EDITORIAL

Early to Dialyze
Healthy and Wise?

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Acute kidney injury (AKI) among hospitalized patients is common, consequential, and costly. Annually in the United States, approximately 10% of the estimated 5 million hospitalizations are complicated by AKI, with 0.4% of cases severe enough to require dialysis. Among patients with AKI requiring extracorporeal kidney support (dialysis), in-hospital mortality rates are consistently in excess of 20%, and may exceed 40% when accompanied by nonrenal organ system failure.[1-3] Acute kidney injury results in prolonged hospital stay, and is associated with marked increase in hospital costs, with attributable costs estimated to be between $5 billion and $10 billion annually.[3-5] Moreover, AKI has been linked with increased longer-term risks of chronic kidney disease (CKD), another condition associated with poor outcomes and high health care resource consumption,[6] as well as of higher risks of hypertension.[7]

Related article

Several cleverly designed and well-conducted trials to prevent AKI or ameliorate its course have been conducted over the past several years; however, findings from these trials have been largely disappointing. Among the interventions tested were anti-inflammatory and pleiotropic drugs (corticosteroids, statins, and aspirin),[8-10] vasoactive or antiplatelet drugs aimed to improve perfusion of the kidneys (fenoldopam, clonidine, and aspirin), different fluid administration strategies (buffered crystalloid solution vs saline),[11] and electronic health records–based alerts of evolving early-stage AKI.[12] Even though off-pump coronary artery bypass graft surgery significantly reduced AKI incidence compared with on-pump coronary artery bypass graft surgery, no improvement in kidney function or in the incidence of CKD was found after 12 months of prospective follow-up.[13] Early excitement about the potential efficacy of remote ischemic preconditioning in preventing AKI[14] was later tempered by larger trials that found no such benefit.[15,16]

As reported in *JAMA*, Zarbock et al[17] report findings from a single-center trial examining the effects of early vs delayed initiation of kidney replacement therapy in the course of patients who are critically ill with AKI. Patients were eligible to be randomized once they had reached stage 2 AKI per Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,[18] which is present if the serum creatinine concentration has doubled from baseline, urine output has decreased to below 0.5 mL/kg/h for at least 12 hours, or both. Eligible patients were also required to have 1 other condition from among severe sepsis, use of vasopressors or catecholamines, refractory fluid overload, or development or progression of organ dysfunction in another (nonkidney) organ. In addition, patients had to exhibit a plasma concentration of 150 ng/mL of neutrophil gelatinase-associated lipocalin (NGAL), a marker of presence and severity of AKI not currently used in routine practice.

Patients were randomized into 2 treatment groups: a group that initiated early kidney replacement therapy (early group; within 8 hours of reaching stage 2 AKI) and a group that delayed initiation of kidney replacement (delayed group; 12 hours after having reached stage 3 AKI per KDIGO criteria [serum creatinine has tripled from baseline, or urine output has decreased to below 0.3 mL/kg/h for at least 24 hours, or serum creatinine concentration of 4 mg/dL with an increase of 0.5 g/dL within 48 hours, or a combination of these outcomes]). Kidney replacement therapy involved continuous venovenous hemodiafiltration, the delivery of which was standardized and had to be strictly adhered to in both groups for at least 7 days. Patients were then followed for the primary end point of all-cause mortality at 90 days as well as several secondary end points focused on kidney outcomes, intensive care unit and hospital length of stay, and selected inflammatory biomarkers.

Of 231 patients enrolled, all 112 patients in the early group and 108 of 119 patients in the delayed group underwent kidney replacement therapy after meeting eligibility criteria (median time to initiation, 6 hours for the early group and 25.5 hours for the delayed group). Mortality after 90 days was 39.3% in the early group compared with 54.7% in the delayed group (P = .03), for an absolute risk reduction of −15.4% (95% CI, −28.1% to −2.6%). Several of the secondary end points were also significantly different between the groups, including shorter duration of kidney replacement therapy (median, 9 days for the early group vs 25 days for the delayed group), mechanical ventilation (125.5 hours for the early group vs 181 hours for the delayed group), and overall hospital length of stay (51 days for the early group vs 82 days for the delayed group). Recovery of kidney function without the need for dialysis was also more common in the early treatment group (53.6% for the early group vs 38.7% for the delayed group).

Zarbock and colleagues were appropriately reserved in their conclusions, highlighting the need for confirmatory data. Although the investigators carefully designed the intervention in a way that could be easily replicated—using widely accepted classification criteria for AKI by stage—the separation between groups (in other words, the difference between earlier and later initiation of dialysis) was modest—less than 24 hours. It is difficult to imagine how such a modest change in the dialytic intervention could yield such significant effects on multiple end points, including a 4-week difference in median hospital length of stay, let alone a 15% absolute reduction in in-hospital mortality. Other single-center, modestly sized published trials of dialytic interventions have yielded similarly remarkable results. In 2003, Marenzi et al[19] published data from a randomized clinical trial of 114 patients undergoing coronary interventions, in which hemofiltration and saline infusion delivered before and after radiocontrast exposure were compared. Rates of all major clinical events, including the development of AKI and the provision of dialysis or hemofiltration were reduced multifold. Moreover, in-hospital mortality was 2% in the hemofiltration group vs 14% in the saline infusion group ($P = .02$) and corresponding 1-year mortality rates were 10% for the hemofiltration group and 30% for the saline infusion group ($P = .01$). At the time many clinicians thought these results were implausible; to date, no confirmatory trials have been conducted. Zarbock et al appropriately acknowledged that single-center trials and trials of relatively modest sample size often overestimate the treatment effect; underpowered trial results showing positive effects with a *P* value less than .05 may be more likely to represent false-positive findings, rather than true-positive results.[20] However, similarly sized trials with less strikingly positive results often go unpublished.

Whether the findings reported by Zarbock et al represent a plausible effect or not, the investigators have performed a rigorous trial and have presented their results appropriately, with responsible and conservative reporting. Two large randomized clinical trials of dialysis "dose" following AKI definitively showed no material benefit for patients given higher intensity hemofiltration, hemodiafiltration, or hemodialysis.[21,22] Although these interventions proved ineffective, the trials were resoundingly successful, in that they were definitive, and informed clinical practice. The question of the optimal timing of dialytic support in critically ill patients is one of high priority and interest. In view of the provocative findings reported by Zarbock et al, it is the responsibility of the nephrology and critical care communities to confirm or refute these findings across multiple sites in a much larger, diverse population.

ARTICLE INFORMATION

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Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury
The ELAIN Randomized Clinical Trial

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IMPORTANCE Optimal timing of initiation of renal replacement therapy (RRT) for severe acute kidney injury (AKI) but without life-threatening indications is still unknown.

OBJECTIVE To determine whether early initiation of RRT in patients who are critically ill with AKI reduces 90-day all-cause mortality.

DESIGN, SETTING, AND PARTICIPANTS Single-center randomized clinical trial of 231 critically ill patients with AKI Kidney Disease: Improving Global Outcomes (KDIGO) stage 2 (≥2 times baseline or urinary output <0.5 mL/kg/h for ≥12 hours) and plasma neutrophil gelatinase–associated lipocalin level higher than 150 ng/mL enrolled between August 2013 and June 2015 from a university hospital in Germany.

INTERVENTIONS Early (within 8 hours of diagnosis of KDIGO stage 2; n = 112) or delayed (within 12 hours of stage 3 AKI or no initiation; n = 119) initiation of RRT.

MAIN OUTCOMES AND MEASURES The primary end point was mortality at 90 days after randomization. Secondary end points included 28- and 60-day mortality, clinical evidence of organ dysfunction, recovery of renal function, requirement of RRT after day 90, duration of renal support, and intensive care unit (ICU) and hospital length of stay.

RESULTS Among 231 patients (mean age, 67 years; men, 146 [63.2%]), all patients in the early group (n = 112) and 108 of 119 patients (90.8%) in the delayed group received RRT. All patients completed follow-up at 90 days. Median time (Q1, Q3) from meeting full eligibility criteria to RRT initiation was significantly shorter in the early group (6.0 hours [Q1, Q3: 4.0, 7.0]) than in the delayed group (25.5 h [Q1, Q3: 18.8, 40.3]; difference, −21.0 [95% CI, −24.0 to −18.0]; *P* < .001). Early initiation of RRT significantly reduced 90-day mortality (44 of 112 patients [39.3%]) compared with delayed initiation of RRT (65 of 119 patients [54.7%]; hazard ratio [HR], 0.66 [95% CI, 0.45 to 0.97]; difference, −15.4% [95% CI, −28.1% to −2.6%]; *P* = .03). More patients in the early group recovered renal function by day 90 (60 of 112 patients [53.6%] in the early group vs 46 of 119 patients [38.7%] in the delayed group; odds ratio [OR], 0.55 [95% CI, 0.32 to 0. 93]; difference, 14.9% [95% CI, 2.2% to 27.6%]; *P* = .02). Duration of RRT and length of hospital stay were significantly shorter in the early group than in the delayed group (RRT: 9 days [Q1, Q3: 4, 44] in the early group vs 25 days [Q1, Q3: 7, >90] in the delayed group; *P* = .04; HR, 0.69 [95% CI, 0.48 to 1.00]; difference, −18 days [95% CI, −41 to 4]; hospital stay: 51 days [Q1, Q3: 31, 74] in the early group vs 82 days [Q1, Q3: 67, >90] in the delayed group; *P* < .001; HR, 0.34 [95% CI, 0.22 to 0.52]; difference, −37 days [95% CI, −∞ to −19.5]), but there was no significant effect on requirement of RRT after day 90, organ dysfunction, and length of ICU stay.

CONCLUSIONS AND RELEVANCE Among critically ill patients with AKI, early RRT compared with delayed initiation of RRT reduced mortality over the first 90 days. Further multicenter trials of this intervention are warranted.

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Acute kidney injury (AKI) is a well-recognized complication of critical illness with a large effect on morbidity and mortality.[1] Despite increases in our knowledge of the management of patients who are critically ill, mortality associated with AKI remains high.[2-4] Although renal replacement therapy (RRT) provokes a considerable escalation in the complexity of treatment, the optimal timing of initiation of RRT in critically ill patients with AKI is still unknown.[5,6] Although the need for RRT in patients with severe AKI and life-threatening complications is unequivocal, the timing of RRT initiation in patients with severe AKI without such complications has not yet been defined. Earlier initiation of RRT may produce benefits by avoiding hypervolemia, eliminating of toxins, establishing acid-base homeostasis, and preventing other complications attributable to AKI. However, early initiation of RRT may unnecessarily expose some patients to potential harm because some patients will spontaneously recover renal function.

AKI *acute kidney injury*

KDIGO *Kidney Disease: Improving Global Outcomes*

NGAL *neutrophil gelatinase–associated lipocalin*

RRT *renal replacement therapy*

SLEDD *sustained low-efficiency daily dialysis*

The optimal timing of RRT initiation has been the focus of several studies. Current evidence suggests reduced mortality and better renal recovery with earlier RRT initiation.[7-9] A recently published pilot multicenter randomized trial investigated the optimal timing of initiation of RRT in critically ill patients with AKI.[10] The authors demonstrated the feasibility of conducting a large definitive trial comparing 2 strategies for RRT initiation among critically ill patients with AKI. In this pilot trial, mortality rates were not different between groups.[10] Thus, a large randomized study with a robust and relevant clinical end point is warranted to resolve this issue. As an initial step to achieve this goal, a single-center randomized clinical trial was performed to investigate whether early initiation of RRT could reduce 90-day all-cause mortality and to analyze other relevant clinical outcomes of RRT in critically ill patients with AKI.

Methods

Study Design and Ethics

A randomized, single-center, 2-group, parallel-group trial of different RRT-implementation strategies for critically ill patients with AKI was conducted between August 2013 and July 2015 (trial protocol in Supplement 1). Institutional review board approval was obtained from the research ethics committee of the Chamber of Physicians Westfalen-Lippe and the Westphalian Wilhelms University Muenster and the trial was registered in the German Clinical Trials Register (DRKS00004367). The study was conducted in accordance with the Declaration of Helsinki, October 2008 (49th General Assembly of the World Medical Association). All consent procedures followed local requirements, as approved by the ethics committee of the University of Muenster. The treating investigator informed the patient about the nature of the trial, its aims, and expected advantages, as well as possible risks. Written informed consent was obtained from eligible patients or by their legally authorized representative. Deferred consent was used in emergencies, and a consultant physician independent of the investigational team gave authorization. Once the participant regained capacity or the legally authorized representative was available, the individual was asked to affirm or withdraw consent.

Patient Recruitment

AKI was diagnosed based on changes in the serum creatinine, urine output, or both. Creatinine measurements were performed twice per day. Every patient had a urinary catheter and urine output was measured every hour. Prior to randomization, investigators obtained consent for participation in the study. Assuming all inclusion criteria were fulfilled and no exclusion criteria were met, each patient received a study identification number and treatment allocation at enrollment. Inclusion criteria were (1) Kidney Disease: Improving Global Outcomes (KDIGO) stage 2 (2-fold increase in serum-creatinine from baseline [for baseline serum creatinine, we used the serum creatinine at hospital admission, the last available serum creatinine within the last 3 months, or an estimated serum creatinine as per the KDIGO guideline[5] in patients with no information about their prior kidney function] or urinary output <0.5 mL/kg/h for ≥12 hours) despite optimal resuscitation (optimizing intravascular volume [fluid resuscitation: pulmonary artery occlusion pressure/central venous pressure of >12 mm Hg, stroke volume variation <12% in ventilated patients]; optimization of cardiac index [>2.6 L/min/m^2]; hemodynamic optimization [mean arterial pressure >65 mm Hg]; normalizing intra-abdominal pressure [<15 mm Hg]); (2) plasma neutrophil gelatinase–associated lipocalin (NGAL) >150 ng/mL; (3) at least 1 of the following conditions: severe sepsis, use of vasopressors or catecholamines (norepinephrine or epinephrine >0.1 µg/kg/min), refractory fluid overload (worsening pulmonary edema, Pa_{O_2}/Fi_{O_2} <300 mm Hg or fluid balance >10% of body weight), development or progression of nonrenal organ dysfunction (Sequential Organ Failure Assessment [SOFA] score ≥2); (4) aged between 18 and 90 years; and (5) intention to provide full intensive care treatment for at least 3 days. Patients with preexisting chronic kidney disease (estimated glomerular filtration rate [GFR] <30 mL/min), previous renal replacement therapy, AKI caused by permanent occlusion or surgical lesion of the renal artery, glomerulonephritis, interstitial nephritis, vasculitis, postrenal obstruction, or hemolytic uremic syndrome or thrombotic thrombocytopenic purpura were excluded. We also excluded patients for pregnancy, prior kidney transplantation, hepatorenal syndrome, AIDS with a CD4 count of <0.05 × 10 E/L, hematologic malignancy with neutrophils of <0.05 × 10 E/L, or participation in another interventional clinical trial.

Randomization and Interventions

Patients were randomized in a 1:1 ratio to 1 of the 2 treatment groups using a computerized system. Randomization was stratified by SOFA Cardiovascular score (0-2 vs 3-4) and by the presence or absence of oliguria. A block randomization within each stratum with block size of 10 was used. Early RRT was initiated within 8 hours of diagnosis of stage 2 AKI using the KDIGO classification (urine output <0.5 mL/kg/h for ≥12h or 2-fold increase in serum creatinine compared with baseline). Delayed RRT was initiated within 12 hours of stage 3 AKI (urine output <0.3 mL/kg/h for ≥24 h and/or >3 fold increase in serum creatinine level compared with baseline or serum creatinine of ≥4 mg/dL with an acute increase of at least 0.5 mg/dL within 48 hours [to convert to µmol/L, multiply by 88.4]) or if any of the following absolute indications for RRT were present: serum urea level higher than 100 mg/dL; serum potassium level higher than 6 mEq/L and/or with electrocardiography abnormalities; serum magnesium level higher than 8 mEq/L (to convert to mmol/L, multiply by 0.5); urine production lower than 200 mL per 12 hours or anuria (according to the KDIGO recommendations); and organ edema in the presence of AKI resistant to diuretic treatment (1 attempt with loop diuretics prior to randomization).

RRT Delivery

Once RRT was initiated, identical settings were used in both treatment groups according to the KDIGO guidelines. To ensure uniformity of treatment between early and delayed RRT groups, specific protocols for the performance of RRT were strictly adhered to. All patients in both groups were treated using continuous venovenous hemodiafiltration. Replacement fluid was delivered into extracorporeal circuit before the filter (ie, predilution), with a ratio of dialysate to replacement fluid of 1:1. The effluent flow prescribed was based on the patient's body weight at the time of randomization and was 30 mL/kg/h (additional fluid removal without replacement was not considered part of the prescribed dose). Blood flow was kept above 110 mL/min. The delivered dose of RRT was monitored based on bloodside urea kinetics. Regional anticoagulation with citrate was used to prevent circuit clotting. RRT was discontinued if renal recovery defined by urine output (>400 mL/24 h without and 2100 mL/24 h with diuretic treatment) and creatinine clearance (>20 mL/min) occurred. If cessation criteria were not fulfilled after 7 days, continuous renal replacement therapy could be changed to an intermittent procedure (sustained low-efficiency daily dialysis [SLEDD], slow continuous ultrafiltration or intermittent hemodialysis).

Follow-up

Following randomization, laboratory and physiologic data, severity of illness as measured by the modified SOFA score, and RRT administration details for 21 days were documented. All patients were followed up for 90 days to ascertain vital status, RRT requirement, and recovery of renal function.

Outcomes

The primary end point was overall mortality in a 90-day follow-up period (from randomization). Secondary outcomes included overall mortality in a 28- and 60-day follow-up period, clinical evidence of organ dysfunction (daily SOFA scores while in the ICU), recovery of renal function, requirement of hemodialysis after day 28 and day 60, duration of renal support, ICU and hospital lengths of stay, and markers of inflammation (interleukin [IL]-6, IL-8, IL-10, IL-18, and macrophage migration inhibitory factor [MIF]).

Biomarker Assay Methods

Blood samples were collected for measurement of inflammatory biomarkers (IL-6, IL-8, IL-10, IL-18 and MIF) on the day of randomization (day 0) and 1 day after randomization (day 1), centrifuged and frozen immediately at −80°C, and then stored until assayed. All inflammatory mediators were analyzed using commercially available assay kits (LEGENDplex; BioLegend).

Sample Size Determination

A group sequential adaptive design with 1 interim analysis and a global (2-sided) significance level α of .05 was used. Power calculations were performed based on the primary end point (ie, the overall mortality in a 90-day follow-up period). The expected 90-day mortality rate in the control group with delayed initiation of RRT was 55% based on the literature.[8,11-19] Differences between treatment groups were to be detected with a power of 80%, if the 90-day mortality rate with early initiation of RRT was 37% or less. The expected treatment effect of 18% was calculated on the mortality differences between early and delayed RRT reported in prior studies.[8,11-19] A required sample size for the final analysis was 115 patients per treatment group, 230 patients in total. One interim analysis was performed after half of the total number of deaths across both treatment groups. Power calculations were performed based on a 2-sided inverse normal log-rank test,[20] using ADDPLAN software (ICON).

Statistical Analyses

Statistical analyses were performed according to the principles of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline E9 using the SAS software for Windows (SAS Institute), version 9.4. Descriptive analyses were performed on all baseline variables including means and standard deviations, medians and quartiles (quartile 1 [Q1], quartile 3 [Q3]), or frequency and percentages, as appropriate. The primary efficacy analysis includes all randomized patients (full analysis set) and was performed according to the intention-to-treat principle (ie, all patients were analyzed in the group to which they were randomized). Patients who received RRT were analyzed in the per-protocol analysis. A group sequential plan according to O'Brien and Fleming with 1 interim analysis was established. To maintain a global significance level α of .05, the interim and the final analysis were performed on local significance levels 0.0052 and 0.0480, respectively. Based on the group sequential plan, in the interim analysis the number of deaths up to the final analysis was recalculated applying the inverse normal method.[21] The effect of early vs delayed initiation of RRT on overall mortality in a 90-day follow-up period was assessed by comparing the randomized groups with a (2-sided) inverse normal log-rank test.[20] The inverse normal log-rank test is performed by computing *P* values for the interim and final log-rank tests separately, and then combining these *P* values so that the overall type I error is controlled. The primary intention-to-treat analysis of the primary outcome provides confirmatory statistical evidence.

The primary statistical analysis was performed first using a hierarchical testing procedure. After reaching a significant result in the primary analysis, each of the secondary outcomes were tested separately using a significance level of .05. No adjustment for multiplicity was applied across the secondary outcomes. Therefore, the results of secondary outcome analyses do not claim confirmatory statistical evidence. The evidence level of the results, however, is more than exploratory, due to the prespecification of secondary outcomes in the protocol, as well as the hierarchical ordering (ie, a required significant result in the primary statistical analysis before the secondary outcomes were tested).

Inferential statistical analyses of time-to-event outcomes that include censored cases were performed using survival analytic methods, such as Kaplan-Meier estimation of the survival function and the log-rank test. Proportional hazards models were fitted after checking the proportionality assumption using the Grambsch and Therneau test, and hazard ratios (HRs) with associated 95% confidence intervals were calculated. A multivariable statistical analysis of the primary outcome was performed using Cox regression. After including all documented baseline characteristics of the patients in the model, backward elimination of variables was applied and a final model was established that included significant factors associated with the primary outcome.

Binary data were tested for significance using the χ^2 test or Fisher exact test where appropriate. Event rates were compared by calculating the odds ratio [OR] and absolute risk reduction with associated asymptotic 95% confidence intervals. Normally distributed data were tested for significance using *t* tests. For non-normal data the Mann-Whitney *U* test was applied, and median values were compared using the Hodges-Lehmann estimation of location shift with associated 95% confidence interval.

All patients completed 90-day follow up (with a tolerance of ±14 days) and vital status was determined. Therefore, in all corresponding statistical analyses (including the primary analysis) an issue of missing data does not arise. In all other statistical analyses, very little missing occurred and were not replaced using any kind of imputation.

Results

Patients

Of 604 patients with AKI screened for the trial, 231 were enrolled and randomized to receive either early initiation of RRT (early group; n = 112) or delayed initiation of RRT (delayed group; n = 119) and included in the primary analysis (**Figure 1**). The baseline characteristics are shown in **Table 1**. Baseline NGAL values were not significantly different between both groups (Table 1). There were no significant differences regarding the criteria for dialysis initiation between both groups (eTable 1 in Supplement 2).

All 112 patients assigned to early group received RRT. However, for the 119 participants assigned to delayed group, only 108 received RRT. RRT was not initiated in 11 patients (9.2%) because 6 patients (5.0%) did not progress to severe AKI (stage 3), 4 patients had protocol violations (3.4%; the patients recovered renal function after reaching stage 3 but without RRT), and 1 patient (0.8%) had no RRT device available. Consistent with the protocol, absolute indications occurred in 18 patients in the delayed group (15.1%) who underwent RRT before reaching KDIGO stage 3 criteria. At randomization, serum creatinine and urine output were not significantly different between early and delayed groups (mean [SD] serum creatinine, 1.95 mg/dL [0.64] for the early group vs 2.00 mg/dL [1.1] for the delayed group, *P* = .67; median [Q1, Q3] urine output, 460 mL/24 h [187.5, 840.0] for the early group vs 500 mL/24 h [156.3, 1042.0] for the delayed group, *P* = .89). The median time from meeting full eligibility criteria to RRT initiation in the early group (6.0 hours [Q1, Q3: 4.0, 7.0]) was significantly shorter compared with the delayed group (25.5 hours [Q1, Q3: 18.8, 40.3]; between-group difference, −21.0 [95% CI, −24.0 to −18.0]; *P* < .001; **Table 2**). In addition, patients in the delayed group were analyzed separately. The median time from randomization to initiation of RRT was similar in those patients reaching KDIGO stage 3 compared with the patients developing an absolute indication (25 hours [Q1, Q3: 19, 40] for patients reaching KDIGO stage 3 vs 27 hours [Q1, Q3: 14, 41] for patients with an absolute indication, *P* = .97). At the time of RRT initiation, serum creatinine and urea concentrations were both higher in the delayed group compared with the early group, whereas urine output was significantly lower in the delayed group compared with the early group (Table 2). All other clinical and biochemical parameters were similar at the time of RRT initiation (Table 2).

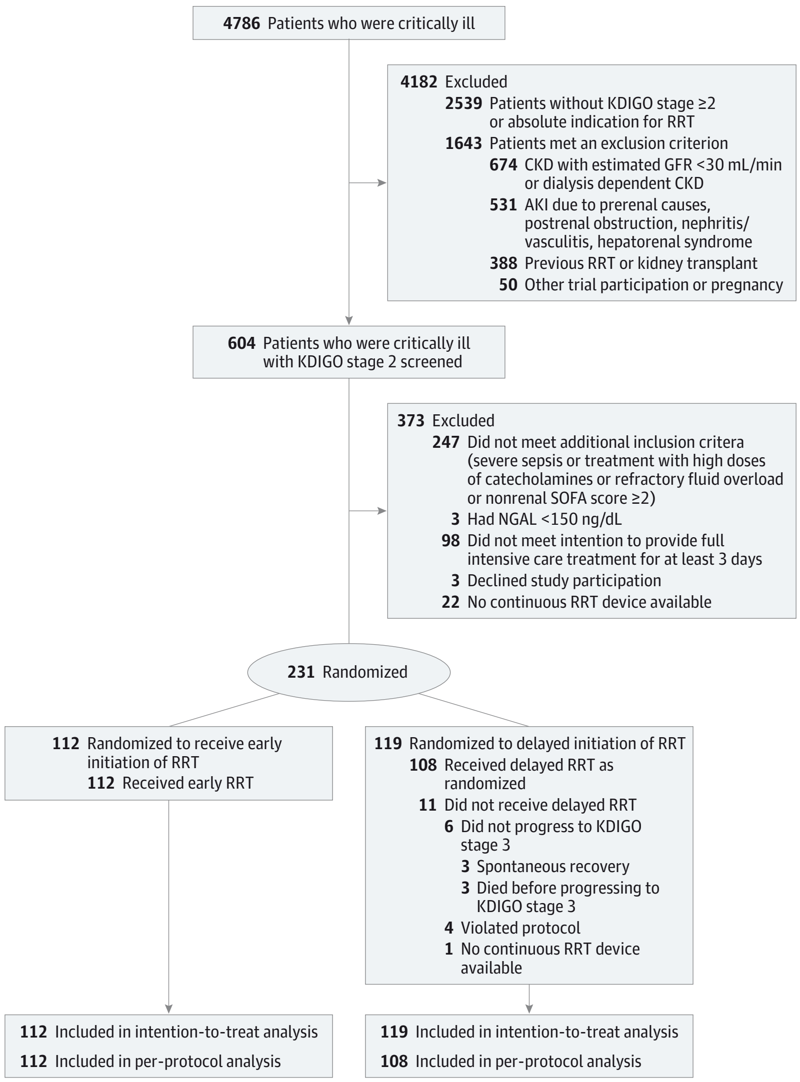
Primary Outcome

Early initiation of RRT significantly reduced 90-day mortality (**Figure 2**) compared with delayed initiation of RRT (44 of 112 patients [39.3%] in the early group vs 65 of 119 patients [54.7%] in the delayed group; *P* = .03; HR, 0.66 [95% CI, 0.45 to 0.97]; between-group difference, −15.4% [95% CI, −28.1% to −2.6%]) (**Table 3**). A subgroup analysis of patients randomized to delayed initiation of RRT found no significant difference between those reaching stage 3 and those developing an absolute indication of RRT for the primary end point (eTable 2 in Supplement 2).

Secondary Outcomes

Early initiation of RRT significantly reduced the median duration of RRT compared with the delayed group (9 days [Q1, Q3: 4, 44] for the early group vs 25 days [Q1, Q3: 7, >90] for the delayed group, *P* = .04; HR, 0.69 [95% CI, 0.48 to 1.00]; between-group difference, −18 [95% CI, −41 to 4]), enhanced recovery of renal function at day 90 (60 of 112 patients [53.6%] for the early group vs 46 of 119 patients [38.7%] for the delayed group, *P* = .02; OR, 0.55 [95% CI, 0.32 to 0.93]; between-group difference, 14.9% [95% CI, 2.2% to 27.6%]), reduced the median duration of mechanical ventilation (125.5 hours [Q1, Q3: 41, 203] for the early group vs 181.0 days [Q1, Q3: 65, 413]

Figure 1. Flow of Patients Through the ELAIN Trial



ELAIN indicates Early vs Late Initiation of Renal Replacement Therapy in Critically Ill Patients With Acute Kidney Injury; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, renal replacement therapy; CKD, chronic kidney disease; GFR, glomerular filtration rate; AKI, acute kidney injury; SOFA, sepsis-related organ failure assessment; NGAL, neutrophil gelatinase–associated lipocalin.

for the delayed group, $P = .002$; between-group difference, −60 [95% CI, −110.0 to −22.0]), and decreased the length of hospital stay (51 days [Q1, Q3: 31, 74] for the early group vs 82 days [Q1, Q3: 67, >90] for the delayed group, $P < .001$; HR, 0.34 [95% CI, 0.22 to 0.52]; between-group difference, −37 [95% CI, −∞ to −19.5]). However, no significant differences between the 2 groups were seen in the requirement of RRT on day 90 (9 of 67 patients [13.4%] for the early group vs 8 of 53 patients [15.1%] for the delayed group; OR, 0.87 [95% CI, 0.31 to 2.44]; between-group difference, −1,7% [95% CI, −14.3% to 11.0%], $P = .80$) and in the length of ICU stay were found (19 days [Q1, Q3: 9, 29] in the early group vs 22 days [Q1, Q3: 12, 36] in the delayed group, $P = .33$; HR, 0.85 [95% CI, 0.61 to 1.19]; between-group difference, −3.0 [95% CI, −12.0 to 4.5]) (Table 3).

Subgroup analysis of patients randomized to the delayed treatment group comparing those reaching stage 3 vs those developing an absolute indication for RRT found no significant differences for the secondary end points of duration of RRT, ICU, and hospital stay (eTable 2 in Supplement 2).

There were no significant differences regarding RRT modalities (blood flow per session, effluent volume per session, and session duration) between the groups (eTable 3 in Supplement 2). Not considering death, 1 serious adverse event (new-onset arrhythmia) and 84 adverse events among 112 patients in the early group were observed, and no serious adverse events and 74 adverse events in 108 patients were observed in the delayed RRT group (eTable 3 in Supplement 2). RRT-related complications were similar in both treatment groups (eTable 3 in Supplement 2). In total, 32 of 112 patients (28.6%) in the early group vs 42 of 108 patients (38.9%) in the delayed group were transitioned to other RRT modalities after receiving continuous RRT: 25 of 112 patients (22.3%) in the early group vs 32 of 108 patients (29.6%) in the delayed group were transitioned to SLEDD, 2 of 112 patients (1.8%) in the early group vs 2 of 108 patients (1.9%) in the delayed group were transitioned to intermittent hemodialysis, and 5 of 112 patients (4.5%) in the early group vs 8 of 108 patients (7.4%) in the delayed group were transitioned to SLEDD and

Table 1. Baseline Characteristics for Critically Ill Patients Receiving Early vs Delayed Initiation of Renal Replacement Therapy

	Early (n = 112)	Delayed (n = 119)
Age, mean (SD), y	65.7 (13.5)	68.2 (12.7)
Sex, No. (%)		
Men	78 (69.6)	68 (57.1)
Women	34 (30.4)	51 (42.9)
Baseline creatinine, mean (SD), mg/dL	1.1 (0.4)	1.1 (0.4)
Estimated GFR, mean (SD), mL/min/1.73 m^2	56.2 (13.8)	55.9 (14.5)
SOFA score, mean (SD)	15.6 (2.3)	16.0 (2.3)
APACHE II, mean (SD)	30.6. (7.5)	32.7 (8.8)
Comorbidities, No. (%)		
Hypertension	97 (86.6)	92 (77.3)
Congestive heart failure	49 (43.8)	47 (39.5)
Diabetes	17 (15.2)	28 (23.5)
Chronic obstructive pulmonary disease	20 (17.9)	21 (17.6)
Chronic kidney disease (estimated GFR<60)	42 (37.8)	52 (44.8)
Cardiac arrhythmia	37 (33.0)	53 (44.5)
Source of admission, No./total No. (%)		
Cardiac		
Total	56/112 (50.0)	52/119 (43.7)
CABG only	11/56 (19.6)	16/52 (30.8)
Valve only	13/56 (23.2)	10/52 (19.2)
Combination or others	32/56 (57.1)	26/52 (50.0)
Trauma	14/112 (12.5)	14/119 (11.8)
Abdominal		
Total	34/112 (30.4)	44/119 (37.0)
Bowel resection	8/34 (23.5)	5/44 (11.4)
Esophageal resection	5/34 (14.7)	2/44 (4.5)
Liver transplant	3/34 (8.8)	7/44 (15.9)
Others	18/34 (52.9)	30/44 (68.2)
Others	8/112 (7.1)	9/119 (7.6)
Neurosurgical	2/8 (25.0)	3/9 (33.3)
Pulmonary	6/8 (75.0)	6/9 (66.7)
Cumulative fluid balance until randomization, median (Q1, Q3), mL	6811.0 (3897.0, 10 189.0)	6334.0 (3951.5, 10 700.5)
Mechanically ventilated, No. (%)	98 (87.5)	105 (88.2)
Medication, No. (%)		
Vasopressors	96 (85.7)	108 (90.8)
Intravenous contrast	38 (33.9)	35 (29.4)
Aminoglycosides	0 (0)	0 (0)
Tacrolimus	4 (3.6)	8 (6.7)
Amphotericin	2 (1.8)	3 (2.5)
SOFA cardiovascular score, No. (%)		
0-2		
Nonoliguric	4 (3.6)	6 (5.0)
Oliguric	11 (9.8)	9 (7.6)
3-4		
Nonoliguric	30 (26.8)	32 (26.9)
Oliguric	67 (59.8)	72 (60.5)
Baseline renal biomarker		
Plasma NGAL, median (Q1, Q3), ng/mL	490.0 (350.0, 822.5)	618.5 (381.8, 941.0)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation Score; CABG, coronary artery bypass graft; GFR, glomerular filtration rate; Q, quartile; NGAL, neutrophil gelatinase associated lipocalin; SOFA, sequential organ failure assessment.

then to intermittent hemodialysis before being discharged (eTable 3 in Supplement 2). Daily fluid balance between early and delayed groups did not differ within the first 3 days after randomization (median [Q1, Q3]: day one, 2773 mL [702, 5280] for the early group vs 2207 mL [441, 4167] for the delayed group, $P = .15$; day two, 1102 mL [−493, 2789] for the early group vs 1077 mL [−80, 2465] for the delayed group, $P = .79$; day three, 384 mL [−913, 1847] for the early group vs 209 mL [−933, 1428] for the delayed group, $P = .41$).

Exploratory Analysis: Inflammatory Mediators

Pro- (MIF, IL-6, IL-8, and IL-18) and anti-inflammatory (IL-10) cytokine concentrations in the blood were measured. These molecules were selected because they are involved in inflammation and have been associated with decreased survival and recovery in prior studies.[22-25] At the time of randomization, the plasma concentrations of biomarkers MIF, IL-6, IL-8, IL-10, and IL-18 did not differ between groups (eTable 4 in Supplement 2). Twenty-four hours after randomization when 100% patients in the early group and 21.8% of patients in the delayed group had received at least 6 hours of RRT, IL-6 and IL-8 concentrations were significantly reduced in the early group compared with the delayed group (IL-6: 399.4 pg/mL in the early group vs 989.3 pg/mL in the delayed group; Hodges-Lehmann estimation of location shift, 310.9 [95% CI, 93.3-663.2]; $P = .02$; IL-8: 65.7 pg/mL for the early group vs 215.5 pg/mL for the delayed group; Hodges-Lehmann estimation of location shift, 105.9 [95% CI, 52.7-160.6]; $P = .001$), whereas the plasma concentrations of MIF, IL-10, and IL-18 did not differ between groups (eTable 4 in Supplement 2). Furthermore, by Cox regression analysis, IL-6 and IL-8 at day 1 were associated with mortality (eTable 5 in Supplement 2).

Discussion

In this randomized clinical trial of critically ill patients with AKI, the use of early RRT compared with delayed therapy reduced mortality over the first 90 days and reduced duration of RRT and length of hospital stay.

Three other trials have evaluated outcomes following early vs delayed initiation of RRT.[8-10] In a randomized clinical trial, Bouman and colleagues[8] enrolled 106 patients with AKI and randomized them to early or delayed RRT initiation. Patients in the early group received RRT soon after meeting criteria for AKI, whereas delayed initiation of RRT was defined when patients developed hyperkalemia or pulmonary edema or had plasma urea levels higher than 440 mmol/L. There was no difference in mortality. One important limitation of this study was that patients who were intended to receive RRT early (early group) received RRT rather late in the course of AKI. Another single-center trial performed in India enrolled 208 patients with community-acquired AKI.[9] In the early group, RRT was started after serum creatinine exceeded 7 mg/dL or serum urea exceeded 25 mmol/L regardless of other AKI complications. In the usual care group, RRT was initiated only in the setting of refractory hyperkalemia, acidosis, or volume overload or if

Table 2. Patient Characteristics at the Time of Renal Replacement Therapy (RRT) Initiation

	Early (n = 112)	Delayed (n = 119)	Absolute Difference Early vs Delayed (95% CI)	*P* Value
Received RRT, No.	112	108		
Time from meeting eligibility criteria to randomization, median (Q1, Q3), h	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.0 (0.0 to 0.0)	.36
Time from KDIGO 2 to RRT, mean (SD), h	5.4 (2.2)	40.0 (54.5)	−34.5 (−45.0 to −24.0)	<.001
Time from KDIGO 2 to RRT, median (Q1, Q3), h	6.0 (4.0, 7.0)	25.5 (18.8, 40.3)	−21.0 (−24.0 to −18.0)	<.001
Urinary output, median (Q1, Q3), mL	445.0 (175.0, 807.5)	270.0 (112.5, 670.0)	115.0 (25.0 to 220.0)	.01
Serum creatinine, mean (SD), mg/dL	1.9 (0.6)	2.4 (1.0)	−0.5 (−0.7 to −0.3)	<.001
Blood urea nitrogen, mean (SD), mg/dL	38.5 (15.5)	47.5 (21.6)	−9.0 (−14.1 to −3.9)	.001
Potassium, mean (SD), mEq/L	5.1 (0.9)	5.1 (0.9)	0.0 (−0.2 to 0.3)	.69
Bicarbonate, mean (SD), mEq/L	20.9 (3.6)	20.7 (3.7)	0.1 (−0.9 to 1.1)	.79
Hemoglobin, mean (SD), g/dL	8.6 (1.3)	8.6 (1.4)	−0.1 (−0.4 to 0.3)	.74
White blood cells, mean (SD), $\times 10^9$/L	16.2 (9.8)	16.5 (9.5)	−0.3 (−2.9 to 2.3)	.83

Abbreviations: KDIGO, Kidney Disease: Improving Global Outcomes, Q, quartile.

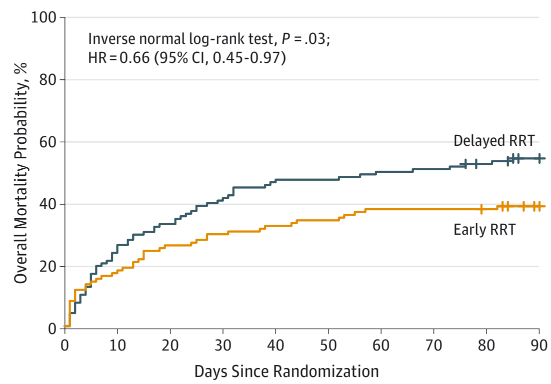
SI conversion factor: To convert creatinine to μmol/L, multiply by 88.4; urea nitrogen to mmol/L, multiply by 0.357.

uremic symptoms developed. No differences in kidney recovery or mortality were observed. In line with these results, a recently published multicenter trial investigating accelerated vs standard initiation of RRT in 101 critically ill patients with AKI also demonstrated no mortality difference between both groups.[10] However, this was a feasibility trial, and the trial was not powered to investigate mortality. Finally, 1 small randomized clinical trial demonstrated that early initiation of RRT was associated with a reduced mortality compared with late initiation of RRT.[18] In this study, the authors evaluated the role of early RRT in 28 patients with AKI following cardiac surgery. Fourteen patients were started on continuous hemodialysis when their urine volume decreased to less than 30 mL/h for 3 hours. In patients in the "late" group (n = 14), RRT was delayed until urine output had fallen to less than 20 mL/h for 2 hours. Survival was significantly better in the group of patients who started RRT earlier. There were no differences between the 2 groups with respect to age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and serum creatinine level at the time of initiation of RRT.

The results of a recently published meta-analysis suggest that earlier initiation of RRT in critically ill patients with AKI may have beneficial association with survival (OR, 0.45 [95% CI, 0.28-0.72]).[7] However, this conclusion is based on heterogeneous studies of variable quality. Therefore, more randomized trials are required to answer this question. This research priority has been articulated by the KDIGO clinical practice guidelines,[5] and the Acute Kidney Injury Network[26] has prioritized this research topic.

Potential benefits of earlier initiation are attributable to more rapid metabolic or uremic control and more effective prevention and management of fluid overload.[27] Some data also suggest that RRT before the onset of severe AKI may attenuate kidney-specific and non-kidney organ injury from acidemia, uremia, fluid overload, and systemic inflammation and could potentially translate into improved survival and earlier

Figure 2. Mortality Probability Within 90 Days After Study Enrollment for Patients Receiving Early and Delayed Initiation of Renal Replacement Therapy (RRT)



No. at risk										
Early RRT	112	92	82	78	75	73	69	69	66	55
Delayed RRT	119	90	79	70	63	62	59	58	54	48

KDIGO indicates Kidney Disease: Improving Global Outcomes. In the delayed group, 18 patients received RRT without reaching KDIGO stage 3 (these patients had an absolute indication). The median (quartile 1 [Q1], quartile 3 [Q3]) duration of follow-up was 90 days (Q1, Q3: 90, 90) in the early group and 90 days (Q1, Q3: 90, 90) in the delayed group. The vertical ticks indicate censored cases.

recovery of kidney function.[28,29] The counterargument is that a strategy of early initiation of RRT might subject patients who would recover renal function with conservative treatment alone to the potential risks associated with RRT. However, AKI confers a substantial increased risk of death even in patients never treated with RRT.[30] As such, although there may be a risk of "unnecessary" RRT, there could be an even greater risk associated with not providing it. To avoid treating patients with RRT who may have otherwise spontaneously recovered kidney function, biomarkers in addition to the KDIGO classification

Table 3. Clinical Outcomes for Early vs Delayed Renal Replacement Therapy (RRT) Among Critically Ill Patients

	Early (n = 112)	Delayed (n = 119)	*P* Value	Absolute Difference, % (95% CI)	OR or HR (95% CI)
Primary Outcome, No. (%)					
90-d All-cause mortality	44 (39.3)	65 (54.7)	.03	−15.4 (−28.1 to −2.6)	HR: 0.66 (0.45 to 0.97)
Secondary Outcomes, No. (%)					
28-d All-cause mortality	34 (30.4)	48 (40.3)	.11	−10.0 (−22.2 to 2.3)	OR: 0.64 (0.37 to 1.11)
Requirement of RRT on day 28, No./total No. patients alive at day 28 (%)	18/78 (23.1)	26/71 (36.6)	.07	−13.5 (−28.1 to 1.1)	OR: 0.52 (0.25 to 1.06)
60-d All-cause mortality	43 (38.4)	60 (50.4)	.07	−12.0 (−24.8 to 0.7)	OR: 0.61 (0.36 to 1.03)
Requirement of RRT on day 60, No./total No. patients alive at day 60 (%)	11/69 (15.9)	14/59 (23.7)	.27	−7.8 (−21.7 to 6.1)	OR: 0.61 (0.25 to 1.47)
Duration of RRT, median (Q1, Q3), d[a]	9 (4, 44) (n = 112)	25 (7, >90) (n = 108)[b]	.04	−18 (−41 to 4)	HR: 0.69 (0.48 to 1.00)[c]
Organ dysfunction, No. (%)[d]	107 (95.5)	118 (99.2)	.11	−3.6 (−7.8 to 0.5)	OR: 0.18 (0.02 to 1.58)
Respiratory	103 (92.0)	116 (97.5)	.06	−5.5 (−11.3 to 0.3)	OR: 0.30 (0.08 to 1.12)
Coagulation	68 (60.7)	87 (73.1)	.05	−12.4 (−24.5 to −0.3)	OR: 0.57 (0.33 to 0.99)
Liver	52 (46.4)	65 (54.6)	.21	−8.2 (−21.1 to 4.7)	OR: 0.72 (0.43 to 1.21)
Cardiovascular	103 (92.0)	115 (96.6)	.12	−4.7 (−10.7 to 1.3)	OR: 0.40 (0.12 to 1.33)
Central nervous system	102 (91.1)	114 (95.8)	.15	−4.7 (−11.1 to 1.7)	OR: 0.45 (0.15 to 1.35)
Recovery of renal function at day 90[e]					
Yes	60 (53.6)	46 (38.7)	.02	14.9 (2.2 to 27.6)	OR: 0.55 (0.32 to 0.93)[f]
No[g]	52 (46.4)	73 (61.3)			
Recovery of renal function at day 90[e]					
Yes	60 (88.2)	46 (85.2)	.62	3.1 (−9.1 to 15.2)	OR: 0.77 (0.27 to 2.17)[h]
No[i]	8 (11.8)	8 (14.8)			
Requirement of RRT on day 90, No./total No. patients alive at day 90 (%)	9/67 (13.4)[j]	8/53 (15.1)[k]	.80	−1.7 (−14.3 to 11.0)	OR: 0.87 (0.31 to 2.44)
ICU stay, median (Q1, Q3), d	15.5 (8.0, 28.0)	16.0 (6.8, 30.0)	.95	0.0 (−3.0 to 3.0)	
ICU stay, median (Q1, Q3), d[l]	19 (9, 29)	22 (12, 36)	.33	−3.0 (−12.0 to 4.5)	HR: 0.85 (0.61 to 1.19)[m]
Hospital stay, median (Q1, Q3), d	33.0 (18.0, 58.0)	43.0 (19.5, 81.3)	.05	−9.0 (−19.0 to 0.0)	
Hospital stay, median (Q1, Q3), d[n]	51 (31, 74)	82 (67, >90)	<.001	−37 (−∞ to −19.5)	HR: 0.34 (0.22 to 0.52)[o]
Duration of mechanical ventilation, median (Q1, Q3), h	125.5 (41, 203)	181.0 (65, 413)	.002	−60.0 (−110.0 to −22.0)	

Abbreviations: HR, hazard ratio; ICU, intensive care unit; Q, quartile; OR, odds ratio.

[a] Duration of RRT was censored at patients' date of death or at day 90 where applicable, whichever occurred first.

[b] Eleven patients did not receive RRT.

[c] An HR less than 1 indicates a shorter duration of RRT in the early group than in the delayed group.

[d] Organ dysfunction is defined as an individual nonrenal Sequential Organ Failure Assessment score of 2 or higher during ICU stay (partial pressure of oxygen/fraction of inspired oxygen [PaO_2/FIO_2] <300 mm Hg, Glasgow coma scale ≤12, requirement of vasopressor administration, bilirubin ≥2 mg/dL, platelets <100 ×10^3/μL).

[e] Renal recovery is defined as dialysis independency at day 90.

[f] An OR less than 1 indicates a higher recovery rate in the early group than in the delayed group.

[g] Including patients who died within 90 days.

[h] An OR less than 1 indicates a higher recovery rate in the early group than in the delayed group.

[i] Excluding patients who died within 90 days.

[j] Patients alive at day 90 (n = 68), 1 patient with missing value.

[k] Patients alive at day 90 (n = 54), 1 patient with missing value.

[l] ICU stay was censored at day 90 or at patients' deaths where applicable.

[m] An HR less than 1 indicates a shorter duration of ICU stay in the early group than in the delayed group.

[n] Hospital stay was censored at day 90 or at patients' deaths where applicable.

[o] An HR less than 1 indicates a shorter duration of hospital stay in the early group than in the delayed group.

system were used in this trial because it has been demonstrated that plasma NGAL is a good predictor for the need of RRT in critically ill patients with AKI.[31,32] Moreover, NGAL concentration can be measured at the bedside within 20 minutes, making this biomarker suitable for a trial testing a time-sensitive intervention. Our data demonstrate that the combination of the KDIGO classification system in combination with plasma NGAL can reliably detect patients with progressively deteriorating AKI. Only 5% (6 of 119 patients) of the patients in the delayed group did not receive RRT, because they spontaneously recovered or died.

Fluid accumulation in patients with AKI is associated with adverse outcomes.[33] However, in our study we could exclude that fluid accumulation was responsible for a worse outcome in the delayed group because there were no differences in daily fluid balance before and within 3 days after randomization. As some data suggest that initiation of RRT before the onset of severe AKI may attenuate kidney-specific and non-kidney organ injury from systemic inflammation.[28,29] It is possible that the reduced plasma levels of inflammatory mediators in the early group are responsible for the reduced mortality. Our data extend the findings of other studies in which pro-inflammatory cytokines were associated with poorer outcomes.[22,34,35] Increased IL-8 concentrations are associated with an increased risk of RRT dependence and death.[36] IL-8, a chemokine, is an important mediator of innate and adaptive immunity and has been implicated in the pathogenesis of AKI.[37-39] Higher IL-8 concentrations may reflect a persistent pro-inflammatory milieu among renal tubular cells impairing renal recovery. IL-6 is a pleiotropic cytokine and higher concentrations have been associated with increased susceptibility to AKI[40] and mortality in patients with AKI.[22]

As several molecules were associated with adverse outcomes in our study, immunomodulation strategies that include inhibition of single molecules are unlikely to be successful, and broad-spectrum modulation of multiple molecules may be needed to improve outcomes in AKI patients.

Study limitations need to be considered. Although a large mortality difference was detected, this was not a multicenter trial, and as with many single-center studies, the observed effect size is likely inflated. Furthermore, larger trials are needed because small trials cannot avoid small baseline differences. Another limitation of this study is the limited generalizability, because almost all patients recruited were surgical patients. Our study provides important feasibility data for an AKI stage-based, biomarker-guided interventional trial in AKI. However, an adequately powered multicenter trial is needed to confirm our results and establish the best time point for the initiation of RRT in critically ill patients with AKI.

Conclusions

Among critically ill patients with AKI, early RRT compared with delayed initiation of RRT reduced mortality over the first 90 days. Further multicenter trials of this intervention are warranted.

ARTICLE INFORMATION

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Study concept and design: Zarbock, Kellum, Aken, Wempe, Pavenstädt, Gerß, Meersch.
Acquisition, analysis, or interpretation of data: Zarbock, Kellum, Schmidt, Boanta, Gerß, Meersch.
Drafting of the manuscript: Zarbock, Wempe, Pavenstädt, Gerß, Meersch.
Critical revision of the manuscript for important intellectual content: Zarbock, Kellum, Schmidt, Aken, Boanta, Gerß, Meersch.
Statistical analysis: Gerß, Meersch.
Obtained funding: Zarbock.
Administrative, technical, or material support: Zarbock, Schmidt, Aken, Wempe, Boanta, Meersch.
Study supervision: Zarbock, Aken, Pavenstädt, Meersch.

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