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Early Serum Creatinine Change and Multidimensional Clinical Determinants of Kidney Replacement Therapy in Acute Kidney Injury

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Abstract

Background: Acute kidney injury (AKI) is a dynamic clinical syndrome, and a single serum creatinine measurement may not adequately reflect the severity or progression of renal dysfunction. The aim of this study was to assess whether early changes in serum creatinine provide better discrimination for renal replacement therapy (RRT) requirement than admission creatinine alone and to identify clinical factors associated with RRT and short-term renal outcomes. **Methods:** This retrospective observational cohort study included 115 adults with AKI admitted to the Nephrology Department or Intensive Care Unit of Sibiu County Clinical Emergency Hospital between January 2018 and December 2025. Clinical, biochemical, hemodynamic, fluid-balance and nephrotoxic exposure data were analyzed. Serum creatinine was assessed at admission or transfer to the Nephrology Department or Intensive Care Unit (time zero) and at 24 and 48 h thereafter. Multivariable logistic regression and receiver operating characteristic analyses were used to evaluate factors associated with RRT requirement and an eGFR below 60 mL/min/1.73 m^2 at 30 days. Creatinine change was defined as the absolute difference from the value measured at study entry. **Results:** Fifty-two patients required RRT. The 48 h change in serum creatinine showed better discrimination for RRT requirement than admission creatinine (AUC 0.758 vs. 0.634; DeLong $p = 0.012$). An exploratory, cohort-derived 48 h creatinine-change threshold of 0.79 mg/dL showed a sensitivity of 90.4% and a specificity of 52.4% for distinguishing RRT status. In multivariable analysis, vasopressor requirement, maximum serum potassium and positive 24 h fluid balance were independently associated with RRT, while the overall model showed high apparent discrimination (AUC 0.925). RRT requirement was also associated with an eGFR below 60 mL/min/1.73 m^2 at 30 days (adjusted OR 2.84, 95% CI 1.02–7.91). **Conclusions:** The 48 h creatinine change showed modest apparent discrimination of RRT status, but these findings are exploratory and do not establish prospective prediction. Patients requiring RRT also had greater hemodynamic instability, hyperkalemia and positive fluid balance and were more likely to have an eGFR below 60 mL/min/1.73 m^2 at 30 days. Serial assessment of renal function, together with the patient's clinical and metabolic status, may therefore be more informative than a single creatinine measurement.

Keywords: acute kidney injury; renal replacement therapy; serial creatinine change; fluid balance; hyperkalemia; renal recovery; nephrotoxic exposure

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1. Introduction

Acute kidney injury (AKI) is a heterogeneous clinical syndrome that is particularly common among critically ill patients and remains associated with substantial short- and long-term morbidity and mortality [1]. Large multinational data have shown that AKI affects a substantial proportion of patients admitted to intensive care and that increasing AKI severity is accompanied by progressively worse clinical outcomes [2].

AKI is no longer regarded solely as an acute and fully reversible event. In some patients, renal dysfunction persists beyond the initial episode and may progress through acute kidney disease to chronic kidney disease [3]. Consequently, increasing attention has been given not only to the diagnosis and staging of AKI, but also to the course of renal function and the likelihood of recovery [4].

Current diagnostic and staging frameworks remain largely dependent on serum creatinine and urine output, both of which are functional markers with important limitations in rapidly evolving kidney injury [5]. Serum creatinine is especially problematic in non-steady-state conditions because its concentration may lag behind abrupt changes in glomerular filtration and is influenced by creatinine generation, distribution volume and critical illness itself [6]. For this reason, a single creatinine value may provide limited information about ongoing renal deterioration, whereas serial measurements can better describe changes in renal function over time [7].

Changes in creatinine during the early course of AKI may therefore be more informative than the admission value alone. Kinetic approaches based on serial creatinine measurements have been investigated as a means of improving assessment of renal function and identifying patients at increased risk of adverse renal outcomes, including the need for renal replacement therapy (RRT) [7]. The decision to initiate RRT in AKI is not based on serum creatinine alone [8]. Electrolyte and acid-base disturbances, fluid overload, hemodynamic instability, persistent oliguria and the overall clinical condition of the patient all influence this decision [9]. Randomized trials have also shown that, in the absence of urgent indications, earlier initiation of RRT does not necessarily improve survival and may result in treatment of patients who might otherwise recover without dialysis [10].

Fluid balance and exposure to nephrotoxic agents may further influence the course and severity of AKI. Positive fluid balance has been associated with more severe AKI and poorer clinical outcomes, while cumulative exposure to nephrotoxic medications has been linked to an increased risk of severe renal injury in hospitalized patients [11,12].

Although these factors have been studied individually, the relationship between early changes in serum creatinine, clinical severity and subsequent RRT requirement is less well characterized in routine clinical practice [13]. Early changes in renal function may also be relevant beyond the acute hospitalization, as patterns of renal recovery after AKI have been associated with subsequent kidney outcomes [14].

The aim of this study was to evaluate the clinical and biochemical factors associated with RRT requirement in patients with AKI, with particular attention to changes in serum creatinine during the first 48 h following admission or transfer to the Nephrology Department or Intensive Care Unit. The discriminatory performance of early creatinine changes was compared with that of admission creatinine, and their relationship with short-term renal outcomes was also examined.

2. Materials and Methods

2.1. Study Design and Population

This retrospective observational cohort study included adult patients (≥18 years) with AKI admitted to the Department of Nephrology or the Intensive Care Unit of Sibiu County Clinical Emergency Hospital, Sibiu, Romania, between 1 January 2018 and 1 December 2025.

Patients were eligible if AKI was documented at the time of admission or transfer to the mentioned departments and sufficient clinical and laboratory data were available for analysis. The cohort was not restricted to patients diagnosed with AKI at their initial hospital presentation and also included patients with AKI occurring in the context of potentially nephrotoxic exposures. For the purposes of the study, the reference time point (0 h) was defined as admission or transfer to the Nephrology Department or Intensive Care Unit.

The final cohort included 115 patients, of whom 52 received renal replacement therapy (RRT) and 63 were managed without RRT. The study population was restricted to selected patients with AKI managed in the 2 mentioned departments and did not represent all patients hospitalized with AKI during the study period.

RRT was defined as the receipt of at least one dialysis session during the index hospitalization. None of the patients received RRT before. RRT was performed using intermittent hemodialysis. The initial session lasted 2 h, followed, when necessary, by a 3 h session and subsequent 4 h sessions at intervals of 1–2 days, according to clinical need. The decision to initiate RRT and the number of sessions were individualized by the treating nephrologist based on clinical indications, including severe hyperkalemia, fluid overload and anuria.

2.2. Data Collection, Study Variables and Outcomes

Demographic characteristics, comorbidities, AKI etiology, precipitating factors, hemodynamic and respiratory parameters, nephrotoxic exposures, fluid intake and urine output, renal function indices, electrolytes, acid–base parameters, inflammatory markers, liver-function and coagulation parameters, and Charlson Comorbidity Index were retrospectively extracted from the available medical records. Infection-associated AKI was defined as AKI primarily attributed to an infectious process, irrespective of whether sepsis was formally documented.

Acute kidney injury was diagnosed according to KDIGO criteria, defined by an increase in serum creatinine of $\geq$0.3 mg/dL within 48 h, an increase to $\geq$1.5 times baseline within 7 days or urine output $<$ 0.5 mL/kg/h for at least 6 h. Serum creatinine was measured at admission or transfer to the Nephrology Department or Intensive Care Unit (Cr0) and at 24 (Cr24) and 48 h (Cr48) thereafter. Absolute changes were calculated as ΔCr0–24 = Cr24 − Cr0 and ΔCr0–48 = Cr48 − Cr0, using Cr0 as the reference for changes following admission or transfer rather than as the pre-AKI baseline.

Measured pre-AKI serum creatinine values were unavailable. Therefore, baseline creatinine was estimated from age and sex using the CKD-EPI 2021 equation, assuming an eGFR of 75 mL/min/1.73 m^2. This estimate was used exclusively for exploratory comparisons with Cr0 and Cr48 and should not be interpreted as an individual patient's true pre-AKI baseline. It was not used for AKI diagnosis, staging, or CKD classification.

Rapid creatinine progression at 24 h and AKI worsening at 48 h were defined as absolute increases in serum creatinine of $\geq$0.3 mg/dL from Cr0 to Cr24 and Cr0 to Cr48, respectively, rather than changes in KDIGO stage. Severe metabolic acidosis was defined as arterial pH $\leq$ 7.20 accompanied by serum bicarbonate $\leq$ 20 mmol/L. The timing of RRT initiation relative to subsequent creatinine measurements, maximum serum potassium, minimum arterial pH and 24 h fluid balance could not be reliably established; therefore, these parameters could not be assumed to have been measured exclusively before RRT initiation.

The primary outcome was RRT requirement during the index hospitalization. Secondary outcomes were an eGFR below 60 mL/min/1.73 m^2 at 30 days and dialysis dependence at hospital discharge among patients treated with RRT. The 30-day renal outcome was based on a single eGFR measurement.

Thirty-day renal outcome data were available for 103 patients, including 28 patients with an eGFR below 60 mL/min/1.73 m^2 and 75 with an eGFR of at least 60 mL/min/1.73 m^2.

Follow-up information was unavailable for 12 patients. Among patients receiving RRT, dialysis dependence at discharge was evaluated as an exploratory outcome because only 9 events were observed.

2.3. Statistical Analysis and Ethics

Continuous variables were summarized as medians with interquartile ranges (IQRs) and compared between patients with and without RRT using the Mann–Whitney U test. Categorical variables were presented as counts and percentages and compared using the chi-square test or Fisher's exact test, as appropriate.

Before multivariable analysis, collinearity among candidate variables was assessed using Spearman correlation coefficients and variance inflation factors (VIFs). Minimum arterial pH and admission bicarbonate showed substantial collinearity (Spearman r = 0.87; VIF 4.92 and 4.38, respectively). Minimum arterial pH was therefore excluded from the final model, while admission bicarbonate was retained as the acid-base variable.

Multivariable logistic regression was used to assess factors associated with RRT requirement. The final model included vasopressor requirement, maximum serum potassium, admission bicarbonate and 24 h fluid balance; sepsis and septic shock were excluded. Associations were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Model discrimination was evaluated using receiver operating characteristic (ROC) analysis and the area under the curve (AUC). A bootstrap-derived 95% CI was calculated for the multivariable RRT model. The added value of ΔCr0–48 was assessed by comparing the multivariable model with and without it using the likelihood ratio test, AIC and DeLong comparison of AUCs.

Separate ROC analyses were performed for admission creatinine, ΔCr0–24, ΔCr0–48, fold change and the two estimated-baseline variables. AUCs were compared using the DeLong test. Optimal thresholds were determined using the Youden index, with corresponding sensitivity and specificity estimates.

A separate multivariable logistic regression model was used to assess factors associated with an eGFR below 60 mL/min/1.73 m^2 at 30 days. This model included ΔCr0–48, RRT requirement, sepsis and Charlson Comorbidity Index. Dialysis dependence at discharge was analyzed exploratorily among patients who received RRT.

All tests were two-sided, and a p value < 0.05 was considered statistically significant. Data processing and statistical analyses were conducted using Python version 3.12, implemented within the PyCharm 2025.3.2.1 integrated development environment.

In accordance with institutional requirements for retrospective analyses of routinely collected clinical data, formal ethics committee approval and individual informed consent were not required. All patient-level data were anonymized before analysis.

3. Results

3.1. Study Population and Baseline Characteristics

A total of 115 patients with acute kidney injury (AKI) were included in the analysis, of whom 52 (45.2%) required renal replacement therapy (RRT) and 63 (54.8%) did not. Baseline demographic characteristics were comparable between groups. The median age was 66.0 years in the non-RRT group and 69.5 years in the RRT group. There were no significant differences in sex distribution, height, body weight, body mass index, smoking status or high-risk alcohol consumption (Table 1).

Table 1. Baseline characteristics, comorbidities, AKI etiology and precipitating factors according to RRT requirement.

Characteristic	No RRT (n = 63)	RRT (n = 52)	*p*
Age, years	66.0 (55.0–75.0)	69.5 (56.0–79.0)	0.549
Female sex	24 (38.1%)	25 (48.1%)	0.375
Male sex	39 (61.9%)	27 (51.9%)	
Height, cm	171.1 (162.6–177.8)	170.0 (165.2–174.6)	0.551
Weight, kg	81.3 (71.2–91.6)	80.2 (67.8–90.7)	0.623
BMI, kg/m^2	28.2 (25.4–30.9)	28.7 (24.5–30.9)	0.989
Current smoker	14 (22.2%)	15 (28.8%)	0.457
Former smoker	15 (23.8%)	15 (28.8%)	
Never smoker	34 (54.0%)	22 (42.3%)	
High-risk alcohol use	12 (19.0%)	7 (13.5%)	0.582
Hypertension	26 (41.3%)	23 (44.2%)	0.896
Diabetes mellitus	25 (39.7%)	18 (34.6%)	0.715
Chronic heart failure	9 (14.3%)	14 (26.9%)	0.146
Coronary artery disease	13 (20.6%)	10 (19.2%)	1.000
Atrial fibrillation	7 (11.1%)	7 (13.5%)	0.923
COPD	10 (15.9%)	7 (13.5%)	0.921
Chronic liver disease	9 (14.3%)	8 (15.4%)	1.000
Active malignancy	3 (4.8%)	5 (9.6%)	0.516
Peripheral vascular disease	5 (7.9%)	6 (11.5%)	0.738
Previous AKI within 12 months	6 (9.5%)	8 (15.4%)	0.503
Home diuretic use	14 (22.2%)	16 (30.8%)	0.409
Home NSAID use	4 (6.3%)	8 (15.4%)	0.204
Cardiorenal AKI	13 (20.6%)	9 (17.3%)	0.008 *
Glomerular/other AKI	8 (12.7%)	5 (9.6%)	
Hypovolemic AKI	14 (22.2%)	11 (21.2%)	
Nephrotoxic AKI	4 (6.3%)	0 (0%)	
Obstructive AKI	8 (12.7%)	0 (0%)	
Infection-associated AKI	16 (25.4%)	27 (51.9%)	
Sepsis	11 (17.5%)	26 (50.0%)	<0.001
Septic shock	1 (1.6%)	23 (44.2%)	<0.001
Hypovolemia	16 (25.4%)	16 (30.8%)	0.667
Acute heart failure	14 (22.2%)	15 (28.8%)	0.550
Contrast exposure within 72 h	12 (19.0%)	15 (28.8%)	0.311
Vancomycin exposure	6 (9.5%)	16 (30.8%)	0.008
Aminoglycoside exposure	1 (1.6%)	2 (3.8%)	0.866
NSAID exposure within 7 days	5 (7.9%)	10 (19.2%)	0.131
Urinary obstruction	8 (12.7%)	0 (0%)	0.022
Hydronephrosis	9 (14.3%)	2 (3.8%)	0.115

Similarly, the prevalence of major chronic comorbidities, including hypertension, diabetes mellitus, chronic heart failure, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, chronic liver disease, active malignancy, peripheral vascular disease and previous AKI within the preceding 12 months, did not differ significantly between groups. Home use of diuretics and NSAIDs was also comparable.

In contrast, the clinical context and etiology of AKI differed substantially according to RRT requirement. The distribution of the primary AKI etiology differed significantly between groups ($p = 0.008$), with infection-associated AKI being more frequent among patients requiring RRT (51.9% vs. 25.4%). Sepsis was present in 50.0% of patients requiring RRT compared with 17.5% of those managed without RRT ($p < 0.001$), while septic shock occurred in 44.2% versus 1.6%, respectively ($p < 0.001$).

Vancomycin exposure was also more frequent in the RRT group (30.8% vs. 9.5%, $p = 0.008$). By contrast, urinary obstruction was observed exclusively among patients not requiring RRT (12.7% vs. 0%, $p = 0.022$). No significant between-group differences were identified for hypovolemia, acute heart failure, contrast exposure, aminoglycoside exposure, recent NSAID exposure or hydronephrosis.

3.2. Clinical Severity, Fluid Balance and Biochemical Profile

Patients requiring RRT showed greater clinical severity. Maximum heart rate during the first 24 h was higher in the RRT group, as was maximum body temperature. Minimum oxygen saturation was lower among patients requiring RRT and vasopressor support was required in 63.5% of patients in the RRT group compared with 12.7% in the non-RRT group (Table 2).

Table 2. Clinical, biochemical and early AKI characteristics according to RRT requirement.

Characteristic	No RRT (n = 63)	RRT (n = 52)	*p*
Maximum heart rate, beats/min	106.8 (96.7–116.2)	116.0 (106.7–133.1)	<0.001
Maximum temperature, °C	36.9 (36.5–37.3)	37.5 (36.8–37.8)	0.001
Minimum SpO_2, %	93.6 (91.2–95.3)	90.6 (88.8–93.0)	<0.001
Vasopressor requirement	8 (12.7%)	33 (63.5%)	<0.001
Fluid intake at 24 h, mL	3206.0 (2897.0–3775.5)	4040.0 (3631.5–4522.2)	<0.001
Urine output at 24 h, mL	1610.0 (1367.5–1807.0)	1089.5 (644.5–1364.2)	<0.001
Admission creatinine, mg/dL	1.6 (1.3–2.3)	1.9 (1.7–2.6)	0.014
Creatinine at 24 h, mg/dL	2.1 (1.7–2.9)	2.4 (2.0–3.3)	0.004
Creatinine at 48 h, mg/dL	2.4 (1.9–3.2)	3.2 (2.5–3.9)	<0.001
Maximum creatinine, mg/dL	2.6 (2.0–3.3)	3.3 (2.6–4.1)	<0.001
Admission potassium, mmol/L	4.8 (4.4–5.1)	5.1 (4.9–5.4)	<0.001
Maximum potassium, mmol/L	5.2 (4.7–5.4)	5.8 (5.3–6.1)	<0.001
Admission sodium, mmol/L	137.7 (135.0–141.0)	135.4 (131.1–138.2)	0.002
Admission chloride, mmol/L	104.3 (101.0–107.8)	104.9 (101.2–107.1)	0.796
Admission bicarbonate, mmol/L	19.9 (16.8–22.5)	15.9 (12.4–18.7)	<0.001
Minimum arterial pH	7.3 (7.3–7.3)	7.2 (7.2–7.3)	<0.001
Maximum lactate, mmol/L	2.2 (1.5–2.9)	2.7 (2.0–3.8)	0.014
Hemoglobin, g/dL	12.1 (10.8–13.4)	12.4 (11.0–13.4)	0.715
Leukocytes, $\times 10^3/\mu L$	11.3 (8.4–14.4)	14.2 (10.0–17.5)	0.006

Table 2. *Cont.*

Characteristic	No RRT (n = 63)	RRT (n = 52)	*p*
Neutrophils, $\times 10^3/\mu L$	6.9 (5.1–9.4)	10.1 (6.2–13.6)	0.003
Lymphocytes, $\times 10^3/\mu L$	3.1 (1.9–4.0)	3.2 (2.0–4.6)	0.555
Platelets, $\times 10^3/\mu L$	185.0 (141.5–236.0)	146.0 (96.5–214.5)	0.022
CRP, mg/L	29.6 (16.2–57.5)	50.8 (24.1–74.6)	0.016
Procalcitonin, ng/mL	0.2 (0.1–0.7)	1.6 (0.3–4.4)	<0.001
AST, U/L	53.0 (37.5–68.0)	78.5 (50.8–126.8)	<0.001
ALT, U/L	45.0 (33.5–68.0)	57.5 (39.8–98.2)	0.054
Total bilirubin, mg/dL	1.0 (0.8–1.5)	1.1 (0.8–1.6)	0.868
INR	1.1 (1.0–1.2)	1.2 (1.1–1.3)	0.006
Charlson Comorbidity Index	3.0 (2.0–5.5)	4.0 (2.0–6.0)	0.564
Rapid progression at 24 h	53 (84.1%)	50 (96.2%)	0.073
AKI worsening at 48 h	61 (96.8%)	52 (100.0%)	0.562
Severe metabolic acidosis	9 (14.3%)	22 (42.3%)	0.002

Fluid balance parameters also differed between groups. Patients in the RRT group received greater fluid volumes during the first 24 h and had lower 24 h urine output.

Serum creatinine was higher in the RRT group at all measured time points. Serum creatinine was higher at admission [1.9 (1.7–2.6) vs. 1.6 (1.3–2.3) mg/dL; $p = 0.014$], at 24 h [2.4 (2.0–3.3) vs. 2.1 (1.7–2.9) mg/dL; $p = 0.004$], at 48 h [3.2 (2.5–3.9) vs. 2.4 (1.9–3.2) mg/dL; $p < 0.001$] and at peak measurement [3.3 (2.6–4.1) vs. 2.6 (2.0–3.3) mg/dL; $p < 0.001$].

Electrolyte and acid-base abnormalities were also more pronounced among patients requiring RRT. Both admission and maximum potassium concentrations were higher ($p < 0.001$ for both), while admission sodium, admission bicarbonate and minimum arterial pH were lower. Severe metabolic acidosis was present in 42.3% of the RRT group compared with 14.3% of the non-RRT group ($p = 0.002$).

Several inflammatory and laboratory parameters also differed between groups. Patients requiring RRT had higher leukocyte and neutrophil counts, C-reactive protein, procalcitonin, lactate, AST and INR, together with lower platelet counts. In contrast, hemoglobin, chloride, lymphocyte count, bilirubin, ALT, Charlson Comorbidity Index, rapid progression at 24 h and AKI worsening at 48 h did not differ significantly between groups.

3.3. Collinearity Among Candidate Determinants of RRT

Collinearity was assessed among seven candidate variables considered for the multivariable RRT model: septic shock, vasopressor requirement, maximum potassium, minimum arterial pH, admission bicarbonate, 24 h fluid balance and sepsis (Table 3). The strongest collinearity was observed between minimum arterial pH and admission bicarbonate, with a Spearman correlation coefficient of 0.87. Consistent with this relationship, variance inflation factors were 4.92 for minimum arterial pH and 4.38 for admission bicarbonate. VIF values for the remaining candidate variables ranged from 1.29 to 3.14 (Figure 1).

Table 3. Collinearity assessment of candidate variables for the RRT model.

Variable	R^2	VIF
Septic shock	0.682	3.14
Vasopressor requirement	0.445	1.80
Maximum potassium	0.222	1.29
Minimum arterial pH	0.797	4.92
Admission bicarbonate	0.772	4.38
24 h fluid balance, per 1000 mL	0.467	1.88
Sepsis	0.466	1.87



Figure 1. Spearman correlation matrix among candidate variables included in the RRT modeling strategy.

Because of the substantial overlap between pH and bicarbonate and the numerical instability observed when both variables were retained, minimum arterial pH was excluded from the final multivariable model, while admission bicarbonate was retained as the marker of acid-base status.

3.4. Independent Clinical Factors Associated with RRT Requirement

Given the clinical overlap between sepsis, septic shock and vasopressor requirement, a more parsimonious multivariable model was preferred. In the initial model, septic shock showed a highly imprecise estimate (adjusted OR 1.39, 95% CI 0.09–21.76), despite acceptable VIF values. Considering the limited number of RRT events (n = 52), vasopressor requirement was retained as the marker of hemodynamic instability, while sepsis and septic shock were excluded from the final model.

The final multivariable logistic regression model included vasopressor requirement, maximum potassium, admission bicarbonate and 24 h fluid balance (Table 4; Figure 2). Three variables remained independently associated with RRT requirement after adjustment. Vasopressor use was associated with almost a sixfold increase in the odds of RRT (adjusted OR 5.81, 95% CI 1.53–22.12; $p = 0.010$). Maximum serum potassium was also strongly associated with RRT, with each 1 mmol/L increase corresponding to an adjusted OR of 4.69 (95% CI 1.50–14.70; $p = 0.008$). Each additional 1000 mL of positive fluid balance at 24 h was associated with an adjusted OR of 4.56 for RRT (95% CI 1.95–10.66; $p < 0.001$). Admission bicarbonate showed an inverse association with RRT (adjusted OR 0.87, 95% CI 0.75–1.01; $p = 0.064$) that approached, but did not reach, conventional statistical significance. Sepsis and septic shock were strongly associated with RRT in the unadjusted analysis, and their effect appears to be captured by vasopressor requirement.

Table 4. Multivariable logistic regression model for RRT requirement.

Variable	Adjusted OR	95% CI	*p*
Vasopressor requirement	5.81	1.53–22.12	0.010
Maximum potassium, per 1 mmol/L	4.69	1.50–14.70	0.008
Admission bicarbonate, per 1 mmol/L	0.87	0.75–1.01	0.064
24 h fluid balance, per +1000 mL	4.56	1.95–10.66	<0.001

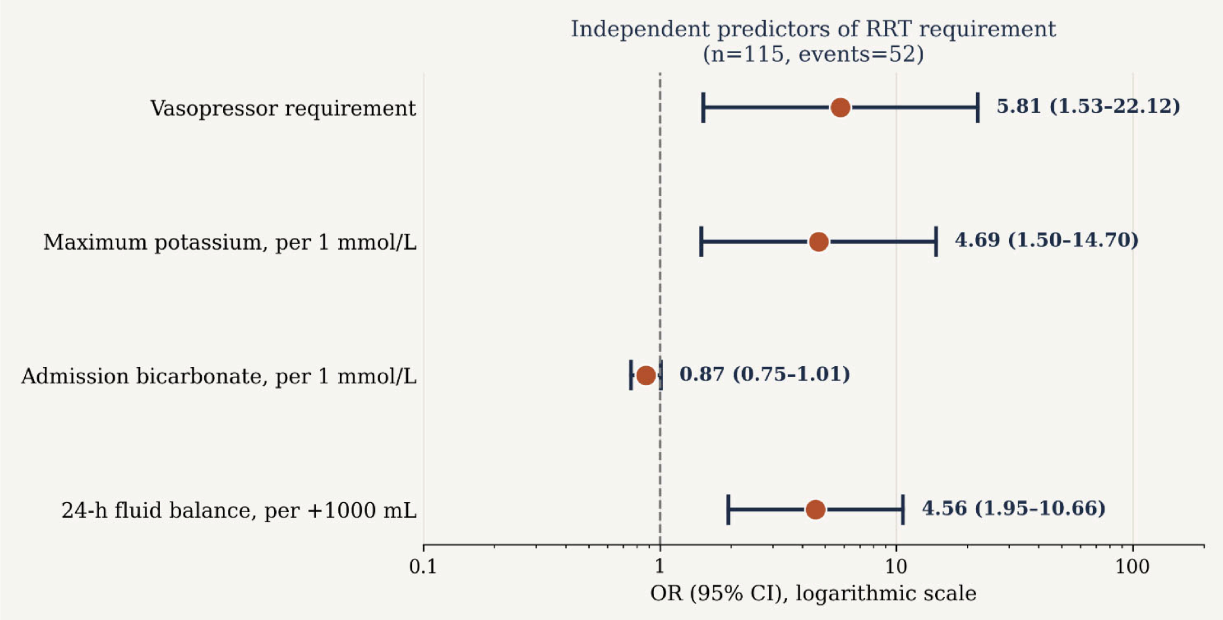


Figure 2. Forest plot of adjusted associations with RRT requirement.

Adding ΔCr0–48 to the clinical model did not improve fit or discrimination (LR test $p = 0.317$; AIC 85.7 vs. 86.7; AUC 0.925 vs. 0.931, DeLong $p = 0.110$), and ΔCr0–48 was not independently associated with RRT (adjusted OR 2.40, 95% CI 0.42–13.71).

The final model demonstrated high apparent discrimination, with an AUC of 0.925 (95% bootstrap CI 0.870–0.967) (Figure 3).

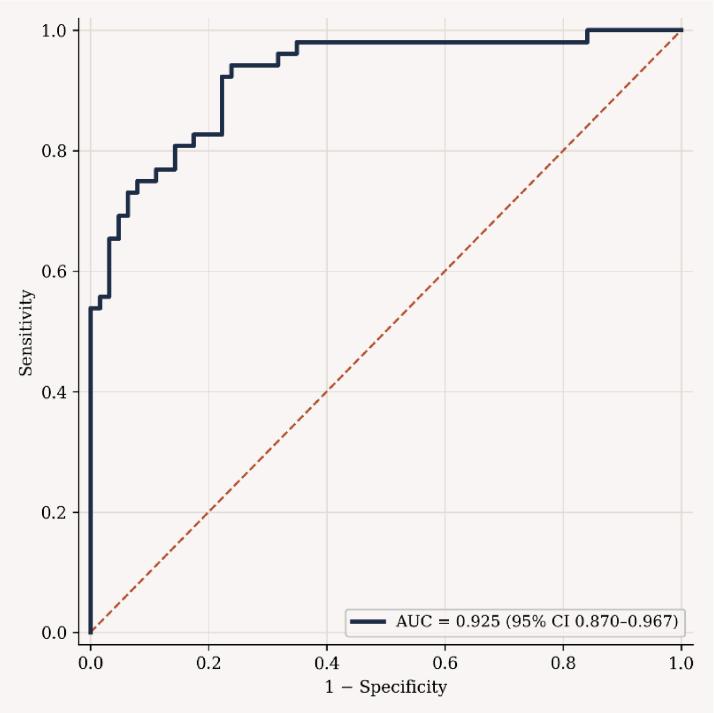


Figure 3. Receiver operating characteristic curve of the multivariable RRT model.

3.5. Early Creatinine Change Provides Greater Discrimination than Admission Creatinine

Early changes in serum creatinine were evaluated to determine whether they provided greater discrimination for RRT requirement than an isolated admission measurement (Table 5; Figure 4). Admission serum creatinine showed modest discriminatory performance, with an AUC of 0.634 (95% CI 0.525–0.733). The change in creatinine during the first 24 h provided a small improvement in discrimination (AUC 0.658, 95% CI 0.561–0.755).

Table 5. Discriminatory performance of creatinine-based measures for RRT requirement.

Predictor	AUC (95% CI)	Youden Threshold	Sensitivity	Specificity
Admission creatinine (mg/dL)	0.634 (0.525–0.733)	1.68	73.1%	55.6%
Δ creatinine 0–24 (mg/dL)	0.658 (0.561–0.755)	0.57	57.7%	76.2%
Δ creatinine 0–48 h (mg/dL)	0.758 (0.661–0.841)	0.79	90.4%	52.4%
Fold change 0–48 h (Cr48/Cr0)	0.679 (0.579–0.771)	×1.38	84.6%	44.4%
Admission − estimated baseline (mg/dL)	0.646 (0.540–0.740)	0.48	86.5%	41.3%
Cr48 − estimated baseline (mg/dL)	0.700 (0.607–0.792)	1.25	94.2%	42.9%

By contrast, the 48 h creatinine change showed higher discrimination, with an AUC of 0.758 (95% CI 0.661–0.841), significantly higher than admission creatinine (DeLong $p = 0.012$). The optimal Youden-derived threshold was an increase of 0.79 mg/dL over 48 h, yielding a sensitivity of 90.4% and a specificity of 52.4%.

To account for differences in kidney function at presentation, the 48 h change was also expressed relative to admission creatinine. Fold change (Cr48/Cr0) showed lower discrimination than the absolute change (AUC 0.679, 95% CI 0.579–0.771; optimal threshold

×1.38, sensitivity 84.6%, specificity 44.4%), although the difference was not statistically significant (DeLong $p = 0.113$).

Because pre-admission creatinine values were not available, a baseline creatinine was estimated from age and sex, using the creatinine value corresponding to an eGFR of 75 mL/min/1.73 m^2 (CKD-EPI 2021). The difference between admission and estimated baseline creatinine yielded an AUC of 0.646 (95% CI 0.540–0.740; threshold 0.48 mg/dL, sensitivity 86.5%, specificity 41.3%), and the difference between 48 h and estimated baseline creatinine yielded an AUC of 0.700 (95% CI 0.607–0.792; threshold 1.25 mg/dL, sensitivity 94.2%, specificity 42.9%).

Neither estimated-baseline measure exceeded the absolute 48 h change from admission (AUC 0.700 vs. 0.758, $p = 0.081$). The 48 h difference from estimated baseline discriminated better than admission creatinine alone ($p = 0.007$).

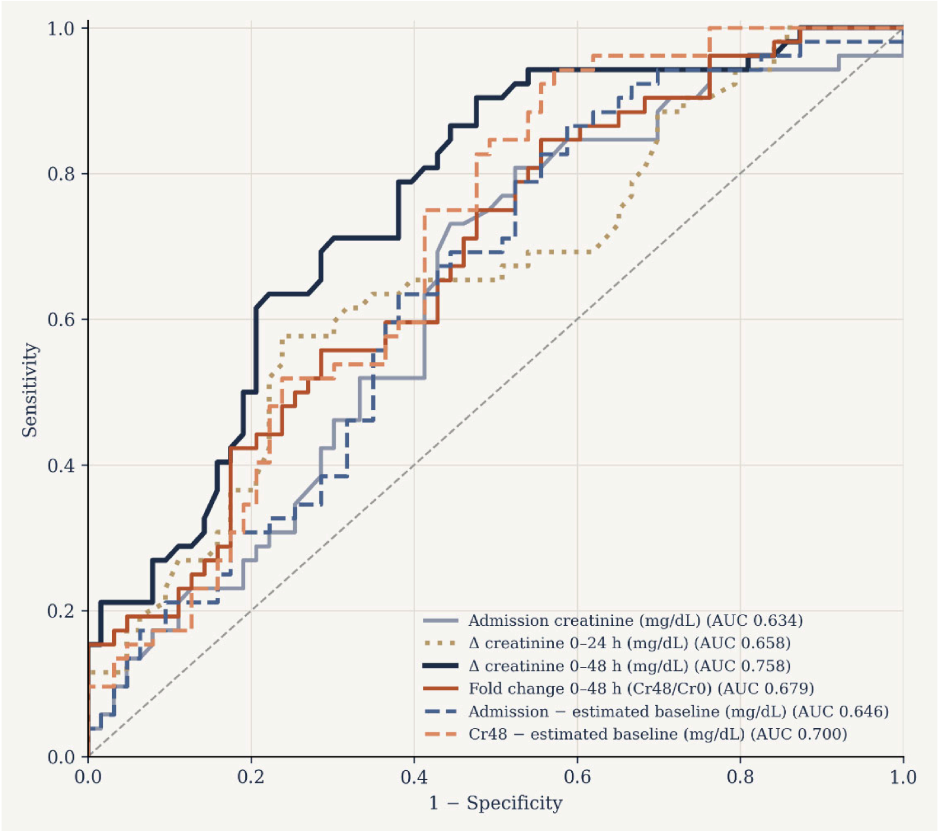


Figure 4. Receiver operating characteristic (ROC) curves of creatinine-based indicators according to renal replacement therapy (RRT) status (n = 115; 52 RRT events). AUC values were: admission creatinine, 0.634; Δ creatinine 0–24 h, 0.658; Δ creatinine 0–48 h, 0.758; fold change 0–48 h (Cr48/Cr0), 0.679; admission creatinine minus estimated baseline, 0.646; and 48 h creatinine minus estimated baseline, 0.700. Baseline creatinine was estimated from age and sex as the value corresponding to an eGFR of 75 mL/min/1.73 m^2 (CKD-EPI 2021). The dashed diagonal line indicates no discrimination.

3.6. Persistent Renal Dysfunction at 30 Days

Thirty-day renal outcome was available for 103 patients: persistent renal dysfunction was documented in 28 patients, while 75 did not meet the outcome and follow-up data were unavailable for 12 patients (Table 6; Figure 5).

Table 6. Multivariable model for an eGFR below 60 mL/min/1.73 m^2 at 30 days.

Variable	Adjusted OR	95% CI	*p*
Δ creatinine 0–48 h, per 1 mg/dL	3.44	0.93–12.66	0.063
RRT requirement	2.84	1.02–7.91	0.046
Sepsis	1.21	0.42–3.51	0.728
Charlson Comorbidity Index, per point	0.95	0.78–1.16	0.624

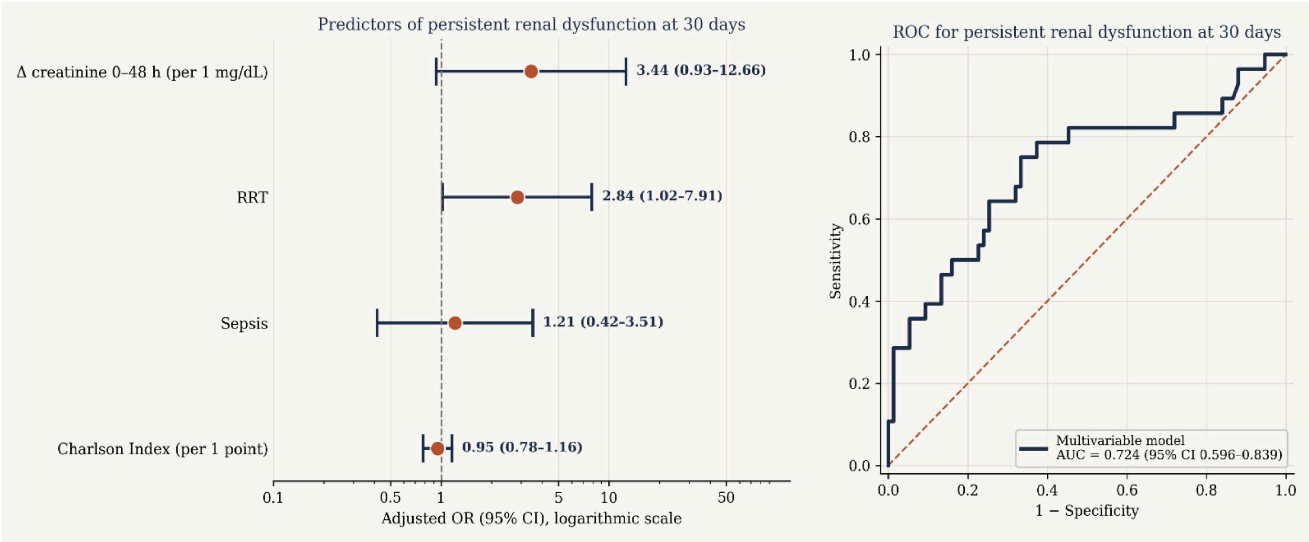


Figure 5. Adjusted associations with an eGFR below 60 mL/min/1.73 m^2 at 30 days and ROC curve of the multivariable model (AUC 0.724).

A multivariable model including 48 h creatinine change, RRT requirement, sepsis and Charlson Comorbidity Index demonstrated moderate overall discrimination, with an AUC of 0.724. RRT requirement during the index AKI episode was independently associated with an eGFR below 60 mL/min/1.73 m^2 at 30 days (adjusted OR 2.84, 95% CI 1.02–7.91; $p = 0.046$).

The 48 h increase in serum creatinine showed a large effect estimate (OR 3.44 per 1 mg/dL increase), although the 95% confidence interval included unity (0.93–12.66), and the association did not reach conventional statistical significance ($p = 0.063$). Neither sepsis nor Charlson Comorbidity Index was significantly associated with an eGFR below 60 mL/min/1.73 m^2 after adjustment.

3.7. Dialysis Dependence at Hospital Discharge

Among patients who underwent RRT, nine remained dialysis-dependent at hospital discharge. Given the limited number of events, estimates from this analysis were imprecise (Table 7; Figure 6). Admission creatinine was not associated with dialysis dependence at discharge. Similarly, no statistically significant associations were observed for maximum creatinine, sepsis or Charlson Comorbidity Index. The wide confidence intervals reflect the low event count and support the interpretation of this analysis as exploratory.

Table 7. Factors associated with dialysis dependence at discharge among patients receiving RRT.

Variable	OR	95% CI	*p*
Admission creatinine, mg/dL	0.53	0.03–10.71	0.679
Maximum creatinine, mg/dL	2.66	0.34–20.84	0.350
Sepsis	0.85	0.15–5.00	0.859
Charlson Comorbidity Index	0.70	0.46–1.07	0.102

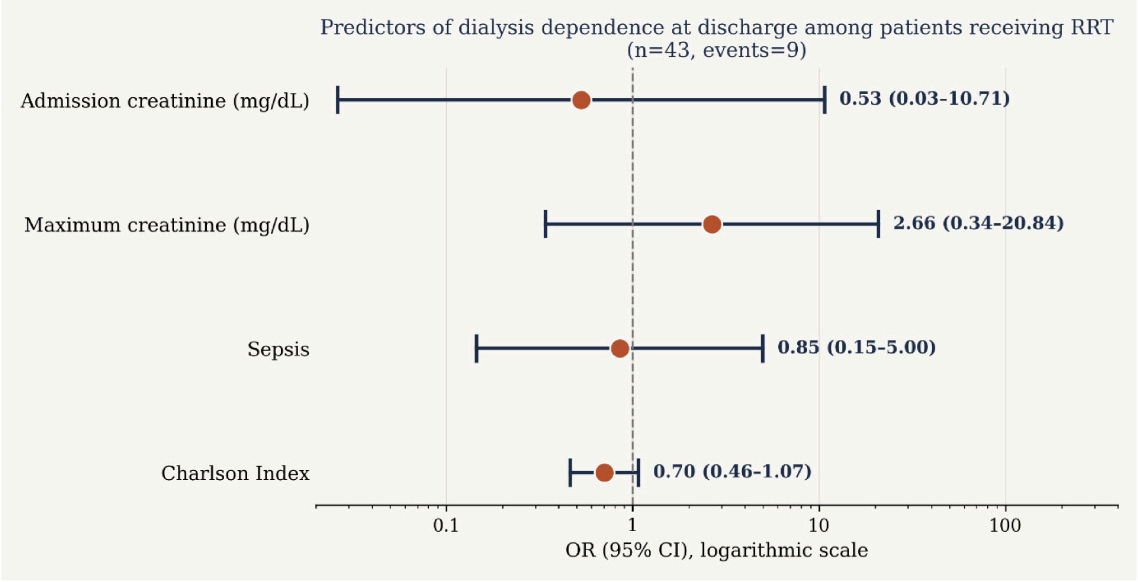


Figure 6. Forest plot of factors associated with dialysis dependence at discharge among patients receiving RRT.

4. Discussion

In this selected cohort, the absolute change in serum creatinine over 48 h showed better discrimination of RRT status than admission creatinine alone. Given the uncertain timing of RRT initiation relative to serial measurements, this finding should be interpreted as an exploratory association rather than evidence of prospective predictive performance. This observation is physiologically plausible because conventional creatinine-based estimates perform poorly when renal function is changing rapidly, whereas kinetic approaches incorporate the direction and magnitude of that change [15]. The same principle has emerged from larger AKI cohorts, in which temporal changes in creatinine contributed meaningfully to the identification of patients who subsequently required renal replacement therapy [16]. Adding ΔCr0–48 to the clinical model did not improve fit or discrimination, indicating that its discriminative value is modest and largely captured by the clinical variables. We analyzed only absolute creatinine changes and did not assess validated kinetic GFR equations or trajectory models. More broadly, early kidney-function trajectories have been shown to distinguish clinically relevant AKI phenotypes that are not fully captured by conventional staging based on peak creatinine alone [14].

This dynamic component is particularly relevant in the context of our second major finding: RRT requirement was not associated with renal dysfunction in isolation, but with a broader phenotype of circulatory, metabolic and volume-related derangement. Positive fluid balance has repeatedly been linked to more severe organ dysfunction and earlier need for continuous renal support in critically ill patients, indicating that fluid accumulation is closely intertwined with the progression of severe AKI [17]. The greater positive fluid balance

in the RRT group may reflect increased fluid administration, reduced urine output and greater disease severity [11]. Fluid accumulation may also dilute serum creatinine, masking the extent of kidney injury [18]. Although 24 h fluid balance remained independently associated with RRT in the multivariable model, this finding does not establish a causal relationship. The association between fluid accumulation and adverse outcomes after initiation of RRT further suggests that volume status remains clinically relevant throughout the course of severe AKI rather than representing only a pre-dialysis phenomenon [19].

The persistence of vasopressor requirement and hyperkalemia in the adjusted model reinforces this interpretation. These variables characterize two different but converging dimensions of severe AKI: systemic hemodynamic instability and loss of renal metabolic homeostasis. Contemporary concepts of sepsis-associated AKI similarly emphasize that kidney dysfunction develops through the interaction of circulatory disturbance, microvascular dysfunction, inflammation, metabolic changes and treatment-related exposures rather than through a single mechanism [20]. Sepsis and septic shock were strongly associated with RRT in the unadjusted analysis, but these associations were no longer significant after adjustment for related clinical variables. This does not diminish their clinical importance, as vasopressor requirement may reflect the hemodynamic instability associated with these conditions. The decision to initiate RRT depends on the overall clinical picture, including electrolyte and acid-base disturbances, fluid balance, organ support requirements and changes in kidney function, rather than the diagnosis alone [10].

RRT requirement was associated with an eGFR below 60 mL/min/1.73 m^2 at 30 days. However, this single measurement cannot establish persistent renal dysfunction or distinguish pre-existing CKD from incomplete renal recovery following AKI. AKI is now recognized as part of a continuum extending from acute injury through acute kidney disease and, in a proportion of patients, to chronic kidney disease, with incomplete recovery identifying patients at particularly high subsequent renal risk [21]. Meta-analytic evidence similarly demonstrates that the risk of chronic kidney disease and kidney failure increases after AKI and is greater after more severe episodes [22]. The lack of an independent association between early creatinine change and the follow-up outcome in our adjusted analysis should therefore not necessarily be interpreted as evidence against a role for early creatinine change, particularly given the limited number of events available for this endpoint. Large longitudinal cohorts have shown that persistent and non-recovering AKI trajectories carry worse outcomes even after accounting for the initial severity of kidney injury [23].

Dialysis dependence at discharge was infrequent, and no clear clinical determinant emerged from the exploratory analysis. Recovery after dialysis-requiring AKI often continues beyond the index hospitalization, with further improvement in kidney function occurring during the following weeks [24]. Predicting which patients will recover remains difficult, even in larger cohorts using routinely available demographic, comorbidity and laboratory data [25]. This prolonged and variable recovery course has also been described in outpatient AKI-D populations, making repeated reassessment more appropriate than early classification of dialysis dependence as permanent kidney failure [26].

The retrospective, single-center design and relatively small sample size limit the generalizability of our findings, while the low number of events for secondary renal outcomes reduces the precision of the estimates. The high proportion of patients requiring RRT (45.2%) likely reflects the selection of more severe AKI cases from nephrology and intensive care settings, making the results less applicable to unselected hospitalized AKI populations.

The absence of measured pre-AKI creatinine values prevented reliable determination of baseline kidney function and pre-existing CKD stage. The estimated baseline creatinine, calculated assuming an eGFR of 75 mL/min/1.73 m^2, was used solely for exploratory purposes and does not represent the true baseline of individual patients. A single eGFR

below 60 mL/min/1.73 m^2 at 30 days may reflect pre-existing CKD, incomplete recovery from AKI, or both. Furthermore, the timing of AKI onset could not be reliably established, and the distribution of community-acquired versus hospital-acquired AKI was unavailable. Consequently, creatinine changes measured from admission or transfer to the Nephrology Department or Intensive Care Unit may reflect different phases of kidney injury. KDIGO stages at diagnosis and during hospitalization were not assessed.

No patient received RRT before admission or transfer to the study departments, but the exact timing of treatment relative to subsequent creatinine measurements and other clinical parameters could not be established. Some measurements may have been influenced by RRT itself, introducing potential reverse causation and limiting the interpretation of the ROC analyses and multivariable model as prospective prediction tools. RRT initiation was individualized according to clinical need, introducing variability related to treatment decisions and local practice beyond AKI severity alone. Randomized evidence also indicates that, in the absence of urgent indications, allowing time for spontaneous recovery can influence whether patients ultimately require RRT [10].

5. Conclusions

In patients with AKI, early absolute change in serum creatinine showed better discrimination for RRT requirement than the admission value alone, although its discriminative value was modest. The need for RRT was associated with a broader pattern of disease severity characterized by hemodynamic instability, positive fluid balance, hyperkalemia and metabolic derangement and was also linked to persistent renal dysfunction at 30 days. These findings support a dynamic, multidimensional assessment of AKI severity rather than reliance on a single creatinine measurement. Given the retrospective single-center design, these observations should be validated in larger prospective cohorts before being translated into clinical risk-stratification tools.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and local institutional requirements governing research involving human participants. Ethical review and approval were not required for this retrospective observational study under the Romanian regulatory framework applicable at the time the study was conducted. Ministerial Order No. 1502/2016, which governed the Ethics Councils of public hospitals, did not establish a general requirement for ethics committee approval of retrospective observational studies. The explicit requirement covering interventional, observational and retrospective studies was subsequently introduced by Ministerial Order No. 6905/2025, published on 23 December 2025. The dataset analyzed in this study did not contain information allowing for the identification of individual patients.

Informed Consent Statement: Informed consent was waived because this retrospective analysis was part of a quality study using anonymized data.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Conflicts of Interest: The authors declare no conflict of interest.

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