney recovery [38]. We also found that in AKI, the need of KRT increased the mortality risk, which may reflect a sicker group of patients. The AKI KDIGO 3 patients (with KRT) clearly demonstrated an increase in mortality, with adjusted ORs of 4.1 [39] compared with less severe grades (1 and 2). These data support the existence of the biological gradient between AKI severity and mortality. A short estimated 2.3-fold increase in the risk of death attributable to AKI has been reported [39]. The pathophysiology of AKI is sufficiently heterogeneous to account for morbidity and mortality on a wide range of timescales.

The strengths of our study are that we separate, for the first time, the effect of some nephrologist interventions on AKI, and with this, we were able to observe the importance of each intervention separately. To our knowledge, the results presented in this study have never been published. Several limitations should be noted. Because of the observational and retrospective nature of the study, no causal relationships could be established. The presented cohort may be associated with its own biases due to its design, and one of them is selection bias. We did not classify the etiology of AKI and did not measure another important nephrologist intervention, such as glucose control and type of sedation. The study was carried out in a single center, and the follow-up of 10 days was relatively short.

Conclusion

In conclusion, in AKI patients, early nephrology consultation, specifically fluid adjustment, could prevent the need for KRT and decrease the progression of AKI.

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Statement of Ethics

The study was approved by the Hospital Civil de Guadalajara Fray Antonio Alcalde Institutional Review Board (HCG 146/18) and was conducted in adherence with the Declaration of Helsinki. Informed and written consent was obtained from all the subjects.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.S.C.I., P.M.A., and C.P.F. designed the protocol, collected the data, analyzed it, and wrote the manuscript. R.C.D.G., A.E.T.Q., F.R.A., G.N.B., R.M.G., J.G.R., F.Y.E., and G.G.G. analyzed it and wrote the manuscript.

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