Supplementary Online Content

Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. *JAMA*. doi:10.1001/jama.2015.12334.

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

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eMethods.

Description of study Intensive Care Units

Center 1 is a tertiary referral ICU that manages all medical and surgical patients except for complex pediatric patients, solid organ transplants (except renal transplants), and patients requiring extracorporeal membrane oxygenation or other advanced mechanical cardiac support

Center 2 is a tertiary referral ICU that predominantly manages adult cardiothoracic and vascular surgical patients, including patients who require extracorporeal membrane oxygenation and other advanced mechanical cardiac support and patients after heart and lung transplants. This ICU also manages some medical patients but does not manage pediatric patients, neurosurgical patients, trauma patients, plastic surgery patients, or major burns.

Center 3 is a tertiary referral ICU that manages all medical and surgical patients except for pediatric patients, patients requiring cardiothoracic surgery, patients requiring extracorporeal membrane oxygenation or other advanced mechanical cardiac support, isolated spinal cord injury patients, plastic surgery patients, and major burns.

Center 4 is a tertiary referral Intensive Care Unit (ICU) that manages all medical and surgical patients except for complex pediatric patients, solid organ transplants (except renal transplants), patients requiring extracorporeal membrane oxygenation or other advanced mechanical cardiac support, isolated spinal cord injury patients, plastic surgery patients, and major burns.

Cointerventions

Apart from randomized study fluid, all other aspects of patient care including the use of non-study crystalloids (e.g. 5% dextrose), colloids, blood products, nutrition, cardiovascular monitoring, pharmacological, cardiorespiratory, and renal support were conducted at the discretion of the treating clinician.

Reporting of ethnicity

Ethnicity was determined by research coordinators who reviewed patients' hospital admission demographic data or asked patients or their next of kin.

Data and study management

Trained research coordinators collected data at each site and entered them into a web-based database (Spinnaker Software, Wellington, New Zealand). Data monitoring and source data verification were conducted according to a pre-specified monitoring plan. An independent Data and Safety Monitoring Committee oversaw the conduct of the study according to a charter that was agreed before the trial commenced.

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Additional details of the statistical analyses

Binomial outcomes were modelled at an individual patient level using mixed generalised linear modelling (PROC GLIMMIX) using a binomial distribution and a logit link function with the most appropriate covariance structures determined based on the generalised chi-square statistic. Main effects were fitted for treatment and sequence with patients nested within sites and sites crossing over, not individual patients. Additional sensitivity analyses adjusting for baseline covariates (Acute Physiology And Chronic Health Evaluation (APACHE)-III admission diagnosis, age, ICU admission source, and APACHE-II score) were also performed with calibration determined at an individual hospital level using Hosmer-Lemeshow statistics. Delta creatinine was additionally adjusted for the baseline serum creatinine level. Heterogeneity across sites was determined by fitting interactions between treatment and site.

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eTable 1. Composition of study fluids

	Concentration (mEq/L)	
Electrolyte	**Buffered crystalloid solution[a]**	**0.9% Saline**
Sodium	140	154
Chloride	98	154
Acetate	27	0
Gluconate	23	0
Potassium	5	0
Magnesium	3	0

[a] The buffered crystalloid used in the study was Plasma-Lyte 148® (Baxter Healthcare Corporation, Deerfield, IL, USA)

eTable 2. Intravenous fluids and blood products administered in the 24 hours prior to enrollment

	Volume of fluid administered (mL) and proportion of patients receiving fluid– mean ± SD; median [IQR]; no. (%)	
Fluid	**Buffered crystalloid group**	**Saline group**
Plasma-Lyte 148 ®	1748 ± 1964; 1200 [0-3000]; 726 (63)	1649 ± 1841;1000 [0-3000]; 675 (61)
0.9% saline	551 ± 1157; 0 [0-875]; 343 (30)	549 ± 1098; 0 [0-1000]; 351 (32)
5% dextrose	47 ± 212; 0 [0-0]; 141 (12)	42 ± 196; 0 [0-0];124 (11)
Pediatric maintenance fluids[a]	0.1 ± 4; 0 [0-0]; 1 (0)	0.3 ± 7; 0 [0-0]; 2 (0)
Other crystalloids	385 ± 1155; 0 [0-0]; 181 (16)	361 ± 1081; 0 [0-0]; 189 (18)
4% albumin	41 ± 253; 0 [0-0]; 40 (3)	34 ± 254; 0 [0-0]; 31 (3)
20% albumin	20 ± 62; 0 [0-0]; 115 (10)	20 ± 83; 0 [0-0]; 98 (9)
Gelofusine ®	13 ±137; 0 [0-0]; 17 (1)	7 ± 68; 0 [0-0]; 15 (1)
Voluven or Volulyte ®	1.7 ± 29; 0 [0-0]; 4 (0)	1.6 ± 34; 0 [0-0]; 3 (0)
Other colloids	0.3 ± 11; 0 [0-0]; 1 (0)	1.6 ± 53; 0 [0-0]; 1 (0)
Blood product		
Packed red cells	149 ± 703; 0 [0-0]; 165 (14)	122 ± 479; 0 [0-0]; 158 (14)
Fresh frozen plasma	91 ± 557; 0 [0-0]; 104 (9)	77 ± 355; 0 [0-0]; 93 (8)
Platelets	51 ± 224; 0 [0-0]; 103 (9)	43 ± 179; 0 [0-0]; 88 (8)
Cryoprecipitate	20 ± 132; 0 [0-0]; 66 (6)	17 ± 81; 0 [0-0]; 63 (6)

[a] 'Pediatric maintenance fluids' were 10% dextrose + 72mmol/L sodium chloride in 500ml + 20mmol/L potassium chloride (for children <6 months); 5% dextrose + 72 mmol/L sodium chloride + 20mmol/L potassium chloride (for children 6 months to 5 years); 2.5% dextrose + 36 mmol/L sodium chloride + 10-20mmol/L (for children >5 years to 16 years).

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eTable 3. Study fluids administered

Fluid	Volume of fluid administered (mL) and proportion of patients receiving fluid– mean ± SD; median [IQR]; no. / total no. (%)	
	Buffered crystalloid group	**Saline group**
Plasma-Lyte 148 (study fluid)		
Day 0[a]	1711 ± 1385; 1250 [650-2500] 1152/1152 (100)	1 ± 45; 0 [0-0] 1/1110 (0)
Day 1	554 ± 1088; 40 [0-780] 562/1102 (51)	0 ± 15; 0 [0-0] 1/1056 (1)
Day 2	285 ± 606; 0 [0-320] 199/530 (38)	0 ± 0; 0 [0-0] 0/494 (0)
Day 3	157 ± 382; 0 [0-102] 89/323 (28)	0 ± 0; 0 [0-0] 0/300 (0)
Day 4 to 90	1285 ± 4590; 0 [0-850] 83/214 (39)	0 ± 0; 0 [0-0] 0/197 (0)
Total	2655 ± 3052; 2000 [1000-3500]	1.8 ± 60; 0 [0-0]
0.9% saline (study fluid)		
Day 0[a]	0 ± 0; 0 [0-0] 0/1152 (0)	1694 ± 1292; 1410 [750-2280] 1105/1110 (100)
Day 1	0 ± 1.5; 0 [0-0] 1/1152 (0)	564 ± 890; 95 [0-875] 572/1056 (54)
Day 2	0 ± 0; 0 [0-0] 0/530 (0)	295 ± 609; 0 [0-440] 176/494 (36)
Day 3	0 ± 0; 0 [0-0] 0/323 (0)	202 ± 542; 0 [0-85] 82/300 (27)
Day 4 to 90	2 ± 34; 0 [0-0] 1/214 (0)	777 ± 1615; 0 [0-760] 85/197 (43)
Total	0.5 ± 15; 0 [0-0]	2554 ± 2120; 2000 [1000-3250]

[a] Day 0 is the day of enrollment

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eTable 4. Non-study fluids administered

Fluid	Volume of fluid administered (mL) and proportion of patients receiving fluid– mean ± SD; median (IQR); no. / total no. (%)	
	Buffered crystalloid group	Saline group
Plasma-Lyte 148 (open label)		
Day 0[a]	27 ± 205; 0 [0-0]; 24/1152 (2)	24 ± 216; 0 [0-0]; 24/1110 (2)
Day 1	17 ± 160; 0 [0-0]; 19/1102 (2)	25 ± 269; 0 [0-0]; 16/1056 (2)
Day 2	7 ± 104; 0 [0-0]; 4/530 (1)	12 ± 170; 0 [0-0]; 4/494 (1)
Day 3	14 ± 175; 0 [0-0]; 5/323 (2)	25 ± 209; 0 [0-0]; 5/300 (2)
Day 4 to 90	126 ± 1761; 0 [0-0]; 2/214 (1)	83 ± 523; 0 [0-0];9/197 (5)
0.9% saline (open label)		
Day 0[a]	23 ± 221; 0 [0-0]; 24/1152 (2)	21 ± 158; 0 [0-0]; 34/1110 (3)
Day 1	14 ± 158; 0 [0-0]; 19/1102 (2)	11 ± 111; 0 [0-0]; 22/1058 (2)
Day 2	8 ± 69; 0 [0-0]; 10/530 (2)	17 ± 149; 0 [0-0]; 9/494 (2)
Day 3	8 ± 85; 0 [0-0]; 4/323 (1)	13 ± 150; 0 [0-0]; 5/300 (2)
Day 4 to 90	93 ± 764; 0 [0-0]; 8/214 (4)	37 ± 207; 0 [0-0]; 9/197 (5)
5% dextrose		
Day 0[a]	146 ± 343; 0 [0-66]; 301/1152 (26)	141 ± 330; 0 [0-40]; 283/1110 (25)
Day 1	154 ± 371; 0 [0-0]; 274/1102 (25)	148 ± 365; 0 [0-0]; 249/1056 (24)
Day 2	103 ± 331; 0 [0-0]; 115/530 (22)	74 ± 243; 0 [0-0]; 89/494 (18)
Day 3	50 ± 214; 0 [0-0]; 42/323 (13)	48 ± 194; 0 [0-0]; 35/300 (12)
Other crystalloids[b]		
Day 0[a]	36 ± 196; 0 [0-0]; 66/1152 (6)	47 ± 302; 0 [0-0]; 65/1110 (6)
Day 1	56 ± 300; 0 [0-0]; 73/1102 (7)	65 ± 314; 0 [0-0]; 75/1056 (7)
Day 2	69 ± 412; 0 [0-0]; 45/530 (8)	89 ± 521; 0 [0-0]; 50/494 (10)
Day 3	87 ± 535; 0 [0-0]; 26/323 (8)	76 ± 588; 0 [0-0]; 26/300 (9)
4% albumin		
Day 0[a]	135 ± 459; 0 [0-0]; 159/1152 (14)	113 ± 384; 0 [0-0]; 137/1110 (12)
Day 1	77 ± 303; 0 [0-0]; 100/1102 (9)	60 ± 270; 0 [0-0]; 74/1056 (7)
Day 2	36 ± 172; 0 [0-0]; 29/530 (5)	26 ± 187; 0 [0-0]; 16/494 (3)
Day 3	22 ± 167; 0 [0-0]; 9/323 (3)	23 ± 163; 0 [0-0]; 12/300 (4)
20% albumin		
Day 0[a]	1 ± 10; 0 [0-0]; 5/1152 (0)	2 ± 22; 0 [0-0]; 11/1110 (1)
Day 1	3 ± 27; 0 [0-0]; 21/1102 (2)	3 ± 27; 0 [0-0]; 17/1056 (2)
Day 2	2 ± 16; 0 [0-0]; 6/530 (1)	4 ± 32; 0 [0-0]; 11/494 (2)
Day 3	1 ± 14; 0 [0-0]; 4/323 (1)	6 ± 40; 0 [0-0]; 8/300 (3)
Gelofusine®		
Day 0[a]	0 ± 0; 0 [0-0]; 0/1152 (0)	0 ± 15; 0 [0-0]; 1/1110 (0)
Day 1	0 ± 0; 0 [0-0]; 0/1102 (0)	0 ± 0; 0 [0-0]; 0/1056 (0)
Day 2	0 ± 0; 0 [0-0]; 0/530 (0)	0 ± 0; 0 [0-0]; 0/494 (0)
Day 3	0 ± 0; 0 [0-0]; 0/323 (0)	0 ± 0; 0 [0-0]; 0/300 (0)
Voluven® or volulyte®		
Day 0[a]	0 ± 0; 0 [0-0]; 0/1152 (0)	2 ± 60; 0 [0-0]; 1/1110 (0)
Day 1	0 ± 0; 0 [0-0]; 0/1102 (0)	0 ± 0; 0 [0-0]; 0/1056 (0)
Day 2	0 ± 0; 0 [0-0]; 0/530 (0)	0 ± 0; 0 [0-0]; 0/494 (0)
Day 3	0 ± 0; 0 [0-0]; 0/323 (0)	0 ± 0; 0 [0-0]; 0/300 (0)
Other colloids		
Day 0[a]	2 ± 48; 0 [0-0]; 2/1152 (0)	3 ± 68; 0 [0-0]; 2/1110 (0)
Day 1	4 ± 108; 0 [0-0]; 2/1102 (0)	4 ± 97; 0 [0-0]; 4/1056 (0)
Day 2	6 ± 148; 0 [0-0]; 1/530 (0)	10 ± 145; 0 [0-0]; 4/494 (1)
Day 3	13 ± 199; 0 [0-0]; 2/323 (1)	30 ± 321; 0 [0-0]; 4/300 (1)

[a] Day 0 is the day of enrollment

[b] Other crystalloids included 5% dextrose, 3% sodium chloride, 23.4% sodium chloride, 0.45% sodium chloride, and 4% dextrose + 0.18% sodium chloride.

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eTable 5. Blood products administered

	Volume of blood product administered (mL) and proportion of patients receiving blood product– mean ± SD; median (IQR); no. / total no. (%)	
Blood product	**Buffered crystalloid group**	**Saline group**
Packed red blood cells		
Day 0[a]	54 ± 220; 0 [0-0]; 103/1152 (9)	30 ± 144; 0 [0-0]; 75/1110 (7)
Day 1	37 ± 143; 0 [0-0]; 93/1102 (8)	27 ± 176; 0 [0-0]; 64/1056 (6)
Day 2	36 ± 122; 0 [0-0]; 54/530 (10)	37 ± 258; 0 [0-0]; 39/494 (8)
Day 3	39 ± 199; 0 [0-0]; 29/323 (9)	45 ± 277; 0 [0-0]; 26/300 (9)
Fresh frozen plasma		
Day 0[a]	33 ± 171; 0 [0-0]; 59/1152 (5)	20 ± 131; 0 [0-0]; 36/1110 (3)
Day 1	8 ± 74; 0 [0-0]; 14/1102 (1)	9 ± 128; 0 [0-0]; 10/1056 (1)
Day 2	6 ± 65; 0 [0-0]; 5/530 (1)	7 ± 78; 0 [0-0]; 5/494 (1)
Day 3	8 ± 100; 0 [0-0]; 3/323 (1)	13 ± 120; 0 [0-0]; 5/300 (2)
Platelets		
Day 0[a]	21 ± 102; 0 [0-0]; 56/1152 (5)	13 ± 80; 0 [0-0]; 36/1110 (3)
Day 1	4 ± 53; 0 [0-0]; 8/1102 (1)	6 ± 67; 0 [0-0]; 12/1056 (1)
Day 2	5 ± 46; 0 [0-0]; 8/530 (2)	12 ± 116; 0 [0-0]; 10/494 (2)
Day 3	8 ± 61; 0 [0-0]; 6/323 (2)	17 ± 132; 0 [0-0]; 9/300 (3)
Cryoprecipitate		
Day 0[a]	5 ± 42; 0 [0-0]; 24/1152 (2)	3 ± 30; 0 [0-0]; 14/1110 (1)
Day 1	2 ± 47; 0 [0-0]; 5/1102 (0)	1 ± 23; 0 [0-0]; 4/1056 (0)
Day 2	0 ± 0; 0 [0-0]; 0/530 (0)	1 ± 14; 0 [0-0]; 1/494 (0)
Day 3	0 ± 5; 0 [0-0]; 1/323 (1)	1 ± 17; 0 [0-0]; 1/300 (0)

[a] Day 0 is the day of enrollment

eTable 6. Sensitivity analysis for missing serum creatinine data

	Acute kidney injury of failure[a] n/N (%)		
Assumption	**Buffered crystalloid group**	**Saline group**	**Relative Risk (95% CI)**
Assume none have acute kidney injury	102/1152 (8.9)	94/1110 (8.5)	1.05 (0.78 to 1.41)
Assume all have acute kidney injury	187/1152 (16.2)	179/1110 (16.1)	1.01 (0.80 to 1.26)

[a] defined as a degree of renal dysfunction of Injury or greater based on the use of a five-category scoring system to evaluate Risk, Injury, Failure, Loss, and End stage renal failure (RIFLE) based solely on defined thresholds of serum creatinine

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eTable 7. Cause-specific in hospital mortality within the 90-day follow-up period

	Buffered crystalloid group	Saline group	Relative Risk (95% CI)	P value
Categories – no. / total no. (%)				
Bleeding	3/1152 (0.3)	2/1110 (0.2)	1.45 (0.24 to 8.63)	1.00
Cardiac	14/1152 (1.2)	20/1110 (1.8)	0.67 (0.34 to 1.33)	0.30
Cerebral	32/1152 (2.8)	39/1110 (3.5)	0.79 (0.5 to 1.25)	0.34
Sepsis	30/1152 (2.6)	23/1110 (2.1)	1.26 (0.73 to 2.15)	0.41
Other	8/1152 (0.7)	11/1110 (1)	0.7 (0.28 to 1.74)	0.50

eTable 8. Raw and Adjusted analyses with patients nested within location

Outcome	OR 95% CI (unadjusted)	P Value	OR 95% CI (nested[a])	P Value	OR 95% CI (nested and adjusted[b])	P Value
Acute kidney injury or failure	1.05 (0.78 to 1.41)	0.76	1.05 (0.78 to 1.41)	0.76	1.01 (0.74 to 1.39)	0.95
RIFLE-R	1.12 (0.85 to 1.47)	0.43	1.12 (0.19 to 6.65)	0.57	1.13 (0.19 to 6.83)	0.54
RIFLE-I	0.77 (0.51 to 1.14)	0.19	0.76 (0.06 to 10.07)	0.41	0.74 (0.49 to 1.12)	0.15
RIFLE-F	1.46 (0.95 to 2.25)	0.08	1.48 (0.96 to 2.29)	0.08	1.45 (0.9 to 2.32)	0.12
KDIGO-1	0.95 (0.76 to 1.19)	0.66	0.95 (0.23 to 3.98)	0.74	0.98 (0.23 to 4.17)	0.89
KDIGO-2	0.89 (0.58 to 1.37)	0.60	0.88 (0.06 to 13.93)	0.67	0.87 (0.57 to 1.35)	0.54
KDIGO-3	1.03 (0.71 to 1.49)	0.88	1.04 (0.72 to 1.51)	0.83	0.99 (0.66 to 1.48)	0.96
RRT in ICU	0.96 (0.61 to 1.52)	0.87	0.98 (0.62 to 1.55)	0.93	0.91 (0.56 to 1.47)	0.69
Died in ICU	0.91 (0.66 to 1.26)	0.57	0.92 (0.66 to 1.28)	0.62	0.88 (0.61 to 1.27)	0.51
Died in Hospital	0.87 (0.64 to 1.18)	0.38	0.88 (0.65 to 1.19)	0.41	0.85 (0.60 to 1.19)	0.34

Abbreviations: Abbreviations: RIFLE: Risk, Injury, Failure, Loss, End stage renal failure Risk, Injury, Failure, Loss, End stage renal failure; KDIGO: Kidney Disease Improving Global Outcomes; RRT: Renal Replacement Therapy; ICU: Intensive Care Unit

[a] Hierarchal analysis with patients nested within site

[b] Multivariable hierarchal analysis adjusting for APACHE-III admission diagnosis, age, ICU admission source, and APACHE-II score with patients nested within site

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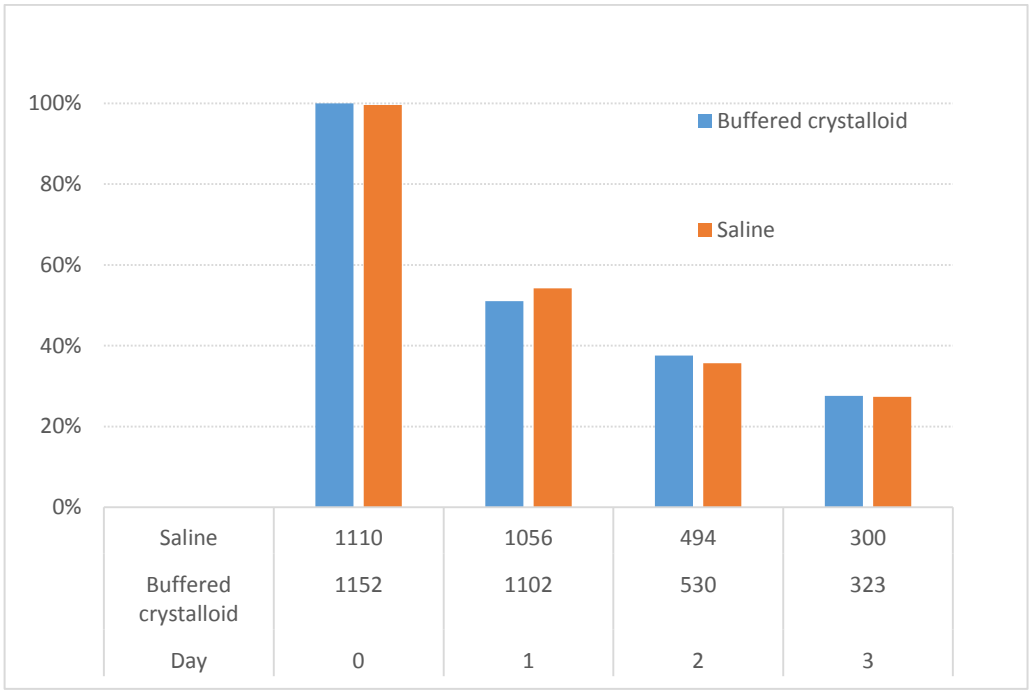
Supplementary figures



eFigure 1: Percentage of patients who received study fluid by treatment group[a]

[a] Day 0 is the day of enrollment. The number of patients remaining in ICU on each study day by treatment group is shown on the horizontal axis.]

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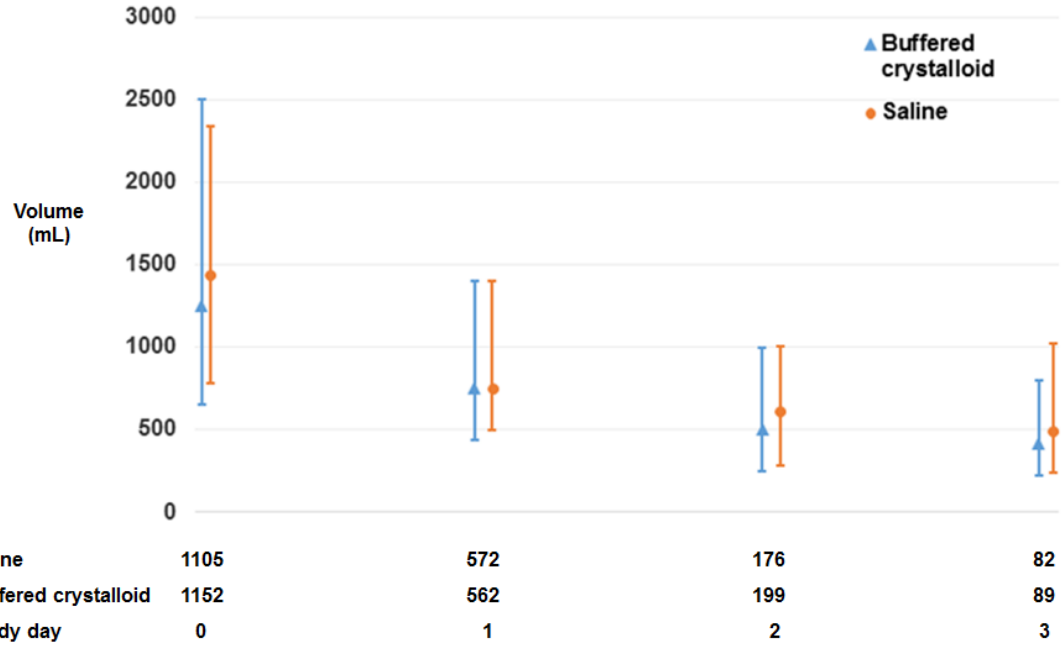

eFigure 2: Median [IQR] volume of fluid per day for those receiving study fluid[a]

[a] Day 0 is the day of enrollment. The number of patients who received study fluid on each study day by treatment group is shown on the horizontal axis.

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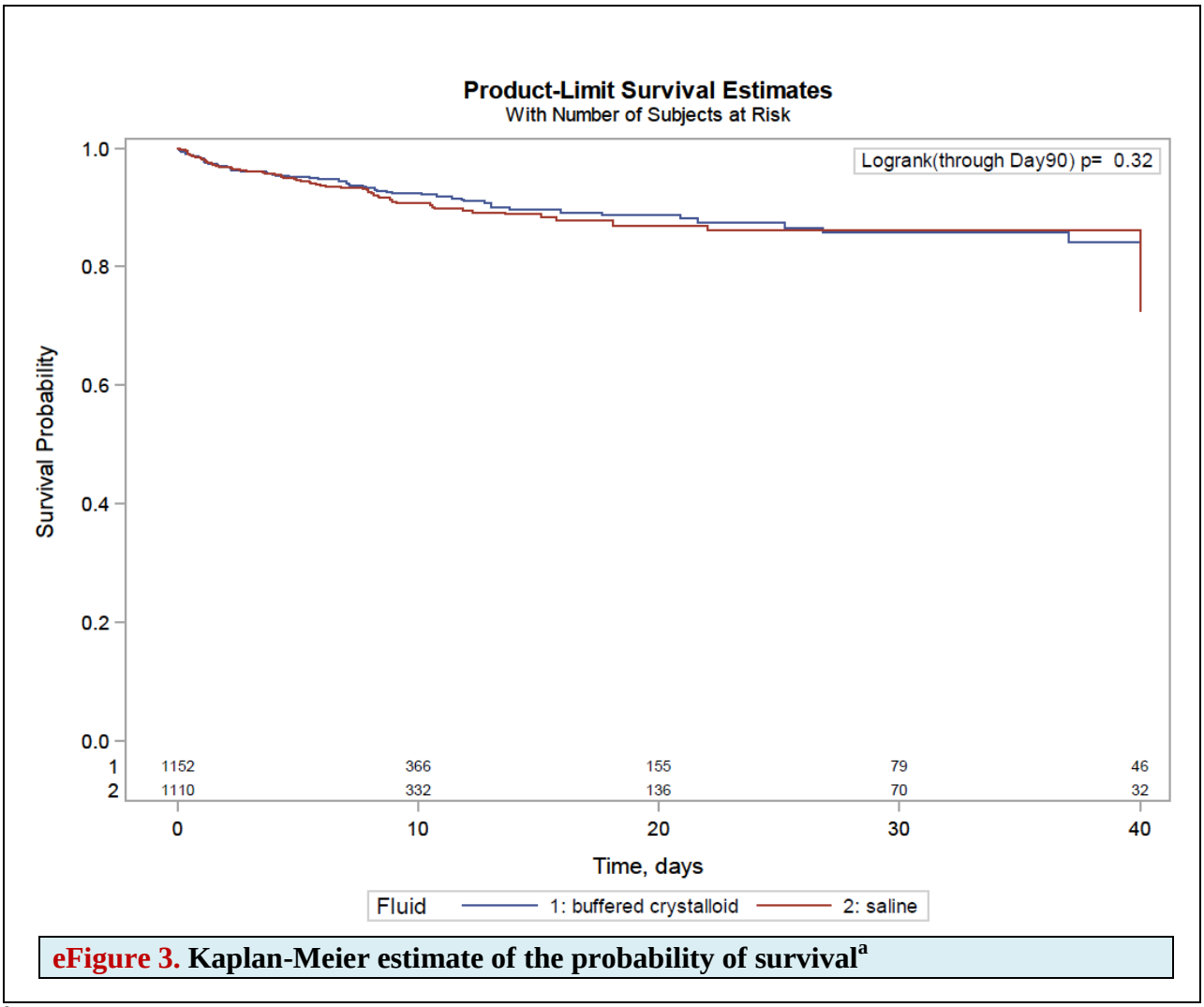

eFigure 3. Kaplan-Meier estimate of the probability of survival[a]

[a] Day 0 is the day of enrollment. The number of patients remaining in ICU on each study day by treatment group is shown on the horizontal axis. The horizontal axis is truncated at 40 days because the number of participants still in follow-up beyond 40 days is small.

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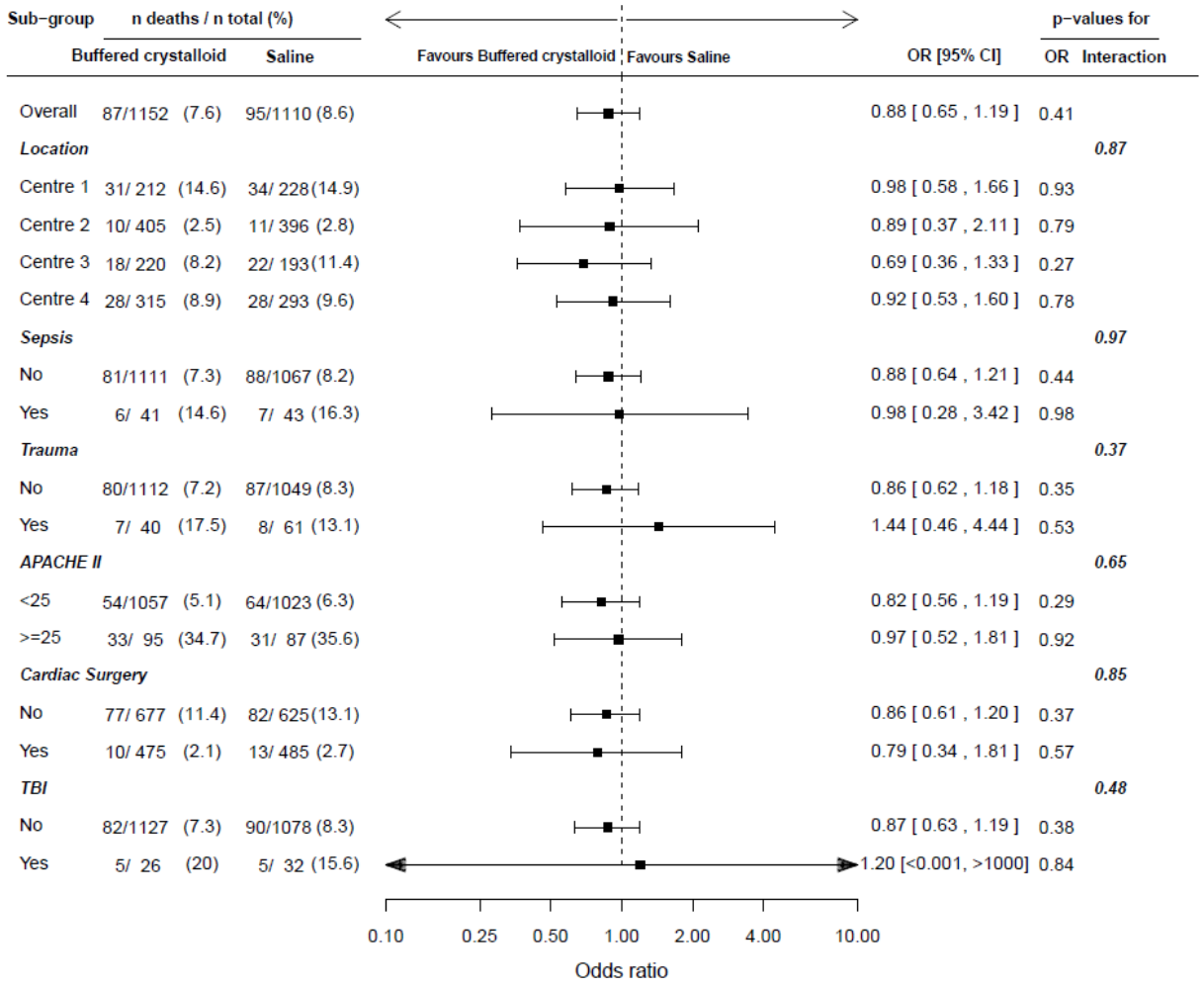

eFigure 4. Risk of in-hospital mortality by subgroup

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