Fluid Management Considerations in CRRT

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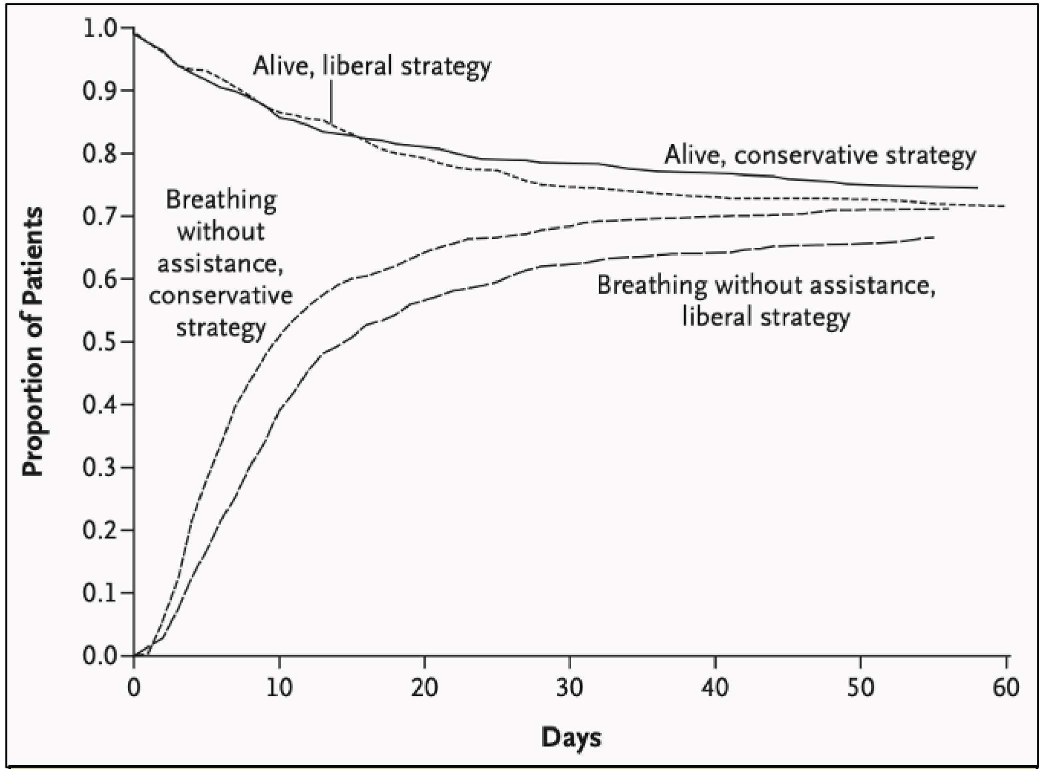
Impact of Fluid Overload on Organ Function and Prognosis in Critical Illness

- For many years, it was recommended that critically ill patients receive large volumes of fluids to enhance renal perfusion and prevent kidney injury.
- Recent studies have changed our understanding of fluid therapy in this population.
- Over the past few decades, research has demonstrated that positive fluid balance is common in critically ill patients and is linked to poor outcomes.
- Fluid overload develops in over two-thirds of critically ill patients with acute kidney injury (AKI) who require kidney replacement therapy (KRT) and is independently associated with morbidity and mortality.

The results of FACTT (Fluid and Catheter Treatment Trial) comparing restrictive versus liberal fluid strategy



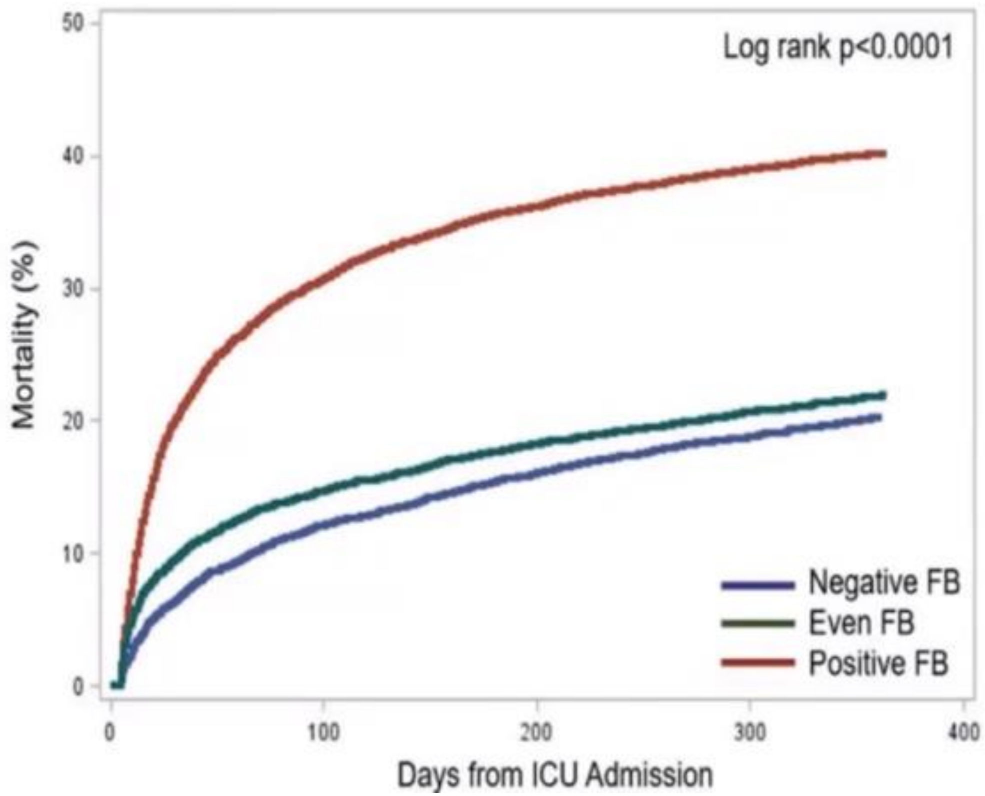
Probability of survival to hospital discharge and breathing without assistance during first 60 days after randomization

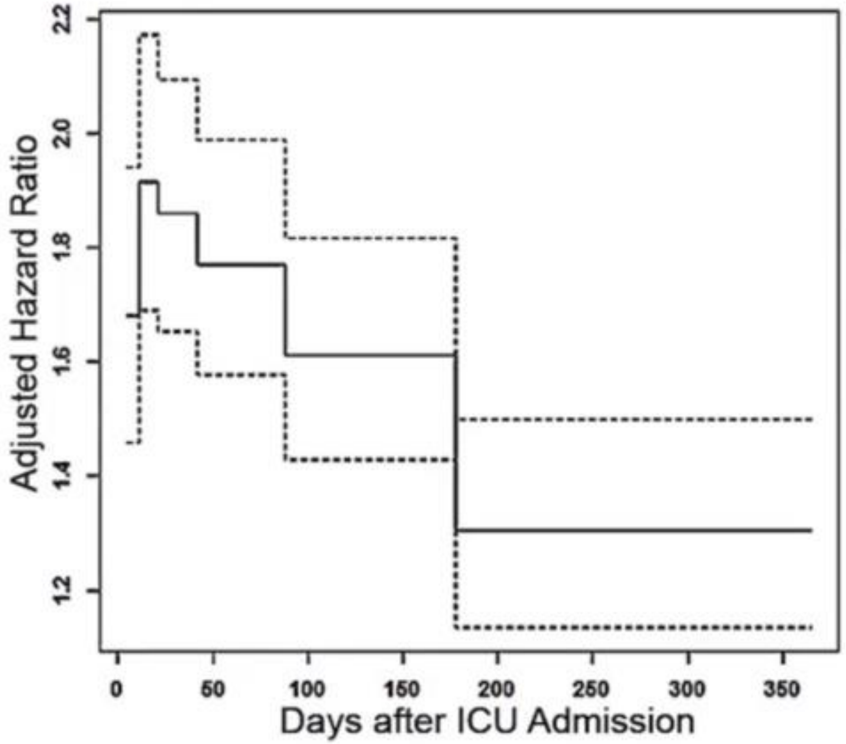
Participants: 1000 patients with ARDS
Type of study: RCT

Outcome	Conservative Strategy	Liberal Strategy	P Value
Death at 60 days (%)	25.5	28.4	0.3
Ventilator-free day from day 1 to 28	14.6 ± 0.5	12.1 ± 0.5	<0.001

Wiedemann HP, et al. N Engl J Med 2006;354(24):2564–75.

Volume overload and mortality in critically ill patients





Balakumar V. , et al. Crit Care Med 2017

Early Reports on the Impact of Fluid Overload in AKI Patients: Increased RRT Need, Worse Recovery, Prolonged Ventilation, and Higher Mortality

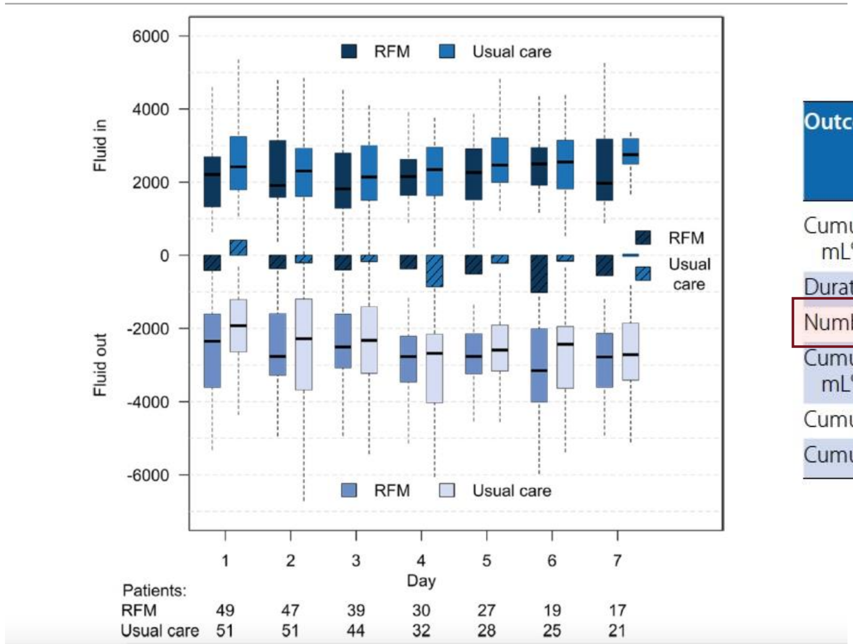
Study	Setting	*n*	Design	Findings
Teixeira *et al.* (2013)[52]	Critically ill adults	601	Secondary analysis of a multicentre observational study	In AKI, higher fluid balance and lower urine volume independently associated with 28-day mortality
Askenazi *et al.* (2013)[130]	Near-term/term sick neonates	58	Prospective single-centre observational study	AKI associated with a net-positive fluid balance and higher mortality
Basu *et al.* (2013)[53]	Paediatric patients undergoing arterial switch operation	92	Retrospective single-centre observational study	AKI associated with higher postoperative day 1 fluid balance and independently associated with prolonged duration of ventilation and hospitalization
Hazle *et al.* (2013)[131]	Infants undergoing congenital heart surgery	49	Prospective single-centre observational study	Fluid overload might be an important risk factor for morbidity at all severities of AKI
Vaara *et al.* (2012)[57]	Critically ill adults with AKI requiring RRT	283	Prospective multicentre observational study	Fluid overload at RRT initiation doubled crude 90-day mortality and remained a significant risk for death after adjustment for demographics and illness severity
Prowle *et al.* (2012)[37]	Studies of perioperative GDT reporting AKI outcomes	24 RCTs	Meta-analysis	GDT significantly reduced risk of postoperative AKI. However, only GDT protocols that were overall fluid neutral were associated with a beneficial renal outcome
Selewski *et al.* (2012)[132]	Paediatric ICU patients requiring ECMO and RRT	53	Retrospective single-centre observational study	Fluid overload at RRT initiation significantly lower in survivors. Correction of fluid overload after initiation of RRT did not improve outcome
Bellomo *et al.* (2012)[62]	Critically ill patients requiring RRT for AKI in the RENAL study	1,453	Retrospective analysis of a multicentre RCT	Negative mean daily fluid balance on RRT consistently associated with risk of death, survival time, RRT-free days, and ICU and hospital-free days
Dass *et al.* (2012)[58]	Cardiovascular surgery patients	94	Retrospective analysis of a single-centre RCT	Positive fluid balance >849 ml in early postoperative period associated with significantly elevated AKI risk
Kambhampati *et al.* (2012)[59]	Adult patients undergoing cardiovascular surgery	100	Prospective single-centre observational study	Progressive severity of positive fluid balance associated with increased AKI risk
Heung *et al.* (2012)[61]	Patients with AKI requiring initiation of RRT	170	Retrospective single-centre observational study	High fluid overload at RRT initiation predicted worse renal recovery at 1 year
Selewski *et al.* (2011)[133]	Critically ill children requiring RRT	113	Retrospective single-centre observational study	Fluid overload at initiation of RRT significantly greater in non-survivors
Grams *et al.* (2011)[55]	Critically ill patients with lung injury enrolled into FACTT	1,000	Retrospective analysis of multicentre RCT	A positive fluid balance after AKI strongly associated with mortality in crude and adjusted analyses; post-AKI diuretic therapy associated with 60 day survival
Fülöp *et al.* (2010)[54]	Critically ill adults with AKI requiring RRT	81	Retrospective single-centre observational study	Volume related weight gain ≥10% and oliguria significantly associated with mortality in multivariable models adjusting for illness severity and diagnosis
Sutherland *et al.* (2010)[56]	Critically ill children with AKI requiring RRT	297	Prospective observational study	≥20% fluid overload at CRRT initiation associated with higher mortality than 10–20% fluid overload, in turn associated with higher mortality than <10% fluid overload; association between degree of fluid overload and mortality remained after adjusting for intergroup differences and severity of illness
Bouchard *et al.* (2009)[51]	Critically ill adults with AKI	618	Secondary analysis of a prospective multicentre observational study	In patients with AKI >10% fluid overload independently associated with 60-day mortality; >10% fluid overload at peak serum creatinine associated with non-recovery of renal function
Payen *et al.* (2008)[50]	Patients enrolled in the SOAP study	3,147	Secondary analysis of a prospective multicentre observational study	Fluid overload an independent risk factor for 60-day mortality in AKI; patients not developing AKI achieved a mean neutral to negative daily fluid balance; AKI associated with daily fluid accumulation

Abbreviations: AKI, acute kidney injury; CRRT, continuous RRT; ECMO, extra-corporeal membrane oxygenation; GDT, goal-directed therapy; ICU, intensive care unit; RCT, randomized controlled trial; RRT, renal replacement therapy.

Prowle, J.R., et al. Nat Rev Nephrol 2014;10, 37–47

Restrictive fluid management versus usual care in AKI (REVERSE-AKI trial)

A multicenter pilot randomized controlled trial on 100 patients with AKI in five European and two Australian ICUs



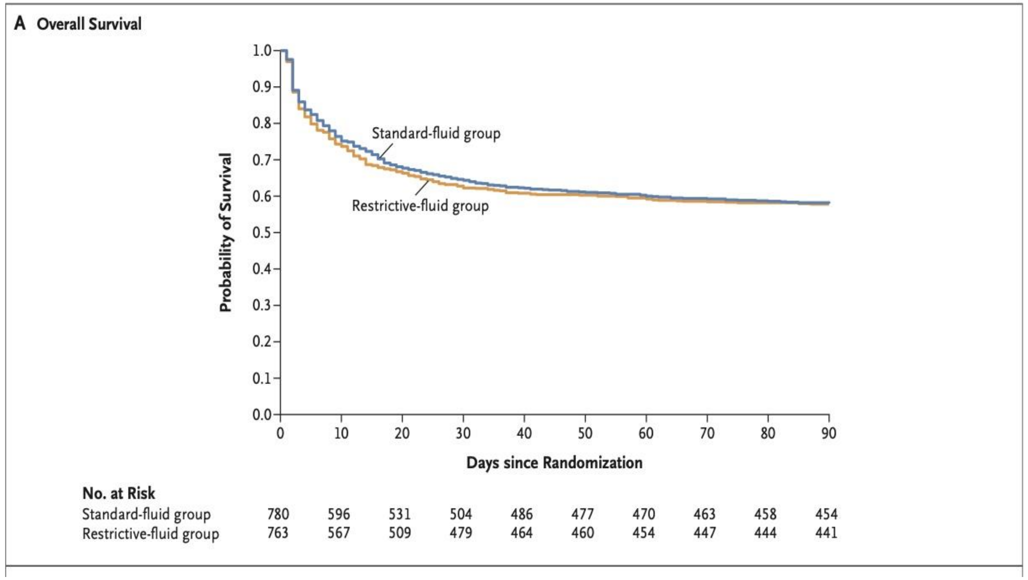
Outcome	Restrictive fluid management ($n=49$)	Usual care ($n=51$)	Restrictive fluid management vs usual care (95% CI)[a]	P value[b]
Cumulative fluid balance at 72 h from randomization, mean (SD) mL[c]	– 1080 (2003)	61 (3131)	– 1148 (– 2200; – 97)	0.033
Duration of AKI (days), median [IQR][d]	2 [1–3]	3 [2–7]	– 1 (– 3; 0)	0.071
Number of patients-receiving RRT, n (%)[e]	6/46 (13)	15/50 (30)	0.42 (0.16; 0.91)	0.043
Cumulative fluid balance at 24 h from randomization, mean (SD) mL[c]	– 416 (1194)	409 (1566)	– 822 (– 1381; – 264)	0.004
Cumulative fluid balance at ICU discharge/day 7, mean (SD) mL[c]	– 2166 (2988)	– 650 (4469)	– 1532 (– 3036; – 29)	0.046
Cumulative dose of furosemide per day, median [IQR] mg[f]	0 (0–19)	1.4 (0–26.2)	0 (– 11; 5.7)	0.700

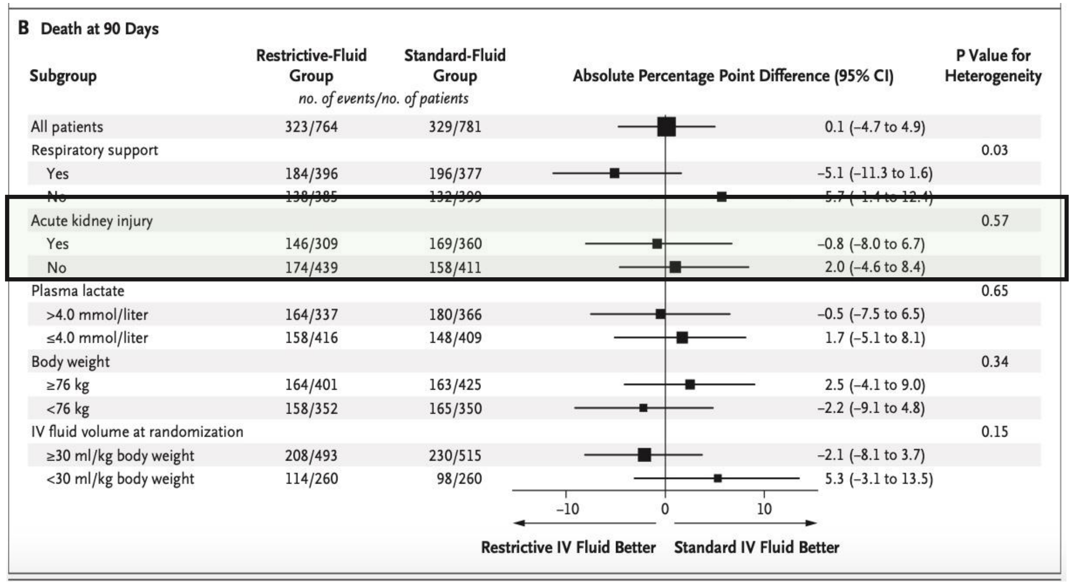
A restrictive fluid management strategy aiming neutral or negative fluid balance after initial resuscitation in patients with AKI was feasible, resulted in low fluid accumulation, and may improve outcome..

Vaara S.T., et al. Intensive Care Med Med 2021

Restriction of Intravenous Fluid in ICU Patients With Septic Shock (CLASSIC trial)

An international RCT on 1545 patient with septic shock

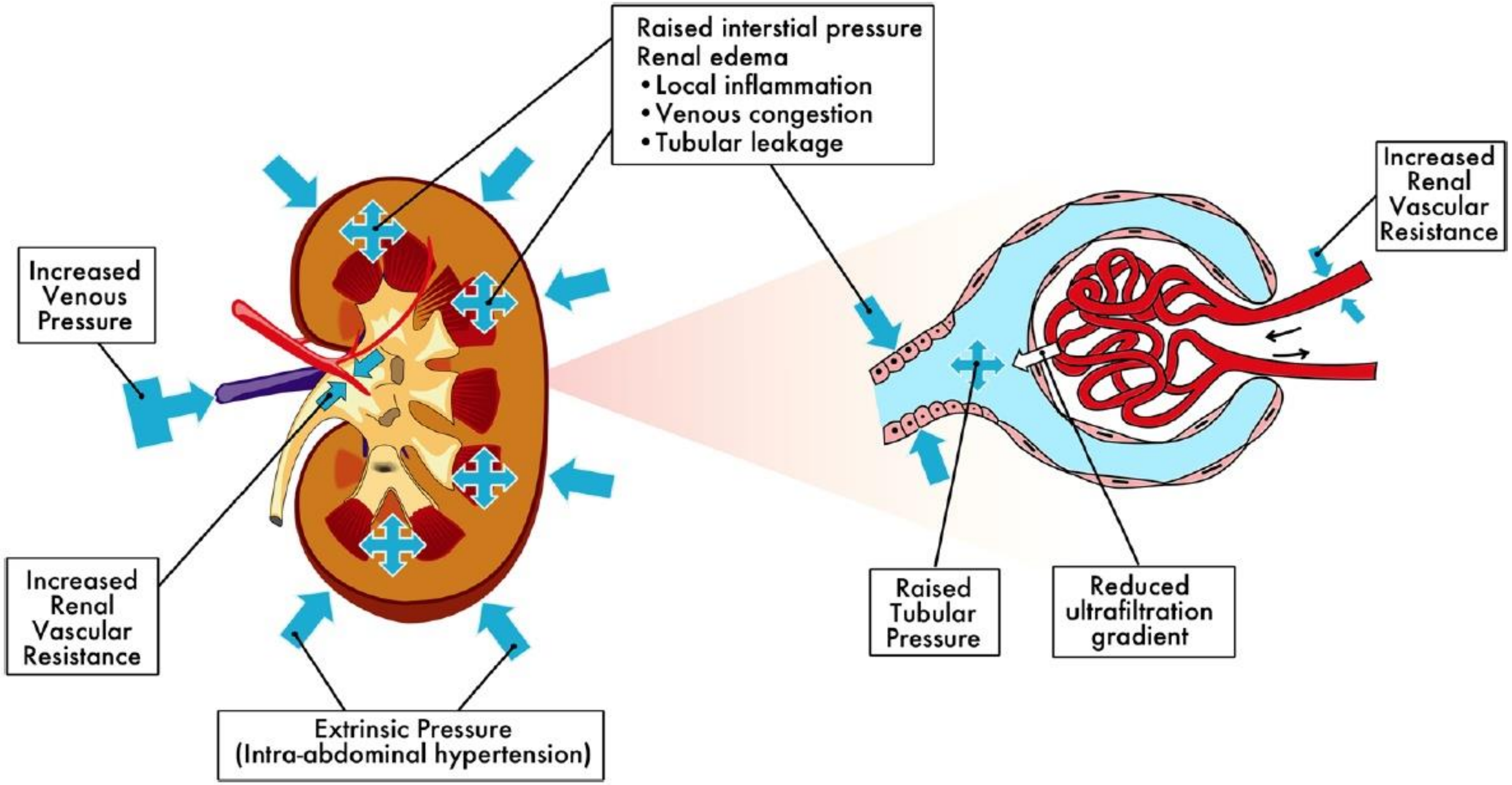




In adult patients with septic shock in the ICU, a restrictive fluid strategy did not lead to a lower 90-day mortality rate compared to standard intravenous fluid therapy. Additionally, there was no significant difference in the incidence of AKI between the two groups.

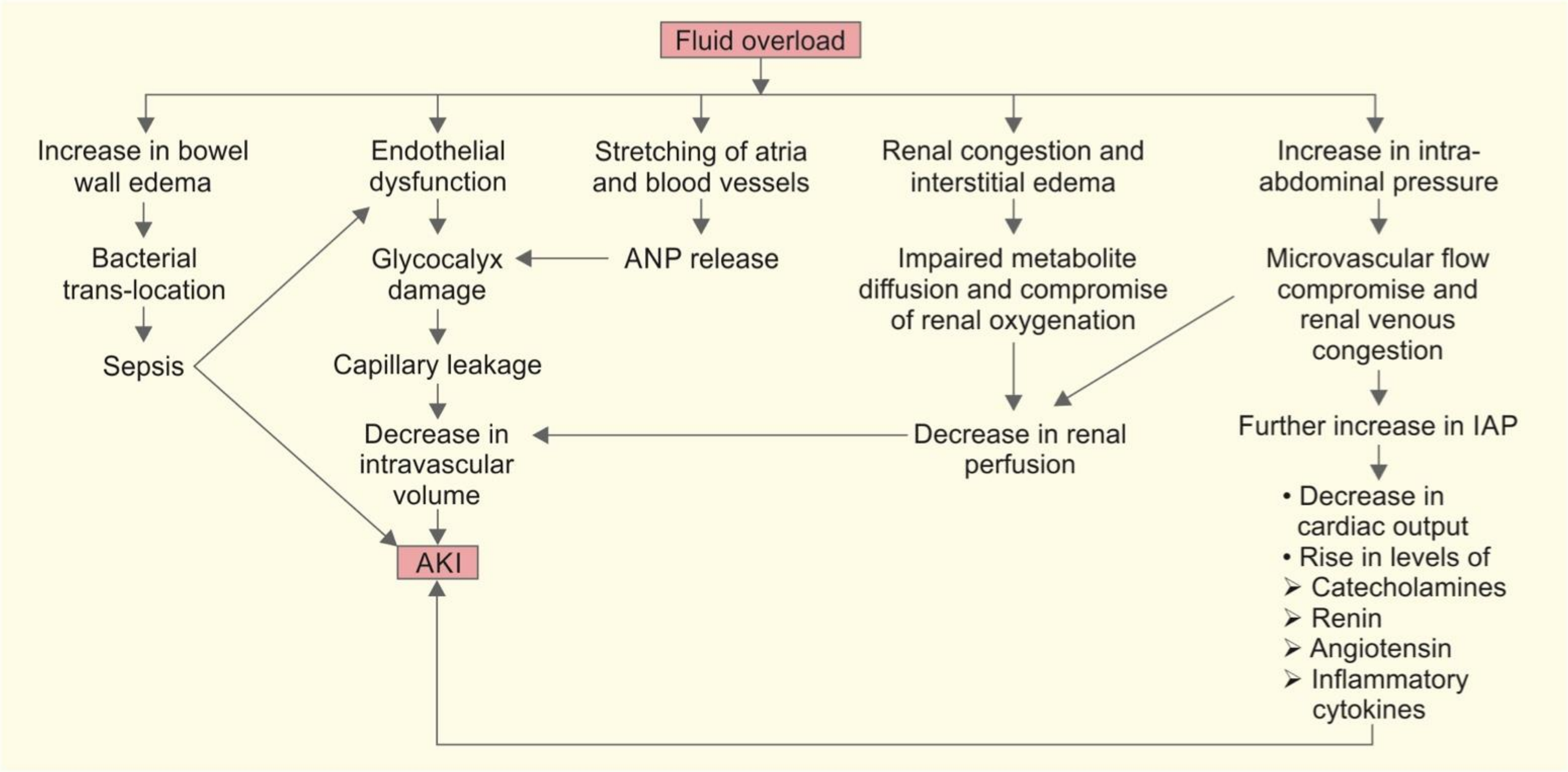
Meyhoff T.S., et al. New Engl J Med 2022;386:2459-2470

Deteriorating Effect of Fluid Overload on Kidney Function



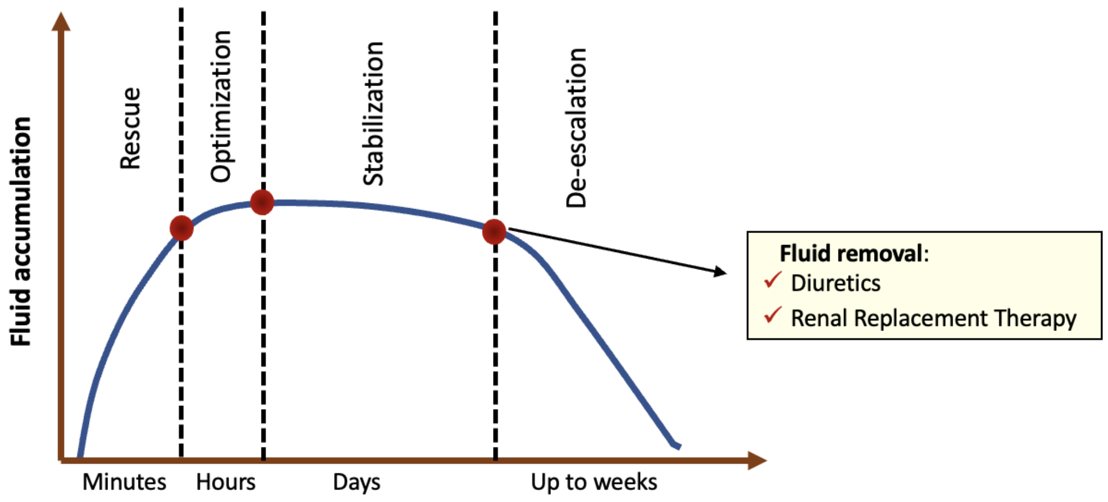
Perner A, et al. Intensive Care Med 2017; 43:807-815

Deteriorating Effect of Fluid Overload



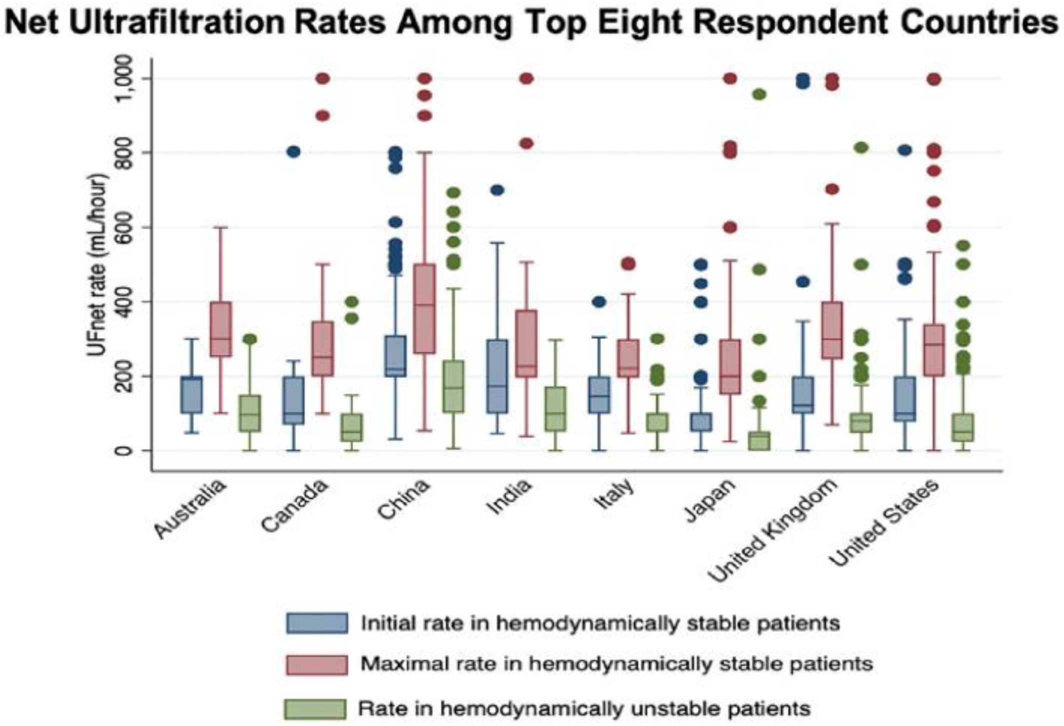
Patil V.P. Indian J Crit Care 2020

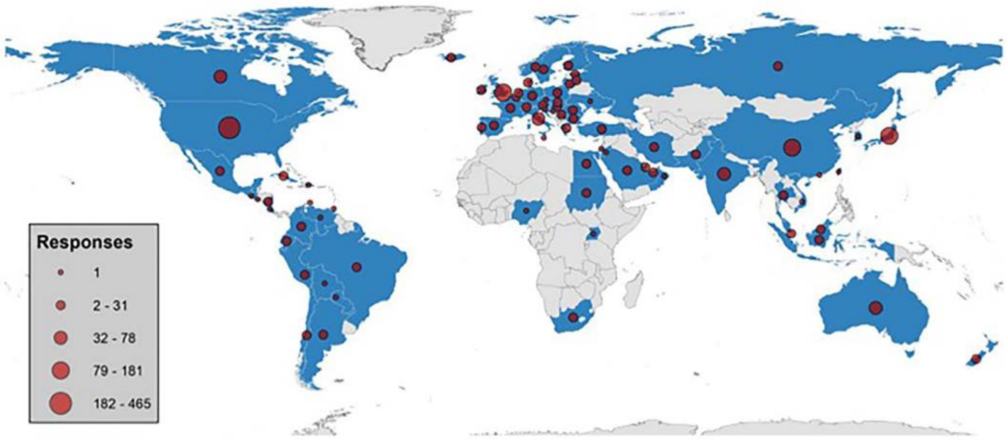
Phases of Fluid Therapy



- When life-threatening fluid overload occurs in patients with oliguric AKI that doesn't respond to diuretics, international guidelines recommend using extracorporeal methods for fluid removal.
- However, the best approach for removing fluid during RRT is still unclear, and clinical practices differ worldwide.

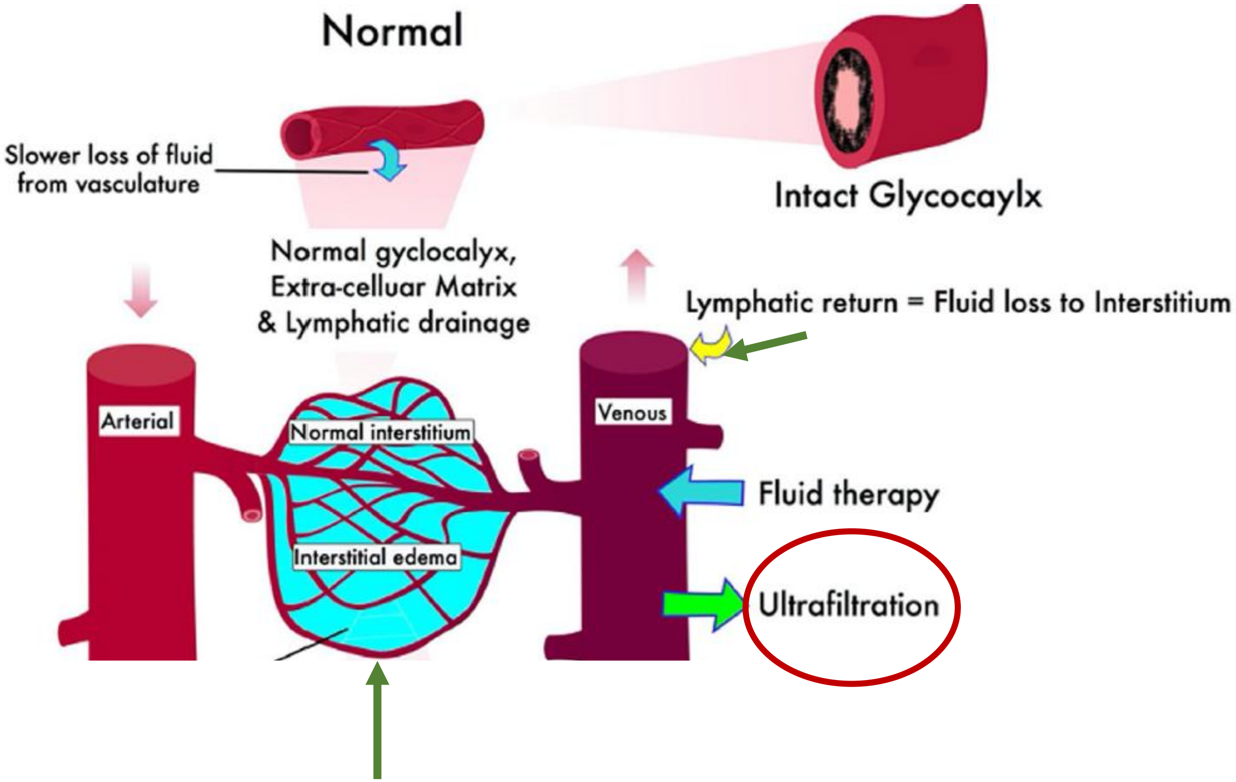
Regional Variation in Prescription and Practice of Net UF

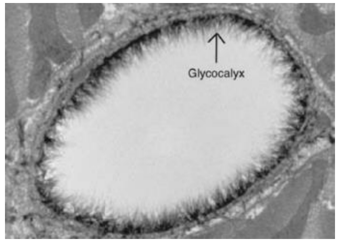




In this multinational study, Net ultrafiltration rates varied significantly across countries ($p < 0.001$ for all three groups), which may be partly due to the absence of evidence-based recommendations and guidelines.

Murugan R et. al. Crit Care Med 2019;

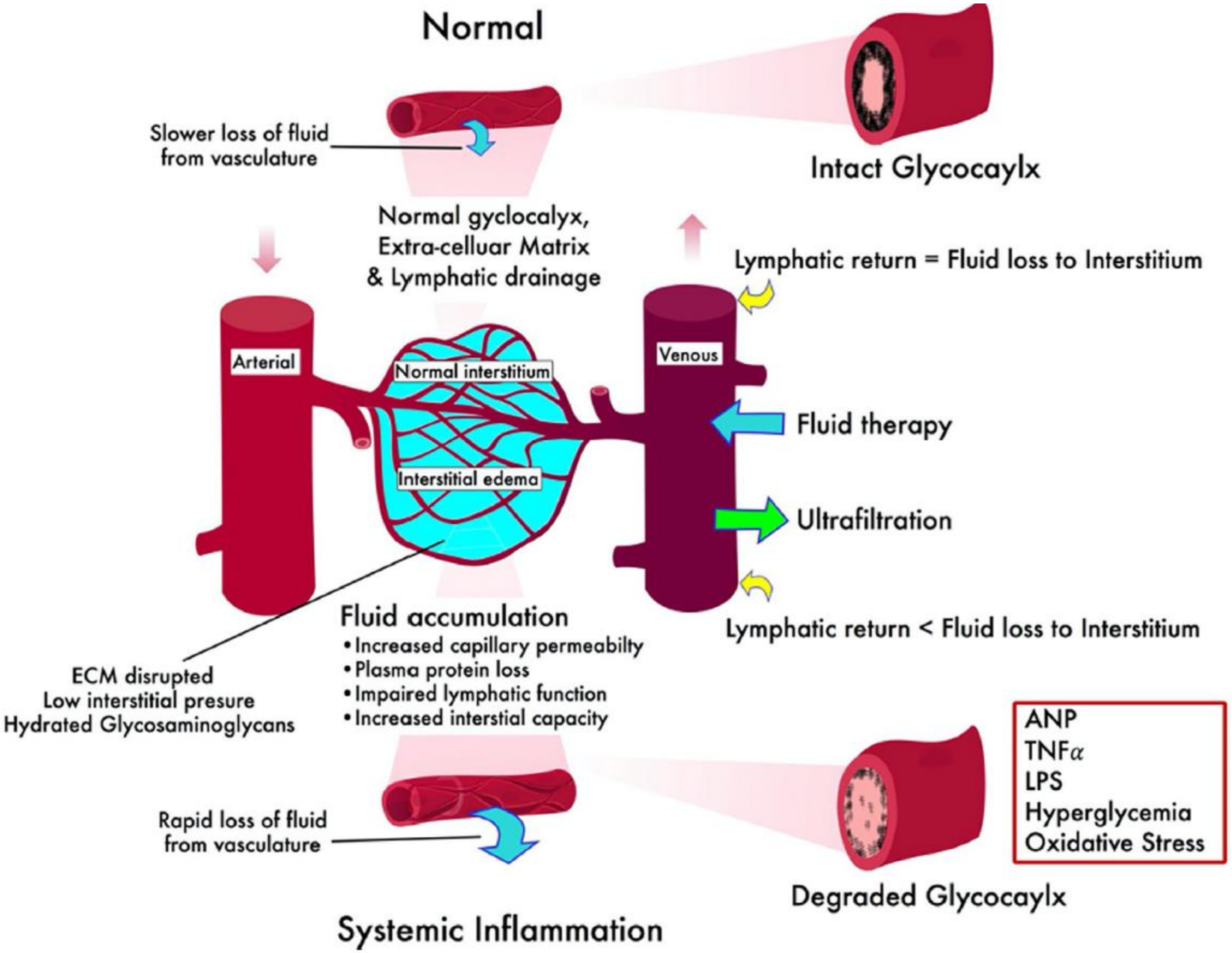


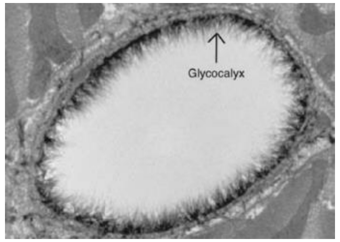


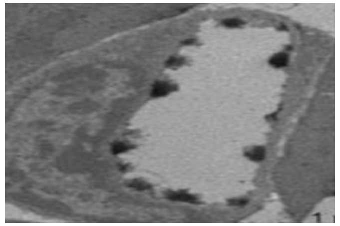
Most vascular refilling happens through the lymphatic return of interstitial fluid. During acute ultrafiltration (UF), this lymphatic flow remains relatively constant. In humans, the total lymph flow through the thoracic duct is approximately 4–5 L/day, or about 200–250 mL/h.

Prowle J., Mehta R. Seminars in Dialysis 2021; 34:440-448

Systemic Inflammation and Fluid Balance

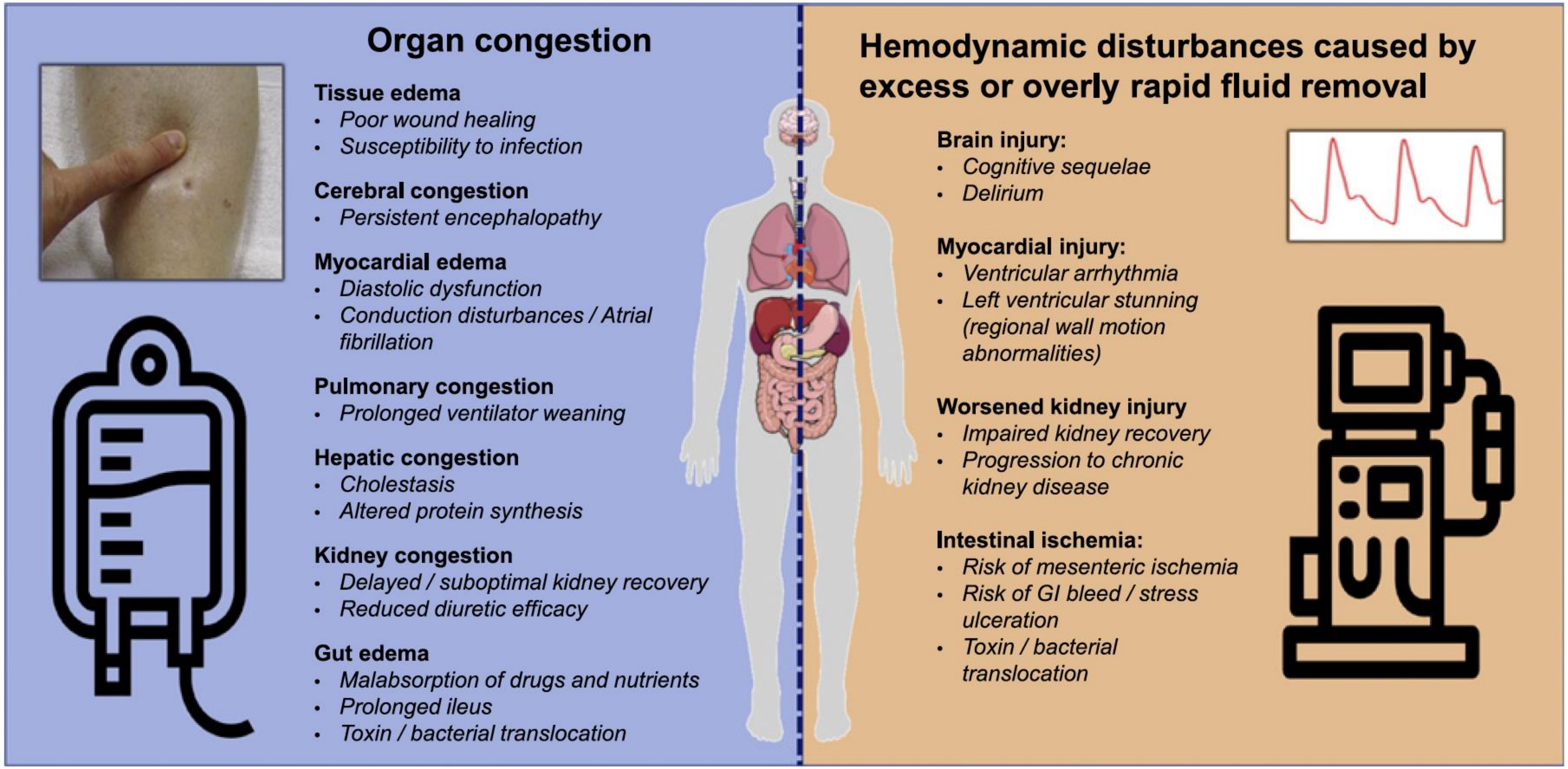






Prowle J., Mehta R. Seminars in Dialysis 2021; 34:440-448

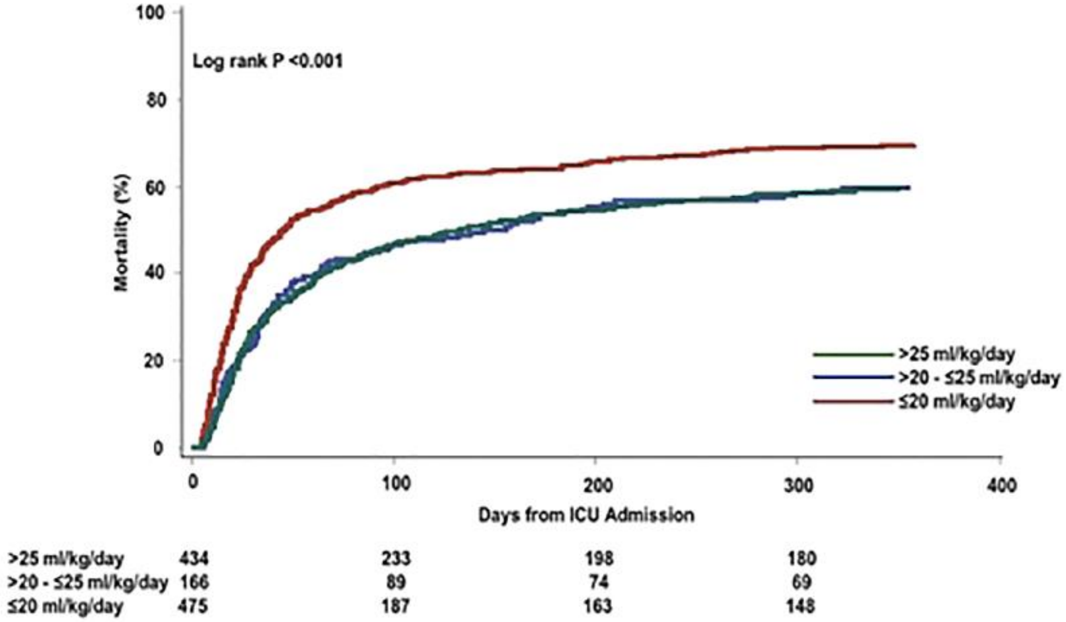
Fluid Management and Adverse Outcomes in Patients with AKI receiving CRRT: Persistent Fluid Accumulation vs. Hemodynamic Disturbance



Teixeira J.P., Blood Purif 2023;52:857–879

Net UF Intensity and Mortality in Critically Ill Patients with AKI and Fluid Overload

Participants: 1075 critically ill patients with fluid overload of >5% ,receiving CRRT or IHD
Type of Study: Observational cohort



Association between intensity of net ultrafiltration and time to mortality from Gray's model

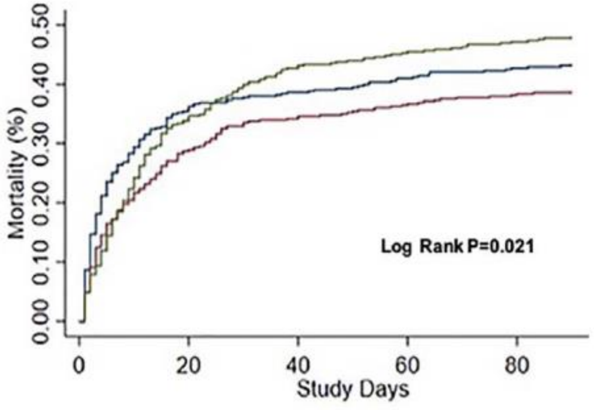
Characteristic	Adjusted hazard ratio (95% CI) by time interval[a]					*p* value
	5–15 days	15–23 days	23–39 days	39–91 days	91–365 days	
High vs low UF^{NET}	0.50 (0.35–0.71)	0.62 (0.46–0.82)	0.73 (0.55–0.97)	0.76 (0.56–1.04)	1.02 (0.71–1.47)	< 0.001
High vs moderate UF^{NET}	0.53 (0.33–0.86)	0.69 (0.46–1.02)	0.75 (0.52–1.09)	0.77 (0.518–1.142)	1.16 (0.72–1.85)	0.039
Moderate vs low UF^{NET}	0.98 (0.62–1.57)	0.87 (0.59–1.27)	0.996 (0.69–1.43)	1.01 (0.69–1.47)	0.844 (0.53–1.34)	0.91

Murugan r., et al. Critical Care 2018; 22:223

Association of Net UF Intensity and Mortality: Secondary Analysis of RENAL Trial Results

Randomized Evaluation of Normal vs Augmented Level of Replacement Therapy (RENAL) trial

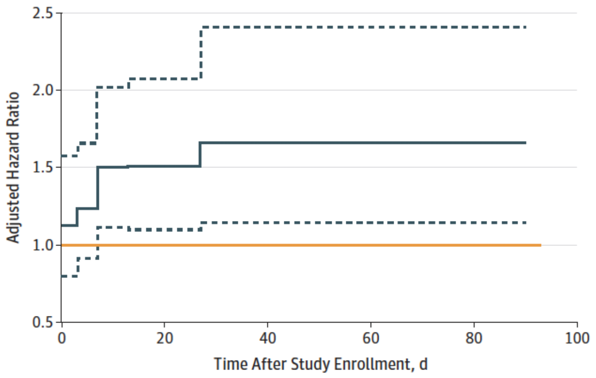
N=1,434



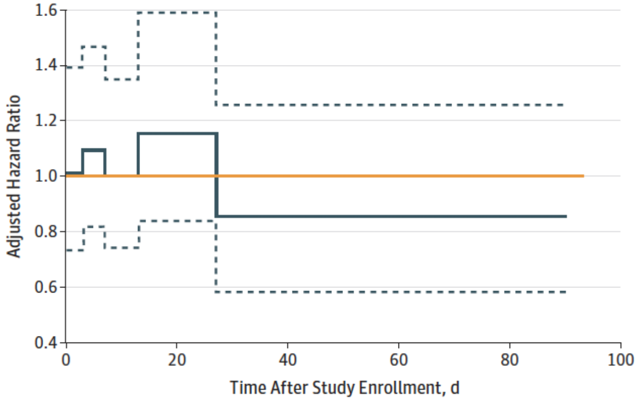
Number at risk					
NUF rate <1.01 mL/kg/h	463	299	284	273	265
NUF rate 1.01 – 1.75 mL/kg/h	474	338	312	301	293
NUF rate >1.75 mL/kg/h	470	311	269	257	248

NUF rate <1.01 mL/kg/h
NUF rate 1.01 – 1.75 mL/kg/h
NUF rate >1.75 mL/kg/h

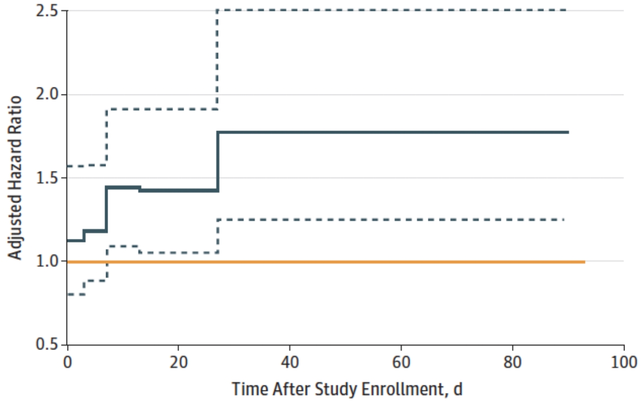
A NUF rate >1.75 mL/kg/h vs NUF rate <1.01 mL/kg/h



B NUF rate 1.01-1.75 mL/kg/h vs NUF rate <1.01 mL/kg/h



C NUF rate >1.75 mL/kg/h vs NUF rate 1.01-1.75 mL/kg/h



Murugan R., et al. JAMA Network Open 2019;2(6):e195418

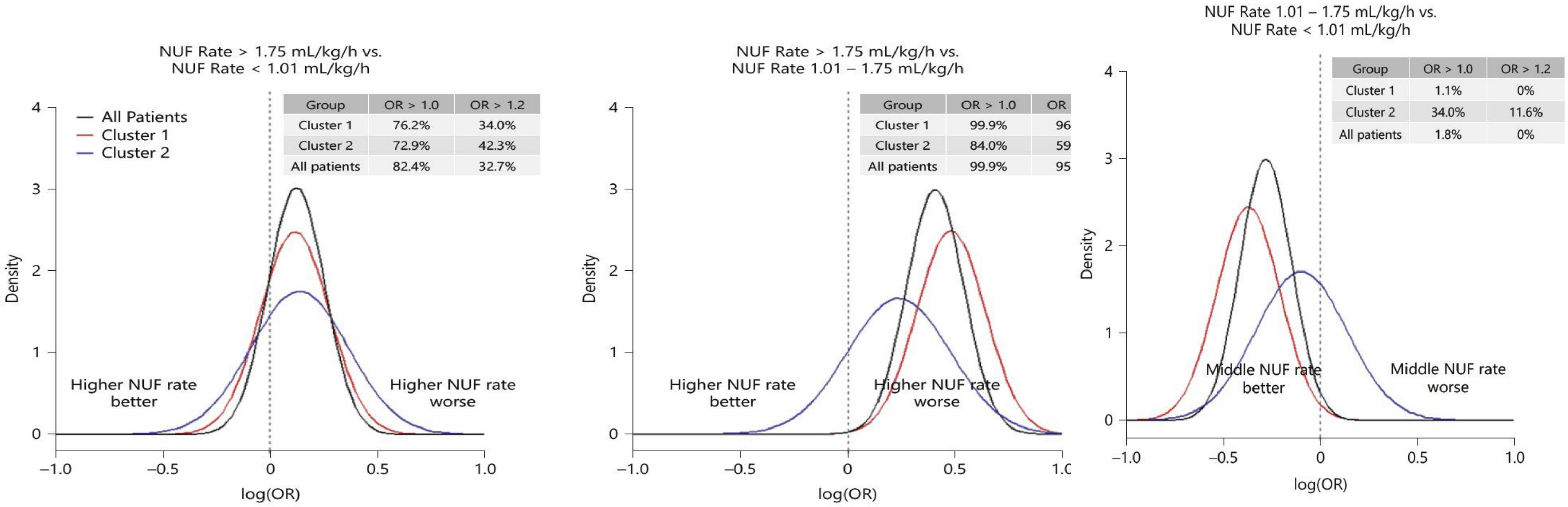
Net UF Intensity and Mortality: Results of a Single Teaching Hospital

NUF rate (mL/kg/h)	Model	Hazard ratio (95% CI) 0–5 days	6–10 days	11–15 days	16–26 days	27–28 days	P-value
No. of patients at risk		347	320	293	274	253	
>1.75 versus <1.01	Unadjusted[a]	0.77 (0.74–0.81)	1.15 (1.12–1.19)	1.49 (1.44–1.54)	1.83 (1.77–1.90)	4.32 (4.15–4.50)	0.004
	Adjusted[b]	1.27 (1.21–1.33)	1.62 (1.55–1.68)	1.87 (1.79–1.94)	1.92 (1.84–2.01)	4.18 (3.98–4.40)	0.031
	No. of deaths, *n*/*N* (%)	34/86 (39.5) versus 41/159 (25.8)	30/82 (36.6) versus 26/144 (18.0)	23/75 (30.7) versus 18/136 (13.2)	36/274 (13.1) versus 8/126 (6.3)	15/253 (5.9) versus 2/120 (1.7)	
>1.75 versus 1.01–1.75	Unadjusted[a]	0.83 (0.80–0.87)	0.85 (0.82–0.88)	1.28 (1.23–1.32)	1.15 (1.11–1.20)	2.23 (2.14–2.32)	0.235
	Adjusted[b]	1.13 (1.08–1.20)	1.05 (1.00–1.09)	1.68 (1.61–1.74)	1.32 (1.27–1.38)	2.27 (2.17–2.38)	0.303
	No. of deaths, *n*/*N* (%)	34/86 (39.5) versus 33/101 (32.7)	30/82 (36.6) versus 26/94 (27.6)	23/75 (30.7) versus 14/82 (17.1)	36/274 (13.1) versus 12/80 (15.0)	15/253 (5.9) versus 4/72 (5.5)	
1.01–1.75 versus <1.01	Unadjusted[a]	0.76 (0.74–0.79)	1.68 (1.62–1.73)	0.91 (0.87–0.94)	1.68 (1.62–1.74)	1.89 (1.81–1.98)	0.053
	Adjusted[b]	0.96 (0.92–1.00)	1.92 (1.85–1.98)	0.83 (0.80–0.86)	1.55 (1.49–1.61)	1.84 (1.76–1.93)	0.061
	No. of deaths, *n*/*N* (%)	33/101 (32.7) versus 41/159 (25.8)	26/94 (27.6) versus 26/144 (18.0)	14/82 (17.1) versus 18/136 (13.2)	12/80 (15.0) versus 8/126 (6.3)	4/72 (5.5) versus 2/120 (1.7)	
Per 0.50 increase	Unadjusted[a]	0.89 (0.88–0.90)	1.01 (1.00–1.01)	1.01 (1.01–1.02)	1.10 (1.09–1.11)	1.30 (1.29–1.31)	0.006
	Adjusted[b]	1.04 (1.03–1.05)	1.12 (1.11–1.13)	1.06 (1.05–1.07)	1.12 (1.11–1.13)	1.33 (1.31–1.34)	0.043

Naorungroj Th., et al., Nephrol Dial Transplant 2021; 36: 1112–1119

Heterogeneity of Effect of Net Ultrafiltration Rate among Critically Ill Adults Receiving CRRT

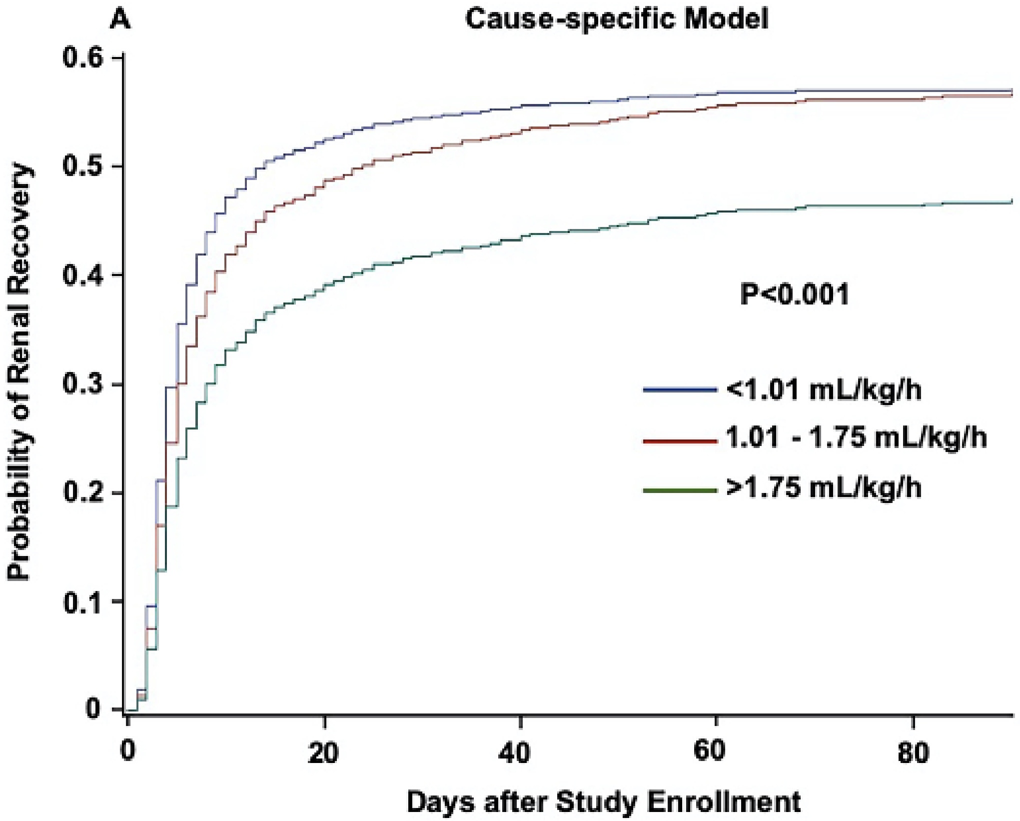
Secondary Analysis of RENAL Trial Results



Cluster 1 vs. cluster 2: more severely ill patients, with more sepsis, more edema, and more vasopressor therapy
Number of patients:1434

Serpa Neto A,et al. Blood Purif 2020;1-11

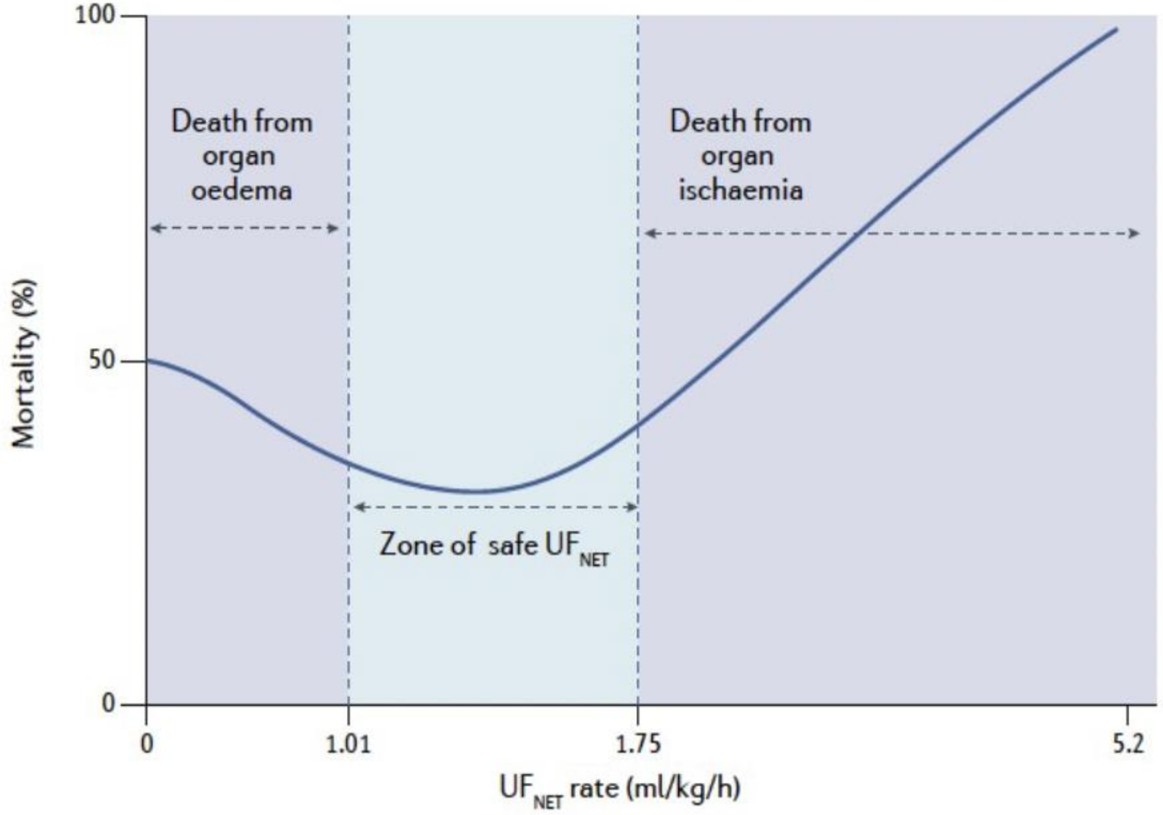
Higher Net UF Rates Are Associated with Lower Renal Recovery



In this study Net UF of more than 1.75 ml/kg per hour was independently associated with lower kidney recovery rates

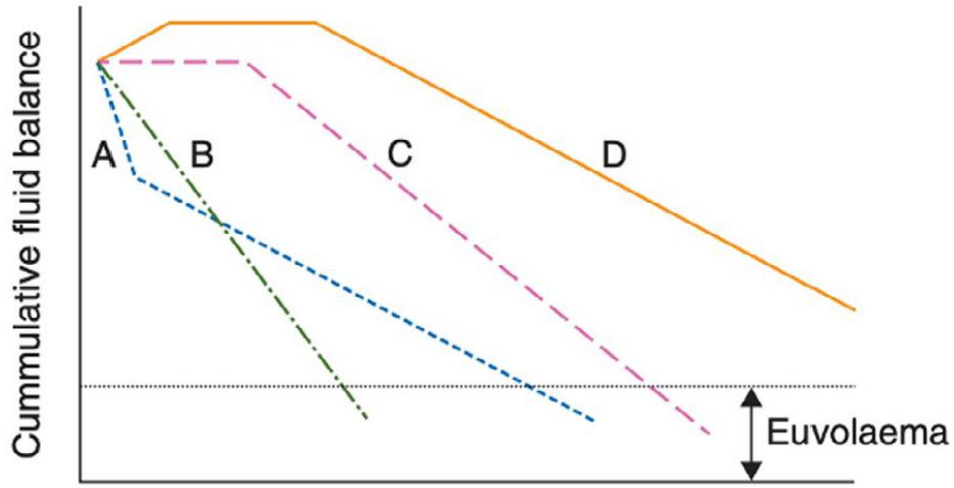
Murugan R et. al. Blood purification 2021

Emerging conceptual model of Net UF rate-outcome relationship



Murugan R et. al. Nature Reviews Nephrology 2021;17: 262-276.

Rate of Mechanical Fluid Removal Based on underlying condition



(A) cardio-renal syndrome
(B) single organ renal failure
(C) AKI complicating severe sepsis
(D) septic shock

Septic shock
UF: 0-100ml/h

Severe sepsis
UF: 0-200ml/h

Single organ AKI
UF: 200-500ml/h

Cardio-renal syndrome
UF: 200-500ml/h

Prowle J., Mehta R. Seminars in Dialysis 2021; 34:440-448

The RELIEVE-AKI trial: Two Strategies of Fluid Removal or Net UF with CRRT

Open access Protocol

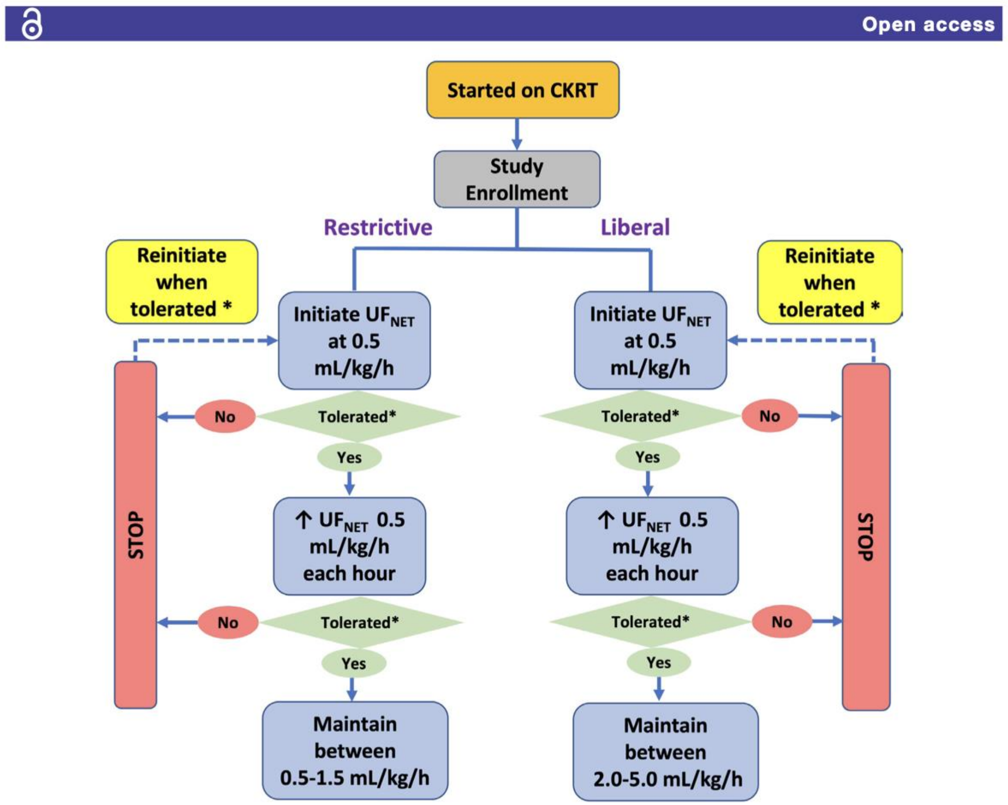
BMJ Open

Restrictive versus Liberal Rate of Extracorporeal Volume Removal Evaluation in Acute Kidney Injury (RELIEVE-AKI): a pilot clinical trial protocol

Raghavan Murugan ,[1] Chung-Chou H Chang,[2] Maham Raza,[3] Nasrin Nikravangolsefid,[4] David T Huang,[3] Paul M Palevsky,[5,6] Kianoush Kashani,[4] for the (RELIEVE-AKI) Study Investigators

Randomized clinical trial funded by NIH to start on April 1st 2022

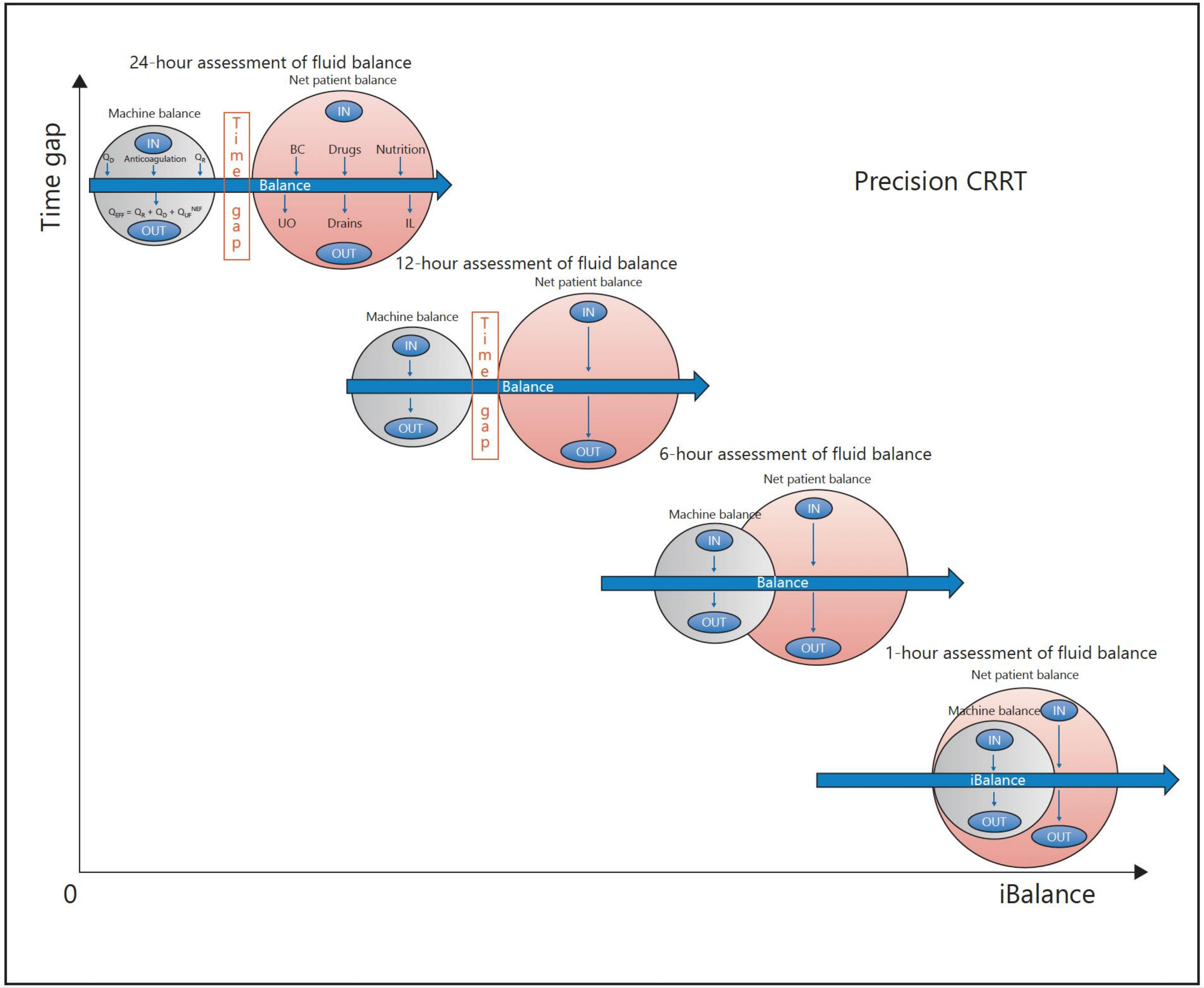
Primary	Secondary
1. Between-group separation in mean delivered UF_{NET} rates of a minimum of 0.53 mL/kg/hour. 2. Protocol deviation defined as UF_{NET} rate out of range of >0.5 mL/kg/hour lower or higher than the assigned UF_{NET} rate range for 6 consecutive hours. 3. Patient recruitment of one patient every 2 months per ICU.	1. Daily fluid balance 2. Cumulative fluid balance 3. Duration of kidney replacement therapy 4. Duration of mechanical ventilation 5. Organ failure-free days 6. ICU length of stay 7. Hospital length of stay 8. Hospital mortality 9. Dialysis dependence at hospital discharge



* Tolerance assessed by MAP ≥65 mmHg and systolic blood pressure ≥90mmHg

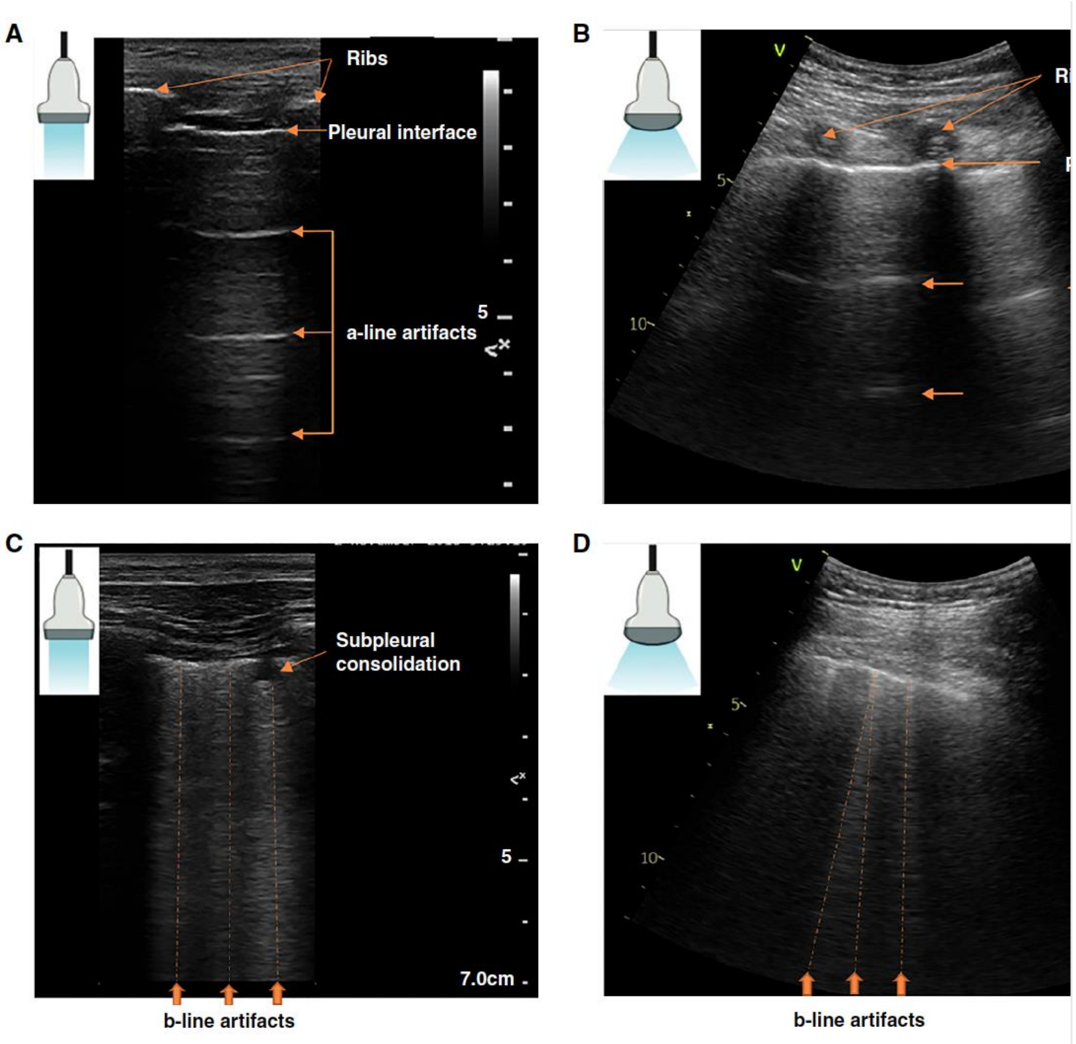
Murugan R, et al. BMJ Open 2023;13:e075960

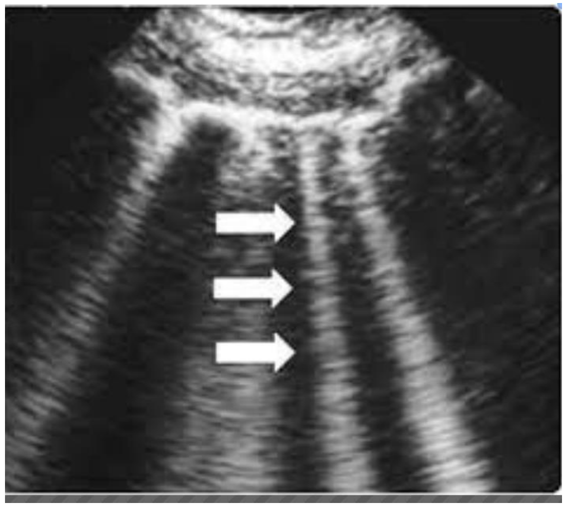
Integrated Fluid Balance: Machine Fluid Balance and Patient Fluid Balance



Murugan R., et al.Blood Purif 2016;42:266–278

Lung Sonography in Assessment of Fluid Status



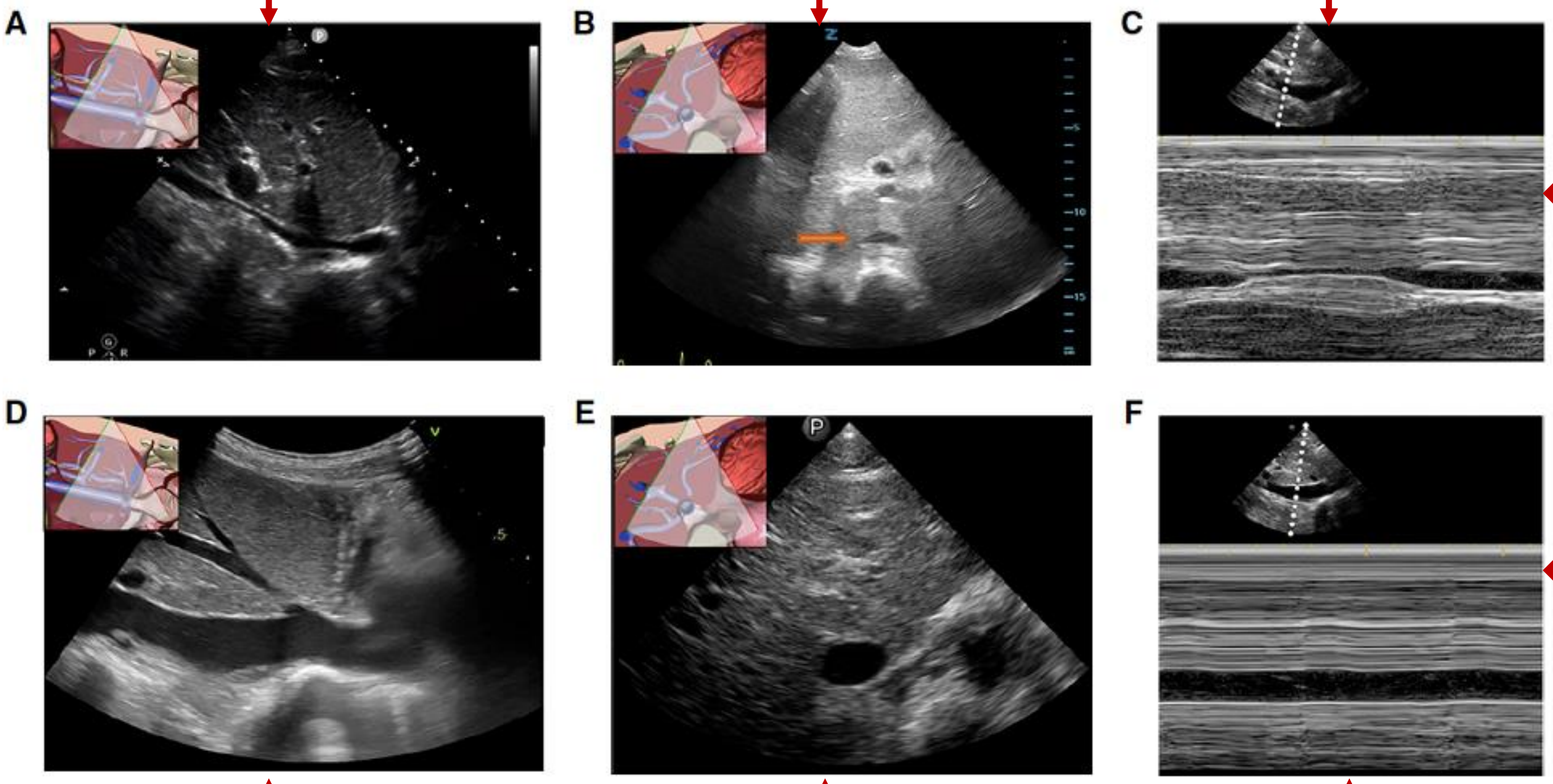


Inferior Vena Cava Diameter and Distensibility in Assessment of fluid Status

Maximum diameter of IVC: < 2.1 cm

An oval appearance in transverse view

Respiratory variations of 50%



Normal/low right atrial pressure (0–5 mm Hg)

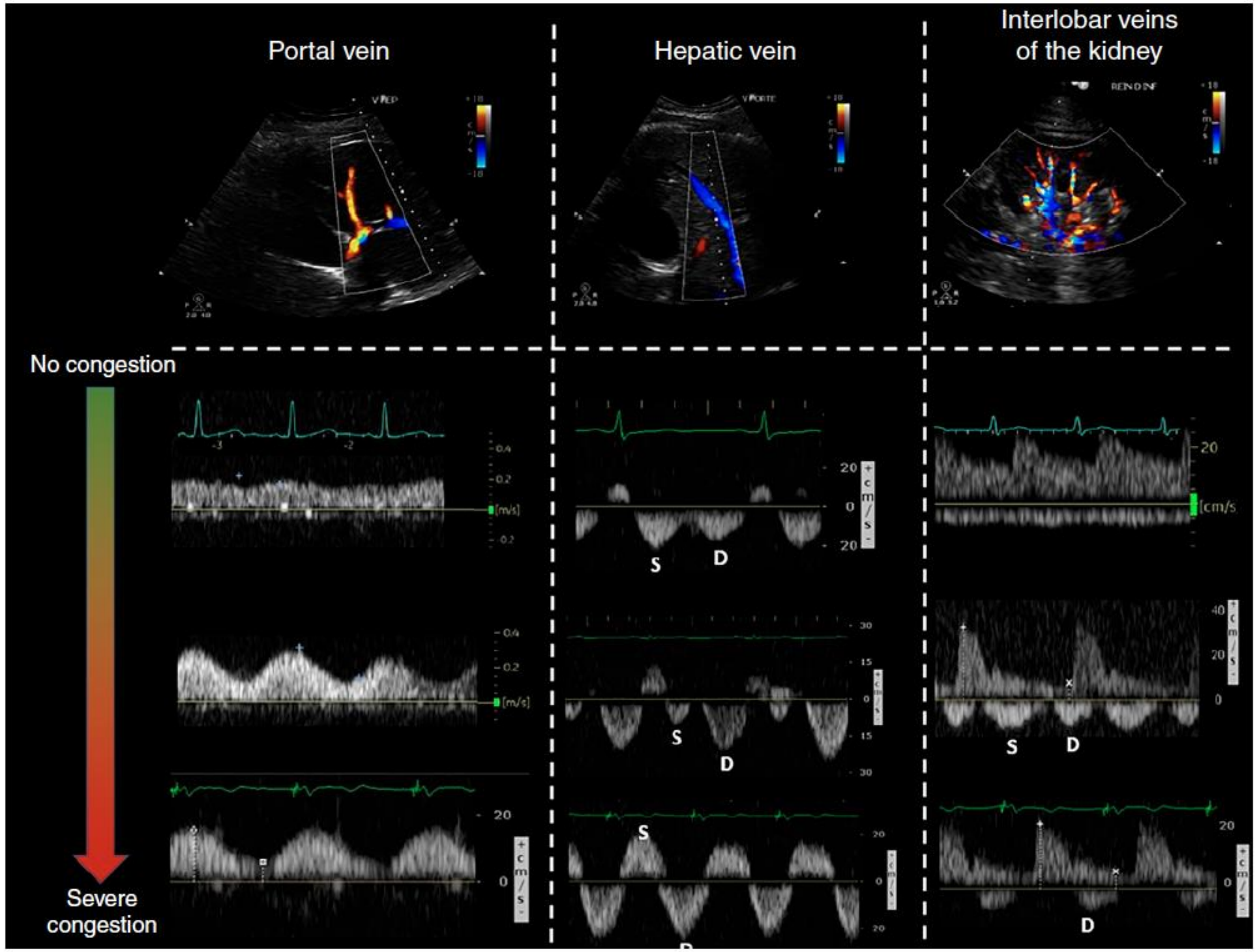
High right atrial pressure (>10 mm Hg).

Distended IVC

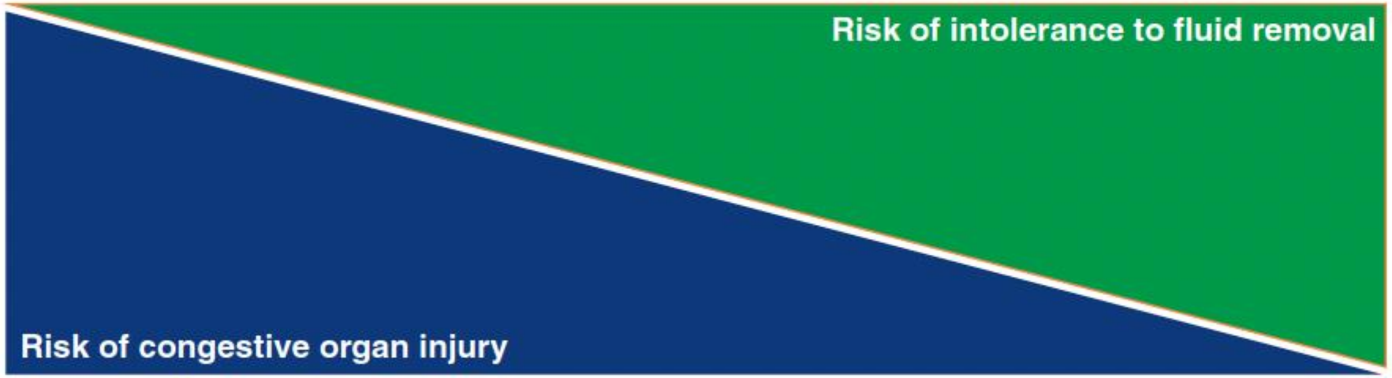
A round appearance in transverse view

Absence of variations of 50%.

Evaluating Systemic Venous Congestion by Venous Doppler Ultrasound



Evaluating the Risk and Benefit of Fluid Removal: Combining Clinical Information and POCUS

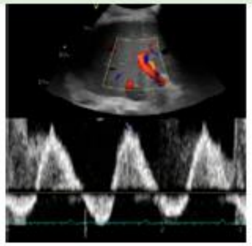


Clinical evaluation

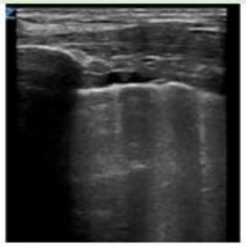
- Fluid accumulation (i.e. cumulative fluid balance)
- Peripheral edema
- Weight increase
- Elevated CVP, PAP
- Vasopressor support
- Mechanical ventilation
- High net UF requirements
- Important pulse pressure variations
- Stage of critical illness

Supporting ultrasonographic features

Abnormal venous Doppler patterns



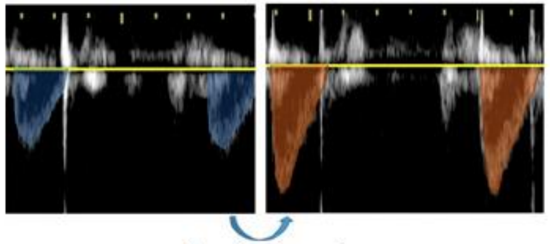
Alveolo-interstitial syndrome



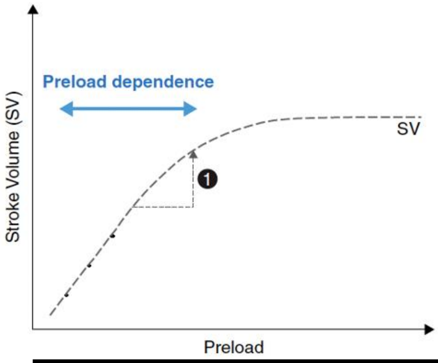
IVC Plethoric

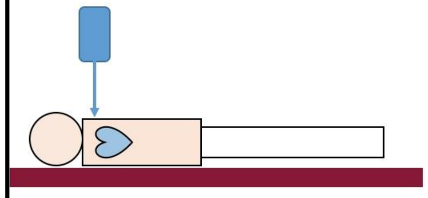
IVC Non-Plethoric

Signs of pre-load dependance

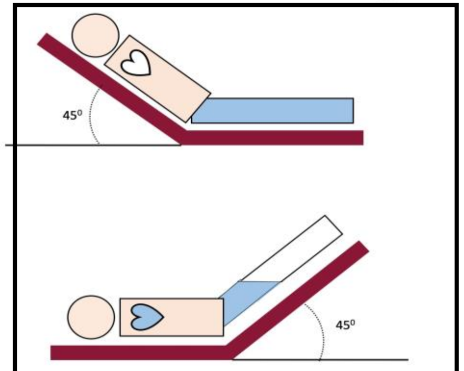


Passive leg raise





fluid challenge tests



leg raising

Conclusion

- Patients with AKI requiring RRT in the ICU are among the most critically ill patients , with a high rate of fluid overload which is associated with poor outcomes such as prolonged AKI and non-recovery.

- There is a bidirectional relationship between net ultrafiltration (UF) and mortality, with rates of 1.01–1.75 mL/kg/h being associated with better survival and renal recovery compared to rates higher than 1.75 mL/kg/h or lower than 1.01 mL/kg/h in CRRT-treated patients.

- These findings emphasize the critical need for ongoing evaluation of fluid management strategies to optimize outcomes.

- To guide fluid management, clinicians integrate several clinical factors, such as bedside physical exams. In addition to evaluating peripheral edema and monitoring hemodynamic data, POCUS has become a useful aid in refining decision-making for fluid removal therapy.