Supplemental Online Content

Gist KM, Menon S, Anton-Martin P, et al; for the WE-ROCK Investigators. Time to continuous renal replacement therapy initiation and 90-day major adverse kidney events in children and young adults. *JAMA Netw Open.* 2024;7(1):e2349871. doi:10.1001/jamanetworkopen.2023.49871

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods. Covariate Balancing Generalized Propensity Score (CBGPS)

The generalized propensity score weights were estimated using the CBGPS method, treating our exposure variable as continuous days to treatment. This method utilized a generalized method-of-moments framework, which ensured a set of moment conditions minimizing the association between the continuous exposure variable and baseline covariates as measured by their correlations when estimating the propensity score. Inverse probability of treatment weights (IPTW) were then computed for each participant to account for measured confounding. Univariate regression was used to estimate the treatment effect by regressing the outcome on the continuous exposure using a weighted regression model incorporating the CBGPS-based IPTW weights. The WeightIt package (version 0.13.1) in R (version 4.1.0) was used to generate the CBGPS and IPTW weights (https://ngreifer.github.io/WeightIt/reference/method_cbps.html). For additional detail on the CBGPS methodology we refer readers to "Fong, C., Hazlett, C., & Imai, K. (2018).[1]

Reference:

1. Fong C, Hazlett C, Imai K. Covariate balancing propensity score for a continuous treatment application to the efficacy of political advertisements. *The Annals of Applied Statistics*. 2018;12(1):156-177.

eTable 1. STROBE Checklist: Time to Continuous Renal Replacement Therapy Initiation and 90-Day Major Adverse Kidney Events in Children and Young Adults

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	8, 9, eMethods
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8, 9*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-11
		(*b*) Describe any methods used to examine subgroups and interactions	9-11
		(*c*) Explain how missing data were addressed	10-11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	N/A
		€ Describe any sensitivity analyses	N/A

eTable 2. Demographics, clinical characteristics, and outcomes of patients with and without volume overload at initiation of continuous renal replacement therapy.

Variable	Overall (n=975)	VO <10% (n=571)	VO ≥ 10% (n=404)	P-Value
Age (years)	8.8 (1.7-15.0)	11.7 (3.5-16.1)	3.7 (0.9-12.0)	<.001
Admission weight (kg)	26.8 (11.6-55.0)	42.0 (15.0-64.4)	16.0 (8.3-35.5	<.001
Female	444 (45.5)	260 (45.5)	184 (45.5)	>.99
Male	531 (54.4)	311 (54.4)	220 (54.4)	
Race				.30
White	56 (76.4)	384 (76.0)	272 (76.8)	
Black	126 (14.7)	68 (13.5)	58 (16.4)	
Native American	16 (1.9)	10 (2.0)	6 (1.7)	
Asian/Pacific Islander	43 (5.0)	31 (6.1)	12 (3.4)	
More than 1 race	18 (2.1)	12 (2.4)	6 (1.7)	
Missing	116	66	50	
Ethnicity				.003
Non-Hispanic or Latino	703 (81.6)	394 (78.2)	309 (86.3)	
Hispanic or Latino	159 (18.4)	110 (21.8)	49 (13.7)	
Missing	113	67	46	
Admit Category				<.001
Shock/infection/Trauma	364 (37.3)	179 (31.3)	185 (45.8)	
Respiratory Failure	194 (19.9)	116 (20.3)	78 (19.3)	
Post-surgical/minor trauma	49 (5.0)	22 (3.9)	27 (6.7)	
CNS dysfunction	39 (3.8)	22 (3.9)	9 (2.2)	
Pain/sedation	8 (0.8)	4 (0.7)	4 (1.0)	
Primary Cardiac disease	30 (3.2)	11 (1.9)	19 (4.7)	
Post Cardiac Surgery	47 (5.1)	21 (3.7)	26 (6.4)	
Heart failure/myopathy	39 (4.0)	32 (5.6)	7 (1.7)	
Other	205 (21.0)	156 (27.3)	49 (12.1)	
Comorbidity				
None	192 (19.7)	116 (20.3)	76 (18.8)	.67
Respiratory	131 (13.4)	67 (11.7)_	64 (15.8)	.08
Cardiac	190 (19.5)	93 (16.3)	97 (24.0)	.004
Neurologic/neuromuscular	131 (13.4)	64 (11.2)	67 (16.6)	.020
Nephrologic/Urologic	89 (9.1)	58 (10.1)	31 (7.7)	.22
Hematologic	132 (13.5)	84 (14.7)	48 (11.9)	.24
Oncologic	221 (22.7)	141 (24.7)	80 (19.8)	.09
Immunologic	153 (15.7)	98 (17.2)	55 (13.6)	.16
Gastrointestinal	184 (18.9)	97 (17.0)	87 (21.5)	.09
Endocrinologic	62 (6.4)	31 (5.4)	31 (7.7)	.20
Comorbidities:				..21
None	192 (19.7)	116 (20.3)	76 (18.8)	
1	478 (49.9)	283 (49.6)	195 (48.3)	
2	191 (19.6)	116 (20.3)	75 (18.6)	
>2	115 (11.8)	57 (10.0)	58 (14.3)	
Baseline measured serum creatinine (mg/dL)	0.4 (0.2-0.6) (n=537)	0.5 (0.3-0.7) (n=305)	0.3 (0.2-0.5) (n=232)	<.001
Sepsis at ICU admission	446 (45.7)	229 (40.1)	217 (53.7)	<.001
PRISM-III at ICU Admission	14 (10-18)	14 (10-18)	15 (10-19)	.079
PELOD-2 CRRT Initiation	7 (4-9)	6 (4-8)	7.5 (5-10)	<.001
VIS at CRRT Initiation	5 (0-20)	2 (0-14)	8 (0-23)	<.001
Indexed UOP 24 hours prior to CRRT Initiation (ml/kg/hr)	0.5 (0.1-1.2)	0.9 (0.5-1.1)	1.0 (0.6-1.7)	.001
Time to CRRT Initiation (days)	2 (1-6)	1 (0-4)	4 (2-10)	<.001

CRRT Duration (days)	6 (3-14)	5 (3-13)	7 (4-15)	.003
Ventilator Free days	13 (0-28)	17 (0-28)	3 (0-28)	<.001
ICU Free days	0 (0-11)	0 (0-15)	0 (0-2)	<.001
90-day Mortality	366 (37.5)	202 (35.4)	164 (40.6)	.11
MAKE-90	626 (64.2)	361 (63.2)	265 (65.6)	.52

The overall sample is 975 (includes all patients with available fluid data). Categorical variables are presented as frequency with percent. Continuous variables are presented as median with interquartile range (IQR). P<0.05 denotes statistical significance.
Abbreviations: MAKE-90 – major adverse kidney events at 90 days (persistent kidney dysfunction, dialysis dependence or death) kg - kilograms; CNS – central nervous system; ICU – intensive care unit; PRISM-III – pediatric risk of mortality score III; PELOD-2 – pediatric logistic organ dysfunction score; VIS – vasoactive inotrope score; VO – percent volume overload; UOP – urine output; ml/kg/hr – milliliters per kilogram per hour, CRRT – continuous renal replacement therapy.

eTable 3. Interquartile odds ratio estimation of time to CRRT initiation, comparing weighted regression by generalized propensity score (GPS) with the outcome model method.

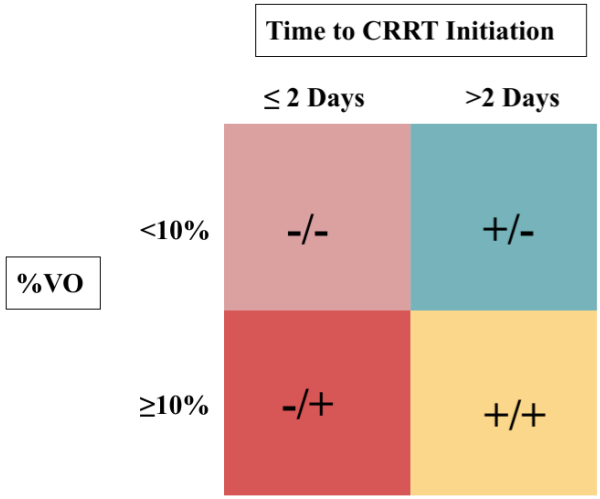
	MAKE-90	Mortality at 90 days	ICU-free days	Ventilator-free days
Approach	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Outcome model estimate	1.14 (1.09-1.19)	1.18 (1.08-1.29)	0.27 (0.25-0.29)	0.79 (0.72-0.87)
GPS weighted estimate	1.21 (1.16-1.26)	1.20 (1.11-1.31)	0.31 (0.29-0.33)	0.78 (0.72-0.84)

eTable 4. Multivariable logistic regression or ordinal regression evaluating the association of time to continuous renal replacement therapy initiation and volume overload sub-phenotypes with outcomes.

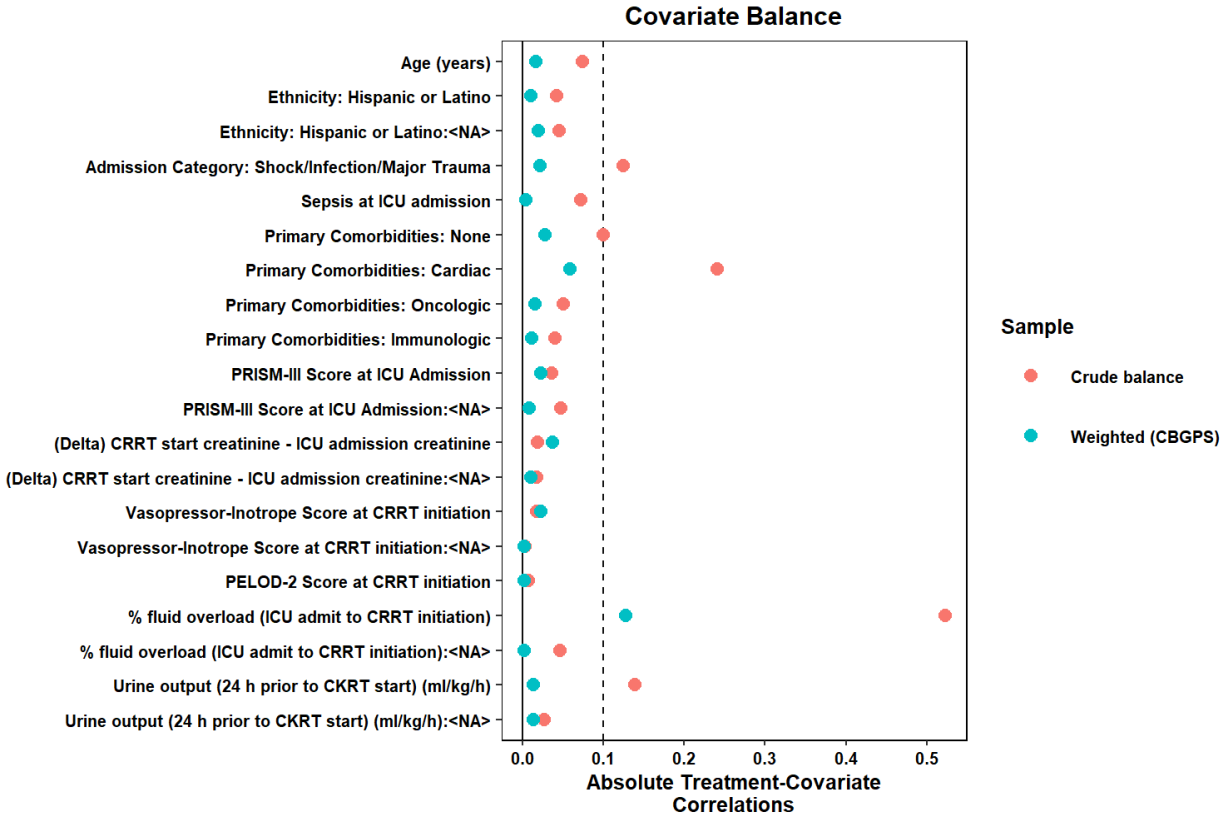
			MAKE-90	Mortality at 90 days	28-day Ventilator-free days	29-Day ICU Free days
Variable	**Reference**	**Contrast**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
No comorbidity	No	Yes	0.5 (0.4-0.6)	0.6 (0.4-0.9)	1.0 (0.7-1.4)	1.6 (1.0-2.4)
Respiratory comorbidity	No	Yes	0.9 (0.6-1.4)	1.2 (0.7-1.9)	0.7 (0.5-1.1)	0.7 (0.5-1.1)
Cardiac comorbidity	No	Yes	1.51 (1.1-2.2)	1.5 (1.0-2.1)	0.7 (0.5-1.1)	0.6 (0.4-0.9)
Oncologic comorbidity	No	Yes	1.3 (0.9-1.9)	1.9 (1.4-2.5)	0.7 (0.5-0.9)	1.0 (0.7-1.4)
Immunologic comorbidity	No	Yes	1.9 (1.2-3.1)	2.2 (1.6-2.9)	0.4 (0.3-0.6)	0.5 (0.4-0.8)
Sepsis at ICU admission	No	Yes	1.12 (0.8-1.7)	1.4 (1.1-1.9)	0.6 (0.5-0.9)	0.7 (0.5-0.9)
VIS at CRRT initiation	0	20	1.1 (1.0-1.3)	1.3 (1.1-1.5)	0.7 (0.6-0.9)	0.6 (0.5-0.8)
CRRT duration (days)	3	14	1.5 (1.3-1.7)	1.0 (0.9-1.0)	0.9 (0.7-1.2)	0.3 (0.2-0.4)
Time to CRRT initiation category	≤2	>2 days	1.0 (0.7-1.4)	1.7 (1.2-2.4)	0.5 (0.4-0.8)	0.2 (0.2-0.3)
Volume overload category	< 10%	≥ 10%	0.9 (0.6-1.3)	1.3 (0.9-1.8)	0.8 (0.6-1.2)	0.6 (0.4-0.8)

Continuous variables (VIS at CRRT initiation and time to CRRT initiation) are presented as interquartile odds ratio with 95% confidence intervals. Multivariable logistic regression was used to assess associations MAKE-90 and 90-day mortality. Ordinal regression was used to assess associations with 28-day ventilator and ICU free days. All other categorical variables are presented as odds ratio with 95% CI). Abbreviations: MAKE-90 – major adverse kidney events at 90 days (persistent kidney dysfunction, dialysis dependence or death), ICU – intensive care unit, VIS = vasoactive inotrope score, CRRT = continuous renal replacement therapy.

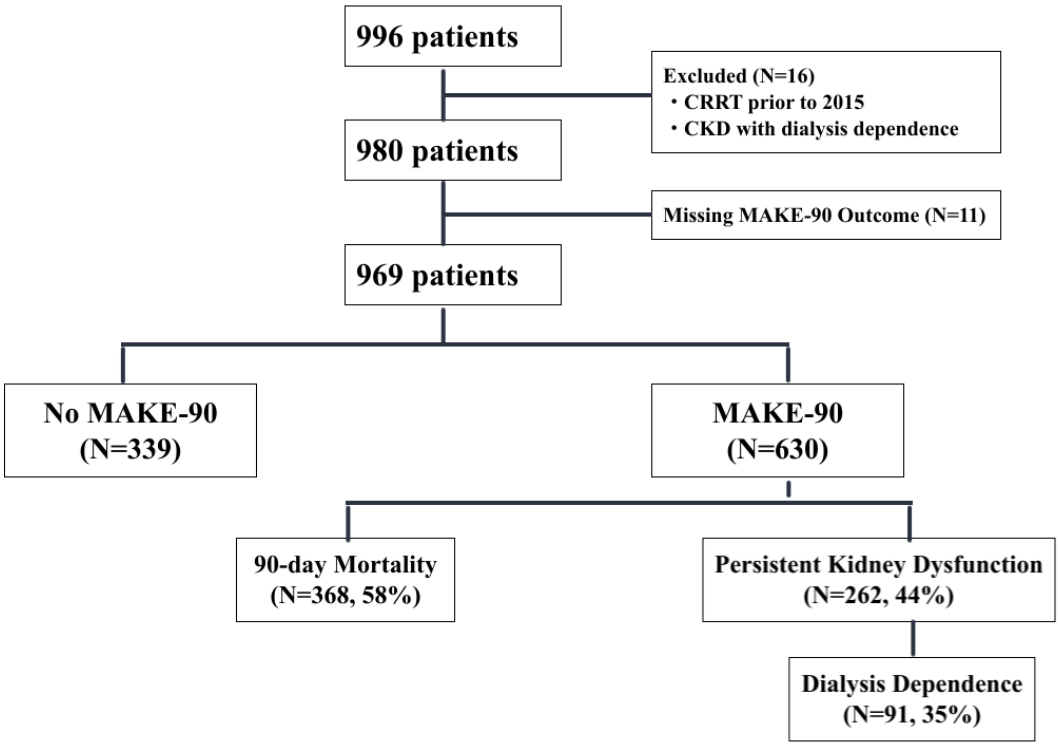
eFigure 1. Sub-phenotypes of time to continuous renal replacement therapy initiation and % volume overload. Four sub-phenotypes delineated by early (≤2 days) and late (≥2 days) continuous renal replacement therapy initiation, and % volume overload (<10% and ≥10%).



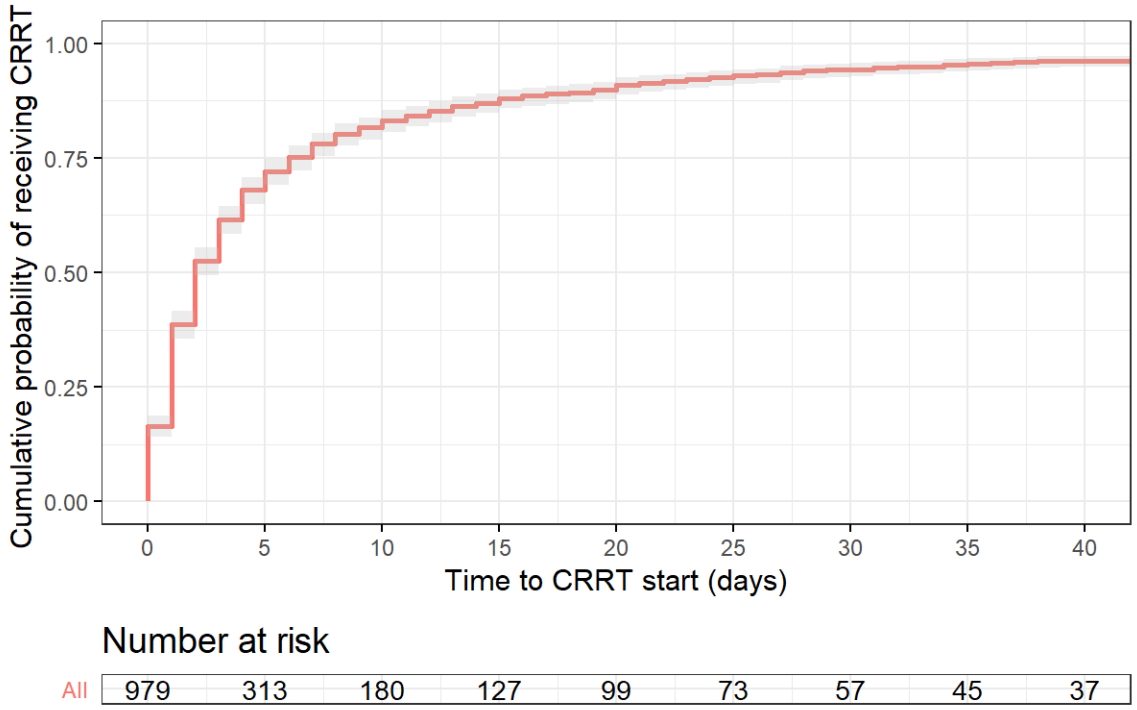
eFigure 2. Covariate balance plot. The balance of each covariate was assessed using the correlation with the continuous exposure (i.e., time to CRRT initiation) before and after the covariate-balancing generalized propensity score (CBGPS) weighting. The missing covariate data (represented by NA) were handled by incorporating missingness in the CBGPS estimation process. The absolute correlation coefficients < 0.1 for most covariates suggest an overall good balance (i.e., minimal confounding) after weighting adjustment.



eFigure 3. Consort flow diagram



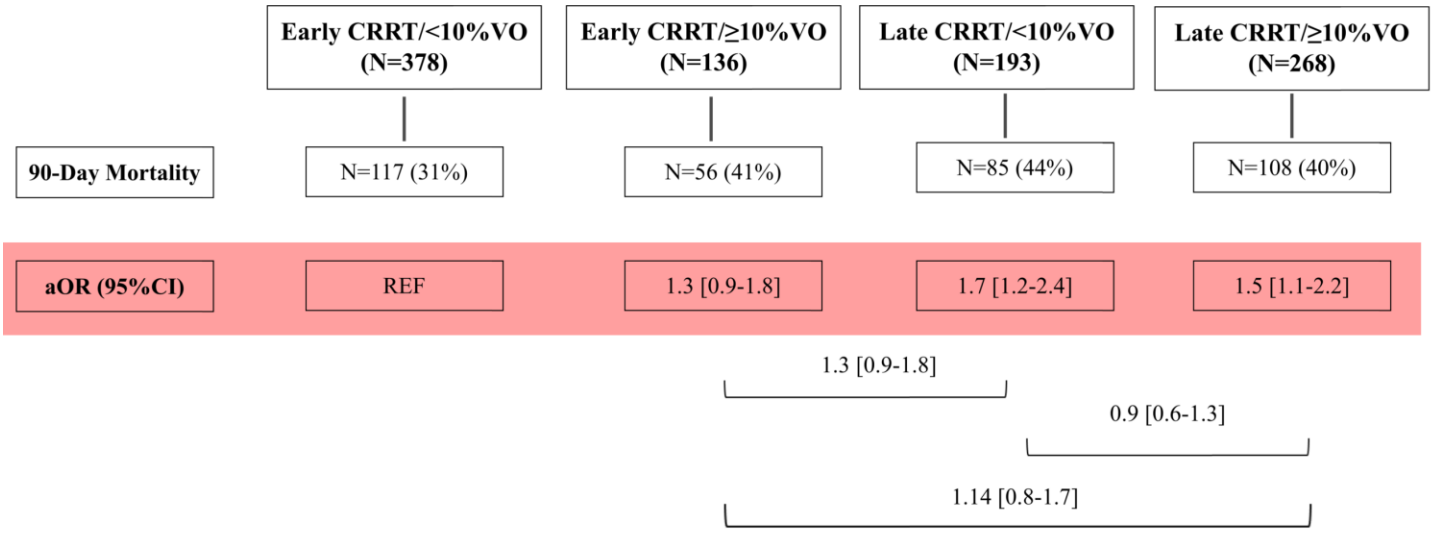
eFigure 4. Kaplan-Meier Curve summarizing the probability of receiving CRRT over time. The probability of receiving CRRT increased within the first 5 days of ICU admission and then started to plateau. The number at risk, in intervals of every 5 days is summarized in the box below the x-axis.



Number at risk

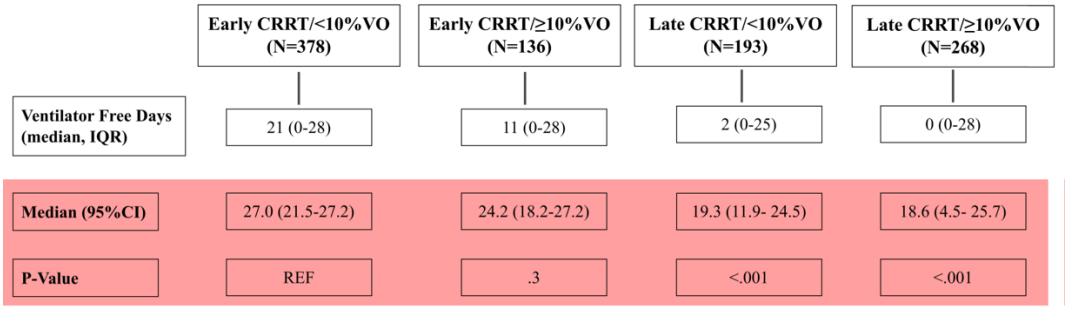
All	979	313	180	127	99	73	57	45	37

eFigure 5. Multivariable logistic regression evaluating the association between continuous renal replacement therapy initiation and volume overload sub-phenotypes and 90-day mortality. Compared to the reference group, early initiation/<10 VO, both late CRRT/<10 VO and late CRRT/≥10 VO had a significantly greater odds of 90-day mortality. Early initiation was defined as ≤2 days and late initiation was defined as >2 days, both anchored to ICU admission. There were no significant between group differences in 90-day mortality after adjusting for confounders.



eFigure 6. Predicted median ventilator and intensive care unit free days among the continuous renal replacement therapy initiation and volume overload phenotypes. Semiparametric ordinal regression models were used to calculate median ventilator (A) and ICU free days (B) across sub-phenotype groups. The models accounted for the nesting of patients within centers via the Huber–White cluster sandwich estimator of variance. The interaction between time to CRRT initiation (≤2 days vs >2 days) and %VO (<10% vs. ≥10%) was assessed and was not significant. The predicted median values were adjusted for no comorbidity, cardiac, respiratory, oncologic, immunologic comorbidities, sepsis at ICU admission and vasoactive inotrope score at CRRT initiation at the most frequent or median level.

A



B