Continuous Renal Replacement Therapy (CRRT): Fluid balance and composition

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The risks of fluid overload

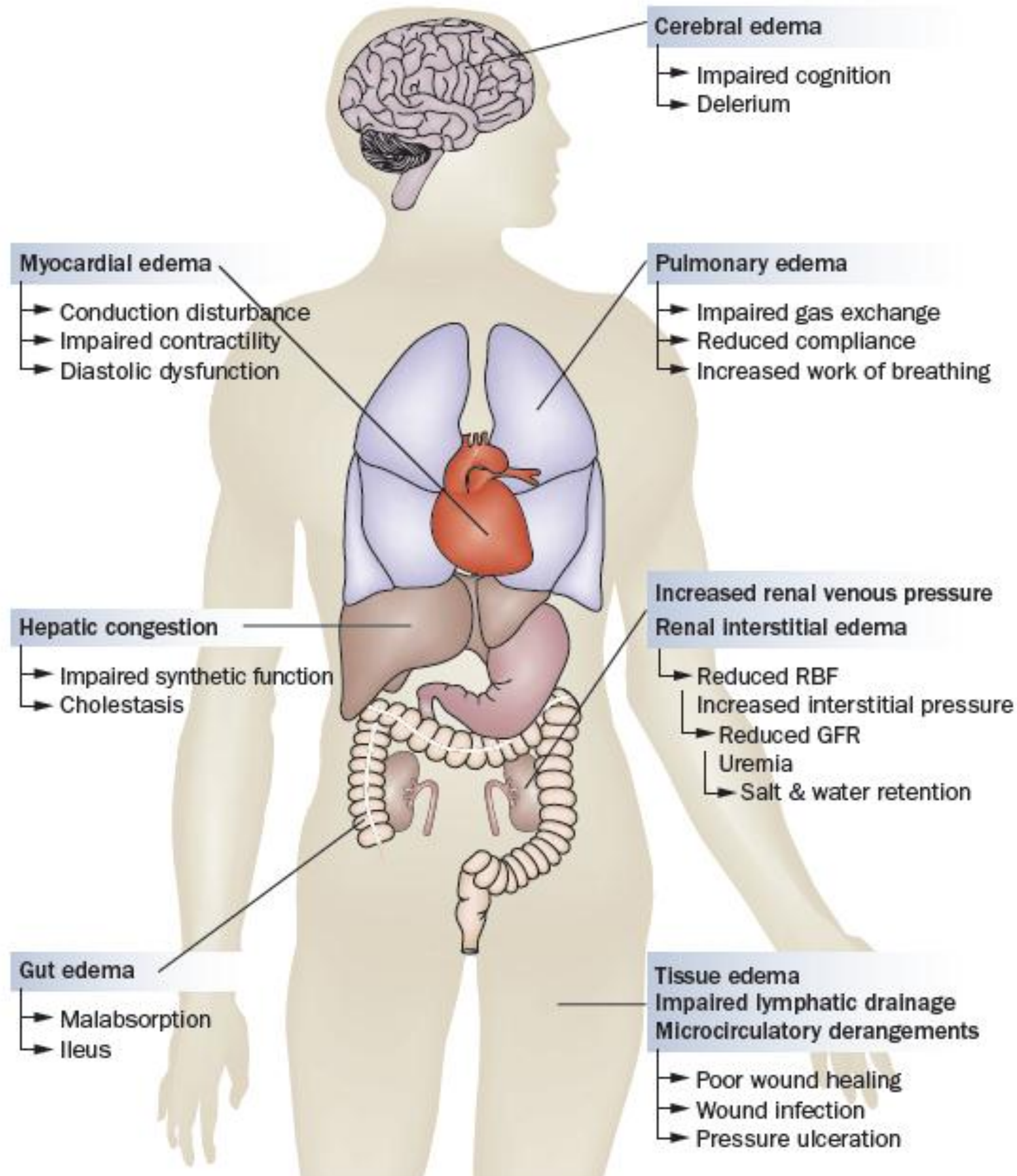


Table 2 | Publications describing two groups of critically ill patients with differing fluid balances where a renal outcome was reported*

Reference	Study type	Population	*n*	Average fluid balance in less-positive group	Average fluid balance in more-positive group	Renal function measure	Renal outcome with more-restrictive fluid balance strategy	Principal outcome with more-restrictive fluid balance strategy
ARDS Clinical Trials Network (2006)[88]	Multicenter RCT	ARDS	1,000	−136 ml on day 7	+6,992 ml on day 7	Need for RRT; change in creatinine	No difference	Shorter duration of ventilation and ICU stay
Martin *et al.* (2005)[86]	Single-center RCT	Mixed ALI	40	−5,480 ml on day 5	−1,490 ml on day 5	Change in creatinine	No difference	Improved oxygenation
Martin *et al.* (2002)[85]	Single-center RCT	ALI after trauma	37	−3,300 ml on day 5	+500 ml on day 5	Change in creatinine	No difference	Improved oxygenation
Mitchell *et al.* (1992)[127]	Single-center RCT	Mixed ICU needing PAC	102	+142 ml	+2,239 ml	Change in creatinine	Small rise in creatinine	Shorter duration of ventilation and ICU stay
Bouchard *et al.* (2009)[25]	Retrospective observational	Mixed ICU with AKI	542	<10% rise	>10% rise	Dialysis independence	Improved	Decrease in mortality
Payen *et al.* (2008)[6]	Retrospective observational	Mixed ICU with or without AKI	3,147	−1,000 ml	+3,000 ml	Renal SOFA score	Improved	Decrease in mortality in patients with AKI
Vidal *et al.* (2008)[72]	Prospective observational	Mixed ICU with elevated or normal IAP	83	+5,000 ml	+9,000 ml	Renal SOFA score	Improved	Normal IAP associated with less organ failure and shorter ICU stay
Adesanya *et al.* (2008)[128]	Retrospective observational	Surgical ICU	41	+5 kg	+8.3 kg	Change in creatinine	No difference	Shorter duration of ventilation and ICU stay
McArdle *et al.* (2007)[87]	Retrospective observational	Surgical ICU	100	+7,500 ml	+10,000 ml	Change in creatinine	No difference	Decrease in postoperative complications
Arlati *et al.* (2007)[99]	Prospective observational	Burns ICU	24	+7,500 ml	+12,000 ml	Urine output	No difference	Decrease in organ dysfunction score

*See Supplementary Information online for systematic search strategy. Abbreviations: AKI, acute kidney injury; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; IAP, intra-abdominal pressure; ICU, intensive care unit; PAC, pulmonary artery catheter; RCT, randomized, controlled trial; RRT, renal replacement therapy; SOFA, sequential organ failure assessment.

Positive fluid balance looks bad!

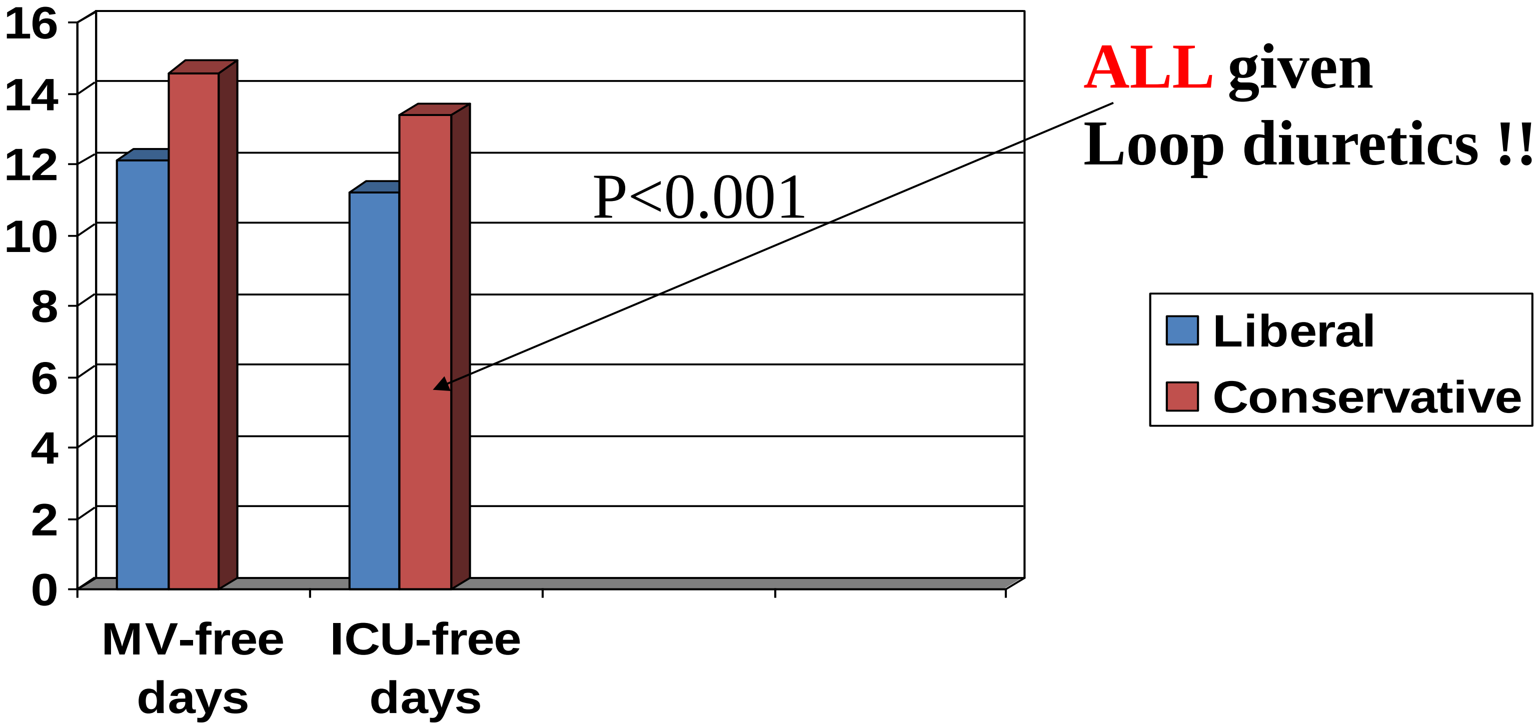
Why we **might** actually need to remove fluid

- Sustained oliguria leads to fluid overload due to obligatory fluid intake in ICU
- Fluid, acid-base, potassium management is much easier if urine output is maintained
- Fluid overload is a real problem
- Let me show you.

The “FACTTs”

- **NEJM 2006; 354: 1-12**
- Comparison of two fluid-management strategies in acute lung injury
- NB: Pneumonia + sepsis >80% of patients
- 503 = conservative strategy
- 497 = liberal strategy

Liberal vs. conservative fluid use



NB: need for RRT 2.8 vs. 1.9% (p=0.06)
Mortality 28.4 vs. 25.5%.
All in favour of "dry"

CJASN ePress. Published on March 10, 2011 as doi: 10.2215/CJN.08781010

Article

Fluid Balance, Diuretic Use, and Mortality in Acute Kidney Injury

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Post-hoc analysis

Clin J Am Soc Nephrol. 2011 May;6(5):966-73.

- Aim: explore association b/w FB, diuretics and mortality in AKI patients from FACTT
- 306 of 1000 patients developed AKI in first 2 days
- Post AKI Fluid Balance was significantly **associated with mortality…higher** frusemide doses had a protective effect which was no longer significant after correction for fluid balance.
- **Conclusion:** Post AKI diuretic therapy was associated with better 60-days survival – this appeared mediated by more negative fluid balance

Table 3. Relative odds of death by FACTT study day 60 associated with average daily fluid balance and furosemide dose following AKI

	Fluid Balance (Post-AKI, in Mean L/Day)		Furosemide Dose (Post-AKI, in Mean 100 mg/Day)	
Adjustment	OR (95% CI)	*P*	OR (95% CI)	*P*
None (univariate)	1.73 (1.47 to 2.03)	<0.001	0.38 (0.23 to 0.63)	<0.001
Full model[a]	1.61 (1.29 to 2.00)	<0.001	0.54 (0.31 to 0.94)	0.028
+Post-AKI fluid balance			0.73 (0.42 to 1.26)	0.255
+Post-AKI furosemide dose	1.56 (1.25 to 1.95)	<0.001		
Final model[b]	1.61 (1.32 to 1.96)	<0.001	0.48 (0.28 to 0.81)	0.007

[a]Full model includes adjustment for the following covariates: age, sex, race, fluid-strategy randomization group, catheter randomization group, day first diagnosed with AKI, fluid balance in the 24 hours prior to randomization, enrollment APACHE III score, sepsis as an etiology for ALI, trauma as an etiology for ALI, pneumonia as an etiology for ALI, multiple transfusions as an etiology for ALI, other etiology for ALI, baseline CVP, baseline presence or absence of shock, use of diuretics in the 24 hours prior to randomization, stage of AKI within 2 study days of randomization (AKIN creatinine-based criteria), mean daily CVP, and mean daily presence or absence of shock. The statistically significant covariates in the full model were race, age, day first diagnosed with AKI, and fluid-strategy randomization group.

[b]Final model includes adjustment for the following covariates: age, race, sex, fluid-strategy randomization arm, catheter randomization arm, enrollment APACHE III score, day first diagnosed with AKI, mean daily CVP, and mean daily presence or absence of shock. The statistically significant covariates in the final model were race, age, day first diagnosed with AKI (with mean fluid balance only), fluid-strategy randomization group (with mean fluid balance only), enrollment APACHE III score, mean daily CVP (with mean furosemide dose only), and mean daily presence or absence of shock.

Positive fluid balance is bad in AKI

original article

http://www.kidney-international.org

Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury

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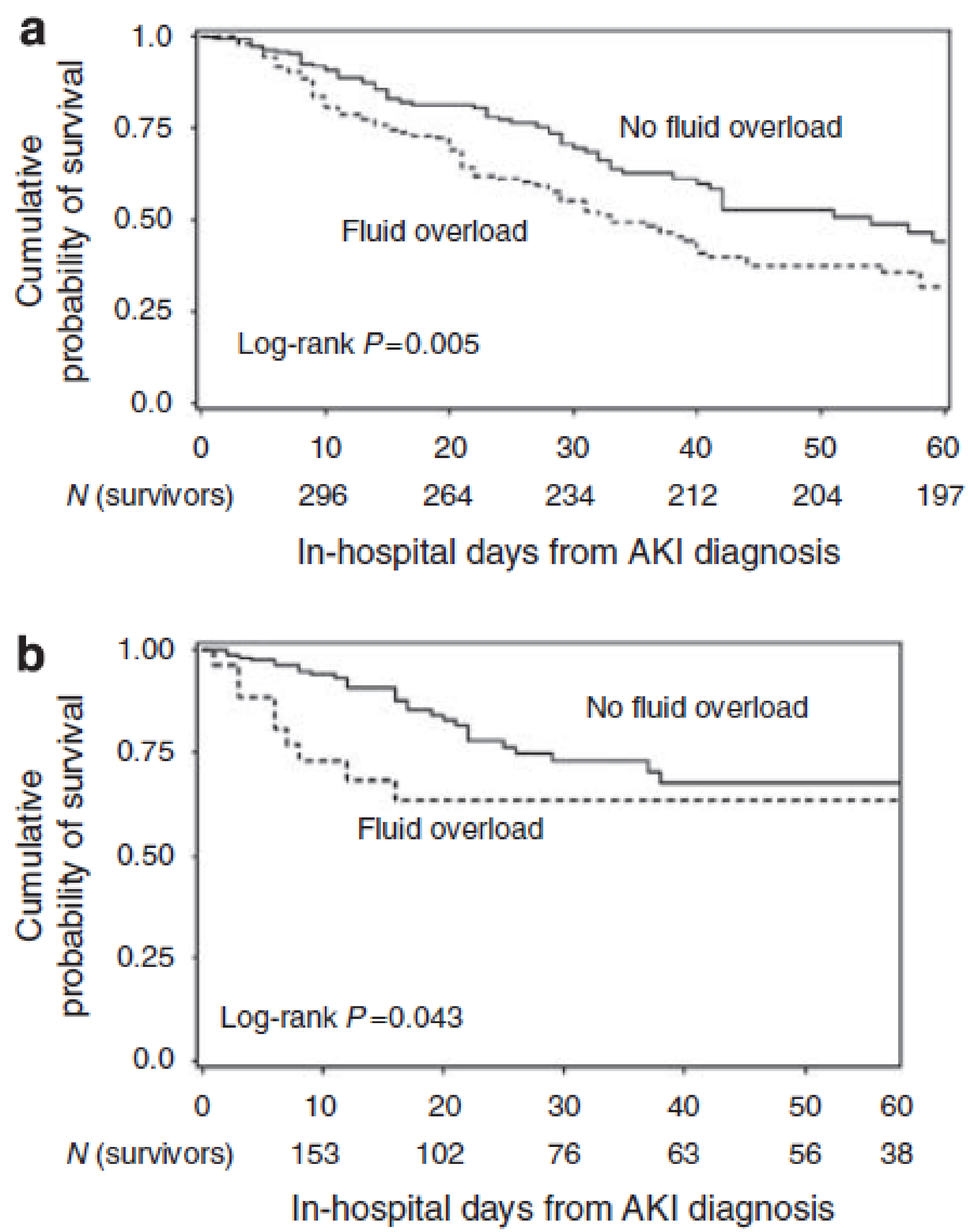
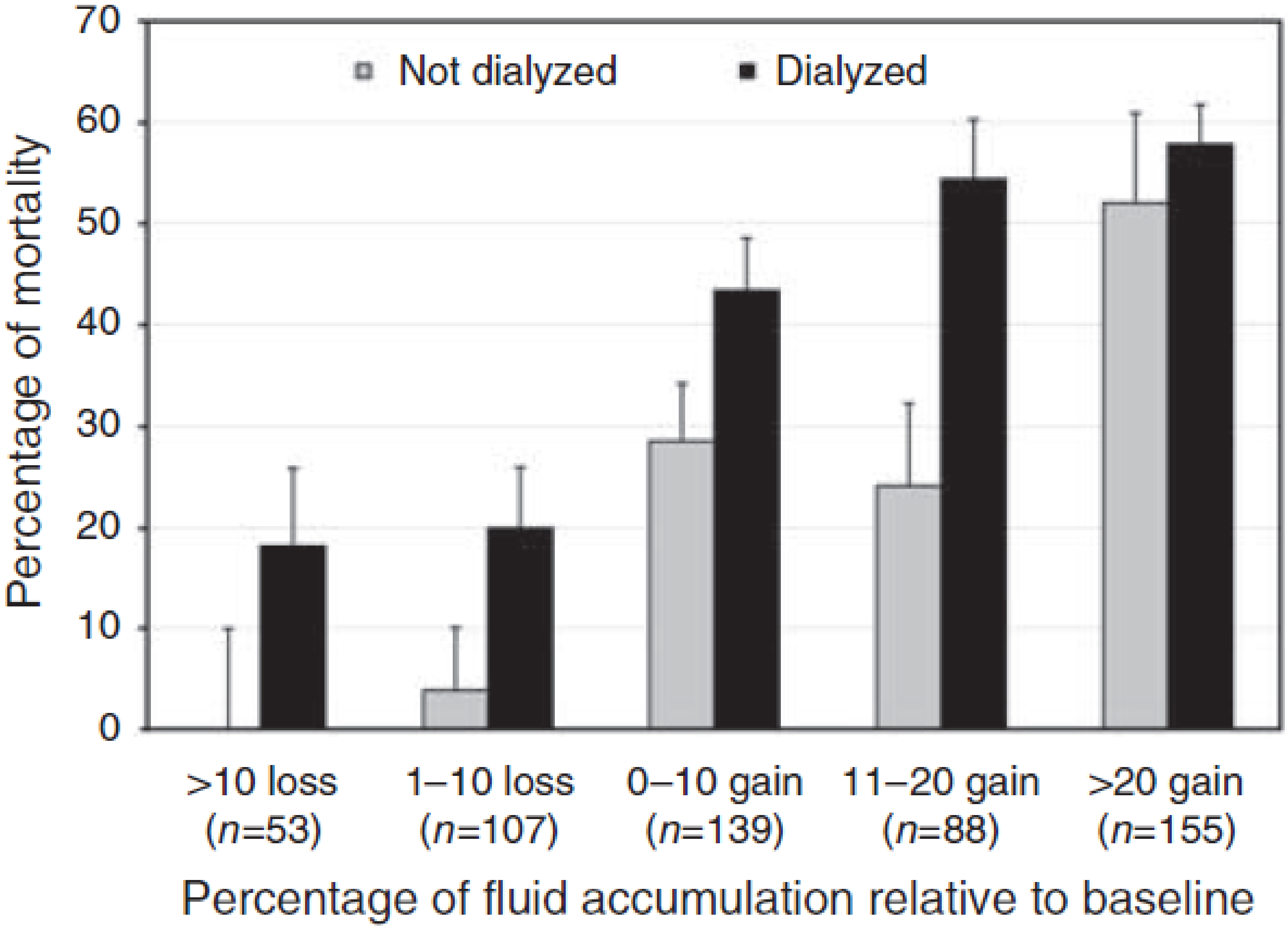

a
Cumulative probability of survival
1.0
0.75
0.50
0.25
0.0
No fluid overload
Fluid overload
Log-rank P=0.005
0
10
20
30
40
50
60
N (survivors)
296
264
234
212
204
197
In-hospital days from AKI diagnosis
b
Cumulative probability of survival
1.00
0.75
0.50
0.25
0.0
No fluid overload
Fluid overload
Log-rank P=0.043
0
10
20
30
40
50
60
N (survivors)
153
102
76
63
56
38
In-hospital days from AKI diagnosis



Not dialyzed
Dialyzed
Percentage of mortality
70
60
50
40
30
20
10
0
>10 loss (n=53)
1–10 loss (n=107)
0–10 gain (n=139)
11–20 gain (n=88)
>20 gain (n=155)
Percentage of fluid accumulation relative to baseline

Research

Open Access

A positive fluid balance is associated with a worse outcome in patients with acute renal failure

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Table 2

Hazard ratios: results of multivariate Cox regression analysis for 60-day mortality in critically ill patients with acute renal failure

Characteristic	Hazard ratio	95% CI	*P* value
Age	1.02	1.01–1.03	<0.001
SAPS II (per point)	1.03	1.02–1.04	<0.001
Heart failure	1.38	1.05–1.81	0.02
Medical admission	1.68	1.35–2.08	<0.001
Mean fluid balance, L/24 hours	1.21	1.13–1.28	<0.001
Mechanical ventilation	1.55	1.14–2.11	<0.001
Liver cirrhosis	2.73	1.88–3.95	<0.001

An observational study fluid balance and patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial*

The RENAL Replacement Therapy Study Investigators

Objective: To examine associations between mean daily fluid balance during intensive care unit study enrollment and clinical outcomes in patients enrolled in the Randomized Evaluation of Normal vs. Augmented Level (RENAL) replacement therapy study.

Design: Statistical analysis of data from multicenter, randomized, controlled trials.

Setting: Thirty-five intensive care units in Australia and New Zealand.

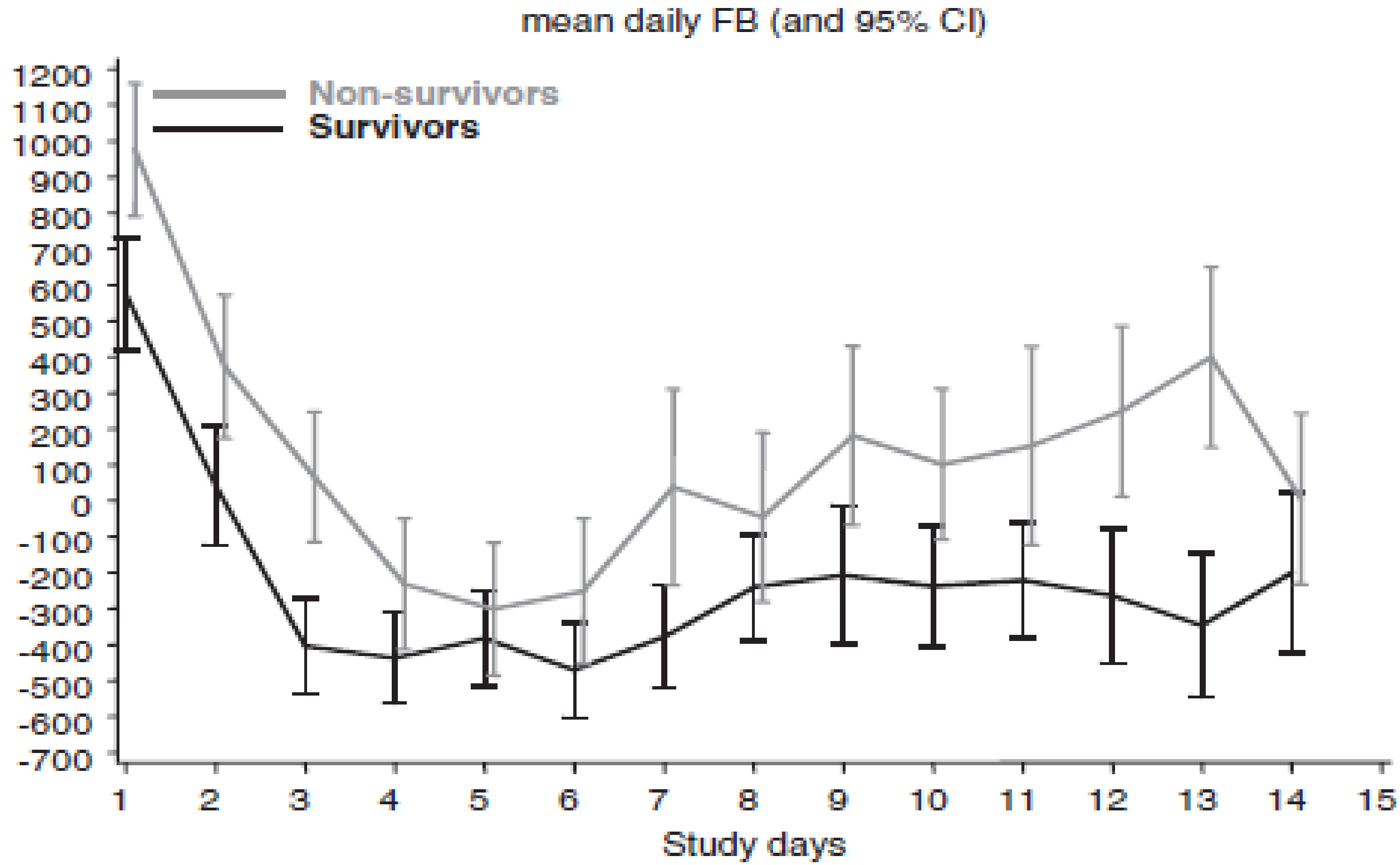
Patients: Cohort of 1453 patients enrolled in the RENAL study.

Interventions: We analyzed the association between daily fluid balance on clinical outcomes using multivariable logistic regression, Cox proportional hazards, time-dependent analysis, and repeated measure analysis models.

Measurements and Main Results: During intensive care unit stay, mean daily fluid balance among survivors was −234 mL/day compared with +560 mL/day among nonsurvivors ($p < .0001$). Mean cumulative fluid balance over the same period was −1941 vs. +1755 mL ($p = .0003$). A negative mean daily fluid balance during study treatment was independently associated with a decreased risk of death at 90 days (odds ratio 0.318; 95% confidence interval 0.24–0.43; $p <$ .000.1) and with increased survival time ($p < .0001$). In addition, a negative mean daily fluid balance was associated with significantly increased renal replacement-free days ($p = .0017$), intensive care unit-free days ($p < .0001$), and hospital-free days ($p = .01$). These findings were unaltered after the application of different statistical models.

Conclusions: In the RENAL study, a negative mean daily fluid balance was consistently associated with improved clinical outcomes. Fluid balance may be a target for specific manipulation in future interventional trials of critically ill patients receiving renal replacement therapy. (Crit Care Med 2012; 40:1753–1760)

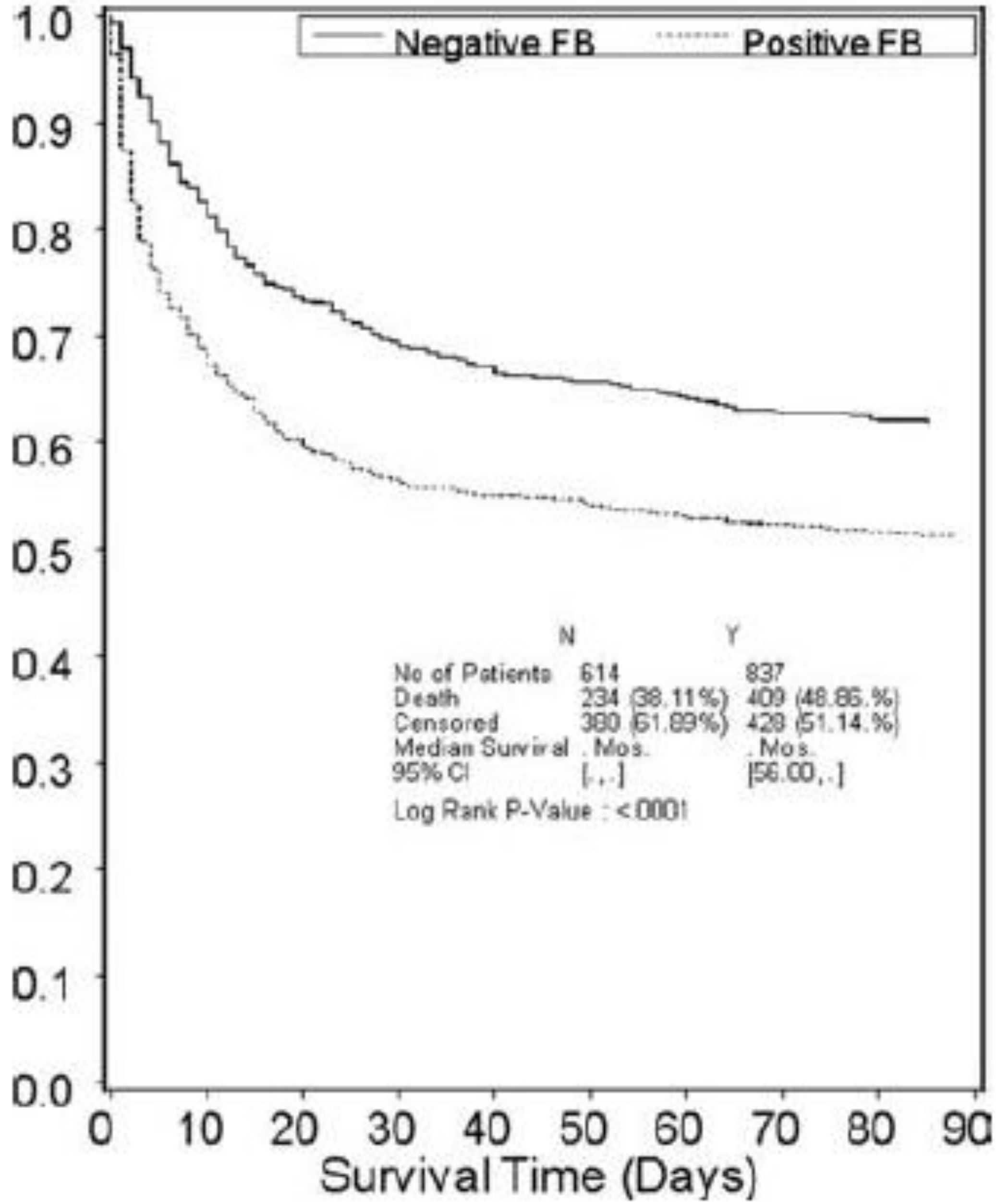
KEY WORDS: acute kidney injury; continuous renal replacement therapy; hemodialysis; hemofiltration; intensive care; kidney



Non-survivors :	643	598	508	441	328	304	304	268	243	218	195	172	152	133
Survivors :	808	805	786	753	618	632	557	505	442	388	346	312	280	253

Table 2. Daily and cumulative fluid balance according to survival status at 90 days after randomization

Fluid Balance, No. of Patients, Mean, SD, Quartile 1 Median, Quartile 3 Days With Missing Data	Nonsurvivors	Survivors	p^a
Mean daily FB during time in ICU[a]	644 560.0 (1494) −274 305.2 1116 10	808 −234 (852) −738 −226 254.9 2	<.0001
Weight-adjusted mean daily FB during time in ICU	644 7.2 (19.1) −3.6, 4.0 14.3 10	808 −2.7 (10.8) −8.7 −2.6 3.1 2	<.0001
Mean cumulative FB during time in ICU	644 1755 (9061) −2310, 1518, 5922 10	808 −1941 (11,000) −6863, −1928, 2240 2	<.0001
Weight-adjusted mean cumulative FB during time in ICU	644 22.5 (119) −29.5, 18.8, 75.2 10	808 −22.3 (131) −85.0, −23.6, 28.4 2	<.0001



Negative FB
Positive FB
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
70
80
90
Survival Time (Days)
N
Y
No of Patients 614 837
Death 234 (38.11%) 409 (48.86.%)
Censored 380 (61.89%) 428 (51.14.%)
Median Survival . Mos. . Mos.
95% CI [.,.] [56.00,.]
Log Rank P-Value : <.0001

Table 3. Multivariable logistic regression with death at 90 days after randomization as outcome[a]

Variable	Effect (Discrete Variable)	Odds Ratio	95% Confidence Interval	p
Negative mean daily fluid balance during index admission to intensive care unit[b]	No vs. yes	0.318	0.24-0.43	<.0001
Age		1.033	1.02-1.04	<.0001
Time from intensive care unit admission to randomization (d)		1.002	1.00-1.04	0.0065
Acute Physiology and Chronic Health Evaluation III score		1.012	1.01-1.02	0.0002
Sequential Organ Failure Assessment liver (score)		1.224	1.07-1.40	0.0033
International normalized ratio for prothrombin time		1.277	1.08-1.51	0.0047

[a]Only variables with $p < .05$ presented; [b]data collected to a maximum of 28 days.

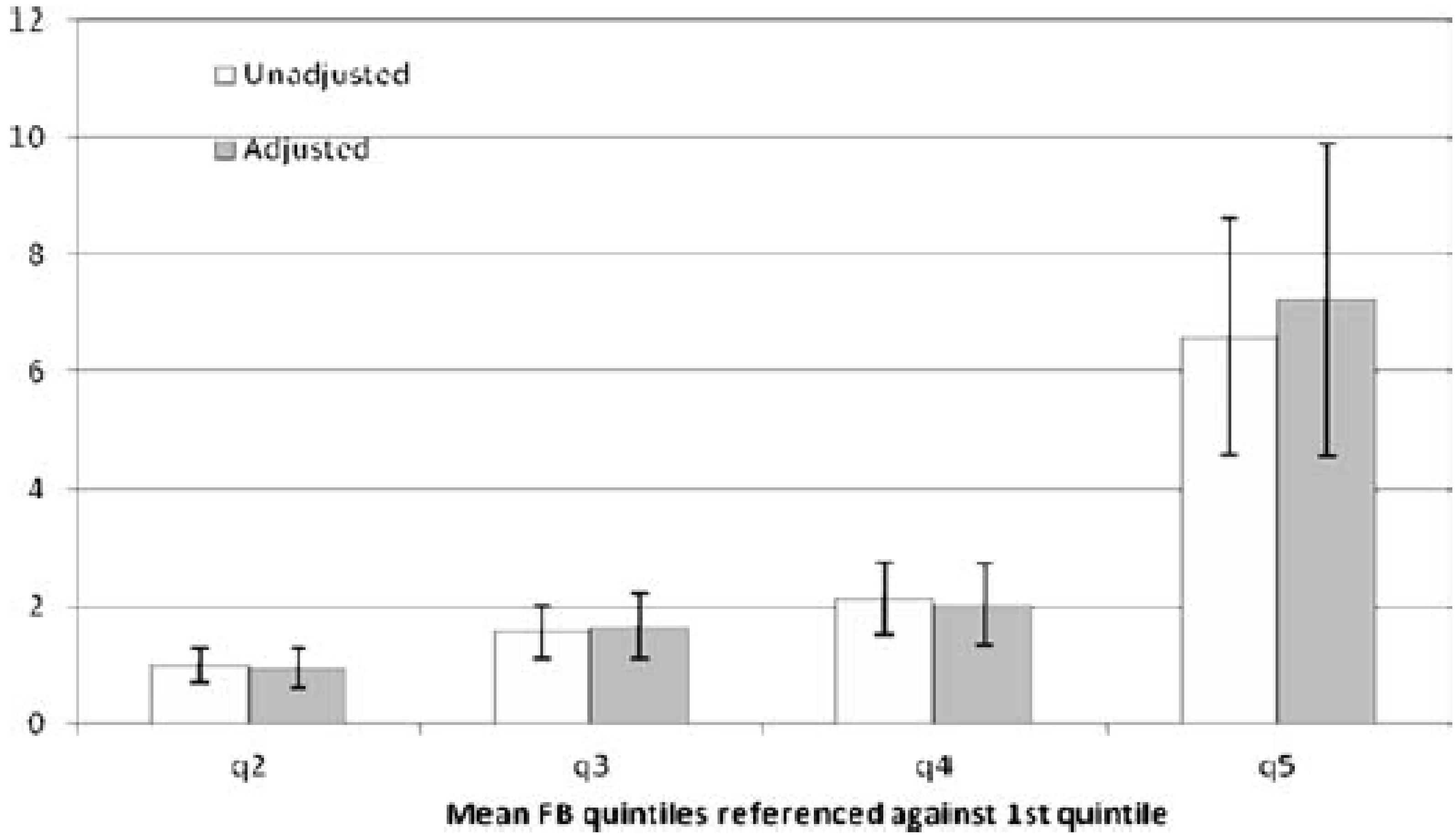

12
10
8
6
4
2
0
Unadjusted
Adjusted
q2
q3
q4
q5
Mean FB quintiles referenced against 1st quintile

Table 4. Multivariable linear regression with renal replacement therapy-free days as outcome

Variable	Estimates	Standard Error	*p*
Intercept	−142.02968	80.90755	.0800
Positive mean daily fluid balance during index intensive care unit admission*	−4.29606	1.35909	.0017
Patients weight (kg)	0.07610	0.03859	.0493
Time from intensive care unit admission to randomization (days)	−0.01299	0.00485	.0077
Overall Sequential Organ Failure Assessment score (all nonmissing organ scores lumped together/5)	−3.68006	1.19039	.0021
Chloride (mmol/L)	0.35592	0.12614	.0050
pH	20.81819	10.26559	.0432

Only variables with $p < .05$ presented.

Murugan *et al. Critical Care* (2018) 22:223
https://doi.org/10.1186/s13054-018-2163-1

Critical Care

RESEARCH Open Access

Net ultrafiltration intensity and mortality in critically ill patients with fluid overload

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Abstract

Background: Although net ultrafiltration (UF^{NET}) is frequently used for treatment of fluid overload in critically ill patients with acute kidney injury, the optimal intensity of UF^{NET} is unclear. Among critically ill patients with fluid overload receiving renal replacement therapy (RRT), we examined the association between UF^{NET} intensity and risk-adjusted 1-year mortality.

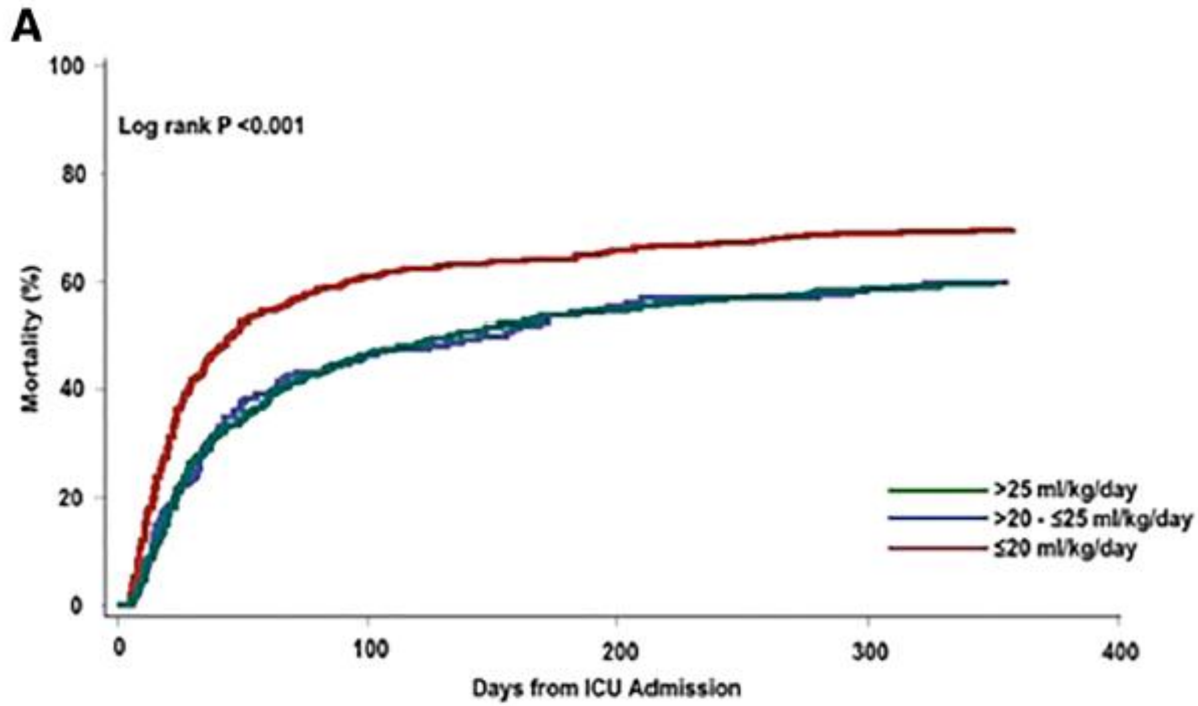
Methods: We selected patients with fluid overload ≥ 5% of body weight prior to initiation of RRT from a large academic medical center ICU dataset. UF^{NET} intensity was calculated as the net volume of fluid ultrafiltered per day from initiation of either continuous or intermittent RRT until the end of ICU stay adjusted for patient hospital admission body weight. We stratified UF^{NET} as low (≤ 20 ml/kg/day), moderate (> 20 to ≤ 25 ml/kg/day) or high (> 25 ml/kg/day) intensity. We adjusted for age, sex, body mass index, race, surgery, baseline estimated glomerular filtration rate, oliguria, first RRT modality, pre-RRT fluid balance, duration of RRT, time to RRT initiation from ICU admission, APACHE III score, mechanical ventilation use, suspected sepsis, mean arterial pressure on day 1 of RRT, cumulative fluid balance during RRT and cumulative vasopressor dose during RRT. We fitted logistic regression for 1-year mortality, Gray's survival model and propensity matching to account for indication bias.

Table 2 Fluid balance, RRT characteristics and outcomes by intensity of net ultrafiltration

	≤ 20 ml/kg/day ($n = 475$)	> 20 to ≤ 25 ml/kg/day ($n = 166$)	> 25 ml/kg/day ($n = 434$)	p value
Fluids administered in the first 24 h of ICU admission (L), median (IQR)	5.3 (3.5–7.9)	5.1 (3.6– 7.8)	5.23 (3.3–8.1)	0.88
Fluid balance after ICU admission (L), median (IQR)				
At 72 h	7.9 (4.4–12)	7.8 (4.7–13.3)	7.6 (4.7–11.6)	0.71
At 7 days	10.1 (6.7–15.2)	10.5 (6.4–15.7)	10.1 (6.4–15.1)	0.78
Average before RRT	2.3 (1.2–4.4)	2.7 (1.5–4.3)	2.3 (1.2–4.2)	0.33
Cumulative before RRT (%)	15.6 (10–25)	17.3 (9.9–28.6)	21 (12.4–33.7)	< 0.001
Duration from ICU admission to RRT (days), median (IQR)	7 (2–13)	5 (3–12)	6 (3–16)	0.27
RRT duration (days), median (IQR)	4.7 (1.5–11.7)	8.7 (4.5–16.7)	7 (3.1–12.7)	< 0.001
Cumulative FB excluding UF^{NET} for duration of RRT (L), median (IQR)[a]	13.5 (4.2–32.8)	22 (8.9–45.1)	19 (7.3–37.2)	< 0.001
MAP for duration of RRT (mmHg), mean (SD)	75.2 (0.6)	77.4 (0.8)	80.1 (0.53)	< 0.001
Cumulative vasopressor dose for duration of RRT (NE), median (IQR)[a]	15.7 (4.3–38.6)	11.4 (1.2–34.7)	8.1 (0.9–25.7)	< 0.001
First RRT modality				
IHD	121 (25.5)	52 (31.3)	127 (29.3)	0.25
CRRT	354 (74.5)	114 (68.7)	307 (70.7)	

Table 2 Fluid balance, RRT characteristics and outcomes by intensity of net ultrafiltration

	≤ 20 ml/kg/day ($n = 475$)	> 20 to ≤ 25 ml/kg/day ($n = 166$)	> 25 ml/kg/day ($n = 434$)	p value
CRRT duration (days), median (IQR)	3.9 (1.5–7.7)	5.8 (3.6–9.4)	5.9 (2.8–9.5)	< 0.001
UF^{NET} volume during CRRT (L), median (IQR)	3.4 (0.9–10.2)	11.6 (5.4–19.2)	16.2 (7.5–28.4)	< 0.001
IHD duration (days), median (IQR)	2 (5–9)	7 (3–13)	4 (2–8)	0.004
UF^{NET} volume during IHD (L), median (IQR)	5.5 (2.2–13.5)	12.6 (4.4–19.7)	9.2 (4–17.2)	< 0.001
Both CRRT and IHD duration (days), median (IQR)	14.7 (9.7–22.9)	15.2 (9.2–21.9)	10.7 (6.9–18.4)	< 0.001
UF^{NET} volume during CRRT and IHD (L), median (IQR)	19.5 (9.5–33.9)	27.9 (18.5–42.1)	26.6 (17.8–46.1)	< 0.001
Hospital length of stay (days), median (IQR)	32 (17–54)	37.5 (23–65)	37 (23–61)	< 0.001
Hospital mortality	272 (57.3)	70 (42.2)	187 (43.1)	< 0.001
1-year mortality	331 (69.7)	100 (60.2)	258 (59.4)	0.003
Renal recovery at 1 year[b]	119 (25.1)	48 (28.9)	138 (31.8)	0.078



>25 ml/kg/day	434	233	198	180
>20 - ≤25 ml/kg/day	166	89	74	69
≤20 ml/kg/day	475	187	163	148

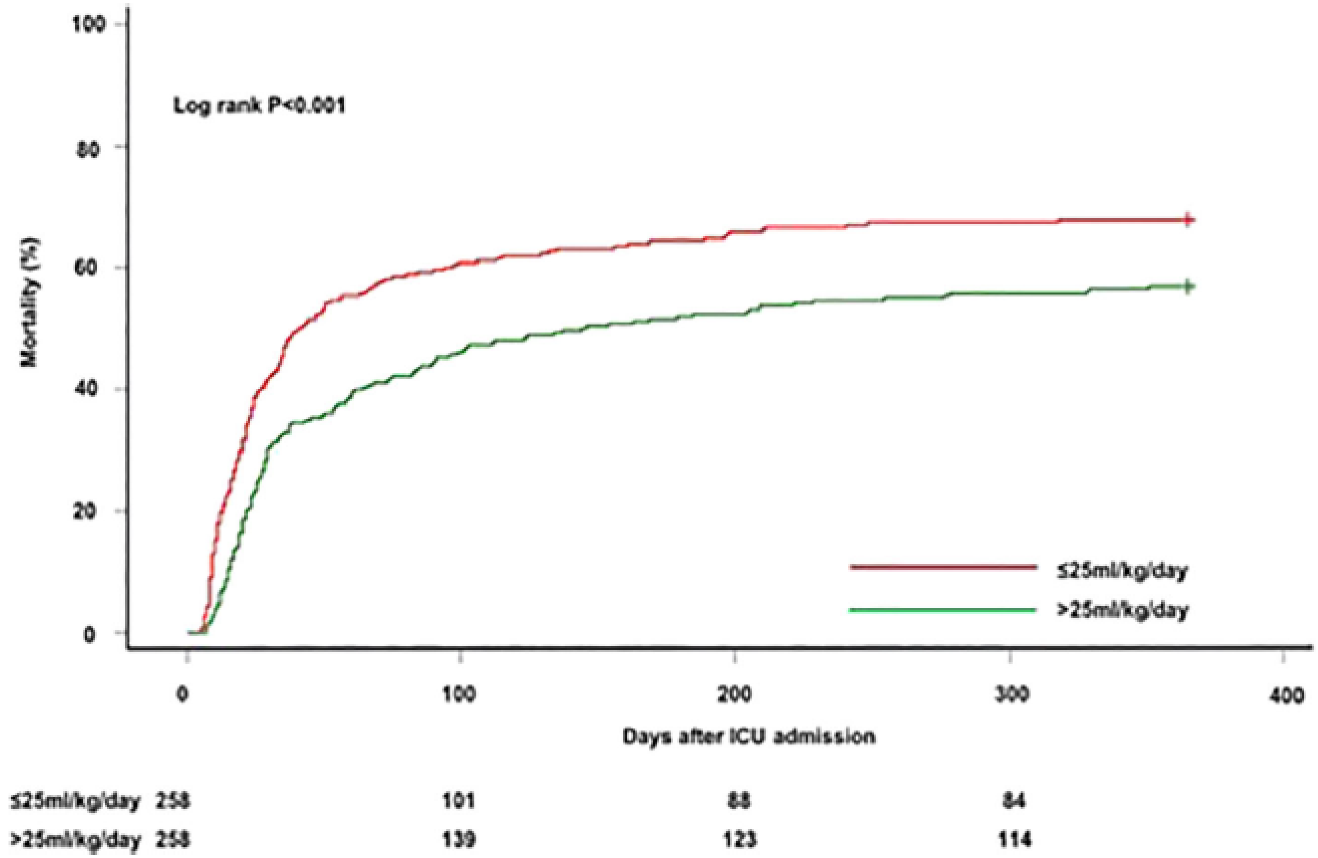


Fig. 2 Association between net ultrafiltration intensity and time to mortality in propensity-matched cohort. Kaplan–Meier failure plots by UF^{NET} for probability of death over 1 year from ICU admission among patients with $UF^{NET} \leq 25$ ml/kg/day ($n = 258$) compared with propensity-matched patients with $UF^{NET} > 25$ ml/kg/day ($n = 258$). Red line, $UF^{NET} \leq 25$ ml/kg/day; green line, $UF^{NET} > 25$ ml/kg/day. Probability of death lower among patients who received $UF^{NET} > 25$ ml/kg/day compared with $UF^{NET} \leq 25$ ml/kg/day (log-rank $p < 0.001$). ICU intensive care unit

Net Ultrafiltration Rate and Mortality Among Critically Ill Adults with Acute Kidney Injury Treated with Continuous Venovenous Hemodiafiltration: A Secondary Analysis of the Randomized Evaluation of Normal Versus Augmented Level of Renal Replacement Therapy Trial

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Importance: Net ultrafiltration is frequently used for treatment of fluid overload among critically ill patients. Whether the rate of net ultrafiltration influences outcome is unclear.

Objective: To examine association between net ultrafiltration rate and survival.

Design: We performed a secondary analysis of the Randomized Evaluation of Normal vs. Augmented Level (RENAL) of Renal Replacement Therapy trial between May, 31st, 2018, and January 31, 2019. The RENAL trial was conducted between December 30, 2005, and November 28, 2008.

Setting: Thirty-five ICUs in Australia and New Zealand.

Participants: Critically ill adults with acute kidney injury and treated with continuous venovenous hemodiafiltration.

Exposure: Net ultrafiltration rate defined as the volume of fluid removed per hour adjusted for patient body weight.

Baseline Patient Characteristics by Net Ultrafiltration Rate

Characteristic	No.(%)				P value
	All Patients (N=1,434)	<1.01 (mL/kg/hr) (N=477)	1.01–1.75 (mL/kg/hr) (N=479)	>1.75 (mL/kg/hr) (N=478)	
Age, years, median(IQR)	67.3 (56.9 - 76.3)	69.3 (61 - 77.4)	68.1 (57.2 - 76.1)	63.8 (51.4 - 74.2)	<0.001
Age category, years					
<53.2	287 (20)	65 (13.6)	96 (20)	126 (26.4)	
53.2 to < 63.6	287 (20)	93 (19.5)	83 (17.3)	111 (23.3)	
63.6 to <71.1	286 (20)	98 (20.5)	97 (20.2)	91 (10)	<0.001
71.1 to <77.7	287 (20)	107 (22.4)	111 (23.2)	69 (14.4)	
≥77.7	287 (20)	114 (24)	92 (19.2)	81 (17)	
Male sex	924 (64.4)	311 (65.2)	330 (69)	283 (59.2)	0.007
Weight, kg, median(IQR)[a]	80 (70 - 90)	81 (73 - 90)	80 (74 - 90)	75 (68 - 85)	<0.001
Preadmission eGFR, mL/min/1.73m^2, median(IQR)[b]	53 (32.6 – 73.9)	48.1 (31 - 68.4)	51 (34 - 72.8)	59 (33.3 - 80.2)	0.009
Patients with known eGFR[b], mL/min/1.73m^2					
46 to <60	143 (30.6)	52 (29.2)	48 (32)	43 (31)	
30 to <46	156 (33.4)	64 (36)	52 (34.7)	40 (28.8)	0.63
<30	168 (36)	62 (34.8)	50 (33.3)	56 (40.3)	
Time in ICU before randomization, hours, median(IQR)	20 (6 – 51)	13 (3 - 41)	21 (6 - 53)	26 (8 - 63)	<0.001
Mechanical ventilation[a]	1057 (73.7)	330 (69.2)	356 (74.3)	371 (77.6)	0.01
Sepsis[a]	709 (49.4)	221 (46.3)	235 (49.1)	253 (53)	0.12

Table 2

Processes of Care During Net Ultrafiltration and Outcomes

Characteristic	No. (%) All Patients (N=1,434)	<1.01 (mL/kg/hr) (N=477)	1.01–1.75 (mL/kg/hr) (N=479)	>1.75 (mL/kg/hr) (N=478)	P value
Intensity of RRT					
High	708 (49.4)	244 (51.1)	216 (45.1)	248 (52)	0.07
Low	726 (50.6)	233 (48.8)	263 (55)	230 (48.1)	
Total SOFA score, median(IQR)	8 (6 – 11)	8 (6 – 11)	8 (6 – 10)	8 (6 – 11)	0.19
Individual daily mean SOFA score, median(IQR)					
Cardiovascular	2.8 (1.5 – 3.7)	3 (1.4 – 4)	2.7 (1.5 – 3.6)	2.7 (1.3 – 3.7)	0.03
Respiratory	3 (2.5 – 3.1)	3 (2.1 – 3)	3 (2.6 – 3.1)	3 (2.6 – 3.2)	0.08
Coagulation	1.8 (0.5 – 2.9)	1.7 (0.4 – 3)	1.7 (0.5 – 2.7)	1.8 (0.7 – 2.7)	0.99
Liver	2 (0.5 – 3)	2 (0.6 – 3.1)	1.8 (0.6 – 3)	1.8 (0.3 – 3)	0.16
Duration of study treatment, days, median(IQR)	3 (2 – 7)	2 (1 – 4)	4 (2 – 8)	5 (2 – 10)	<0.001
Effluent flow rate, mL/kg/hr, median(IQR)	25 (25 – 40)	40 (25 – 40)	25 (25 – 40)	40 (25 – 40)	0.07
Daily fluid balance, mL/day, median(IQR)	-38 (-812 – 727)	641 (-91 – 1,793)	-55.5 (-678.5 – 490)	-658 (-1,445 – 55)	<0.001
Cumulative fluid balance, mL, median(IQR)	-107 (-4,061 – 3,087)	2,335 (-177 – 5,548)	-368 (-3,538 – 2,437)	-3,553.5 (-7,747 – 408)	<0.001

Association Between Net Ultrafiltration Rate and Survival from Gray's Model

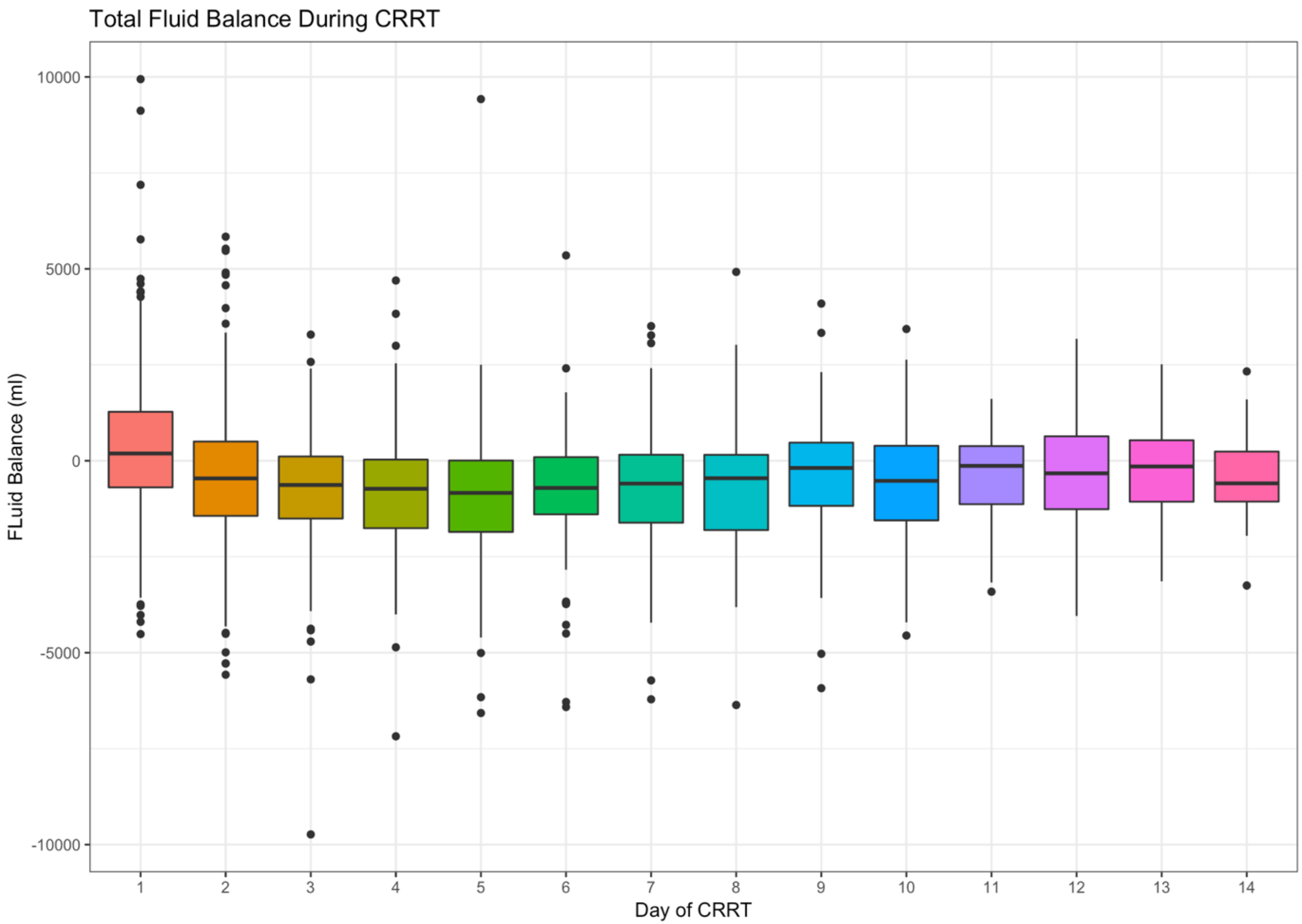
Characteristic	Model	Hazard Ratio Range (95% CI) by Time Interval[a] 0 – 3 days (N=1,390)	3 – 7 days (N=1,216)	7 – 13 days (N=1,085)	13 – 27 days (N=976)	27 – 90 days (N=862)	P value
>1.75 vs. <1.01 mL/kg/hr, (ref)	Unadjusted	0.62 (0.47–0.82)	0.86 (0.67–1.10)	1.31 (1.02–1.68)	1.46 (1.11–1.91)	1.70 (1.23–2.34)	<0.001
	Adjusted[b]	1.13 (0.81–1.57)	1.24 (0.93–1.66)	1.51 (1.13–2.02)	1.52 (1.11–2.07)	1.66 (1.16–2.39)	0.01
>1.75 vs. 1.01 – 1.75 mL/kg/hr, (ref)	Unadjusted	0.97 (0.72–1.30)	1.16 (0.89–1.49)	1.49 (1.16–1.91)	1.40 (1.07–1.82)	1.66 (1.21–2.28)	0.002
	Adjusted[b]	1.12 (0.81–1.56)	1.18 (0.89–1.57)	1.44 (1.10–1.90)	1.42 (1.07–1.89)	1.77 (1.26–2.49)	0.004
1.01 – 1.75 vs. <1.01 mL/kg/hr, (ref)	Unadjusted	0.64 (0.48–0.85)	0.74 (0.57–0.96)	0.84 (0.64–1.09)	1.14 (0.86–1.52)	0.97 (0.69–1.37)	0.006
	Adjusted[b]	1.01 (0.74–1.39)	1.09 (0.82–1.46)	1.00 (0.74–1.34)	1.15 (0.84–1.52)	0.85 (0.58–1.25)	0.59
UF^{NET} per 0.50 mL/kg/hr increase	Unadjusted	0.90 (0.85–0.97)	0.97 (0.92–1.03)	1.06 (1.00–1.12)	1.09 (1.03–1.16)	1.11 (1.04–1.19)	<0.001
	Adjusted[b]	1.03 (0.97–1.09)	1.05 (1.00–1.11)	1.08 (1.02–1.15)	1.11 (1.04–1.18)	1.13 (1.05–1.22)	0.003

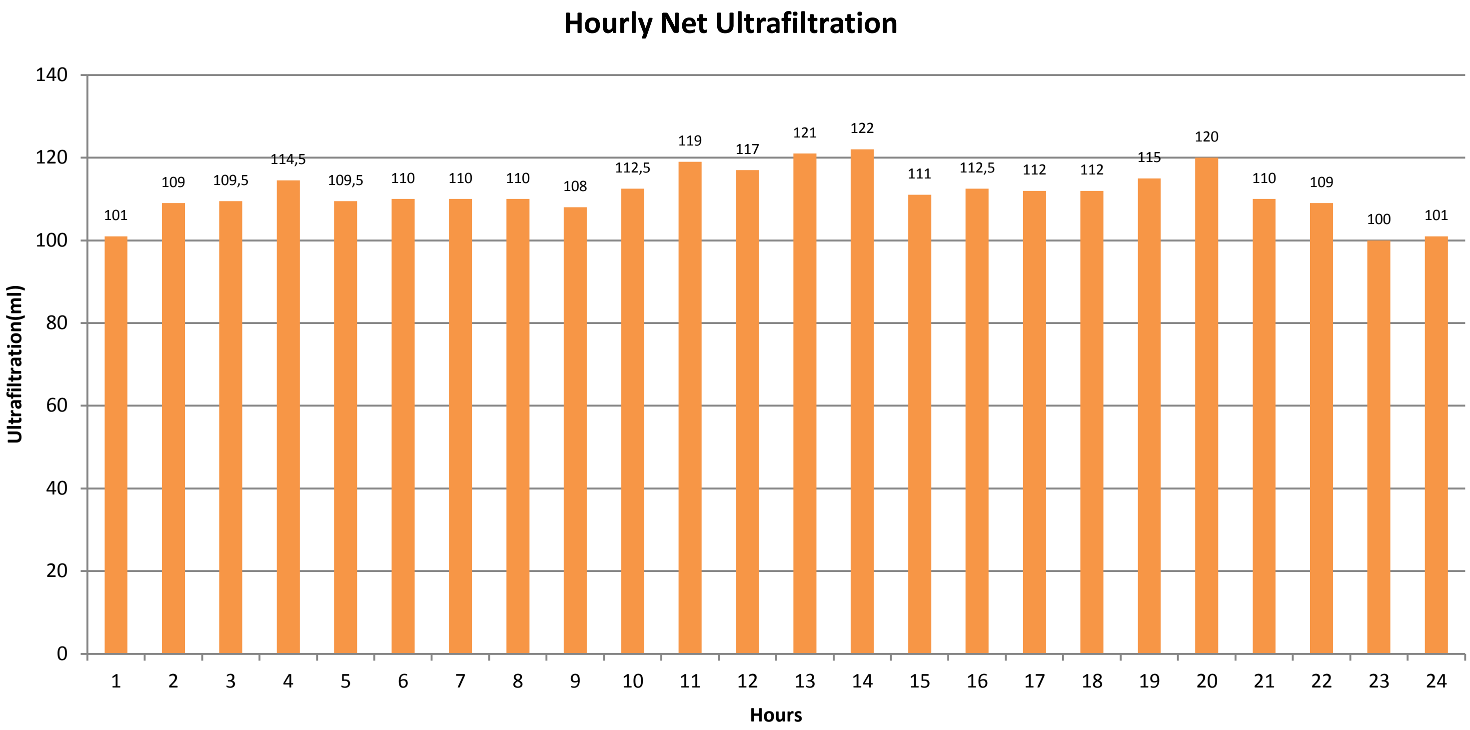
[a] Shown are unadjusted and adjusted hazard ratios estimated from Gray's model for association between UF^{NET} rate and mortality within each time interval. Models included five intervals and four nodes with the default timing of nodes chosen by the statistical program based on number of events within each time interval. A hazard ratio <1 suggests that UF^{NET} rate is associated with lower mortality and a hazard ratio >1 suggests UF^{NET} rate is associated with higher mortality within each time interval. P values reported are for the ranges of hazard ratios across times intervals from the model.

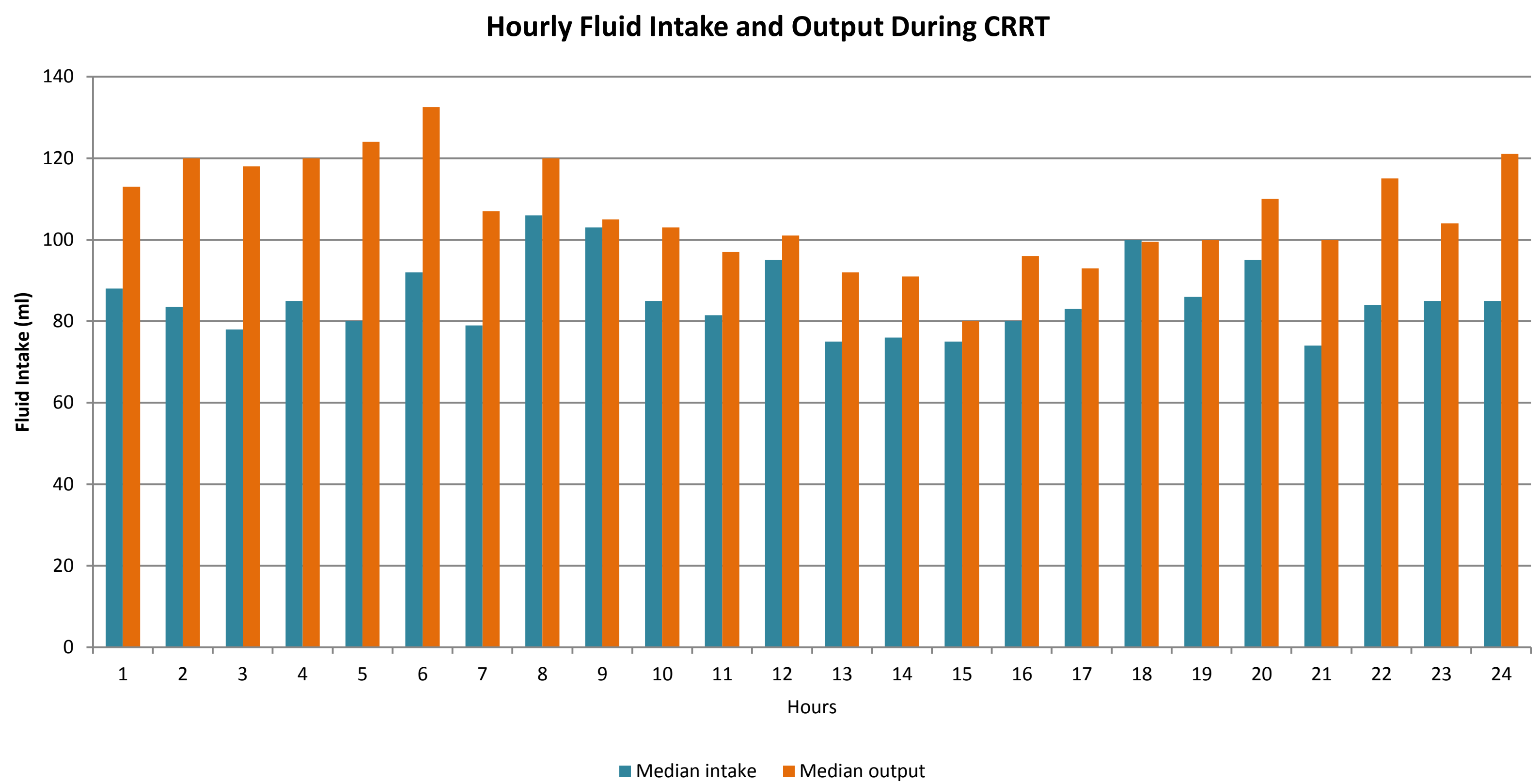
Table 2 Continued

Characteristic	No. (%) All Patients (N=1,434)	<1.01 (mL/kg/hr) (N=477)	1.01–1.75 (mL/kg/hr) (N=479)	>1.75 (mL/kg/hr) (N=478)	P Value
Hourly UF^{NET} volume, mL/hr, median(IQR)	104.7 (56.2 – 150.3)	31.7 (0.66 – 62.5)	106 (89.5 –131)	167.4 (141.5 – 203)	<0.001
Cumulative UF^{NET} volume, mL, median(IQR)	6,977 (2,370 – 16,950)	1,708 (100 – 4007)	8,535 (4,504 – 16,436)	16,560.5 (8,509 – 28,380)	<0.001
Daily fluid balance excluding UF^{NET}, mL/day, median(IQR)[a]	1,739.5 (971 – 2,563)	1,370 (561– 2,259)	1,683 (989 – 2,440.5)	2,058.5 (1,385 – 2,882)	<0.001
Cumulative fluid balance excluding UF^{NET}, mL, median(IQR)[a]	7,406 (3,079 – 15,284)	4,582 (1,276 – 8,690)	8,476 (3,590 – 15,878)	11,092 (5,127 – 22,385)	<0.001
Duration of mechanical ventilation, days, median(IQR)	5 (2 – 10)	3 (1 - 7)	6 (2 - 12)	7 (3 - 12)	<0.001
ICU length of stay, days, median(IQR)	7 (3 – 14)	5 (2 - 10)	8 (4 - 15)	9 (5 - 16)	<0.001
Hospital length of stay, days, median(IQR)	8 (5 - 15)	6 (3 - 11)	9 (5 - 16)	10 (6 - 16)	<0.001
No. of days of RRT, days, median(IQR)	5 (3 – 11)	3 (2 – 6)	6 (3 – 11)	7 (4 – 17)	<0.001
RRT dependence among survivors					
By day 28	120 (13.4)	19 (6.5)	37 (11.6)	64 (22)	<0.001
By day 90	44 (5.5)	10 (3.8)	17 (5.8)	17 (6.9)	0.28

Cohort of 370 patients from Austin Hospital ICU




Hourly Net Ultrafiltration
Ultrafiltration(ml)
Hours
0
20
40
60
80
100
120
140
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
101 109 109,5 114,5 109,5 110 110 110 108 112,5 119 117 121 122 111 112,5 112 112 115 120 110 109 100 101


Hourly Fluid Intake and Output During CRRT
Fluid Intake (ml)
0
20
40
60
80
100
120
140
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
Hours
Median intake
Median output

Fluid composition

- Bicarbonate-buffered fluid is the standard composition
- However, citrate CRRT is becoming dominant and commercial products use a combination of citrate and bicarbonate
- If citrate is used appropriate adjustments need t be made to ensure a near physiologic buffer concentration (25-35 mEq/L)

The data are clear!

Crit Care Med 2015;

A Randomized Controlled Trial of Regional Citrate Versus Regional Heparin Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Adults

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Dorrilyn Rajbhandari, RN Post Grad Dip (Clinical Nursing)[1,2]; Celia Bradford, MD, FCICM[3];
Heidi Buhr, RN, MClinTPrac[1]; Serigne Lo, PhD, AStat[2];
Rinaldo Bellomo, MBBS, MD (Hons), FRACP, FCICM, PG Dip Echo[4,5]

Design: Multicenter, parallel group randomized controlled trial.
Setting: Seven ICUs in Australia and New Zealand.
Patients: Critically ill adults requiring continuous renal replacement therapy.
Interventions: Patients were randomized to receive one of two methods of regional circuit anticoagulation: citrate and calcium or heparin and protamine.

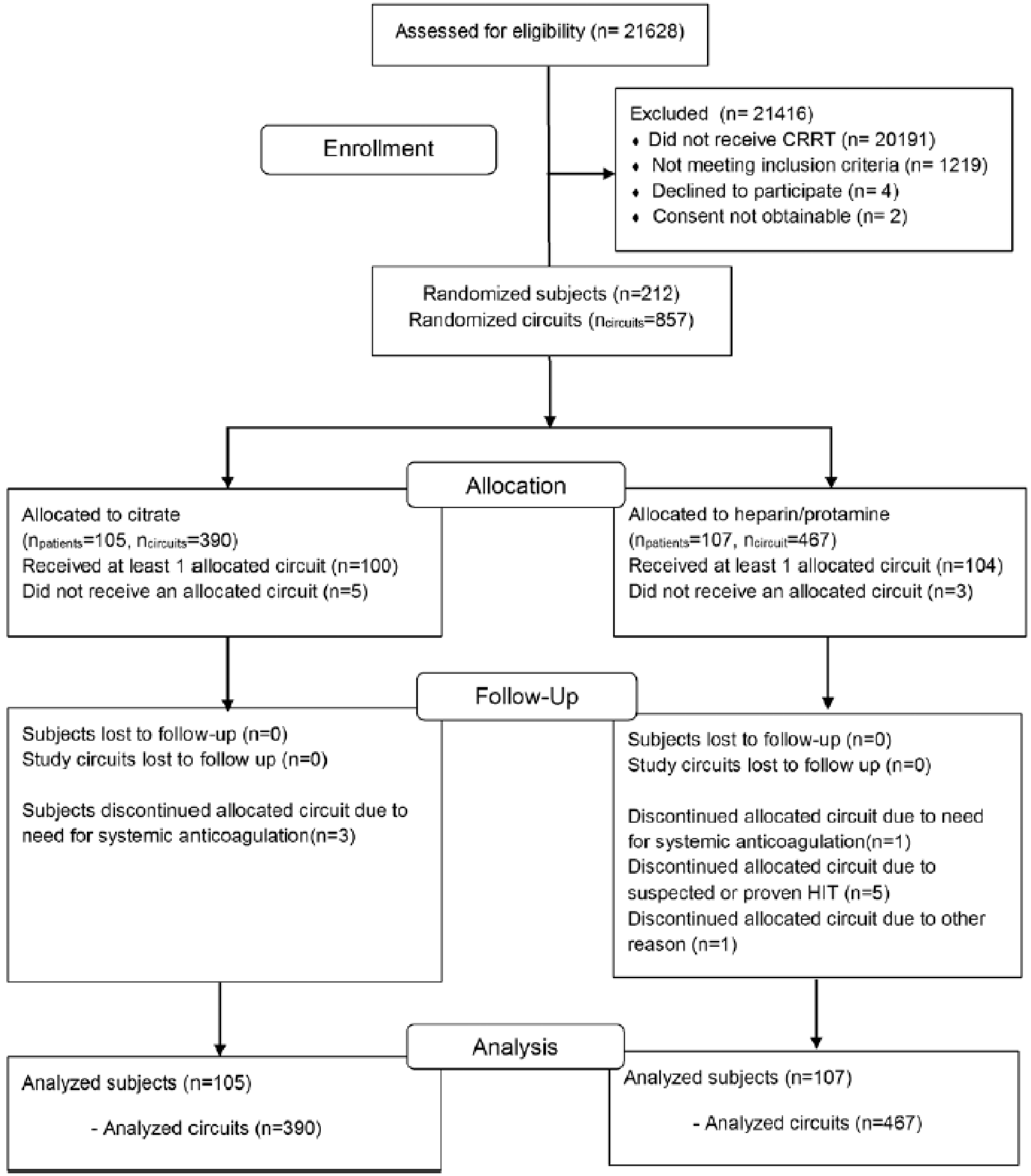
Assessed for eligibility (n= 21628)
Enrollment
Excluded (n= 21416)
Did not receive CRRT (n= 20191)
Not meeting inclusion criteria (n= 1219)
Declined to participate (n= 4)
Consent not obtainable (n= 2)
Randomized subjects (n=212)
Randomized circuits ($n_{circuits}$=857)
Allocation
Allocated to citrate
($n_{patients}$=105, $n_{circuits}$=390)
Received at least 1 allocated circuit (n=100)
Did not receive an allocated circuit (n=5)
Allocated to heparin/protamine
($n_{patients}$=107, $n_{circuit}$=467)
Received at least 1 allocated circuit (n=104)
Did not receive an allocated circuit (n=3)
Follow-Up
Subjects lost to follow-up (n=0)
Study circuits lost to follow up (n=0)
Subjects discontinued allocated circuit due to need for systemic anticoagulation(n=3)
Subjects lost to follow-up (n=0)
Study circuits lost to follow up (n=0)
Discontinued allocated circuit due to need for systemic anticoagulation(n=1)
Discontinued allocated circuit due to suspected or proven HIT (n=5)
Discontinued allocated circuit due to other reason (n=1)
Analysis
Analyzed subjects (n=105)
- Analyzed circuits (n=390)
Analyzed subjects (n=107)
- Analyzed circuits (n=467)

TABLE 1. Baseline Demographic and Clinical Characteristics of the Intervention and Control Groups

Variable	Citrate ($n = 105$)	Heparin ($n = 107$)
Age, yr	66.4 (14.3)	66.8 (14.9)
Male gender, *n*/total (%)	74/105 (71)	72/107 (67)
Weight		
Measured (vs estimated), *n*/total (%)	46/105 (44)	50/107 (47)
Weight (kg)	85.0 (20.6)	84.3 (22.9)
Source of admission to ICU, *n*/total (%)		
Emergency department	24/105 (22.9)	38/107 (35.5)
Hospital ward	27/105 (25.7)	19/107 (17.8)
Operating theatre, elective	31/105 (29.5)	33/107 (30.8)
Operating theatre, emergency	4/105 (3.8)	3/107 (2.8)
Transfer from another hospital	4/105 (3.8)	6/107 (5.6)
Transfer from other ICU	9/105 (8.6)	6/107 (5.6)
Not available	6/105 (5.7)	2/107 (1.9)
Time from ICU admission to randomization (hr)		
Median (interquartile range)	25.1 (44.5)	21.5 (44.0)
APACHE III diagnostic group, *n*/total (%)		
Coronary artery bypass grafts	14/105 (13.3)	13/107 (12.1)
Renal disorders	10/105 (9.5)	7/107 (6.5)
Sepsis with shock, nonurinary	8/105 (7.6)	7/107 (6.5)
Other respiratory diseases	6/105 (5.7)	7/107 (6.5)
Valvular heart surgery	5/105 (4.8)	6/107 (5.6)
Other	62/105 (59.0)	67/107 (62.6)
APACHE II score, mean (SD)	25.6 (7.6)	25.0 (6.9)

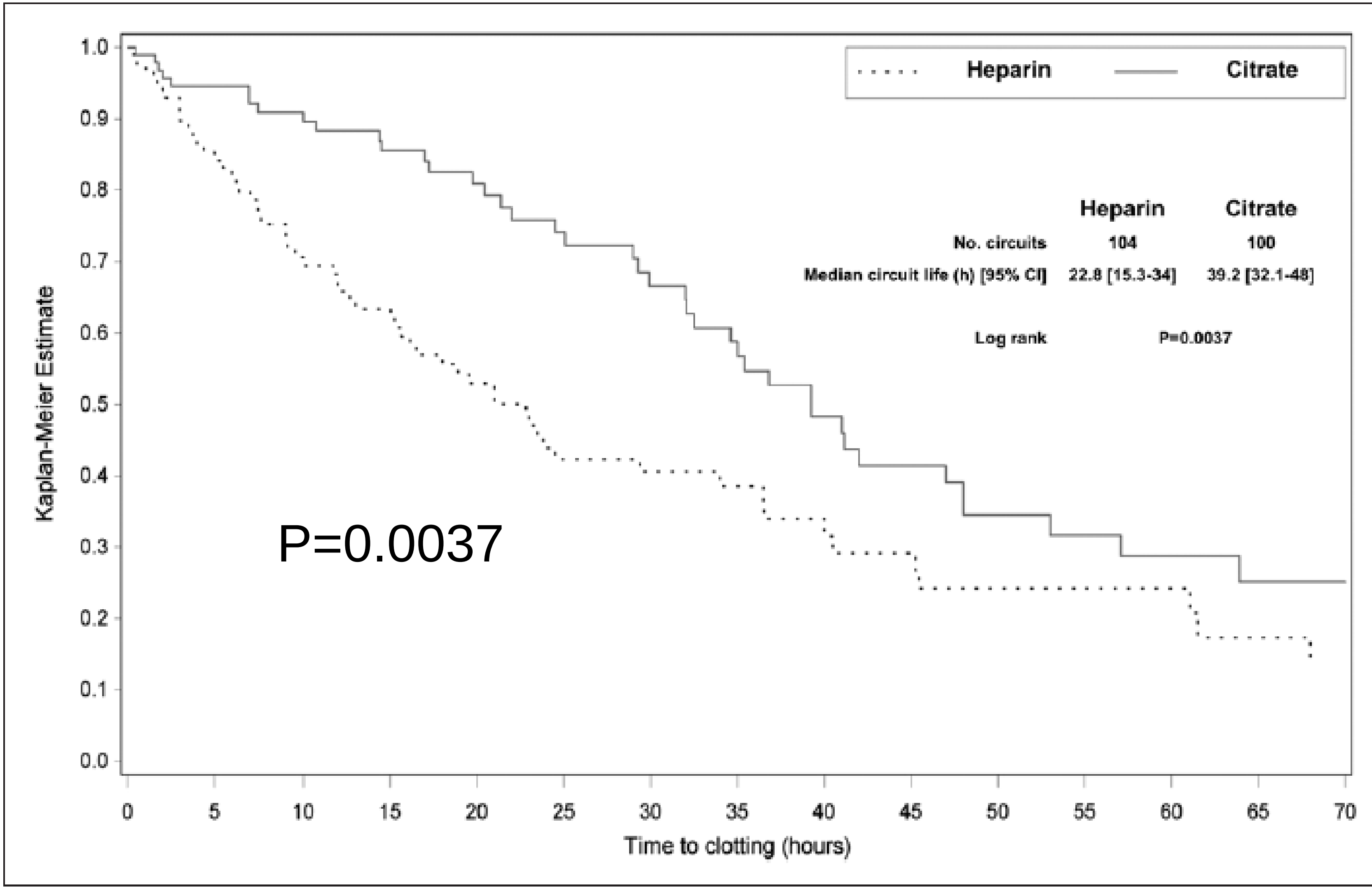

Figure 2. Kaplan-Meier estimate of the probability of continuous renal replacement therapy circuit survival for the first circuit.

For all circuits: HR for clotting 2.03 using frailty model

Conclusions

- Avoidance of fluid overload is important during RRT
- Higher net UF aimed at achieving near dry weight after the initial resuscitation phase is desirable
- Very high net UF rates may be a marker of illness severity and may be undesirable as well
- Much more work is needed in the field of volume control during RRT in ICU
- Fluid composition is moving toward citrate. If citrate CRRT is not applied bicarbonate is the standard