# Time to Renal Replacement Therapy Initiation in Critically Ill Patients With Acute Kidney Injury: A Secondary Analysis of the Standard Versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) Trial

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**OBJECTIVES:** Among critically ill patients with severe acute kidney injury (AKI) who lack emergent indications for renal replacement therapy (RRT), a strategy of preemptive RRT initiation does not lead to improved outcomes. However, for patients with persistent AKI and without urgent indications for RRT, the safety of prolonged delays in RRT initiation is unclear. We sought to assess the association between progressively longer delays in RRT initiation and clinical outcomes.

**DESIGN:** A post hoc secondary analysis.

**SETTING:** The multinational STandard vs. Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial.

**PATIENTS:** Participants allocated to the standard strategy of the STARRT-AKI trial.

**INTERVENTIONS:** The exposure was time from randomization to RRT initiation, evaluated in quartiles and as a continuous variable.

**MEASUREMENTS AND MAIN RESULTS:** The primary outcome was all-cause mortality at 90 days. Secondary outcomes were RRT dependence, RRT-free days, and hospital-free days, all at 90 days, as well length of ICU and hospital stay. Of the 1462 participants allocated to the standard strategy group, 903 (62%) received RRT. Median time (interquartile range) to RRT initiation was 12.1 hours (8.3–13.8 hr), 24.5 hours (21.8–26.5 hr), 46.8 hours (35.2–52.1 hr), and 96.1 hours (76.7–139.2 hr) in quartiles 1–4, respectively. Prolonged time to RRT initiation was associated with a lower risk of death at 90 days (quartile 4 vs. 1: adjusted odds ratio, 0.63 [95% CI, 0.42–0.94]); further analyses using cubic splines and inverse probability weighting to account for immortal time bias showed no association with the risk of death. There was no association between time to RRT initiation and RRT-free days, hospital-free days, or lengths of ICU or hospital stay. Longer delay to RRT initiation had a linear association with RRT dependence at 90 days.

**CONCLUSIONS:** Among patients with no urgent indications and who received RRT in the standard strategy of the STARRT-AKI trial, longer deferral of RRT initiation was not associated with a higher risk of mortality.

**KEYWORDS:** acute kidney injury; critical care; dialysis; renal replacement therapy; timing

Acute kidney injury (AKI) is a common complication of critical illness occurring in more than half of patients admitted to the ICU (1, 2). In patients with severe AKI, renal replacement therapy (RRT) is often



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## KEY POINTS

**Question:** In critically ill patients with severe acute kidney injury (AKI) but without conventional indications for renal replacement therapy (RRT), does prolonged delay in RRT initiation associate with a higher risk of death?

**Findings:** In this post hoc secondary analysis of the STandard vs. Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial, after accounting for potential immortal time bias, longer time to RRT initiation in critically ill patients with severe AKI was not associated with increased risk of death at 90 days.

**Meaning:** In the absence of conventional indications for RRT, a strategy of careful monitoring and RRT deferral is not associated with excess mortality.

used to manage medically refractory hyperkalemia, metabolic acidosis, or complications of volume accumulation (3). However, in the absence of these urgent indications, the preponderance of evidence from recent trials has suggested that a strategy of preemptive or earlier commencement of RRT does not yield a survival advantage and may confer harm (4–6). The implication of these findings is that a strategy of RRT deferral in the absence of urgent AKI-associated emergencies may be an acceptable strategy.

There is no definitive evidence around how long RRT may be deferred in the setting of prolonged unremitting severe AKI. The recent Artificial Kidney Initiation for Kidney Injury 2 (AKIKI-2) trial found that in patients with oliguria for more than 72 hours without an urgent indication for RRT, further delays in starting RRT did not result in more RRT-free days. However, longer delays in RRT initiation were associated with a higher risk of death and a lower chance of transitioning from coma to awakening (7, 8).

We conducted a post hoc analysis of patients allocated to the standard RRT initiation arm of the STandard vs. Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial to describe the association between progressively longer delays in RRT initiation and clinical outcomes. We hypothesized that longer delays to RRT initiation, in the absence of urgent indications, would not be associated with worse clinical outcomes.

## MATERIALS AND METHODS

### Design and Setting

We conducted a cohort study that comprised participants allocated to the standard strategy of the STARRT-AKI trial, an international randomized control trial of 3019 patients that was conducted at 168 hospitals in 15 countries (6). Details of the trial protocol, statistical analysis plan and main results have been published previously (6, 9, 10). The trial was approved by the Research Ethics Boards at Unity Health Toronto (CTO 16-009, approval date: February 23, 2016) and the University of Alberta (File Number Pro00060023, approval date: November 19, 2015) (**Table S1**, http://links.lww.com/CCM/H692). All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975. This study followed The Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies (**Table S2**, http://links.lww.com/CCM/H692) (11).

### Population

We included participants allocated to the standard strategy arm of the STARRT-AKI trial who received RRT. The STARRT-AKI trial included patients 18 years old or older who were admitted to an ICU with severe AKI, defined as fulfilling stage 2 or 3 based on the Kidney Disease: Improving Global Outcomes classification (3). Serum creatinine was to exceed 100 μmol/L in women and 130 μmol/L in men. Key exclusion criteria were an urgent need for RRT, the recent receipt of RRT, advanced chronic kidney disease (defined by an estimated glomerular filtration rate < 20 mL/min/1.73 $m^2$), or the presence of an AKI etiology with a specific intervention. Eligible patients were randomized 1:1 to a strategy of accelerated or standard RRT initiation. In the accelerated strategy, all patients were to commence RRT within 12 hours of meeting eligibility criteria. For patients allocated to the standard strategy, which is the cohort investigated in this secondary analysis, clinicians were discouraged from initiating RRT unless one of the following indications was present: a serum

potassium of greater than or equal to 6.0 mmol/L, a pH of less than or equal to 7.20 with a serum bicarbonate level of less than or equal to 12 mmol/L, evidence of severe respiratory failure based on a ratio of the $Pao_2$ to the $Fio_2$ of less than or equal to 200 and clinical perception of volume overload, or persistent severe AKI lasting more than 72 hours. There was no obligation to start RRT even in the presence of one or more of the aforementioned indications. In addition, RRT could be initiated at the clinicians' discretion if there was a perception that deferral was no longer in the patient's best interest. The initiation of RRT within 12 hours of eligibility criteria being met was considered a protocol violation.

## Exposure

The primary exposure was the time, measured in hours, from randomization to RRT initiation among patients allocated to the standard strategy. Time was evaluated both in quartiles and as a continuous variable.

## Outcomes

The primary outcome was death from any cause at 90 days after randomization. Secondary outcomes were RRT dependence at 90 days, RRT-free and hospitalization-free days at 90 days, and ICU and hospital length of stay.

## Statistical Analysis

Baseline characteristics were expressed as numbers and percentages or medians and interquartile ranges (IQRs), as appropriate. We compared the baseline characteristics of the participants allocated to the standard strategy group who did and did not receive RRT using Pearson chi-square test or univariable regression analysis as appropriate. Baseline characteristics at the time of randomization and clinical characteristics at the time of RRT initiation were described across quartiles of time to RRT initiation. Clinical characteristics at the time of RRT initiation in the subset of patients who initiated RRT less than 12 hours from randomization were also described.

We performed multivariable logistic regression to evaluate the association between time from randomization to RRT initiation, categorized in quartiles, and all-cause death and RRT dependence at day 90, respectively. A multivariable linear regression was used to assess the association between quartiles of time from randomization to RRT initiation and all other outcomes (adjusted mean difference [aMD]). All models were adjusted for the following baseline variables: age, sex, baseline estimated glomerular filtration rate, Simplified Acute Physiology Score (SAPS) II, sepsis, and admission type.

In additional analyses, we assessed time to RRT initiation as a continuous exposure, using restricted cubic splines (RCSs). Three knots were used for RCS based on the model's lower Akaike information criteria. To control for potential immortal time bias, binomial regression was used to determine the probability of patients receiving RRT. This was performed using a generalized linear model with an indicator for RRT as the outcome using baseline characteristics (age, sex, baseline estimated glomerular filtration rate, SAPS II, sepsis, and admission type) and physiologic pre-randomization parameters (urine output, platelet, hemoglobin, Sequential Organ Failure Assessment [SOFA] score, cumulative fluid balance, temperature, arterial pH, heart rate, creatinine, potassium, WBCs, bicarbonate, and weight). Missing values in covariates were imputed with the median value of the covariate to get a probability estimate for every patient. The inverse of the predicted probabilities generated in the aforementioned model was then used to weight each patient. A sensitivity analysis was performed in the subset of patients who survived for at least 96 hours, the median time to RRT initiation in the fourth quartile.

For the outcome of the number of RRT-free and hospital-free days at 90 days, we used an inverse probability weighted ordinary least squares model to control for immortal time bias. An RCS was used to account for possible nonlinear relationship between the variables. For the outcome of RRT dependence at 90 days, multivariable logistic regression with RCS was performed with the sample restricted to those who were alive at 90 days since being alive was a requirement for this outcome. For this model, weights were the inverse of the probabilities of receiving RRT and being alive at day 90. For the outcomes of ICU and hospital length of stay, we used a multistate time-to-event analysis with death and ICU or hospital discharge as competing events. Time to RRT was again used in RCS form to capture its nonlinear relationship with the outcomes.

**TABLE 1.**

**Clinical Condition at Initiation of Renal Replacement Therapy in the Standard Strategy Group Who Received Renal Replacement Therapy, Across Quartiles of Time From Randomization to Renal Replacement Therapy Initiation**

| Quartile | Q1, *n* = 226 | Q2, *n* = 226 | Q3, *n* = 226 | Q4, *n* = 225 | *p*[d] |
|---|---|---|---|---|---|
| Time to RRT initiation, hr | 12.1 (8.3–13.8) | 24.5 (21.8–26.5) | 46.8 (35.2–52.1) | 96.1 (76.7–139.2) | |
| Sequential Organ Failure Assessment score[a] | 13.0 (10.0–15.0) | 12.0 (10.0–14.0) | 12.0 (9.0–15.0) | 11.0 (9.0–14.0) | < 0.001 |
| Sepsis | 126 (61) | 100 (55) | 119 (62) | 125 (63) | 0.33 |
| Heart rate, beats/min | 101 (83–112) | 90 (75–103) | 89 (78–103) | 90 (76–105) | < 0.001 |
| Systolic blood pressure, mm Hg | 110 (100–124) | 118 (105–135) | 118 (106–136) | 121 (105–138) | < 0.001 |
| Temperature, degrees Celsius | 37.00 (36.50–37.70) | 37.00 (36.50–37.60) | 36.90 (36.38–37.60) | 36.90 (36.32–37.40) | 0.14 |
| Glasgow Coma Scale | 9.0 (3.0–15.0) | 6.0 (3.0–14.0) | 7.0 (3.0–13.0) | 8.0 (3.0–14.0) | 0.048 |
| Urine output, mL/24 hr | 295 (112–670) | 270 (65–755) | 302 (72–832) | 700 (195–1795) | < 0.001 |
| Oliguria or anuria[b] | 139 (63) | 130 (58) | 124 (56) | 78 (36) | < 0.001 |
| Cumulative fluid balance[c], mL | 2588 (1011–5113) | 3269 (1317–6762) | 3157 (1405–7069) | 2020 (441–8211) | 0.007 |
| Hemoglobin, g/L | 92 (82–107) | 90 (80–104) | 88 (80–103) | 85 (77–100) | < 0.001 |
| Arterial pH | 7.30 (7.23–7.38) | 7.32 (7.26–7.37) | 7.32 (7.25–7.39) | 7.33 (7.25–7.40) | 0.020 |
| Serum creatinine, µmol/L | 303 (233–402) | 410 (309–515) | 456 (336–578) | 462 (323–619) | < 0.001 |
| Serum potassium, mmol/L | 4.60 (4.00–5.20) | 4.70 (4.20–5.20) | 4.60 (4.10–5.10) | 4.30 (3.80–4.90) | 0.002 |
| Serum bicarbonate, mmol/L | 18.0 (16.0–22.0) | 19.0 (16.0–21.0) | 20.0 (17.0–22.0) | 20.0 (16.0–23.0) | 0.024 |
| Serum urea, mmol/L | 20 (16–28) | 24 (18–33) | 30 (22–38) | 38 (29–46) | < 0.001 |
| Region | | | | | < 0.001 |
| Asia/South America | 62 (27) | 12 (5.3) | 7 (3.1) | 4 (1.8) | |
| Australia/New Zealand | 49 (22) | 51 (23) | 48 (21) | 26 (12) | |
| Europe | 54 (24) | 63 (28) | 88 (39) | 118 (52) | |
| North America | 61 (27) | 100 (44) | 83 (37) | 77 (34) | |
| Diuretic use at RRT initiation | 100 (44) | 85 (38) | 78 (35) | 86 (38) | 0.20 |

(*Continued*)

**TABLE 1. (*Continued*)**
**Clinical Condition at Initiation of Renal Replacement Therapy in the Standard Strategy Group Who Received Renal Replacement Therapy, Across Quartiles of Time From Randomization to Renal Replacement Therapy Initiation**

| Quartile | Q1, *n* = 226 | Q2, *n* = 226 | Q3, *n* = 226 | Q4, *n* = 225 | *p*[d] |
|---|---|---|---|---|---|
| Presence of ≥ 1 indication for RRT at time of RRT initiation in the standard arm | 135 (60) | 129 (60) | 113 (54) | 220 (98) | < 0.001 |
| Serum potassium ≥ 6 mmol/L | 17 (7.5) | 13 (5.8) | 8 (3.5) | 10 (4.4) | 0.26 |
| pH ≤ 7.2 or bicarbonate ≤ 12 mmol/L | 51 (23) | 33 (15) | 32 (15) | 35 (18) | 0.13 |
| $Pao_2/Fio_2$ ≤ 200 and clinical perception of volume overload | 115 (51) | 105 (46) | 96 (42) | 78 (35) | 0.005 |
| Persistent acute kidney injury ≥ 72 hr | 0 (0) | 0 (0) | 0 (0) | 214 (95) | < 0.001 |

RRT = renal replacement therapy.
[a]Scores range from 0 to 24, with higher scores indicating more severe disease and a higher risk of death.
[b]Oliguria was defined as a urinary output of < 400 mL per 24-hr period.
[c]Data regarding cumulative fluid balance after admission to an ICU were available for 880 in the standard strategy group who received RRT at the time of initiation.
[d]Pearson $\chi^2$ test; Kruskal-Wallis rank-sum test.
Data are presented as *n* (%) or median (interquartile range). Quartiles represent time from randomization to RRT initiation: Q1: 0–17.3 hr; Q2: 17.3–29.1 hr; Q3: 29.1–68.4 hr; and Q4: 68.4–1466.7 hr.

Statistical analyses were performed with the use of Stata software, Version 15 (StataCorp, College Station, TX), and R software, Version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). A *p* value of less than0.05 was used to define statistical significance.

## RESULTS

### Baseline Characteristics

There were 1462 participants in the standard strategy arm, of whom 903 (62%) received RRT (**Fig. S1**, http://links.lww.com/CCM/H692). Baseline characteristics of all participants in the standard strategy group, categorized by the receipt of RRT, are shown in **Table S3** (http://links.lww.com/CCM/H692). Among the 903 participants who commenced RRT, the median (IQR) time to RRT initiation in quartiles 1, 2, 3, and 4 was 12.1 hours (IQR, 8.3–13.8 hr), 24.5 hours (IQR, 21.8–26.5 hr), 46.8 hours (IQR, 35.2–52.1 hr), and 96.1 hours (IQR, 76.7–139.2 hr), respectively. The baseline characteristics of patients in the standard strategy group who received RRT are described by quartiles of time to RRT initiation in **Table S4** (http://links.lww.com/CCM/H692). There were no significant differences in demographics, preexisting conditions, admission categories, or hospital-acquired risk factors for AKI across quartiles. However, patients in quartile 4, as compared with quartile 1, had higher urine output, higher cumulative fluid balance, higher arterial pH, lower potassium, and higher bicarbonate, respectively, at the time of randomization. There were 107 participants who, despite being allocated to the standard strategy, commenced RRT less than 12 hours from randomization; clinical characteristics for this group are described in **Table S5** (http://links.lww.com/CCM/H692).

Clinical characteristics at the time of RRT initiation are summarized across quartiles of time to RRT initiation in **Table 1**. Patients in quartile 4, as compared with quartile 1, had lower SOFA scores, less oliguria or anuria, higher arterial pH, higher serum creatinine, lower serum potassium, higher bicarbonate, and higher serum urea at the time of RRT initiation.

### Outcomes

***Primary Outcome.*** A longer time from randomization to RRT initiation was associated with a lower risk of death at 90 days (quartile 3 vs. 1: adjusted odds ratio

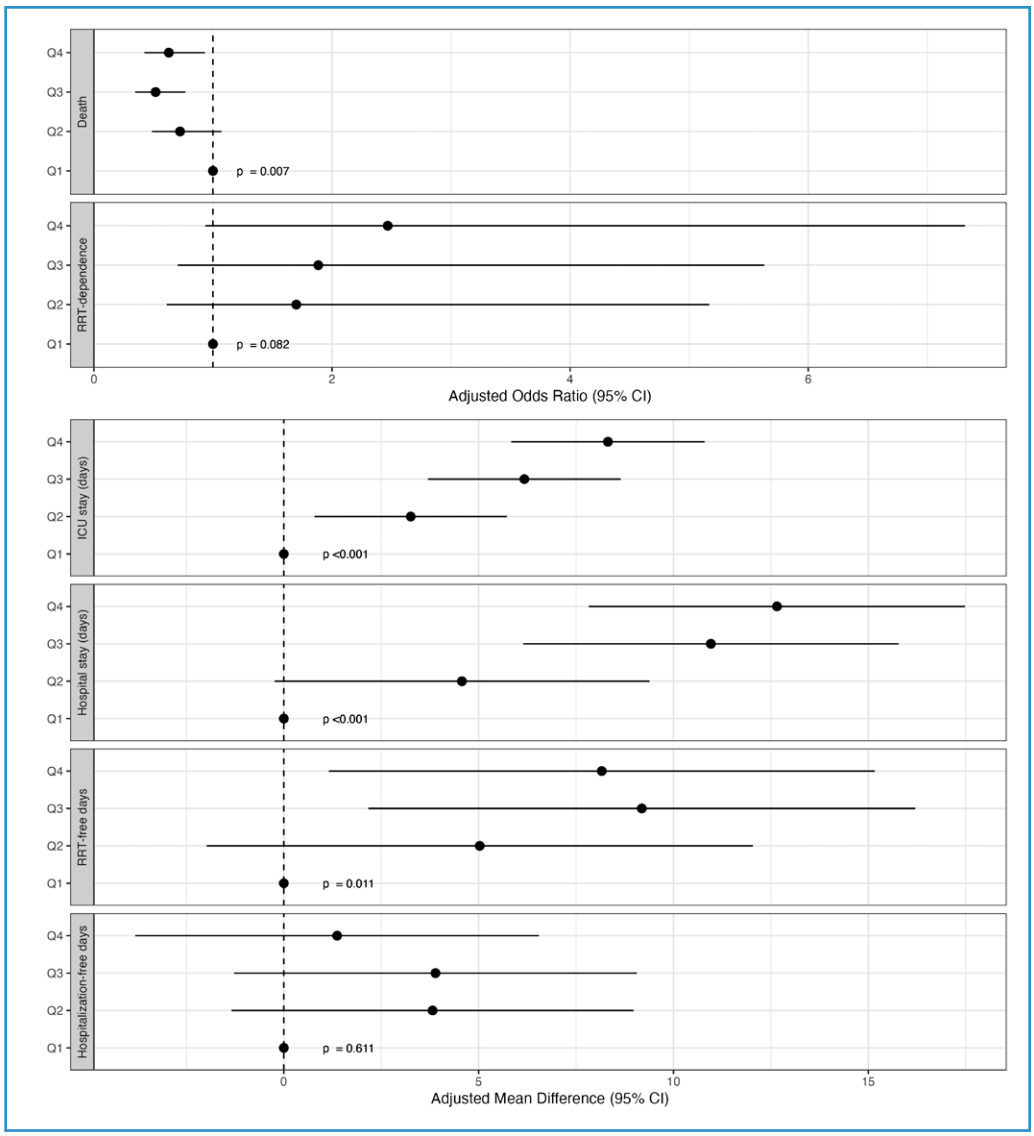


**Figure 1.** Adjusted associations of time to renal replacement therapy (RRT) initiation (by quartiles) and outcomes. *p* values for trend are shown.

[aOR], 0.52 [95% CI, 0.35–0.77] and quartile 4 vs. 1: aOR, 0.63 [95% CI, 0.42–0.93]) (**Fig. 1**; and **Table S6**, http://links.lww.com/CCM/H692). However, when examining time to RRT initiation as a continuous variable, there was no linear or nonlinear association between time to RRT initiation and 90-day mortality (**Fig. 2**; and **Table S7**, http://links.lww.com/CCM/H692). Results were similar among patients who survived for at least 96 hours (**Fig. S2** and **Table S8**, http://links.lww.com/CCM/H692).

***Secondary Outcomes.*** Time to RRT initiation, assessed in quartiles, was not associated with RRT dependence, number of RRT-free days, or hospitalization-free days at 90 days (Fig. 1; and Table S6, http://links.lww.com/CCM/H692). Similarly, when examined as a continuous variable, time to RRT initiation was not associated with the number of RRT-free or hospitalization-free days (**Fig. 3**, ***B*** and ***C***; and **Tables S9** and **S10**, http://links.lww.com/CCM/H692). Among the 388 survivors to 90 days with complete data, a longer delay in initiation of RRT had a linear association with higher probability of RRT dependence at 90 days ($p$ = 0.01) (**Fig. 3*A***; and **Table S11**, http://links.lww.com/CCM/H692).

Longer delays to RRT initiation were associated with longer duration of ICU length of stay (quartile 4 vs. 1: aMD, 8.3 d [95% CI, 5.8–10.8 d] and quartile 3 vs. 1: aMD, 6.2 d [95% CI, 3.7–8.6 d]) and a longer duration of hospital stay (quartile 4 vs. 1: aMD, 12.7 d [95% CI, 7.8–17.5 d] and quartile 3 vs. 1: aMD, 11.0 d [95% CI, 6.2–15.8 d]) (Fig. 1; and Table S6, http://links.lww.com/CCM/H692). However, in the inverse probability weighted analysis after accounting for the death as a competing risk, time to RRT initiation was not associated with length of ICU or hospital stay (**Fig. 4**; and **Tables S12** and **S13**, http://links.lww.com/CCM/H692).

## DISCUSSION

Among patients with severe AKI but no urgent indications for RRT initiation, delaying the initiation of RRT was not associated with incremental mortality risk, and there was no time threshold above which mortality appeared to significantly increase. In addition, deferral of RRT initiation was not associated with

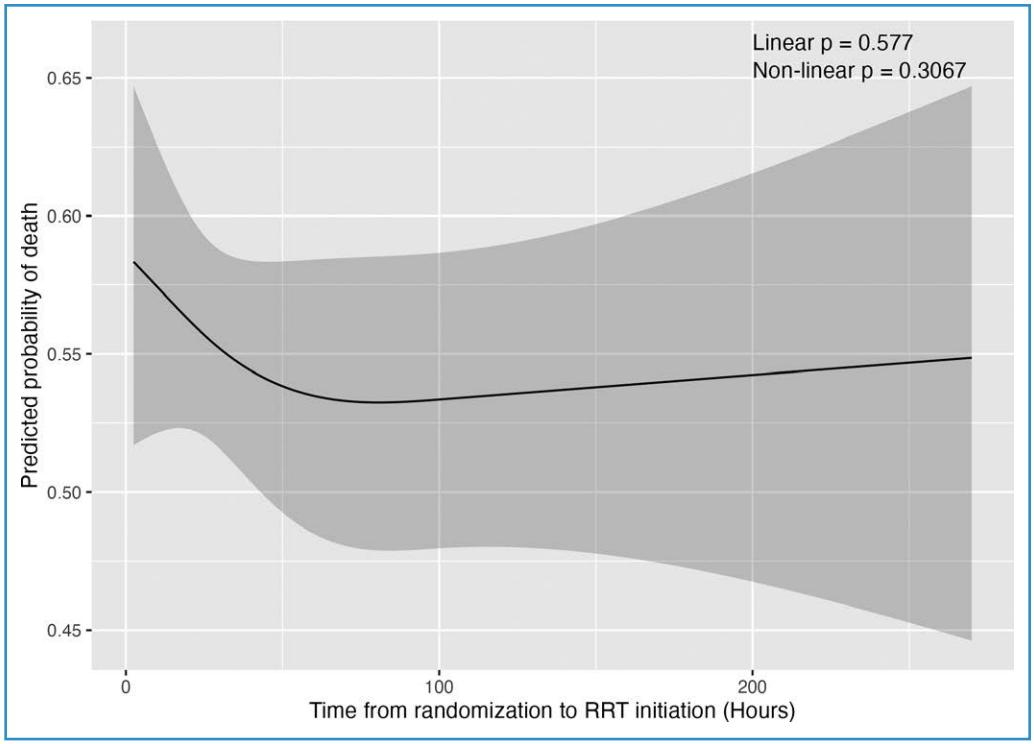


**Figure 2.** The association between time from randomization to renal replacement therapy (RRT) initiation and the predicted probability of death at 90 d. The *solid line* represents the fitted line of the association between time to RRT initiation (hr) and the probability of death after adjustment for age, sex, baseline estimated glomerular filtration rate, Simplified Acute Physiology Score II, sepsis, admission type, urine output, platelet, hemoglobin, Sequential Organ Failure Assessment score, cumulative fluid balance, temperature, arterial pH, heart rate, creatinine, potassium, WBCs, bicarbonate, and weight and the *shaded region* represents the 95% CI.

differences in the number of RRT-free or hospital-free days at 90 days. However, we observed an association with longer time to RRT initiation and the higher risk of RRT dependence at 90 days.

Although recent randomized trials did not show that early RRT initiation leads to superior outcomes as compared with strategies of RRT deferral (4–6, 12), the patients in the "delayed" arms of these trials who commenced RRT did so within a median range of 31–57 hours from randomization. It thus remains unclear if further deferral of RRT, in the setting of severe persistent AKI and no urgent indication for RRT initiation, is a safe and acceptable practice. The AKIKI-2 trial randomized 278 patients with persistent stage 3 AKI, to a strategy of immediate RRT initiation ("delayed" RRT) compared with further delay in RRT initiation until there was a conventional indication or serum urea exceeded 50 mmol/L ("more-delayed" RRT). The "more-delayed" group had a median time of 94 hours to RRT initiation. Contrary to the intuitive hypothesis that patients with more protracted delays in RRT initiation would have more RRT-free days, patients in the "more-delayed" arm had a comparable number of RRT-free days compared with those in the "delayed" arm. In addition, a post hoc adjusted analysis suggested that a more-delayed strategy to starting RRT conferred a higher hazard of death.

Contrary to our hypothesis, we found a lower risk of 90-day all-cause mortality in quartiles reflecting the longest time from randomization to RRT initiation. However, these associations were no longer evident in analyses that treated time to RRT as a continuous variable and accounted for the likelihood of surviving to the receipt of RRT. We speculate that patients who remain clinically stable despite severe AKI are able to tolerate prolonged deferral of RRT initiation without any impact on mortality. Overall, these findings suggest that with close surveillance, RRT can be safely deferred in patients with severe AKI, and there is no fixed time beyond which waiting to commence RRT confers net harm. STARRT-AKI participants who were allocated to the standard arm and started RRT relatively earlier were generally sicker, as suggested by higher SOFA scores, lower urine output, and higher cumulative fluid balance in the earliest quartile at RRT initiation. This may indicate that the relative severity in illness acuity is important in predicting mortality and therefore influences the perceived "need" to commence RRT by clinicians.

When assessed in quartiles, patients with longer time to RRT initiation had more RRT-free days. By the same token such patients had longer ICU stays suggesting that nonrecovery of kidney function and uncertainty around RRT initiation may contribute to

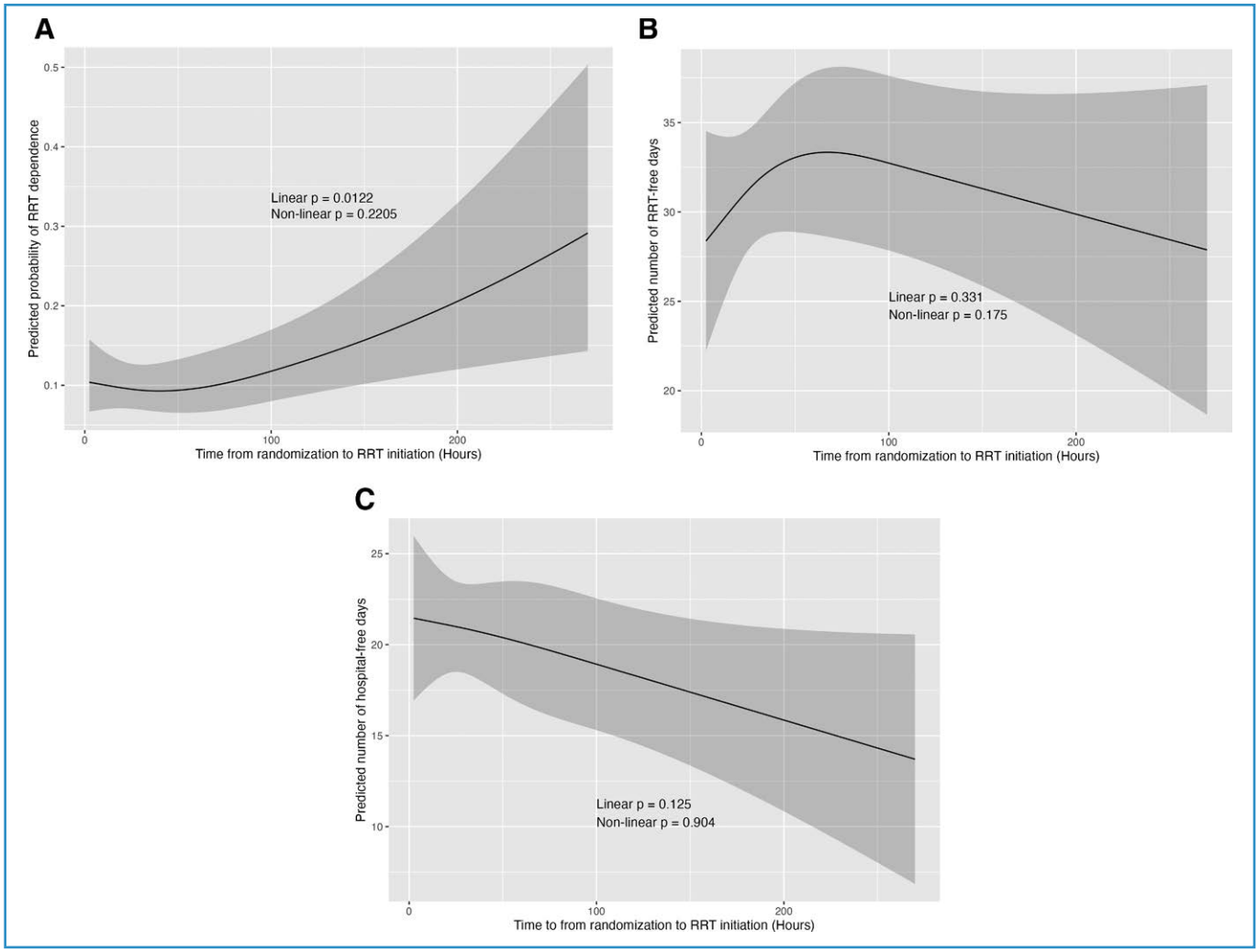


**Figure 3.** The association between time from randomization to renal replacement therapy (RRT) initiation and secondary outcomes. The association between time from randomization to RRT initiation and the predicted probability of RRT dependence (**A**), the number of RRT-free days (**B**), and the number of hospital-free days at 90 d (**C**). The *solid lines* represent the fitted lines of the association and the *shaded region* represents the 95% CI.

longer ICU stay. However, after accounting for immortal time bias and the likelihood of a patient surviving to receive RRT (as well as other variables) these relationships were negated. When time to RRT initiation was treated as a continuous variable, we observed a statistically significant association with RRT dependence at 90 days. The reason for this relationship is unclear from this study, although it could be speculated that cumulative fluid balance, sustained inflammation, or preexisting individual patient characteristics (such as chronic kidney disease) could play a role. We believe this result should be interpreted with caution given the small number of trial participants who were alive and RRT dependent at 90 days.

Our study has several strengths. By focusing on participants in the standard arm of the STARRT-AKI trial, for whom there was a great deal of flexibility with respect to the initiation or deferral of RRT, we were able to study the effects of protracted RRT deferral on patient outcomes in the context of usual care. As the study was embedded in a clinical trial, we had access to a comprehensive database with variables that were rigorously collected and verified. The trial database afforded access to a broad array of clinical data at both the time of randomization and the initiation of RRT, which enabled robust adjustment for potential confounders. We also performed analyses that accounted for patients randomized to the standard arm but who did not commence RRT, either because of death or kidney recovery. By doing so, we addressed the key "competing risks" with which clinicians are faced when considering the initiation of RRT in patients with AKI.

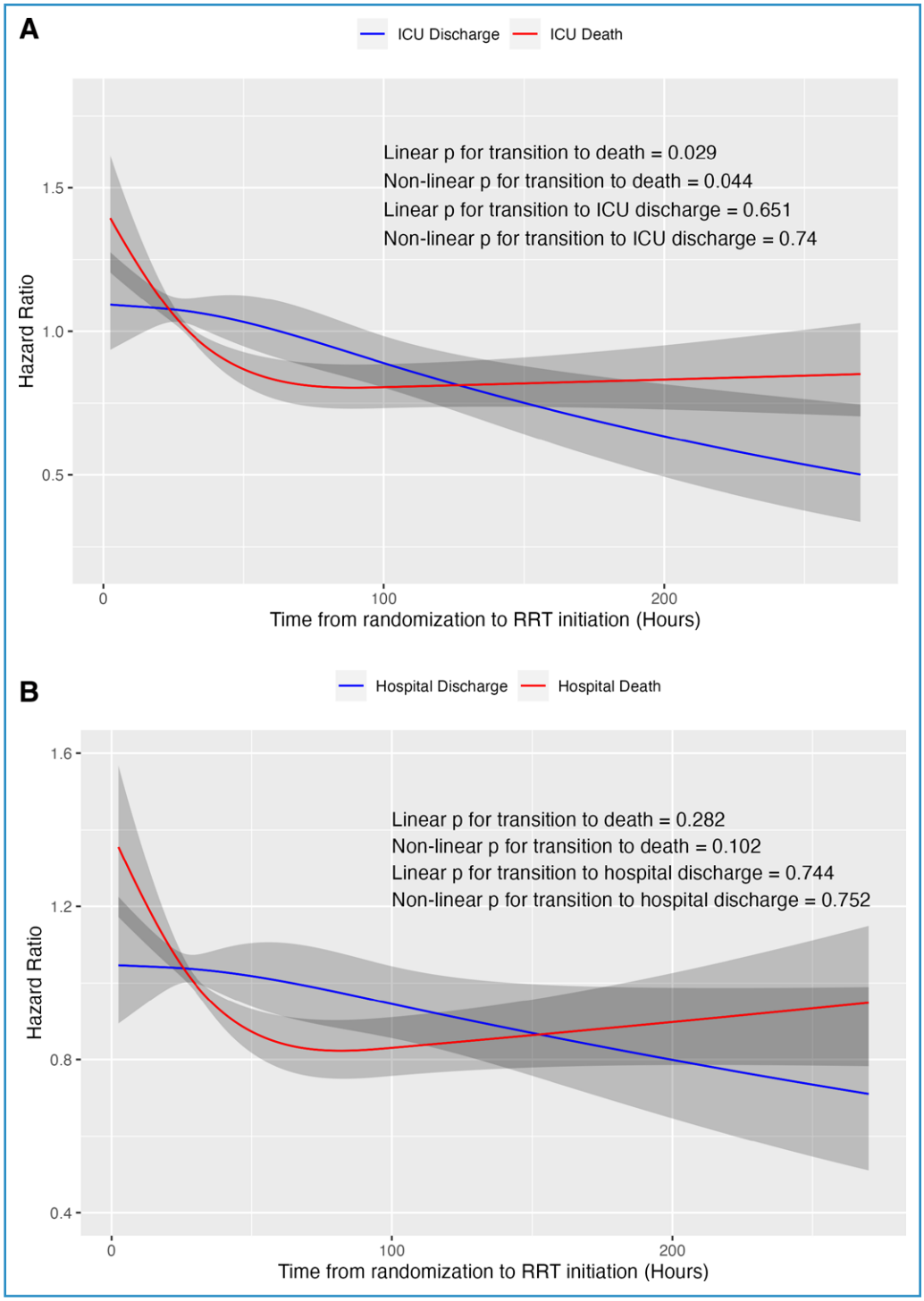


**Figure 4.** The association between time from randomization to renal replacement therapy (RRT) initiation and secondary outcomes. The association between the time from randomization to RRT initiation and the predicted probability of ICU discharge and ICU death (**A**) and the predicted probability of hospital discharge and hospital death (**B**). The *solid lines* represent the fitted line of the associations and the *shaded region* represents the 95% CI.

There are key limitations to acknowledge. Our principal analysis was subject to immortal time bias, as patients who commenced RRT in the intervals comprising the highest quartiles must have survived to enable the delayed receipt of RRT. Notwithstanding our attempts to address this by accounting for patients who did not receive RRT and adjustment for key covariates, it is possible that patients whose time to RRT initiation was protracted were inherently healthier than those who started earlier. A large proportion of our cohort were patients admitted to the ICU for medical diagnoses as opposed to those admitted to the ICU following surgery; notably, less than 10% having had cardiopulmonary bypass in the preceding 7 days. Therefore, our results may not readily extend to patients with critical illness driven by a surgical diagnosis. Although participants were recruited at a diverse array of hospitals around the world, patients enrolled in clinical trials may be inherently different than the broader ICU population, which may limit the generalizability of our findings. Furthermore, the eligibility criteria for the STARRT-AKI deliberately excluded individuals who were perceived by clinicians to have an immediate need to start RRT or who were felt to be likely to recover kidney function without RRT. Finally, we were not able to assess other important clinical outcomes such as the duration of coma and quality of life.

## CONCLUSIONS

We found that among critically ill patients with severe AKI but without conventional indications for RRT, the time to RRT initiation was not associated with a higher risk of death at 90 days. Prolonged deferral of RRT initiation in severe AKI may be associated with a higher risk of RRT dependence at 90 days.

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*The STandard vs. Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) steering committee investigators listed are available at: https://www.ualberta.ca/critical-care/research/starrtaki/documents.html.*

*The STandard vs. Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) data sharing statement will generally align with the data sharing policy of The George Institute for Global Health (https://www.georgeinstitute.org/*

*data-sharing-policy). The STARRT-AKI Co-Chairs and Steering Committee support the view that research data generated from publicly funded research should be made available for sharing to enhance public well-being, to maximize the potential knowledge gained, to reduce redundant research, and to facilitate scientific discovery and innovation. Data sharing will be for the purposes of medical research and under the auspices of the consent under which the data were originally gathered. De-identified individual participant data collected during the STARRT-AKI trial will be shared beginning 2 years after the publication of the primary and secondary analyses, with no end date. Data will be made available to qualified researchers who provide a detailed and methodologically sound proposal with specific aims that are clearly outlined. To gain access, qualified researchers will need to sign a data sharing and access agreement and will need to confirm that data will only be used for the purpose for which data access was granted. Proposals should be directed to the trial Co-Chairs via email: bagshaw@ualberta.ca and Ron.Wald@unityhealth.to.*

## REFERENCES


1. Hoste EA, Bagshaw SM, Bellomo R, et al: Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med* 2015; 41:1411–1423
2. James MT, Bhatt M, Pannu N, et al: Long-term outcomes of acute kidney injury and strategies for improved care. *Nat Rev Nephrol* 2020; 16:193–205
3. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kid Inter Supp* 2012; 2:1–138
4. Gaudry S, Hajage D, Schortgen F, et al; AKIKI Study Group: Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016; 375:122–133
5. Barbar SD, Clere-Jehl R, Bourredjem A, et al; IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network: Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *N Engl J Med* 2018; 379:1431–1442
6. Bagshaw SM, Wald R, Adhikari NKJ, et al; STARRT-AKI Investigators; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; United Kingdom Critical Care Research Group; Canadian Nephrology Trials Network; Irish Critical Care Trials Group: Timing of initiation of renal-replacement therapy in acute kidney injury. *N Engl J Med* 2020; 383:240–251
7. Gaudry S, Hajage D, Martin-Lefevre L, et al: Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): A multicentre, open-label, randomised, controlled trial. *Lancet* 2021; 397:1293–1300
8. Rambaud T, Hajage D, Dreyfuss D, et al: Renal replacement therapy initiation strategies in comatose patients with severe acute kidney injury: A secondary analysis of a multicenter randomized controlled trial. *Intensive Care Med* 2024; 50:385–394
9. The STARRT-AKI Investigators: STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury: Study protocol for a multi-national, multi-center, randomized controlled trial. *Can J Kidney Health Dis* 2019; 6:2054358119852937
10. The STARRT-AKI Investigators: Statistical analysis plan for the Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial. *Crit Care Resusc* 2019; 21:162–170
11. von EE, Altman DG, Egger M, et al: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Prev Med* 2007; 45:247–251
12. Li X, Liu C, Mao Z, et al: Timing of renal replacement therapy initiation for acute kidney injury in critically ill patients: A systematic review of randomized clinical trials with meta-analysis and trial sequential analysis. *Crit Care* 2021; 25:15