Supplementary Appendix

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

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SUPPLEMENTARY APPENDIX

Balanced Crystalloids versus Saline in Non-critically Ill Adults

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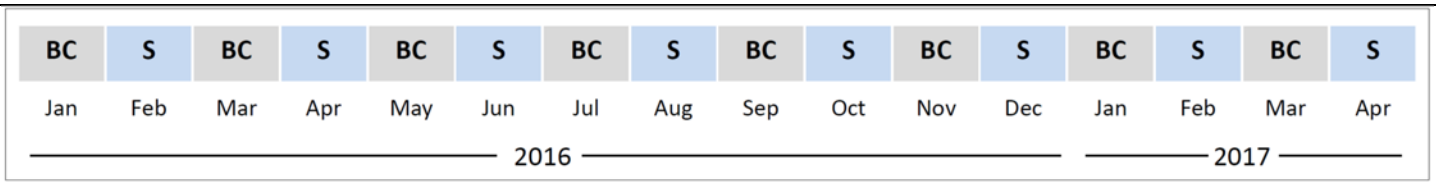
Investigators

In addition to the authors, the following investigators participated in the SALTED trial: All investigators listed below are from Vanderbilt University Medical Center, Nashville, Tennessee - I.D. Jones, S. Russ, R.M. Brown, H.J. Domenico, L. Atchison, M. Felbinger, J. L. Stollings, and M. Knostman.

Figure S1. Schedule of treatment allocation by the cluster multiple-crossover design. All patients in the study emergency department were assigned to the same isotonic crystalloid type, with crossover between balanced crystalloids and saline each month. Additional details about treatment allocation are also described.



BC: balanced crystalloids; S: saline

Topic	Explanation
Patients in the ED at the beginning of the trial	Patients who presented to the ED after midnight on January 1, 2016 were eligible for the trial. Patients who presented to the ED on December 31, 2015 and remained in the ED after midnight were not included in the trial. Clinicians were trained to begin study procedures at midnight, with selection of balanced crystalloids as the isotonic crystalloid of choice for the month of January. Electronic alerts embedded into the order entry system were activated at midnight on January 1, 2016.
Patients in the ED at the end of the trial	Patients who presented to the ED on April 30, 2017 before 23:59 were eligible for the trial. Electronic alerts embedded into the order entry system were turned off at midnight. Patients who were otherwise eligible for the trial who presented to the ED on April 30, 2017 and remained in the ED past midnight into May 1, 2017 were included; crystalloids delivered to these patients in the ED on May 1, 2017 were selected by the treating clinicians without guidance from the study protocol. Ten patients (0.07% of the study population) presented to the ED in the 6 hours before the end of the trial.
Patients in the ED during a crossover	Patients who remained in the ED during a crossover (midnight on the 1st of each month) were analyzed based on the month in which they presented to the ED. For example, patients presenting to the ED on January 31, 2016 who remained in the ED after midnight into February 1, 2016 were analyzed in the balanced crystalloids group. The electronic alerts encouraged saline for all patients in the ED on February 1, 2016; saline delivered to patients on February 1 who presented to the ED on January 31 were considered "off-protocol" during analysis. Therefore, the electronic alerts encouraged "off protocol" crystalloids for patients remaining in the ED during a crossover; this led to some contamination of study intervention in the intention-to-treat analysis. During the trial, 111 patients (0.8% of the study population) presented to the ED during the 6 hours preceding one of the 15 crossovers (ie, between 18:00 and 23:59 on the last day of the month).
Crystalloid selection after admission to a hospital floor	Crystalloid selection after transfer out of the ED into an in-hospital floor bed was not part of the study intervention. Crystalloid selection after admission to a hospital floor bed was based on routine care.
Crystalloid selection after admission to an ICU	Patients admitted from the ED to an ICU were not included in this trial. As part of the companion ICU trial (isotonic Solutions and Major Adverse Renal Events Trial, SMART), crystalloid selection in the ED for patients admitted to an ICU followed the same multiple crossover schedule described here for patients admitted to the floor. Crystalloid selection after ICU admission followed the schedule described in SMART. ICUs that commonly admitted patients from the ED (medical ICU, trauma ICU, and surgical ICU) were on the same crystalloid schedule as the ED.

Figure S2. Flow diagram of patient enrollment.

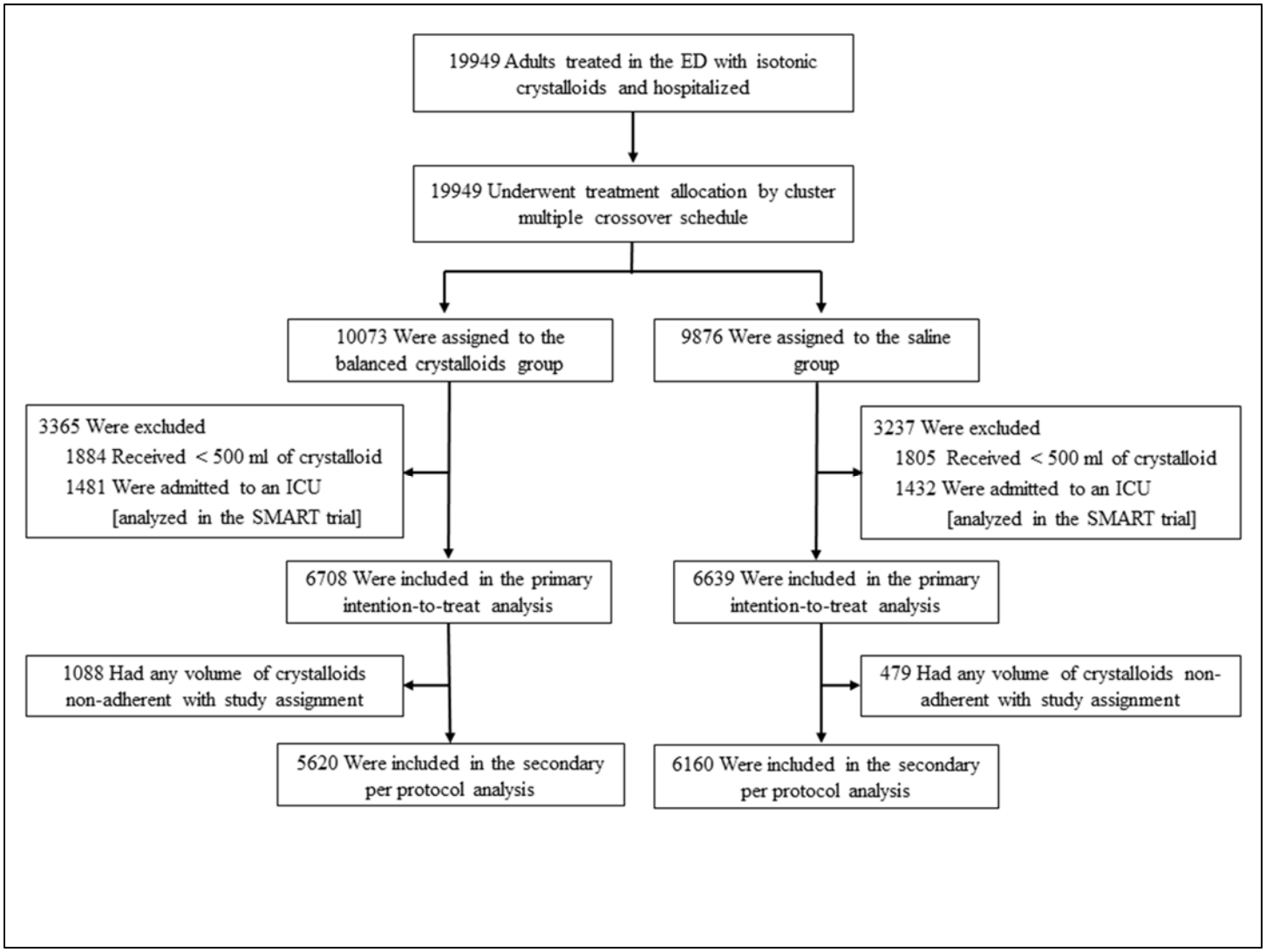


Figure S3. Histograms of total crystalloid volumes administered in the ED by assigned treatment group in the intention-to-treat analysis.

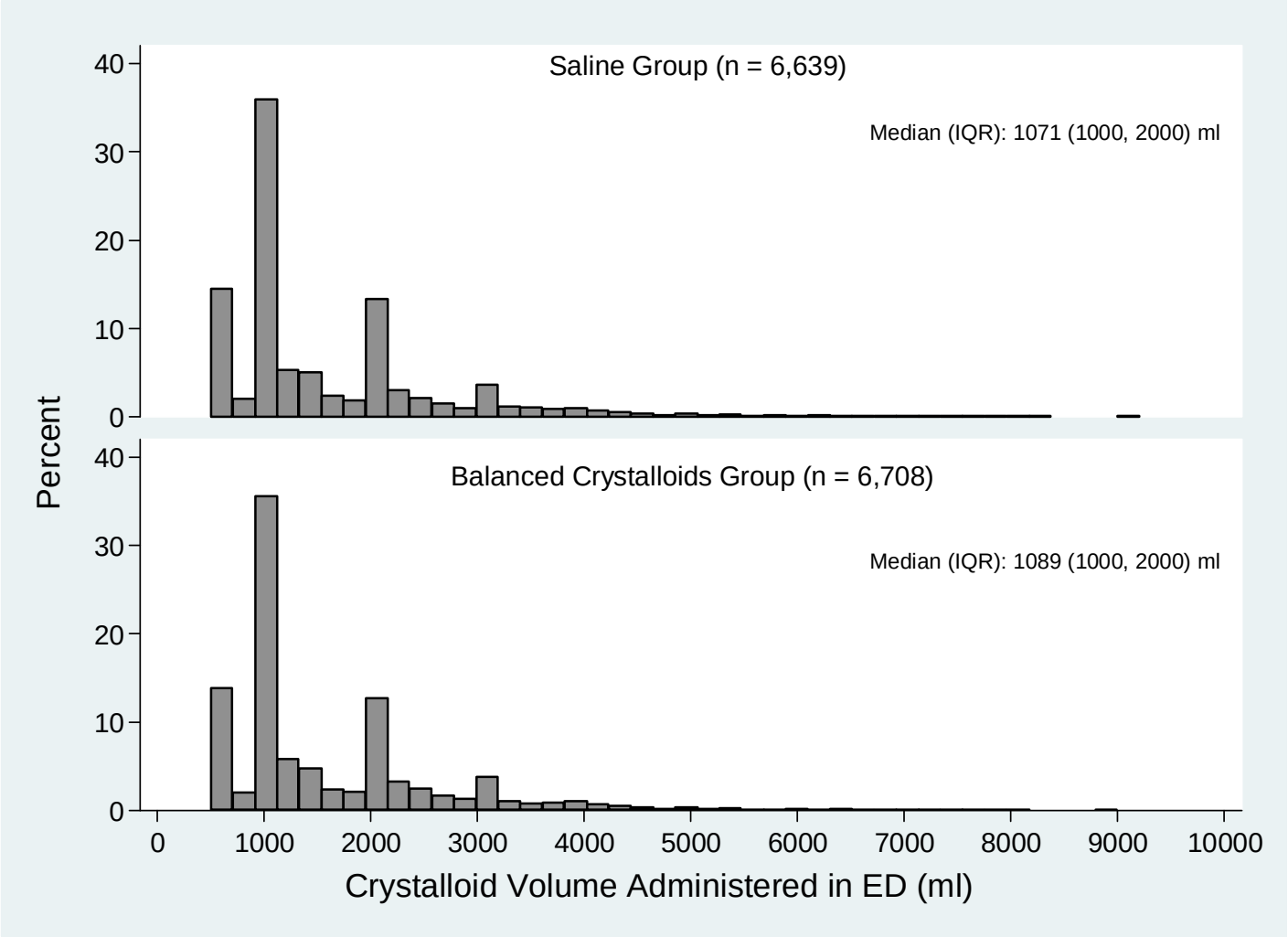


Figure S4. Histograms of hospital-free days to day 28 by assigned treatment group in the intention-to-treat analysis.

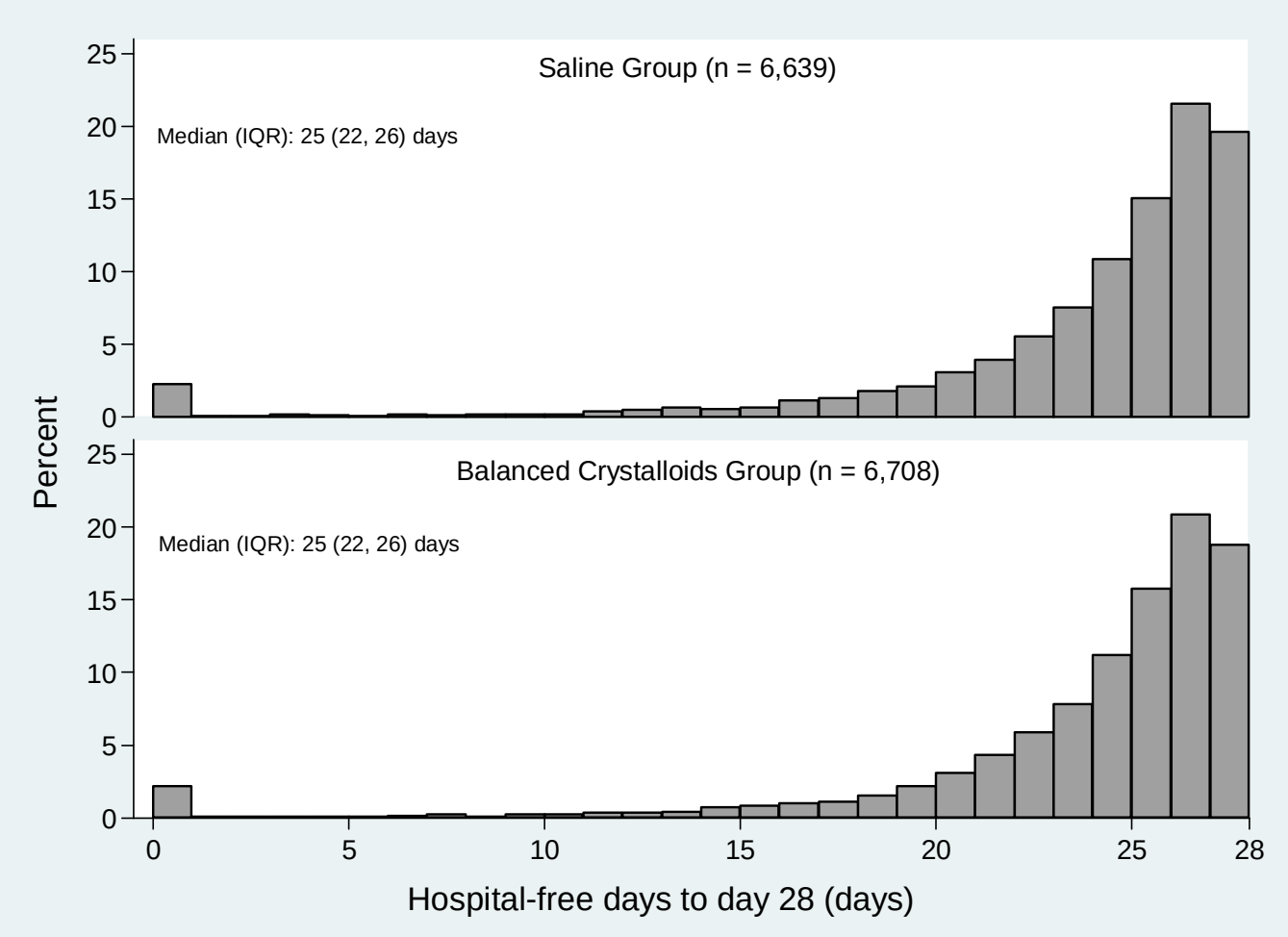


Figure S5. Incidence of Major Adverse Kidney Events within 30 days (MAKE30) and its components, by assigned treatment group in the intention-to-treat analysis. Patients were classified by the most severe component of MAKE30 they fulfilled, with severity ordered from highest to lowest as: death, new renal replacement therapy (RRT), and persistent renal dysfunction with final serum creatinine ≥ 200% of baseline. The displayed p value is an adjusted value for the full MAKE30 outcome adjusted for the following variables: age, sex, race, admitting service, and days elapsed since initiation of the trial.

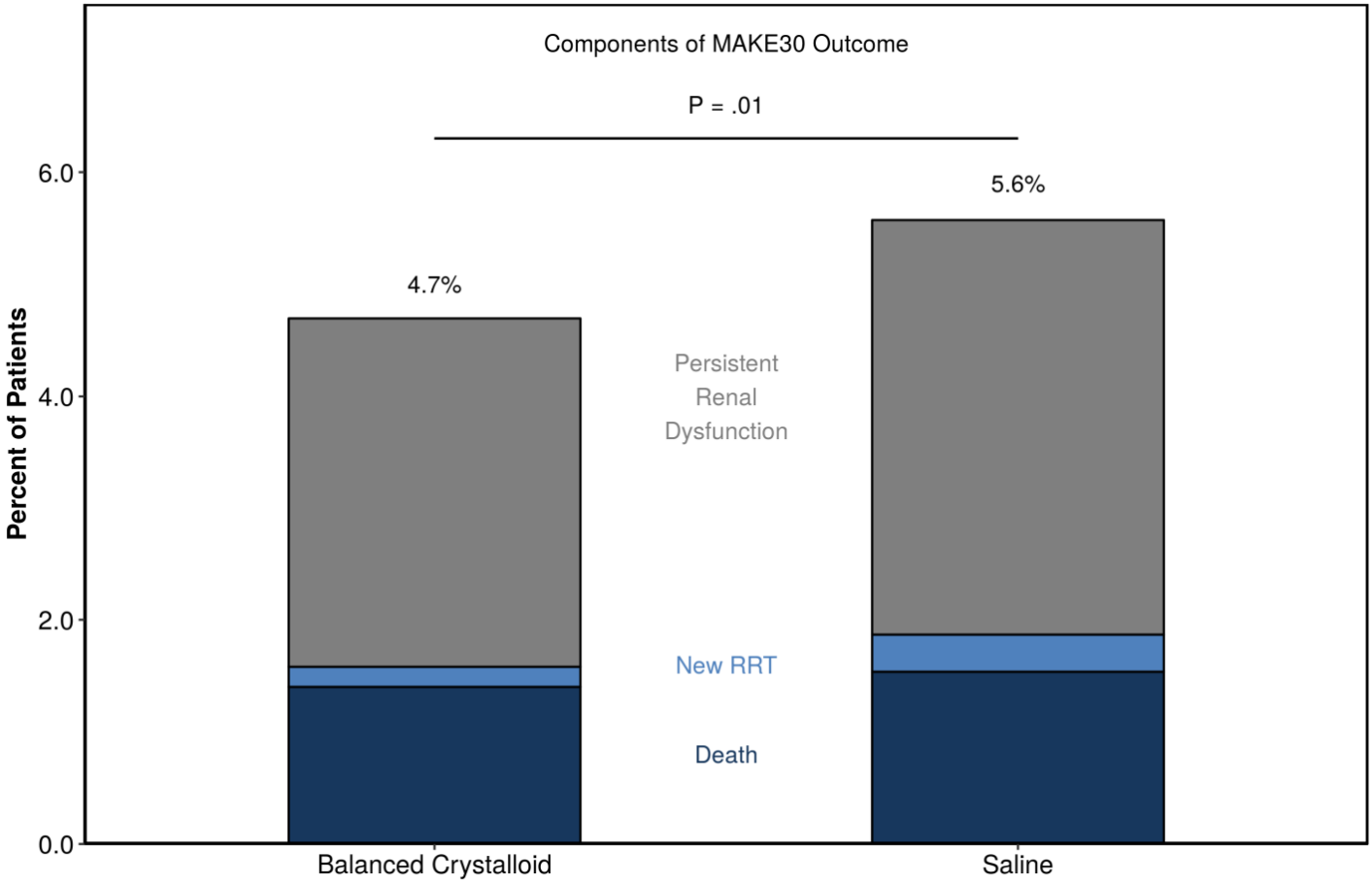


Figure S6. Incidence of Major Adverse Kidney Events within 30 Days (MAKE30) according to volume of isotonic crystalloid received in the emergency department (ED), by fluid type (balanced crystalloids [blue line] vs saline [red line]). Vertical lines represent patient sample sizes along the continuum of volume administration (balanced crystalloids = blue lines along bottom axis; saline = red lines along top axis). The x-axis was truncated at 3000 ml due to the small sample size of patients who received > 3000 ml.

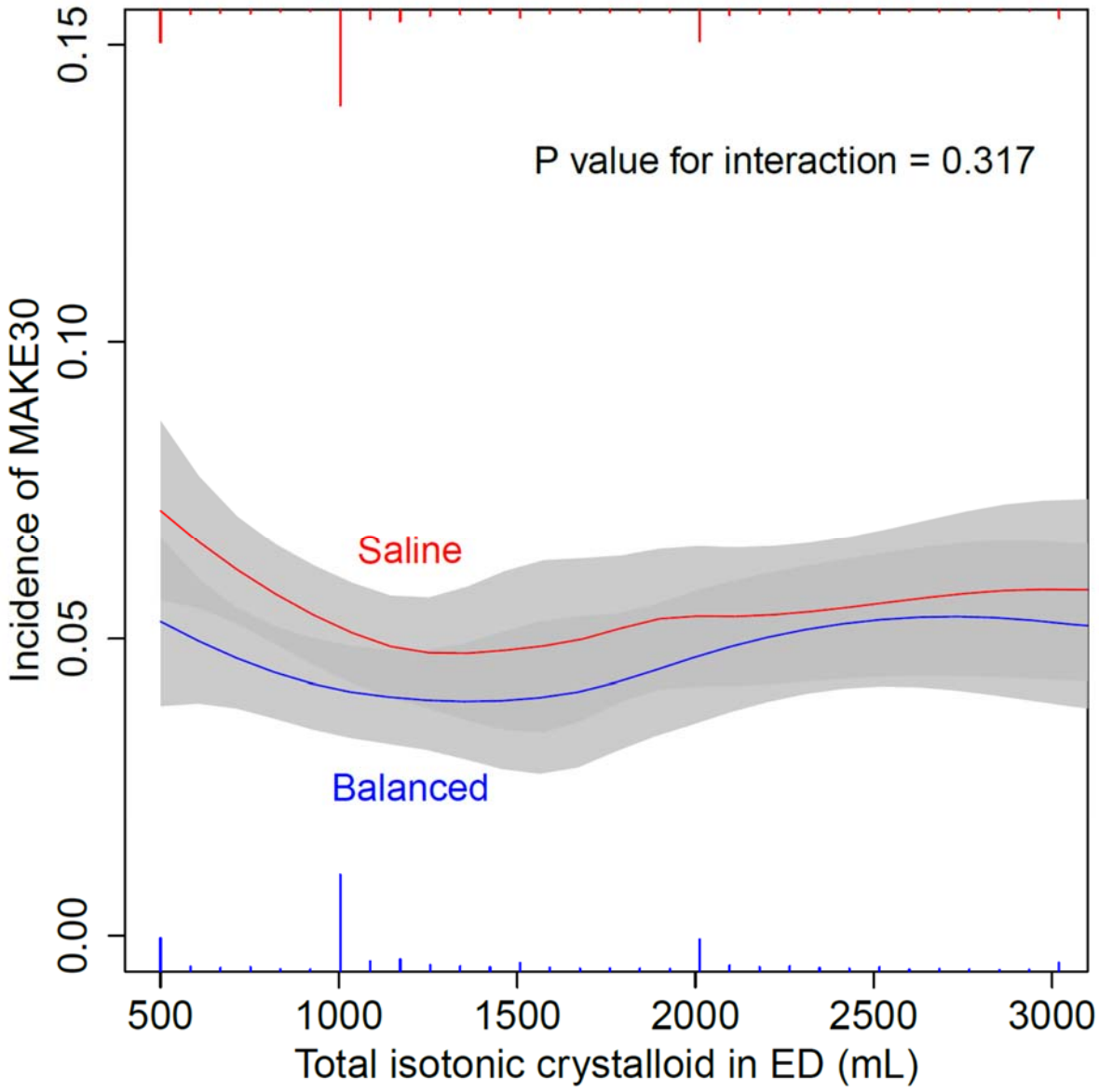


Table S1. Description of Major Adverse Kidney Events within 30 days (MAKE30).

Definition of MAKE30	In this trial, Major Adverse Kidney Events within 30 days (MAKE30) was defined as a composite of death, new renal replacement therapy, or final serum creatinine ≥ 200% of baseline at the earliest of hospital discharge or 30 days after the index ED visit. MAKE30 was a dichotomous outcome. All patients in the trial were eligible for MAKE30. Patients who presented to the ED with end stage renal disease on chronic renal replacement therapy were eligible for MAKE30 only through death. All other patients were eligible for MAKE30 through all three components—death, new renal replacement therapy, and final serum creatinine ≥ 200% of baseline.
Follow-up time for MAKE30	Outcomes were assessed during the index hospitalization following the ED visit in which each patient was enrolled. Hospitalization began at the time of an admission order to an inpatient team. Hospitalization ended at the time of physical departure of the patient from the hospital. The components of MAKE30 were assessed during hospitalization until 30 days following ED presentation. The follow-up period ended at the earliest of death, hospital discharge or day 30. Patients who were discharged or died prior to day 30 had a follow-up period equal to their hospital length of stay. Patients who died or were discharged after day 30 had a follow-up period of 30 days.
Death within MAKE30	Patients met the death component of MAKE30 if they died after hospital admission, prior to hospital discharge, and prior to day 30.
New renal replacement therapy within MAKE30	Patients met the new renal replacement therapy component of MAKE30 if they presented to the ED without end stage renal disease on chronic renal replacement therapy and then started renal replacement therapy after hospital admission, prior to hospital discharge, and prior to day 30. Intermittent hemodialysis, continuous renal replacement therapy, and initiation of peritoneal dialysis were all considered new renal replacement therapy. Patients with end stage renal disease on chronic renal replacement therapy prior to the ED visit were not eligible for the new renal replacement therapy endpoint.
Final serum creatinine ≥ 200% of baseline within MAKE30	Patients met the final serum creatinine ≥ 200% of baseline component of MAKE30 if they presented to the ED without end stage renal disease on chronic renal replacement therapy and then the last serum creatinine value drawn prior to hospital discharge and before day 30 was at least twice the baseline serum value. Baseline creatinine was defined as the lowest recorded value within the electronic medical record at the study institution in the year prior to ED presentation. Patients with no recorded creatinine values in the prior year had a baseline creatinine value calculated assuming normal baseline renal function using the following equation: [creatinine = 0.74 – 0.2 (if female) + 0.08 (if Black) + 0.003 x age (in years)].[1] Patients with end stage renal disease on chronic renal replacement therapy prior to the ED visit were not eligible for the final serum creatinine ≥ 200% of baseline endpoint. Final serum creatinine ≥ 200% of baseline was also called persistent renal dysfunction.
Rationale for MAKE30	Use of MAKE30 as an outcome in this trial was consistent with recommendations from the 2010 taskforce convened by the National Institute of Diabetes and Digestive and Kidney Diseases to discuss trials investigating acute kidney injury.[1,2] For trials evaluating early interventions, such as the intervention used in the current trial (crystalloids in the ED), the taskforce recommended a composite endpoint of death, dialysis, or a sustained loss of kidney function. One recommended option for a definition of sustained loss of kidney function was doubling of baseline serum creatinine. A composite outcome was recommended because of the competing risks of death, new dialysis, and doubling of creatinine. Patients who die early may not progress to dialysis. Patients started on dialysis for acute renal failure may not have persistent doubling of creatinine due to the effects of dialysis. Since publication of these taskforce recommendations, MAKE30 defined with the same criteria as outlined in the current trial has been used as an endpoint in clinical studies.[3,4]

Table S2. Definitions for additional exploratory clinical outcomes.

Outcome	Definition
Hospital length of stay among survivors	Days between ED arrival and hospital discharge among survivors.
Delayed transfer to ICU after initial floor admission	Initial admission from the ED to a hospital ward and then transfer from the hospital ward to an ICU during the index hospitalization.
ICU free days to day 28	Number of days alive and not admitted to an ICU between ED arrival and 28 days later. In-hospital death coded as 0.
Mechanical ventilation	Initiation of invasive or noninvasive mechanical ventilation after ED arrival and before hospital discharge.
Ventilator free days to day 28	Number of days alive and not receiving mechanical ventilation between ED arrival and 28 days later. In-hospital death coded as 0.
Vasopressor use	Initiation of a vasopressor therapy by continuous intravenous infusion after ED arrival and before hospital discharge.
Vasopressor free days to day 28	Number of days alive and not receiving vasopressors between ED arrival and 28 days later. In-hospital death coded as 0.
Peak serum creatinine	Highest serum creatinine (mg/dL) between hospital admission and the earliest of hospital discharge or 30 days after ED arrival. Values at ED arrival (before crystalloid therapy) not included.
Change in serum creatinine from baseline to peak	Difference between peak and baseline serum creatinine values (mg/dL).
Lowest serum bicarbonate < 20 mmol/L	Lowest serum bicarbonate value < 20 mmol/L between hospital admission and the earliest of hospital discharge or 30 days after ED arrival. Values at ED arrival (before crystalloid therapy) not included.
Highest serum bicarbonate > 30 mmol/L	Highest serum bicarbonate value > 30 mmol/L between hospital admission and the earliest of hospital discharge or 30 days after ED arrival. Values at ED arrival (before crystalloid therapy) not included.
Lowest serum chloride < 90 mmol/L	Lowest serum chloride value < 90 mmol/L between hospital admission and the earliest of hospital discharge or 30 days after ED arrival. Values at ED arrival (before crystalloid therapy) not included.
Highest serum chloride > 110 mmol/L	Highest serum bicarbonate value > 110 mmol/L between hospital admission and the earliest of hospital discharge or 30 days after ED arrival. Values at ED arrival (before crystalloid therapy) not included.

Table S3: Additional exploratory outcomes by assigned treatment group in the intention-to-treat analysis.

Outcome	**Balanced (n = 6708)**	**Saline (n = 6639)**	**aOR* (95% CI^)**	**Adjusted p^**
Hospital length of stay among survivors, median (IQR) [days] †	3.0 (1.8, 5.3)	3.0 (1.8, 5.3)	1.03 (0.97, 1.09)	0.37
Delayed transfer to ICU after initial floor admission, n (%)	543 (8.1)	517 (7.8)	1.03 (0.91, 1.07)	0.64
ICU free days to day 28	28 (28, 28)	28 (28, 28)	0.98 (0.87, 1.11)	0.78
Mechanical ventilation, n (%)	127 (1.9)	135 (2.0)	0.94 (0.73, 1.20)	0.60
Ventilator free days to day 28	28 (28, 28)	28 (28, 28)	1.08 (0.88, 1.32)	0.48
Vasopressor use, n (%)	132 (2.0)	134 (2.0)	0.97 (0.76, 1.25)	0.84
Vasopressor free days to day 28	28 (28, 28)	28 (28, 28)	1.01 (0.83, 1.24)	0.91
Peak serum creatinine, median (IQR) [mg/dL] ‡	0.90 (0.74, 1.28)	0.89 (0.74, 1.25)	1.03 (0.96, 1.10	0.43
Change in serum creatinine from baseline to peak, median (IQR) [mg/dL] ‡	0.13 (-0.03, 0.36)	0.12 (-0.04, 0.34)	1.04 (0.97, 1.11)	0.28
Lowest serum bicarbonate < 20 mmol/L, n (%)	1668 (24.9)	1859 (28.0)	0.85 (0.79, 0.92)	< 0.01
Highest serum bicarbonate > 30 mmol/L, n (%)	397 (5.9)	347 (5.2)	1.14 (0.98, 1.32)	0.09
Lowest serum chloride < 90 mmol/L, n (%)	124 (1.9)	128 (1.9)	0.93 (0.73, 1.20)	0.59
Highest serum chloride > 110 mmol/L, n (%)	1020 (15.2)	1280 (19.3)	0.77 (.071, 0.85)	<0.01

*Multivariable models adjusted for: age, sex, race, admitting service, time (days since trial initiation).

^ Confidence intervals and p-values for exploratory outcomes were not adjusted for multiplicity. With 13 exploratory outcomes, there was a 49% chance of observing a p-value <0.05 for least one exploratory outcome by chance alone.

† Patients who died during the hospitalization (95 in balanced group and 105 in saline group) were not eligible for length of hospital stay among survivors. Hence, sample sizes for this outcome were: balanced 6613 and saline 6534.

‡ Patients with end stage renal disease on chronic renal replacement therapy prior to ED presentation (126 in balance group and 109 in saline group) were not eligible for the following outcomes: peak serum creatinine, change in serum creatinine from baseline to peak. Hence, sample sizes for these outcomes were: balanced 6582 and saline 6530.

Table S4. Sensitivity analyses conducted for hospital-free days to 28 days, Major Adverse Kidney Events within 30 Days (MAKE30), acute kidney injury, and in-patient mortality. Four sensitivity analyses were conducted: 1) adjustment for period effect; 2) population limited to patients without end stage renal disease at ED presentation; 3) population limited to patients with a measured baseline serum creatinine; 4) population limited to the first ED visit among unique patients in the trial.

Population / Outcome	**Balanced**	**Saline**	**aOR* (95% CI)**	**Adjusted p**
Adjustment for period effect (full study population)†	n = 6708	n = 6639		
Hospital free days to day 28, median (IQR) [days]	25 (22, 26)	25 (22, 26)	0.98 (0.90, 1.06)	0.53
Major Adverse Kidney Event within 30 days, n (%)	315 (4.7)	370 (5.6)	0.82 (0.70, 0.95)	0.01
Acute kidney injury (KDIGO stage ≥ II), n (%)‡	528 (8.0)	560 (8.6)	0.91 (0.80, 1.03)	0.14
In-hospital mortality during entire hospitalization, n (%)	95 (1.4)	105 (1.6)	0.88 (0.66, 1.16)	0.36
Patients without end stage renal disease at ED presentation	n = 6582	n = 6530		
Hospital free days to day 28, median (IQR) [days]	25 (22, 26)	25 (22, 26)	0.97 (0.92, 1.03)	0.36
Major Adverse Kidney Event within 30 days, n (%)	314 (4.8)	364 (5.6)	0.83 (0.71, 0.97)	0.02
Acute kidney injury (KDIGO stage ≥ II), n (%)	528 (8.0)	560 (8.6)	0.91 (0.80, 1.03)	0.14
In-hospital mortality during entire hospitalization, n (%)	94 (1.4)	99 (1.5)	0.92 (0.69, 1.22)	0.55
Patients with measured baseline creatinine	n = 4405	n = 4276		
Hospital free days to day 28, median (IQR) [days]	25 (22, 26)	25 (22, 26)	0.96 (0.89, 1.03)	0.26
Major Adverse Kidney Event within 30 days, n (%)	229 (5.2)	266 (6.2)	0.81 (0.68, 0.98)	0.03
Acute kidney injury (KDIGO stage ≥ II), n (%)‡†	417 (9.7)	413 (9.9)	0.97 (0.84, 1.12)	0.66
In-hospital mortality during entire hospitalization, n (%)	62 (1.4)	73 (1.7)	0.79 (0.56, 1.11)	0.18
First ED visit among unique patients in trial	n = 5364	n = 5209		
Hospital free days to day 28, median (IQR) [days]	25 (23, 26)	25 (23, 26)	0.96 (0.89, 1.02	0.20
Major Adverse Kidney Event within 30 days, n (%)	237 (4.4)	264 (5.1)	0.84 (0.70, 1.00)	0.05
Acute kidney injury (KDIGO stage ≥ II), n (%)‡†	378 (7.2)	404 (7.9)	0.87 (0.75, 1.01)	0.07
In-hospital mortality during entire hospitalization, n (%)	81 (1.5)	83 (1.6)	0.93 (0.68, 1.27)	0.64

*All multivariable models adjusted for: age, sex, race, admitting service, time (days since trial initiation). In the analysis adjusting for period effect, a variable for period (ie, study month) was also included in the multivariable models.

†Description of models adjusting for period effect: For hospital free days, a proportional odds regression model was used with a cluster sandwich covariance estimator to adjust for within-period correlation. For the dichotomous outcomes (MAKE30, acute kidney injury, and in-hospital mortality), generalized linear mixed-effects models with period as a random effect were used.

‡Patients with end stage renal disease on chronic renal replacement therapy prior to ED presentation were not eligible for the following outcomes and were removed from the denominator for calculation of percentages: new renal replacement therapy within 30 days, final creatinine within 30 days ≥ 200% of baseline, acute kidney injury KDIGO stage ≥ II.

Table S5. Baseline characteristics for patients in the per-protocol analysis (patients who exclusively received the assigned crystalloid type in the ED).

			Balanced (n = 5620)	**Saline (n = 6160)**
Age, median (IQR) [years]			53 (36, 67)	54 (37, 67)
Female, n (%)			2976 (53.0)	3132 (50.8)
Race, n (%)				
	White		4330 (77.1)	4796 (77.9)
	Black		1111 (19.8)	1179 (19.1)
	Other		179 (3.2)	185 (3.0)
Elixhauser Comorbidity Index, median (IQR)			7 (3, 15)	7 (2, 14)
Admission service, n (%)				
	Medicine services			
		General medicine	3975 (70.7)	4464 (72.5)
		Cardiology	256 (4.6)	320 (5.2)
		Neurology	84 (1.5)	140 (2.3)
	Surgery services			
		General surgery	1056 (18.8)	1012 (16.4)
		Trauma	249 (4.4)	224 (3.6)
Baseline serum creatinine, median (IQR) [mg/dL]			0.86 (0.72, 0.96)	0.84 (0.70, 0.94)
Kidney function at ED arrival				
	ED serum creatinine, mean (St Dev) [mg/dL]		1.25 (1.24)	1.32 (1.40)
	Serum creatinine, median (IQR) [mg/dL]		0.92 (0.77, 1.27)	0.94 (0.77, 1.33)
	Serum creatinine ≥ 1.5 mg/dL, n (%)		930 (16.6)	1168 (19.0)
	End Stage Renal Disease on chronic renal replacement therapy, n (%)		89 (1.6)	107 (1.7)
	Acute kidney injury KDIGO stage ≥II, n (%)*		469 (8.5)	587 (9.7)
Serum electrolytes at ED arrival, median (IQR)				
	Sodium [mmol/L]		138 (135, 140)	138 (135, 140)
	Chloride [mmol/L]		104 (100, 106)	104 (100, 107)
	Bicarbonate [mmol/L]		23 (21, 25)	23 (21, 25)
	Blood Urea Nitrogen [mg/dL]		15 (10, 22)	15 (11, 22)

* Patients with end stage renal disease on chronic renal replacement therapy at the time of ED arrival were not eligible for acute kidney injury; hence, sample sizes for patients eligible for acute kidney injury at ED arrival were: balanced: 5531; saline: 6053.

Table S6. Clinical outcomes by treatment group in the per-protocol analysis (patients who exclusively received the assigned crystalloid type in the ED).

Outcome		**Balanced (n = 5620)**	**Saline (n = 6160)**	**aOR* (95% CI)**	**Adjusted p**
Hospital free days to day 28, median (IQR) [days]		25 (23, 26)	25 (22, 26)	1.01 (0.95, 1.08)	0.74
Major Adverse Kidney Event within 30 days, n (%)		239 (4.3)	343 (5.6)	0.76 (0.64, 0.91)	< 0.01
	Death	78 (1.4)	96 (1.6)	0.89	
	New renal replacement therapy†	15 (0.3)	28 (0.5)	0.57	
	Final creatinine ≥ 200% of baseline†	183 (3.3)	273 (4.5)	0.72	
Acute kidney injury KDIGO stage ≥ II, n (%)†		399 (7.2)	518 (8.6)	0.82 (0.72, 0.94)	0.01
In-hospital mortality during entire hospitalization, n (%)		79 (1.4)	99 (1.6)	0.88 (0.65, 1.18)	0.39

*Multivariable models adjusted for: age, sex, race, admitting service, time (days since trial initiation)

† Patients with end stage renal disease on chronic renal replacement therapy prior to ED presentation (89 in balance group and 107 in saline group) were not eligible for the following outcomes: new renal replacement therapy within 30 days, final creatinine within 30 days ≥ 200% of baseline, acute kidney injury KDIGO stage ≥ II. Hence, sample sizes for these outcomes were: balanced 5531 and 6053 saline.

Supplementary Appendix References:

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2. Molitoris BA, Okusa MD, Palevsky PM, et al. Design of clinical trials in AKI: a report from an NIDDK workshop. Trials of patients with sepsis and in selected hospital settings. Clin J Am Soc Nephrol CJASN 2012;7(5):856–60.
3. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care Lond Engl 2013;17(1):R25.
4. Semler MW, Wanderer JP, Ehrenfeld JM, et al. Balanced crystalloids versus saline in the intensive care unit: The SALT randomized trial. Am J Resp Crit Care Med. 2017; 195: 1362-1372.