The Effect of an Accelerated Renal Replacement Therapy Initiation Is Not Modified by Baseline Risk

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To the Editor:

Acute kidney injury (AKI) is a common feature of critical illness (1), and up to 10-15% of patients admitted to ICU receive renal-replacement therapy (RRT) (2). In the STARRT-AKI trial, accelerated RRT initiation did not reduce the risk of 90-day mortality in critically ill adults with AKI without an urgent indication for RRT (3). However, whether patients at higher risk of progressive AKI and destined to require RRT would benefit from an accelerated RRT initiation strategy remains unknown.

Using data from the STARRT-AKI trial (3), we sought to derive a model to predict baseline risk of RRT initiation among critically ill adults with AKI randomized to the standard strategy and estimate whether such risk modifies the effect of an accelerated RRT strategy on mortality. We hypothesized that patients at higher risk of receiving RRT would benefit from accelerated RRT initiation.

Methods

We conducted a *post hoc* secondary analysis of the STARRT-AKI trial (3, 4). Patients were eligible for the trial if they were adults, admitted to ICU and had stage 2-3 AKI according to the Kidney Disease: Improving Global Outcomes classification (5). Patients with urgent indications for RRT were excluded. Eligible patients were randomized to accelerated (within 12 hours of trial eligibility) or standard RRT initiation (whereby RRT was discouraged unless a conventional indication supervened). The primary outcome was 90-day mortality. The main effect modifier in this secondary analysis was the baseline risk of RRT initiation.

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To derive a model for risk of RRT initiation, we only included patients randomized to the standard strategy. This cohort was split in half, using calendar time of enrolment, into distinct derivation and validation sets. Within the derivation subset, we utilized a multivariable logistic regression model based on the least absolute shrinkage and selection operator (LASSO) (6), which included RRT initiation as the dependent variable and, initially, all demographics, clinical and laboratory covariates as predictors (Table 1). Ten-fold cross-validation was used to select the optimal lambda value that minimized mean squared prediction error (7). This model identified the set of variables predicting baseline RRT risk. Calibration (Brier score) and discrimination (area under the receiver operating curve, AUC) were reported in the validation subset. This final model was then applied to the entire STARRT-AKI population (i.e., both accelerated and standard strategies) to estimate each participant's baseline (pre-randomization) risk of RRT initiation.

To determine whether the baseline risk of RRT initiation modified the effect of the accelerated strategy on 90-day mortality, we fitted a multivariable logistic regression model with the randomized group (i.e., accelerated or standard strategy) as the main exposure, the baseline risk as estimated by the LASSO model, and their interaction. Sensitivity analyses included a model considering interaction on the additive scale and another with site-specific random effects. We used 0.05 as threshold for statistical significance, and all reported tests are two-sided. Reported associations are shown as odds ratios (ORs) with 95% confidence intervals (CIs). All analyses were performed using STATA Version 14.2 (StataCorp, College Station, TX).

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Results

Baseline characteristics of randomized patients are shown in Table 1. Approximately 62% of patients allocated to the standard strategy started RRT. At baseline, these patients had a higher illness severity and were more likely to be receiving mechanical ventilation and vasopressors compared to those not started on RRT. More patients who started RRT had oliguria, while scheduled surgery was more common among those not started on RRT. Patients in both groups had a similarly low risk of mortality during the first two days (2.3% and 1.0% for the standard and accelerated strategies, respectively).

Table 2 shows predictors of RRT initiation identified by our parsimonious model. SOFA score (OR 1.16 per 1-point increase; 95%CI 1.12–1.19) and cumulative fluid balance (OR 1.02 per 500 mL increase; 95%CI 1.01–1.03) were associated with a higher likelihood of RRT initiation. Conversely, diuretic use preceding randomization (OR 0.63; 95%CI 0.50–0.79) and greater urine output (OR 0.85 per 500-ml increase; 95%CI 0.80–0.91) were associated with a lower likelihood of RRT initiation. The Brier score and AUC in the validation set were 0.21 and 0.68 respectively.

The baseline risk of RRT initiation did not modify the effect of an accelerated strategy compared to standard strategy on the risk of 90-day mortality (interaction p-value=0.64; Figure 1). In addition, no interaction was noted on the additive scale (interaction p-value=0.68) and when incorporating site-specific random effects (interaction p-value=0.40) in the risk model.

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Discussion

Among critically ill adults with AKI randomized to the standard strategy in the STARRT-AKI trial, a higher SOFA score, non-receipt of diuretics, oliguria, and higher cumulative fluid balance at baseline were associated with a higher risk of RRT initiation. However, this higher baseline risk did not modify the effect of an accelerated RRT initiation strategy on mortality.

Although an accelerated strategy of RRT initiation did not confer improved survival in STARRT-AKI and other recent trials (3, 8), in the ELAIN trial, earlier initiation was found to be beneficial in a predominantly surgical population (9). While patients with peri-operative AKI did not benefit from accelerated RRT initiation in the STARRT-AKI trial, it is still possible that patients with certain features do benefit from earlier RRT initiation. Our study shows that, even for those patients at highest risk of subsequently receiving RRT, an accelerated strategy is unlikely to be beneficial. These findings are in line with published subgroup analyses of the STARRT-AKI and AKIKI trials showing no differential effect of an accelerated strategy by baseline illness severity (3, 8) the presence of sepsis or acute respiratory distress syndrome (10).

Several limitations need to be considered. It is unclear if our findings reflect a true absence of heterogeneity of treatment effect or imperfect subgroup identification. We did not have information on time-changing covariates prior to randomization, which could increase the model performance. Finally, we did not have clinician level characteristics to include in the model to estimate the risk of RRT initiation; however, a sensitivity analysis considering site-specific differences yielded similar findings.

In conclusion, a higher baseline risk of RRT initiation did not modify the effect of an accelerated strategy on 90-day mortality among critically ill adult patients with AKI. In the

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absence of an urgent AKI-related complication, close monitoring and initial deferral of RRT initiation for critically ill adults with AKI, even if the eventual initiation of RRT appears likely, is a reasonable approach.

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Figure legend

Figure 1. Modification of the effect of an accelerated renal replacement therapy initiation on mortality by baseline probability of RRT initiation, derived using a logistic model based on the least absolute shrinkage and selection operator. The P value is based on a logistic model (see text). RRT, renal replacement therapy.

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Table 1. Baseline characteristics of patients

Characteristic	Accelerated RRT (N = 1465)	Standard strategy (N = 1462)			p value[1]
		Overall (N = 1462)	Started RRT (N = 903)	Did not start RRT (N = 559)	
Age – years	64.6 (14.3)	64.7 (13.4)	64.1 (13.6)	65.7 (12.9)	0.02
Female sex – no. (%)	470 (32.1)	467 (31.9)	285 (31.6)	182 (32.6)	0.73
Weight – Kg	88.0 (27.4)	88.0 (25.1)	87.7 (25.1)	88.5 (25.1)	0.52
Serum creatinine – mg/dL	1.4 (1.0)	1.3 (1.0)	1.4 (1.0)	1.3 (0.9)	0.25
Glomerular filtration rate – ml/min/1.73 m^2	66.0 (29.8)	67.3 (29.8)	67.1 (30.4)	67.6 (29.0)	0.76
Preexisting conditions – no. (%)					
Chronic kidney disease	658 (44.9)	626 (42.8)	389 (43.1)	237 (42.4)	0.83
Hypertension	814 (55.6)	823 (56.3)	496 (54.9)	327 (58.6)	0.19
Diabetes mellitus	439 (30.0)	459 (31.4)	289 (32)	170 (30.4)	0.56
Heart failure	204 (13.9)	204 (14.0)	118 (13.1)	86 (15.4)	0.24
Coronary artery disease	320 (21.8)	328 (22.4)	202 (22.4)	126 (22.6)	0.98
Liver disease	172 (11.7)	165 (11.3)	109 (12.1)	56 (10.0)	0.27
Metastatic cancer	77 (5.3)	84 (5.7)	54 (6)	30 (5.4)	0.71
Hematologic cancer	87 (5.9)	83 (5.7)	53 (5.9)	30 (5.4)	0.77
HIV infection or AIDS	13 (0.9)	13 (0.9)	7 (0.8)	6 (1.1)	0.76
Admission category – no. (%)					
Scheduled surgery	207 (14.1)	184 (12.6)	108 (12)	76 (13.6)	0.40
Unscheduled surgery	285 (19.5)	289 (19.8)	161 (17.8)	128 (22.9)	0.02
Medical	973 (66.4)	989 (67.6)	634 (70.2)	355 (63.5)	0.01
Hospital acquired risk factor for acute kidney injury in previous week – no. (%)					
Cardiopulmonary bypass	112 (7.6)	118 (8.1)	67 (7.4)	51 (9.1)	0.29
Aortic aneurysm repair	71 (4.8)	74 (5.1)	47 (5.2)	27 (4.8)	0.84
Vascular surgery	76 (5.2)	77 (5.3)	45 (5.0)	32 (5.7)	0.62
Major trauma	62 (4.2)	55 (3.8)	28 (3.1)	27 (4.8)	0.12
Intravenous contrast material	382 (1463)	375 (25.6)	233 (25.8)	142 (25.4)	0.92
Aminoglycoside use	154 (10.5)	148 (10.1)	86 (9.5)	62 (11.1)	0.38
Amphotericin use	9 (0.6)	12 (0.8)	9 (1.0)	3 (0.5)	0.52
Clinical condition at baseline					
SOFA score	11.6 (3.6)	11.8 (3.6)	12.5 (3.5)	10.5 (3.4)	<0.01
SAPS II score	58.1 (17.4)	59.4 (17.4)	62.1 (16.9)	55.1 (17.2)	<0.01
Mechanical ventilation – no. (%)	1103 (75.3)	1148 (78.5)	741 (82.1)	407 (72.8)	<0.01
Vasoactive support – no. (%)	1008 (68.8)	1052 (72.0)	674 (74.6)	378 (67.6)	<0.01
Oliguria or anuria – no. (%)	647 (45.7)	618 (42.3)	451 (49.9)	167 (29.9)	<0.01

Continuous variables are shown as mean (standard deviation). AIDS: acquired immunodeficiency syndrome, AKI: acute kidney injury, HIV: human immunodeficiency virus, RRT: renal replacement therapy, SOFA: sequential organ failure assessment, SAPS II: simplified acute physiology score.

[1]P-value is for the comparison, among those randomized to the standard-strategy, between those that started or not RRT. Means are compared with Student's T test and proportions with Chi square test.

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Table 2. Factors associated with initiation of renal replacement therapy among critically ill adult patients with acute kidney injury

Characteristic	**Odds ratio[1] (95% confidence interval)**	**p value[2]**	**Comment**
Age	0.91 (0.84 – 0.99)	0.03	For every 10 year increase
Weight	0.99 (0.95 – 1.03)	0.52	For every 10 kg increase
Systolic blood pressure	1.01 (0.98 – 1.05)	0.45	For every 10 mmHg increase
Cardiovascular comorbidity[3]	1.15 (0.91 – 1.45)	0.24	Yes vs. no
Intravenous contrast exposure	0.98 (0.77 – 1.25)	0.87	Yes vs. no
SOFA score pre randomization	1.16 (1.12 – 1.19)	< 0.01	For every 1 point increase
Cumulative fluid balance[4]	1.02 (1.01 – 1.03)	< 0.01	For every 500 ml increase
Diuretic treatment over 24 hours pre-randomization	0.63 (0.50 – 0.79)	< 0.01	Yes vs. no
Urine output over 24 hours pre-randomization	0.85 (0.80 – 0.91)	< 0.01	For every 500 ml increase
Serum potassium	1.08 (0.95 – 1.22)	0.25	For every 1 mmol/L increase

SOFA: sequential organ failure assessment

1. Associations shown for final least absolute shrinkage and selection operator (LASSO) model fitted in validation subset; optimal lambda chosen based on mean square error
2. Based on a multivariable LASSO logistic model
3. Either heart failure or coronary heart disease
4. From admission to the intensive care unit to randomization

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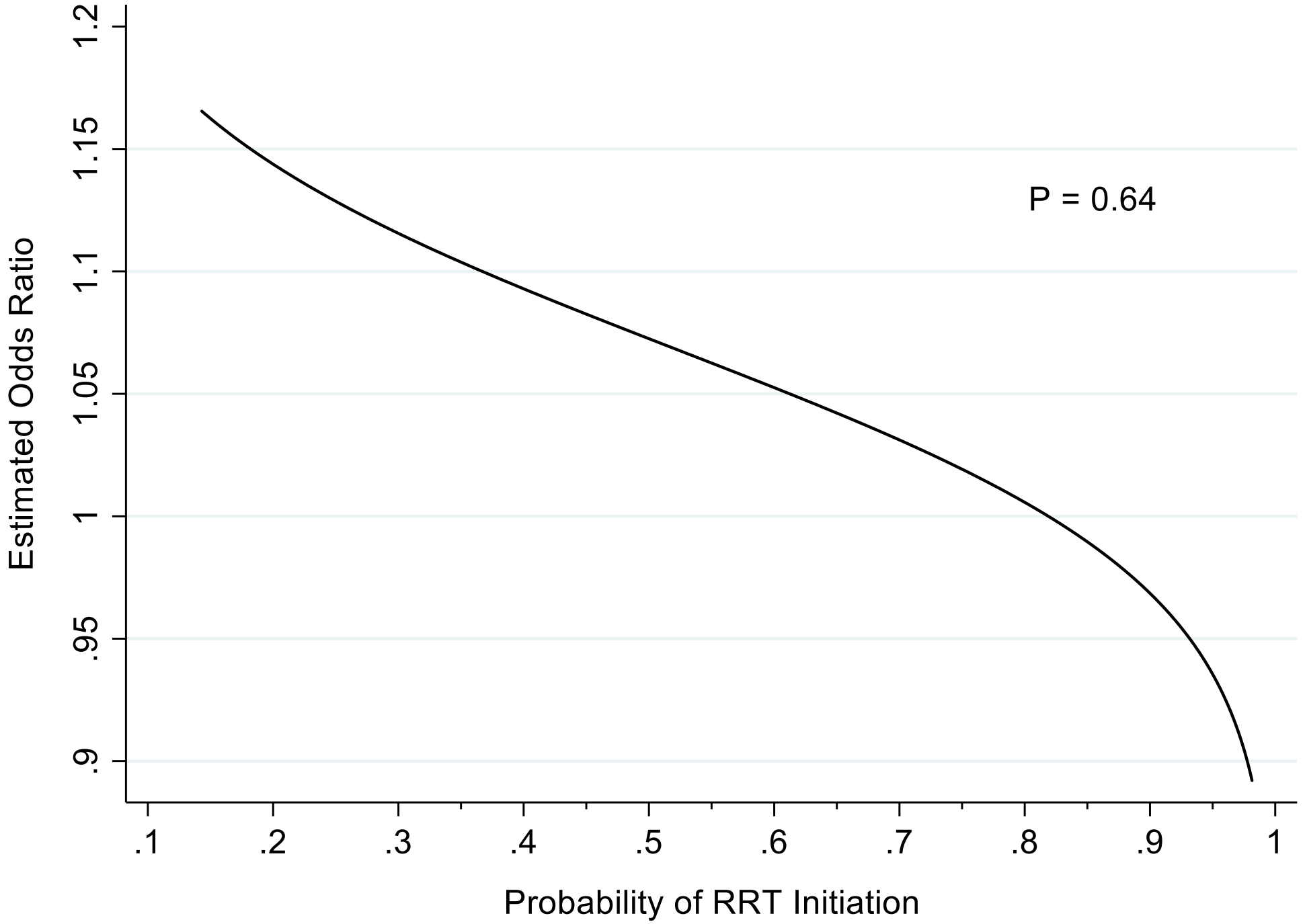

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