RRT in Critically ill Patient

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outline:

- Time of initiation
- Therapy dose
- Filter membrane
- Modality choice
- RRT discontinuation

Indications for RRT in patients with AKI

Indications for RRT in patients with AKI

- Renal replacement therapy (RRT) : mainstay of supportive therapy in severe AKI

- Severe AKI, requiring renal replacement therapy, occurs in 5-13% of patients and has a mortality rate of 50-80%

Indications for RRT in patients with AKI

Appropriate time

Absolute indication for RRT

- Refractory fluid overload
- Severe hyperkalemia (k>6.5 mEq/L) or rapidly rising k
- Signs of uremia(pericarditis, encephalopathy, or an otherwise unexplained decline in mental status)
- Severe metabolic acidosis (pH <7.1)
- Certain alcohol and drug intoxications

ELECTIVE INITIATION for RRT

- Serum potassium >6.0 mEq/L, or >5.5 mEq/L if there is ongoing tissue breakdown or ongoing potassium absorption (GI bleeding)
- Severe metabolic acidosis (pH <7.2) despite optimal medical management
- Hypervolemic patients who remain in persistent positive fluid balance despite aggressive attempts at diuresis

Is early dialysis better than late ?

Is early dialysis better?

- What is meant by early dialysis?

- What is meant by late dialysis?

❖Urea or cr

❖Urine output

❖Time to ICU admission

No clear definitions

Appropriate time for initiation RRT: Is there potential benefit for early RRT??

Most of the evidence available from studies published between 2000 and 2010 came from observational studies

observational studies, as well as study-level meta-analyses including them, suggested a potential benefit for early RRT

Early RRT [redacted]

The ELAIN Trial

THE BOTTOM LINE

	ELAIN trial (N=231)	AKIKI trial (N=620)
Centers	1 (Germany)	31 (France)
Inclusion Criteria		
AKI Stage	Stage 2	Stage 3
Other Criteria	At least 1 of: • Severe sepsis • On vasopressors • Refractory fluid overload • SOFA score ≥2	At least 1 of: • Mechanically ventilated • On vasopressors
Biomarker	Serum NGAL >150 ng/mL	None
Dialysis Triggers		
Early Group	Within 8 h of stage 2	Within 6 h of stage 3
Delayed Group	12 h after progressing to KDIGO stage 3 AKI or any of the following dialysis triggers: • BUN >100 mg/dL • K >6 mEq/L (or ECG changes) • Mg >4 mmol/L • Urine <200 mL/24 h • Organ edema despite diuretics	Any of the following dialysis triggers: • BUN >112 mg/dL • K >6 mEq/L (or 5.5 mEq/L with treatment) • pH <7.15 (pure metabolic or mixed) • Pulmonary edema with Fio_2 >0.5 (or O_2 >5 L/min or oligo/anuria >72 h)
Various criteria		
Outcomes		
90-d Mortality; early vs delayed (%)	39.3 vs 54.7 ($P = .03$) Absolute risk reduction 15.34%, Number needed to treat (NNT) is 7, Fragility Index 3	48.5 vs 49.7 ($P = .79$)
Patients Needing Dialysis in Delayed Group (%)	90.8	51.0

Does early initiation of Kidney Replacement Therapy (KRT) decrease mortality? A comparison of the RCTs

	ELAIN	AKIKI	IDEAL-ICU
Design (all were RCTs)	Single-surgical center Germany N = 231	Multicenter France N = 620	Multicenter France N = 488
AKI severity & Early KRT criteria	KDIGO Stage 2 AKI + NGAL >150ng/ml	KDIGO stage 3 on ventilator &/or vasopressors	RIFLE-F AKI Early septic shock
Time-frame early KRT start within...	8 hours	6 hours	12 hours
% Received KRT (early vs late)	100% vs 91%	98% vs 51%	97% vs 62%
Mortality (early vs late)	90-day 39% vs 54%	60-day 49% vs 50%	90-day 58% vs 54%
Unique findings	Time on KRT, Kidney recovery, and ventilator time favored early group	61% of survivors did not receive KRT & fewer catheter infections in delayed group	Time on KRT, Kidney recovery, and ventilator time favored early group
ICU Length of stay	No difference	No difference	No difference
Limitations & Critiques	Results potentially skewed as many early start patients may have recovered without KRT	Limited generalizability as ≅ 50% received iHD and 30% CRRT	Inconsistencies between KDIGO and RIFLE AKI criteria
References	Zarbock et al. JAMA 2016	Gaudry et al. NEJM 2016	Barbar et al. NEJM 2018

better survival outcome

Pasin *et al. BMC Anesthesiology* (2019) 19:62
https://doi.org/10.1186/s12871-019-0733-7

BMC Anesthesiology

RESEARCH ARTICLE Open Access

Early initiation of renal replacement therapy in critically ill patients: a meta-analysis of randomized clinical trials

Laura Pasin*, Sabrina Boraso and Ivo Tiberio

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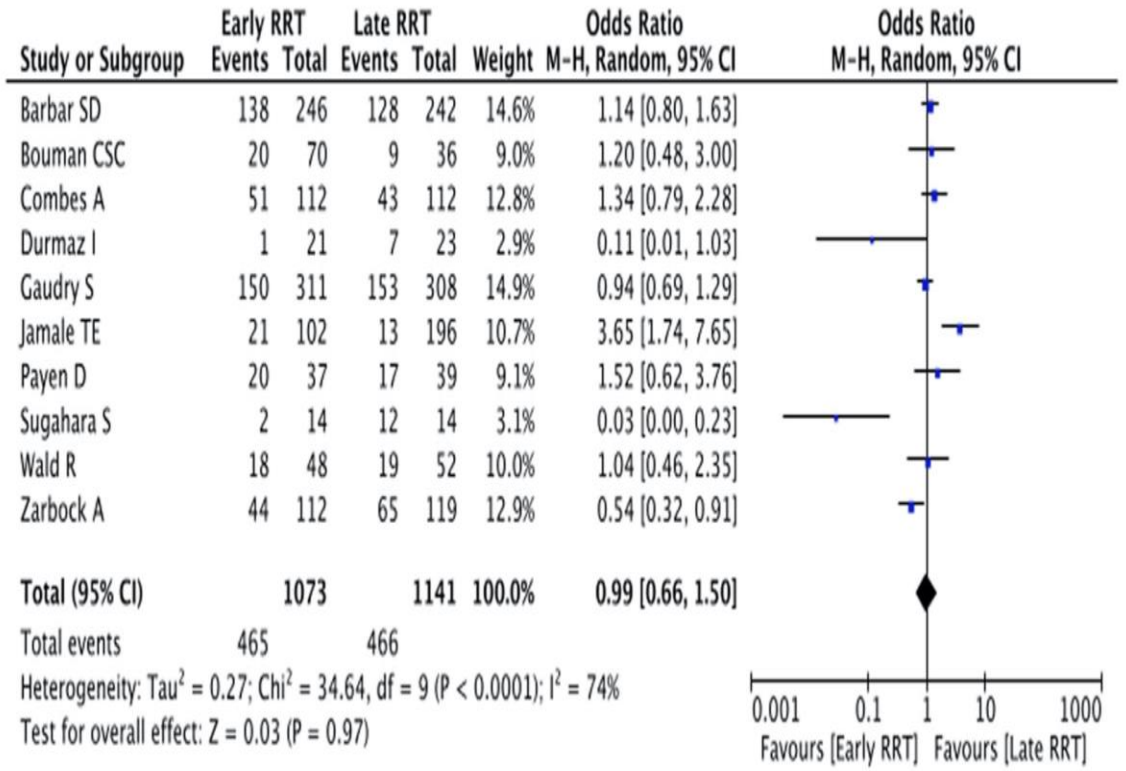

Fig. 2 Forest plot for mortality

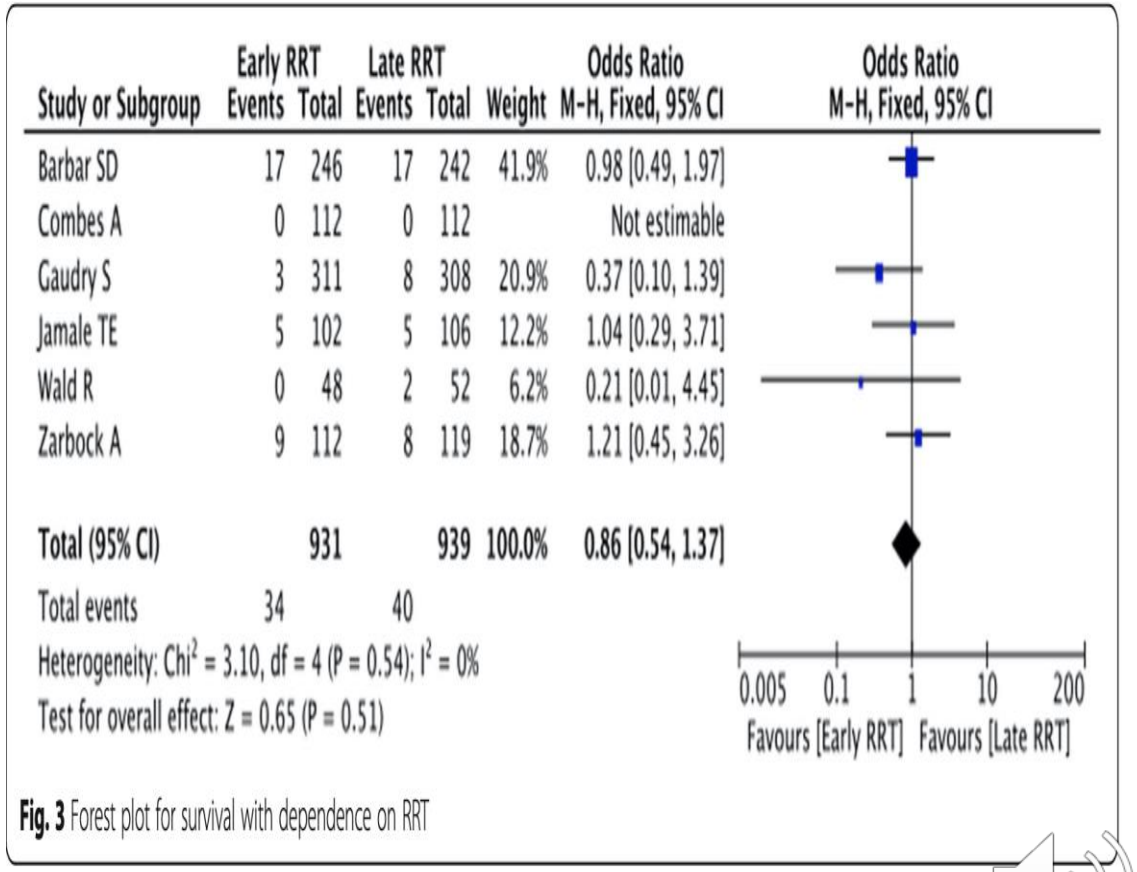

Fig. 3 Forest plot for survival with dependence on RRT

Conclusions: early initiation of RRT in critically ill patients with AKI does not provide a clinically relevant advantage when compared with standard/late initiation

Pasin *et al. BMC Anesthesiology* (2019) 19:62
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- Problem in this study:

(1) standardized definition of “early” and “late” initiation of RRT

(2) special populations such as the septic shock patients or post cardiac surgery patients

- Not probably allow to draw definitive conclusions on the optimal timing of starting RRT in critically ill patients

PLOS ONE

RESEARCH ARTICLE

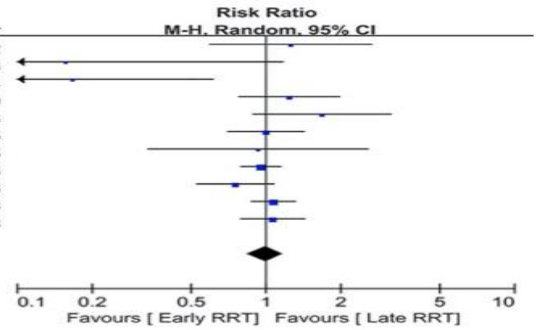
Early versus late initiation of renal replacement therapy for acute kidney injury in critically ill patients: A systematic review and meta-analysis

Li Xiao[1☯], Lu Jia[2☯], Rongshan Li[2], Yu Zhang[3], Hongming Ji[2]*, Andrew Faramand[4]

Short-term mortality (≤ 31days)

Study or Subgroup	Early initiation of RRT Events	Total	Late initiation of RRT Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Bouman 2002	11	35	9	36	4.2%	1.26 [0.59, 2.66]	2002
Durmaz 2003	1	21	7	23	0.7%	0.16 [0.02, 1.17]	2003
Sugahara 2004	2	14	12	14	1.5%	0.17 [0.05, 0.61]	2004
Payen 2009	20	37	17	39	8.6%	1.24 [0.78, 1.97]	2009
Jamale 2013	21	102	13	106	5.4%	1.68 [0.89, 3.17]	2013
Combes 2015	40	112	40	112	12.1%	1.00 [0.70, 1.42]	2015
Wald 2015	6	48	7	52	2.4%	0.93 [0.34, 2.57]	2015
Gaudry 2016	129	311	134	308	19.8%	0.95 [0.79, 1.15]	2016
Zarbock 2016	34	112	48	119	11.9%	0.75 [0.53, 1.07]	2016
Barbar 2018	111	246	102	242	18.9%	1.07 [0.87, 1.31]	2018
Lumlertgul 2018	36	58	35	60	14.4%	1.06 [0.79, 1.43]	2018
Total (95% CI)		**1096**		**1111**	**100.0%**	**0.99 [0.84, 1.17]**	
Total events	411		424				

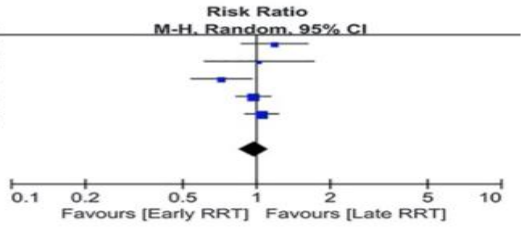
Heterogeneity: Tau² = 0.03; Chi² = 17.79, df = 10 (P = 0.06); I² = 44%
Test for overall effect: Z = 0.08 (P = 0.93)



Long-term mortality (60-180 days)

Study or Subgroup	Early initiation of RRT Events	Total	Late initiation of RRT Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Combes 2015	51	112	43	112	14.6%	1.19 [0.87, 1.62]	2015
Wald 2015	18	48	19	52	6.6%	1.03 [0.62, 1.71]	2015
Zarbock 2016	44	112	65	119	16.6%	0.72 [0.54, 0.95]	2016
Gaudry 2016	150	311	153	308	30.6%	0.97 [0.83, 1.14]	2016
Barbar 2018	143	246	134	242	31.5%	1.05 [0.90, 1.23]	2018
Total (95% CI)		**829**		**833**	**100.0%**	**0.98 [0.85, 1.13]**	
Total events	406		414				

Heterogeneity: Tau² = 0.01; Chi² = 6.85, df = 4 (P = 0.14); I² = 42%
Test for overall effect: Z = 0.31 (P = 0.76)



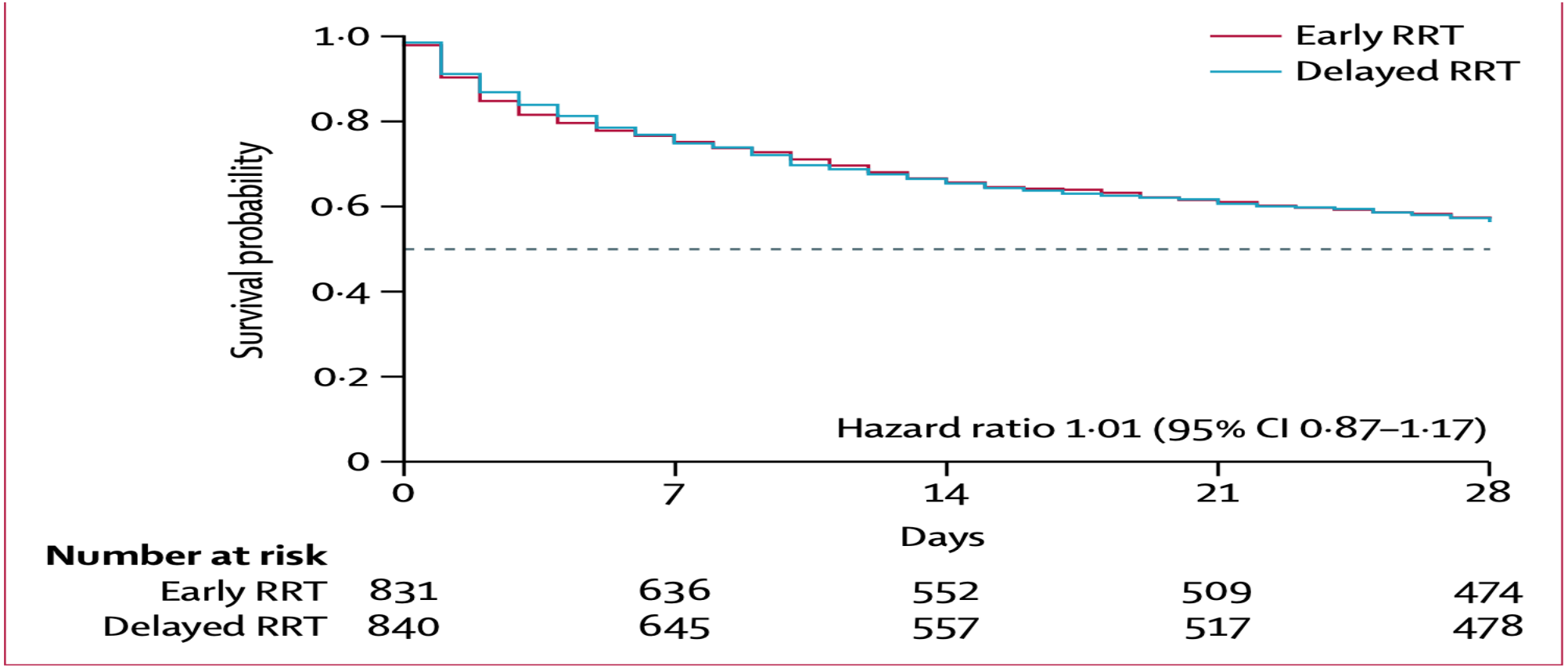
In critically ill patients with acute kidney injury, early compared with late initiation of RRT is not associated wi… favorable mortality outcomes, although it appears to reduce the risk of metabolic acidosis

Lancet 2020; 395: 1506–15

Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials

Stéphane Gaudry, David Hajage*, Nicolas Benichou†, Khalil Chaïbi†, Saber Barbar, Alexander Zarbock, Nuttha Lumlertgul, Ron Wald, Sean M Bagshaw, Nattachai Srisawat, Alain Combes, Guillaume Geri, Tukaram Jamale, Agnès Dechartres, Jean-Pierre Quenot‡, Didier Dreyfuss‡*

Probability of survival up to day 28 in the intention-to-treat population according to RRT initiation strategy



The timing of RRT initiation does not affect survival in critically ill patients with severe acute kidney injury in the absence of urgent indications for RRT. Delaying RRT initiation, with close patient monitoring, might lead to a reduced

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

The STARRT-AKI Investigators, for the Canadian Critical Care Trials Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group, the United Kingdom Critical Care Research Group, the Canadian Nephrology Trials Network, and the Irish Critical Care Trials Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

- **Design**
- Multinational, RCT, critically ill patients with AKI, comparing accelerated strategy vs standard strategy of KRT initiation
- 168 hospitals from 15 countries participated randomizing 3019 patients
- Inclusion criteria:
- >18 year old
- Admitted to the ICU with kidney dysfunction (Creatinine >1.13 in woman and >1.47 in men)
- Severe AKI (doubling of serum Cr from baseline or a serum Cr of ≥ 4 mg/dl or a urine output of less than 6ml/kg for the preceding 12 hours)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

- **Interventions**
- **Accelerated strategy group**: After randomization a 12 hour window was given for consent and initiation of KRT
- **Standard strategy group**: KRT was not started until one or more of the following was present:
- Potassium ≥ 6 mmol/L
- pH ≤ 7.2
- Bicarbonate ≤ 12 mmol/L
- PaO2/FiO2 ≤ 200 + Volume overload
- Persistent AKI for 72 hours after randomization

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

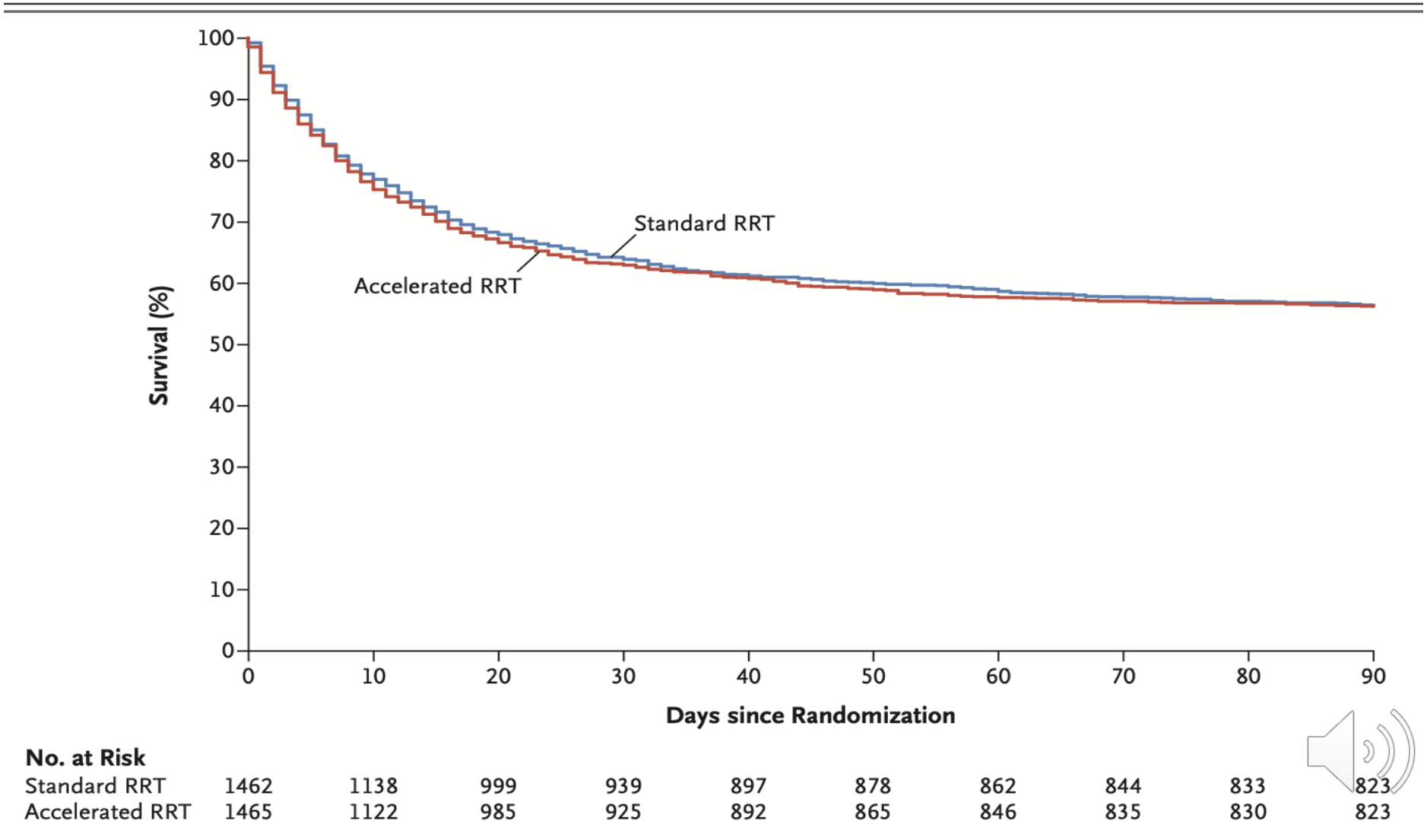
Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

Primary outcome: Death from any cause at 90 days

Key secondary outcomes: Dependence of KRT Composite: death or dependence of KRT and major kidney event

Primary outcome: Death from any cause at 90 days

: 43.9% in accelerated strategy
43.7% in Standard strategy (relative risk, 1.00; 95% CI 0.93-1.09)



STARRT–AKI: Does early initiation of kidney replacement therapy (KRT) decrease mortality?

#NephJC

Methods

Multinational open-label RCT
168 hospitals
15 countries

October 2015 - September 2019

Critically ill patients
+
Kidney dysfunction
+
Severe AKI
(KDIGO Stage 2 or 3)
N=3019

Standard strategy
Standard of care
n=1462

Accelerated Strategy
KRT within 12 hours of meeting eligibility criteria
n=1465

Findings

Mortality at 90 days	KRT Dependence	Any Adverse Event
43.7%	6%	17%
43.9%	10%	23%
RR 1 p=0.92	RR 1.7 95% CI (1.2-2.4)	p < 0.001

Conclusion Among critically ill patients with acute kidney injury, an accelerated renal replacement strategy was not associated with a lower risk of death at 90 days than a standard strategy.

Reference: Sean Bagshaw MD, Ron Wald MD, CM, MPH., Neill Adhikari, MD, CM, et al. **Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury.** NEJM 2020 doi: 10.1056/ NEJMoa2000741

@ DTomacruzMD

NEPHROLOGY SOCIAL MEDIA COLLECTIVE EST 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

- **Secondary outcomes**
- Higher dependence on KRT in the accelerated strategy 10.4% vs 6%
- Higher risk of rehospitalization in accelerated strategy (21 versus 17)
- Adverse events more common in early strategy (23.0% vs 16.5%) (P<0.001)
- The most common adverse events :Hypotension and hypophosphatemia
- No difference in serious adverse events between the two strategies

Does early initiation of Kidney Replacement Therapy (KRT) decrease mortality? A comparison of the RCTs

#NephJC

	ELAIN	AKIKI	IDEAL-ICU	STARRT-AKI
Design (all were RCTs)	Single-surgical center Germany N = 231	Multicenter France N = 620	Multicenter France N = 488	Multicenter Multinational N = 2927
AKI severity & Early KRT criteria	KDIGO Stage 2 AKI + NGAL >150ng/ml	KDIGO stage 3 on ventilator &/or vasopressors	RIFLE-F AKI Early septic shock	KDIGO stage 2 or 3 Critically ill
Time-frame early KRT start within...	8 hours	6 hours	12 hours	12 hours
% Received KRT (early vs late)	100% vs 91%	98% vs 51%	97% vs 62%	97% vs 62%
Mortality (early vs late)	90-day 39% vs 54%	60-day 49% vs 50%	90-day 58% vs 54%	90-day 44% vs 44%
Unique findings	Time on KRT, Kidney recovery, and ventilator time favored early group	61% of survivors did not receive KRT & fewer catheter infections in delayed group	Time on KRT, Kidney recovery, and ventilator time favored early group	Greater % adverse events, KRT dependence & rehospitalization in early (accelerated) group
ICU Length of stay	No difference	No difference	No difference	↓ accelerated group
Limitations & Critiques	Results potentially skewed as many early start patients may have recovered without KRT	Limited generalizability as ≅ 50% received iHD and 30% CRRT	Inconsistencies between KDIGO and RIFLE AKI criteria	Heterogeneity of KRT start time in delayed (standard) group
References	Zarbock et al. JAMA 2016	Gaudry et al. NEJM 2016	Barbar et al. NEJM 2018	Bagshaw et al. NEJM 2020

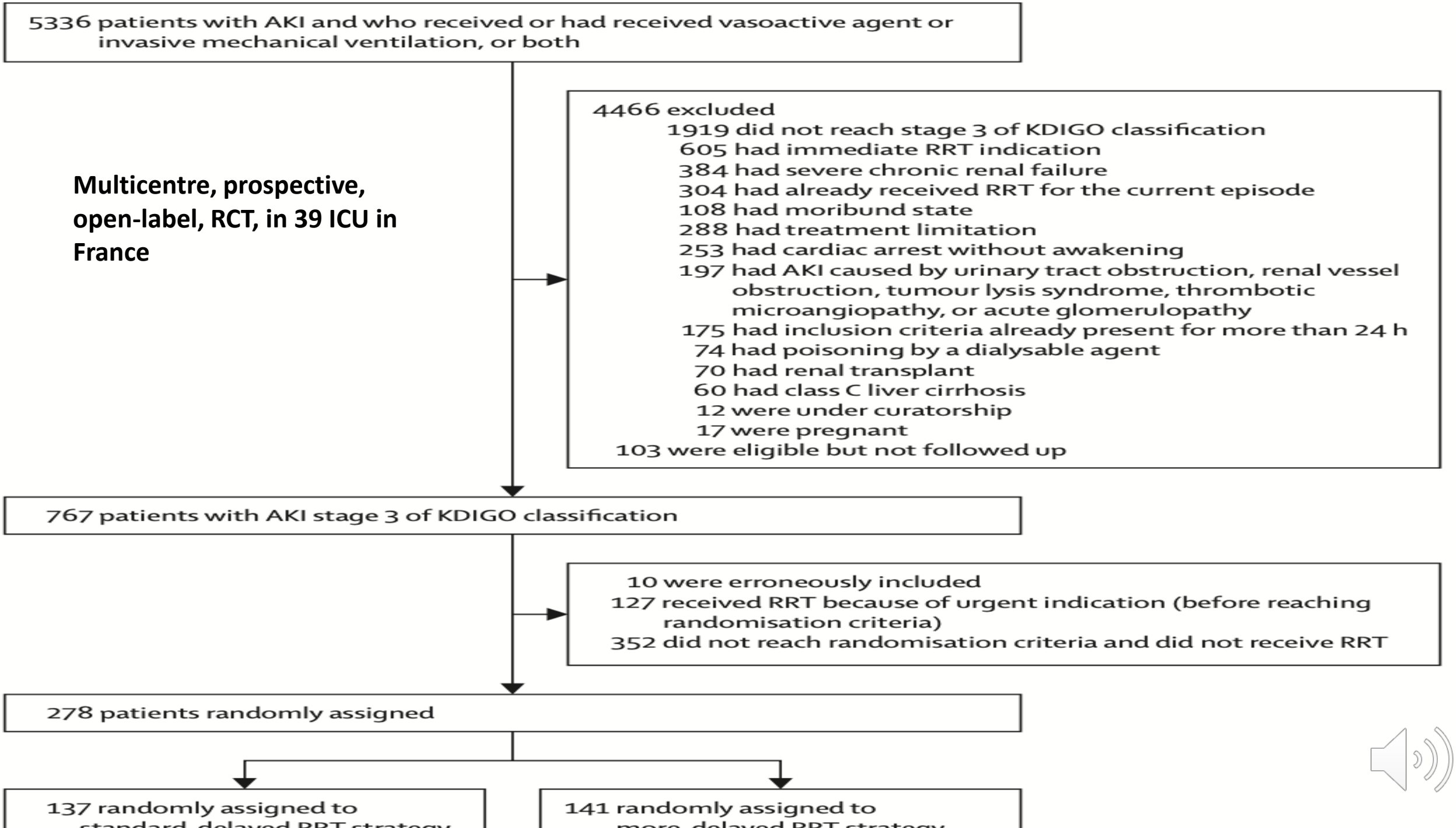
Visual abstract by @Sophia_Kidney


Time to Stop
Starting RRT
Early in AKI

Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial

Lancet 2021; 397: 1293–300

more-delayed initiation strategy would result in more RRT-free days, compared with a delayed strategy


5336 patients with AKI and who received or had received vasoactive agent or invasive mechanical ventilation, or both
Multicentre, prospective, open-label, RCT, in 39 ICU in France
4466 excluded
1919 did not reach stage 3 of KDIGO classification
605 had immediate RRT indication
384 had severe chronic renal failure
304 had already received RRT for the current episode
108 had moribund state
288 had treatment limitation
253 had cardiac arrest without awakening
197 had AKI caused by urinary tract obstruction, renal vessel obstruction, tumour lysis syndrome, thrombotic microangiopathy, or acute glomerulopathy
175 had inclusion criteria already present for more than 24 h
74 had poisoning by a dialysable agent
70 had renal transplant
60 had class C liver cirrhosis
12 were under curatorship
17 were pregnant
103 were eligible but not followed up
767 patients with AKI stage 3 of KDIGO classification
10 were erroneously included
127 received RRT because of urgent indication (before reaching randomisation criteria)
352 did not reach randomisation criteria and did not receive RRT
278 patients randomly assigned
137 randomly assigned to
141 randomly assigned to

Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial

- *Inclusion criteria*
- Age >18 years
- Receiving ICU care - on mechanical ventilation or catecholamine infusion
- KDIGO Stage 3 AKI
- Oliguria or azotemia
  - oliguria: urine output < 0.3 ml/kg/h or < 500 ml/d) or anuria (urine output < 100 ml/d) for > 72 hours
  - azotemia: blood urea nitrogen concentration between 112 mg/dl (40 mmol/l) and 140 mg/dl (50 mmol/l)

Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial

- **Procedures**
- delayed strategy

KRT to be initiated within 12 hours of fulfilling randomization criteria

- more-delayed-strategy

KRT postponed until an urgent indication occurred or BUN reached 140 mg/dl for one day. (*note that duration of anuria was not a criterion*)

Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial

- **More-delayed RRT strategy:**

1. Fewer patients receiving treatment
2. No association with more RRT-free days(12 days in the delayed strategy and 10 days in the more-delayed strategy
3. **higher 60-day mortality**
4. similar complications related to AKI or to RRT

Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial

- Conclusion: Severe AKI patients with oliguria >72 h or BUN>112 mg/dL and no severe complication that would mandate immediate RRT, longer postponing of RRT initiation did not confer additional benefit and was associated with potential harm

Early vs Late Initiation Of Kidney Replacement Therapy : A Comparison Of RCTs

#NephJC

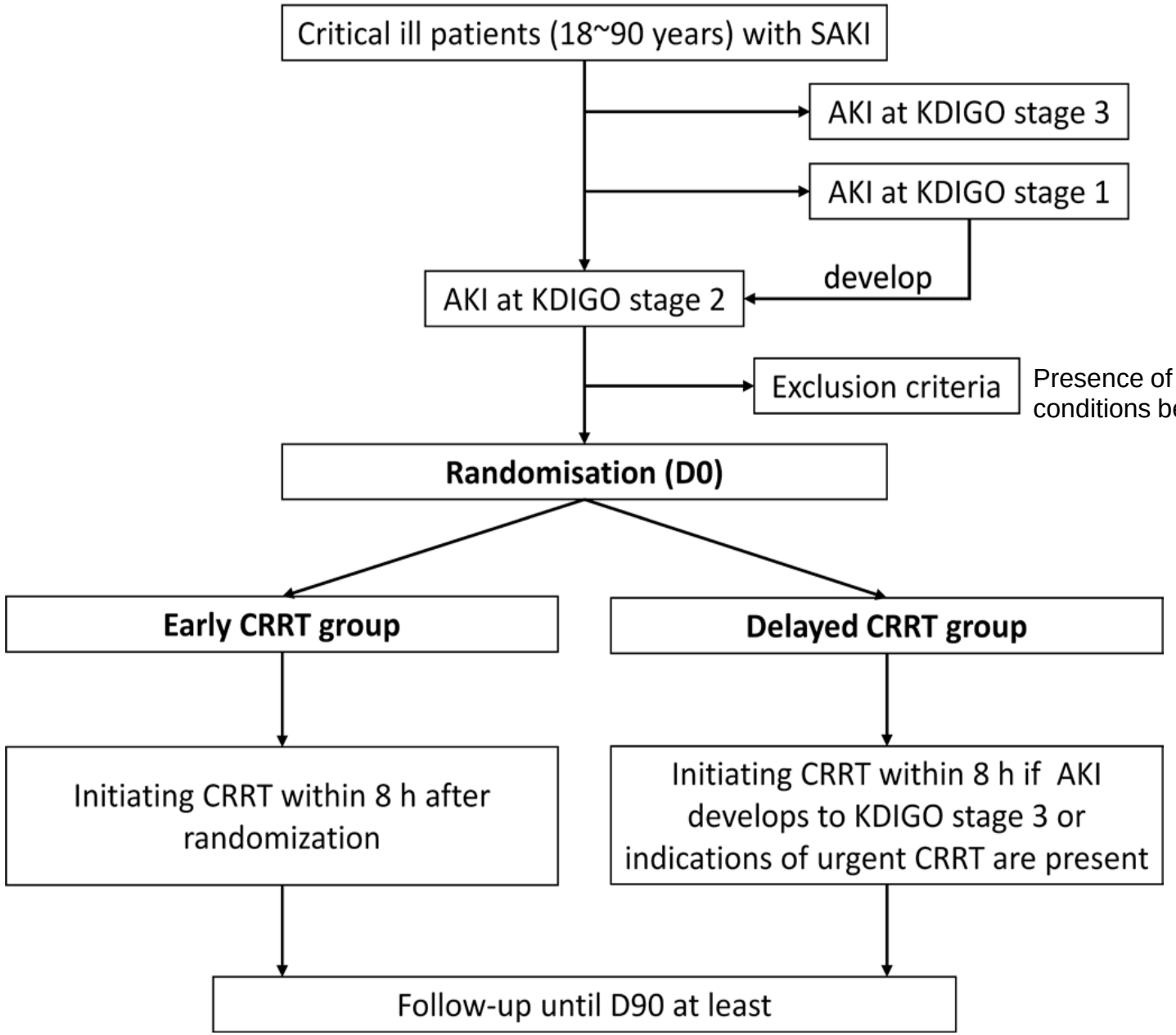
	ELAIN	AKIKI	IDEAL-ICU	STARRT-AKI	AKIKI-2
Study Design	RCT, Single center France	RCT, Multi-Centre France	RCT, Multi-Centre	RCT, Multinational	RCT, Multi-Centre France
Study participants (N)	231	620	488	2927	278
Eligibility criterion	KDIGO stage 2 AKI	KDIGO stage 3 AKI	RIFLE - FAILURE	KDIGO Stage 2 or 3	KDIGO stage 3 with oliguria >72 hrs or BUN 40-50 mmol/l
Early KRT criterion	Within 8 hrs	Within 6 hrs	Within 12 hrs	Within 12 hrs	Within 12 hrs
Delayed KRT criterion	Within 12 hrs or no initiation	• Life-threatening complications of AKI • BUN > 40mmol/l • Oliguria persisting >72 hrs	48 hrs after randomisation in the absence of kidney recovery	• Life-threatening complications of AKI • Persistent AKI for ≥ 72 hrs	• BUN >50 mmol/l • Life-threatening complication of AKI
Difference in mortality (Early Vs Late)	At 90 d 39.3% vs 54.7% **(p=0.03)**	At 60 d 48.5% vs 49.7% **(p=0.79)**	At 90 d 58% vs 54% **(p= 0.38)**	At 90 d 43.9% vs 43.7% **(p=0.92)**	At 60 d 44% vs 55% **(p=0.07)**
Other Key outcomes	Shorter KRT duration and hospital stay in early group	Diuresis occurred earlier in delayed arm	No difference in length of ICU and hospital stay	Higher KRT dependency at 90 d in accelerated arm	KRT free days between D0 and D28 10 vs 12 days (p=0.93)
Complications related to AKI OR KRT (Early Vs delayed)	No difference	CRBSI higher in early group	Hyperkalaemia more in delayed group	More in accelerated arm	No difference
Limitations	Small sample, single centre, mostly surgical patients	Included pts with advanced AKI, 50% pts received IHD	Non blinded, stopped early due to futility	Heterogeneity in groups, Decision of KRT at physician discretion	Small sample size, Debate over BUN levels for KRT initiation
	JAMA 2016	NEJM 2016	NEJM 2018	NEJM 2020	Lancet 2021

@Dilushiwijay @Priti899

Ongoing trial

The timing of continuous renal replacement therapy initiation in sepsis associated acute kidney injury in the intensive care unit: the CRTSAKI Study (Continuous RRT Timing in Sepsis-associated AKI in ICU): study protocol for a multicentre, randomised controlled trial

CRTSAKI Study



TIMING OF RENAL REPLACEMENT THERAPY

- **serum urea, serum creatinine and urine output** :

usual parameters used to guide

serum urea and creatinine are imprecise biomarkers of renal function (variable rates of production during critical illness)

- **Renal biomarkers such as NGAL, tissue inhibitor of metalloproteinases (TIMP), and insulin-like growth factor binding protein-7 (IGFBP7)** :

Better triggers to commence RRT in septic AKI

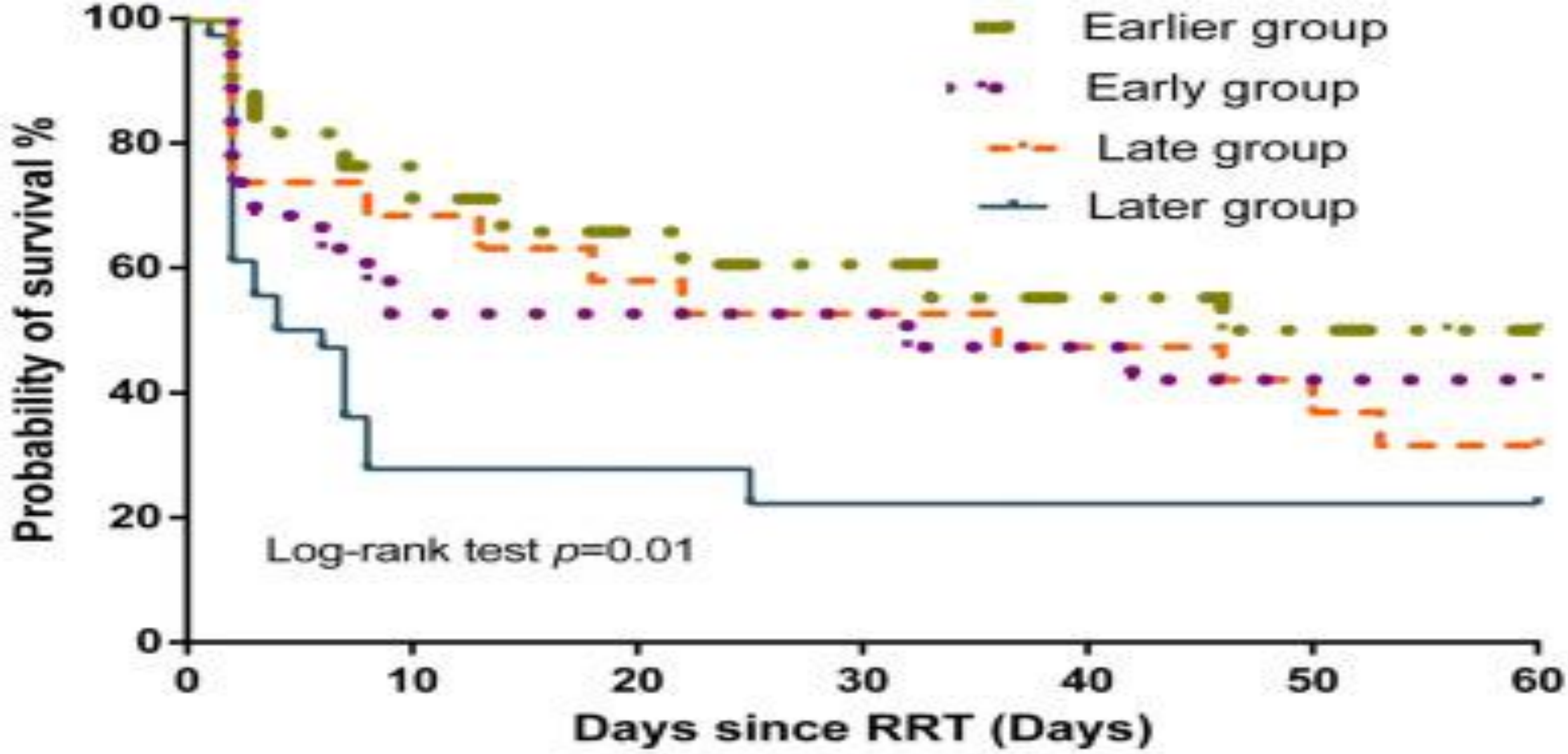
Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Corrigendum to "Timing of continuous renal replacement therapy in severe acute kidney injury patients with fluid overload: A retrospective cohort study" [J Crit Care. 2021 Aug; 64: 226–236]

- Retrospective cohort study
- Patients with fluid overload treated with CRRT due to severe AKI
- Mixed medical intensive care unit of China
- Patients were divided into early (≤15 h) and late (>15 h) groups based on the median time from ICU admission to CRRT initiation
- Primary outcome was all-cause mortality at day 60

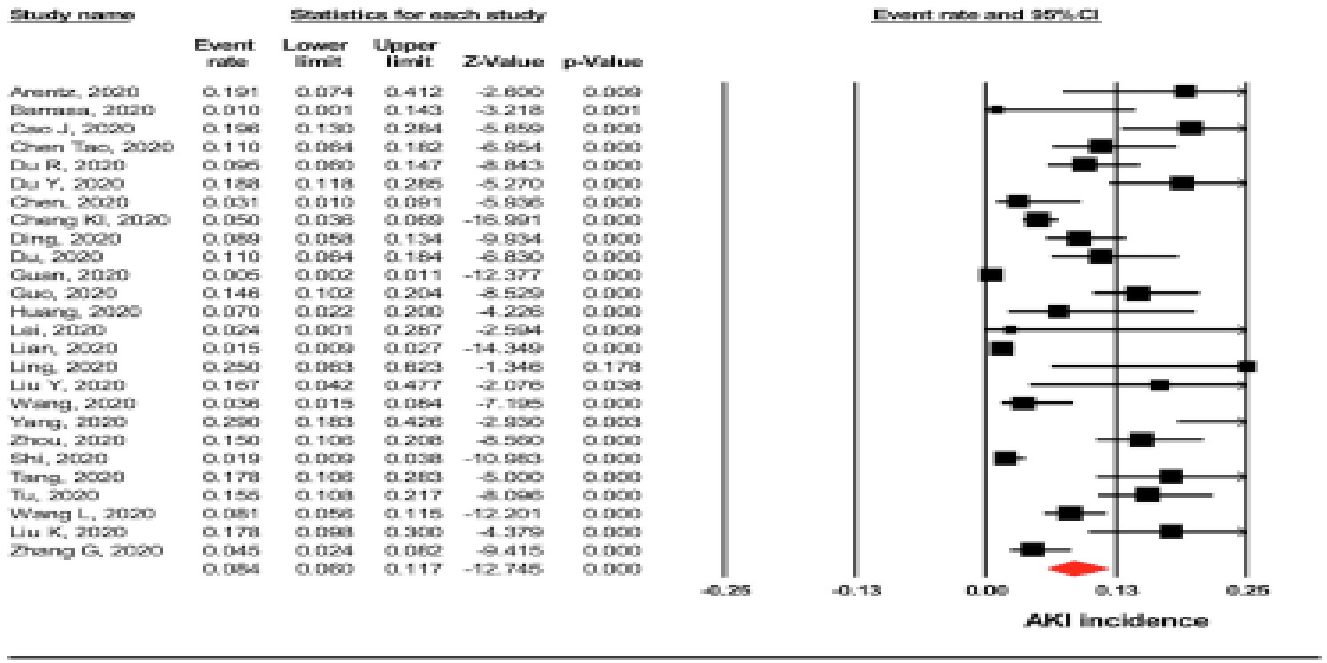


Early initiation of CRRT was independently associated with survival benefits in severe AKI patients with fluid overload.

Incidence of acute kidney injury and its association with mortality in patients with COVID-19: a meta-analysis

14 studies included with a total of 3364 patients

A) Incidence of AKI

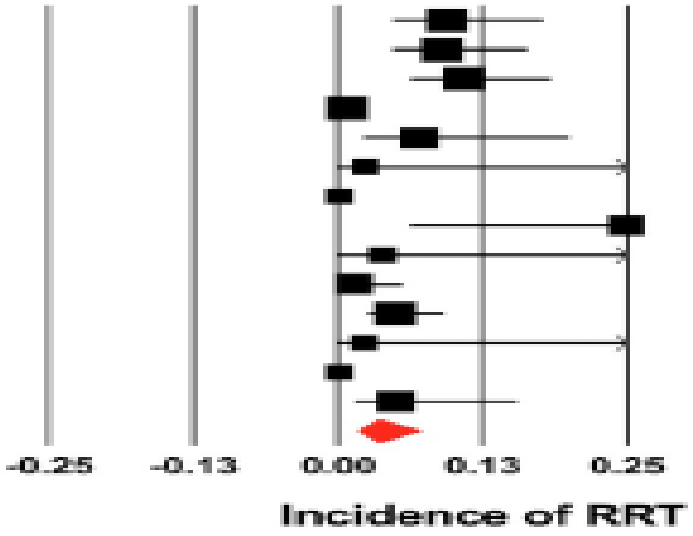


Incidence of AKI in patients with confirmed SARS-CoV-2 infection : 8.4%

Incidence of acute kidney injury and its association with mortality in patients with COVID-19: a meta-analysis

C) Incidence of RRT

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Du Y, 2020	0.094	0.048	0.177	-6.096	0.000
Chen, 2020	0.090	0.047	0.164	-6.588	0.000
Du, 2020	0.110	0.064	0.184	-6.830	0.000
Guan, 2020	0.008	0.004	0.015	-14.235	0.000
Huang, 2020	0.070	0.022	0.200	-4.226	0.000
Lei, 2020	0.024	0.001	0.287	-2.594	0.009
Lian, 2020	0.001	0.000	0.010	-5.205	0.000
Ling, 2020	0.250	0.063	0.623	-1.346	0.178
Liu Y, 2020	0.038	0.002	0.403	-2.232	0.026
Wang, 2020	0.015	0.004	0.056	-5.925	0.000
Zhou, 2020	0.050	0.027	0.092	-8.869	0.000
Arentz, 2020	0.023	0.001	0.277	-2.629	0.009
Cheng KI, 2020	0.001	0.000	0.011	-5.122	0.000
Yang, 2020	0.050	0.015	0.155	-4.628	0.000
	0.036	0.018	0.071	-8.950	0.000



incidence of RRT : 3.6%

Indications of renal replacement therapy in COVID-19 patients

- Renal indications : severe AKI (KIDGO AKI 2–3 stages) with hemodynamic instability
- Non-renal indications:

1. severe ARDS and persistent inflammatory fever, which cannot be controlled not even with corticosteroid therapy
2. hypernatremia refractory to conservative medical treatment
3. volume overload or urine output, which cannot meet the needs of drug infusion and energy supply and diuretic resistance

https://doi.org/10.1186/s13613-020-00689-1

www.aging-us.com AGING 2021, Vol. 13, No. 7

Research Paper

The effectiveness of continuous renal replacement therapy in critical COVID-19 patients with cytokine release syndrome: a retrospective, multicenter, descriptive study from Wuhan, China

Huiling Xiang[1,*], Bin Song[2,*], Yuanyuan Zhang[3], Jianduan Zhang[3], Jing Xiong[1]

- retrospective, multi-center study
- 83 patients diagnosed with COVID-19 and CRS
- 67 critical patients, 38 cases were treated with CRRT

- inclusion criteria :peak IL-6 >100 pg/mL, or a peak IL-6 >50-100 pg/mL with concurrent ARDS or multiple organ disease syndrome (MODS)
- Indications for CRRT include hyperkalemia, acidosis, multiple organ dysfunction, or severe CRS

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- For the 38 patients treated with CRRT, the changes of inflammation-related indicators before and after CRRT were compared
- WBC counts (P=0.039), neutrophil counts (P=0.014), CRP (P=0.049), D-dimer (P=0.006) : declined significantly from the values before CRRT
- lymphocytes, PCT and IL-6 : not change significantly

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LIMITATION OF STUDY:

Compared to the non-CRRT group, the CRRT group had more patients with an IL-6 value >4000 pg/mL (24.1% vs. 34.2%)

SO2in patients who received CRRT was lower than in the non-CRRT group

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Huiling Xiang[1,*], Bin Song[2,*], Yuanyuan Zhang[3], Jianduan Zhang[3], Jing Xiong[1]

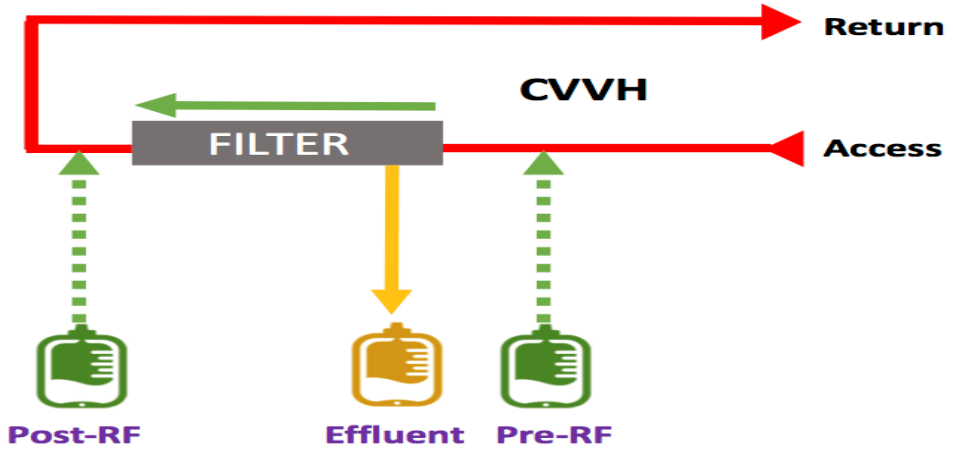
- Fatality rate higher in CRRT group (P=0.005)
- Inflammatory markers such as C-reactive protein, neutrophil counts, and D-dimer decreased after CRRT (P<0.05)
- **Conclusions: CRRT significantly reduced the inflammation, it did not decrease the fatality rate of patients with CRS. Therefore, the choice of CRRT indication, dialysis time and dialysis mode should be more careful and accurate in COVID-19 patients with CRS.**

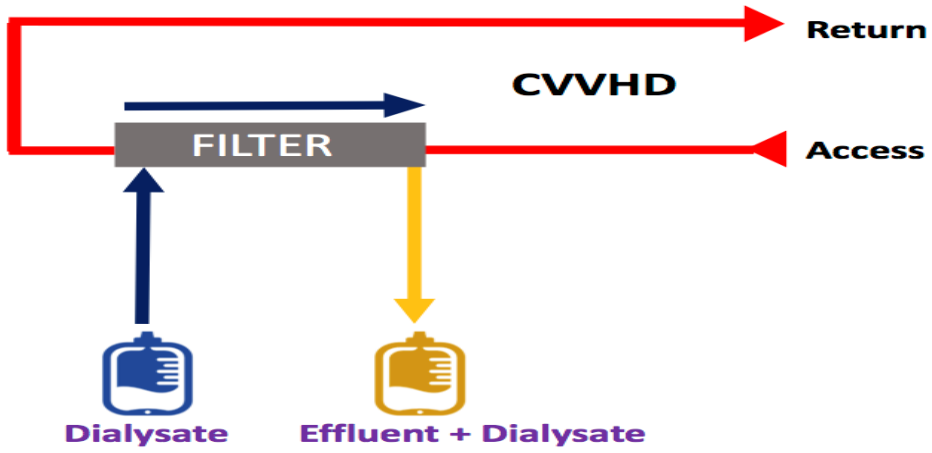
Dialysis dose prescription

Target dose of RRT in AKI :

Modality of KRT	Typical Target Dose
Intermittent hemodialysis (delivered on a 3×/wk schedule) IHD /SLED	Kt/V_{urea} >1.2 per treatment; or URR > 0.67
Continuous kidney replacement therapy	Total effluent flow of 20-25 mL/kg/hr

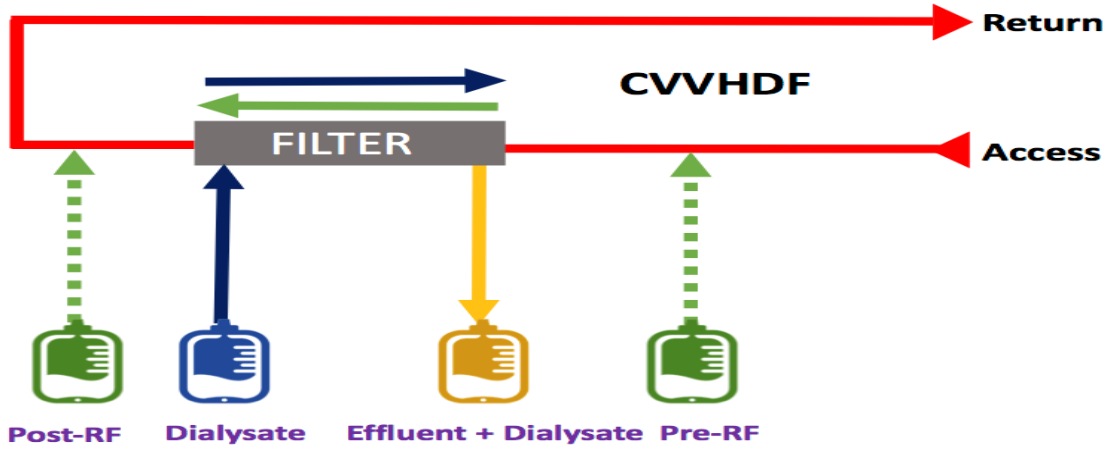
CRRT DOSE:





CVVH: Continuous venous-venous hemofiltration
CVVHD: Continuous veno-venous hemodialysis
CVVHDF: Continuous veno-venous hemodiafiltration
Post-RF: post-dilutional replacement fluid
Pre-RF: pre-dilutional replacement fluid

Renal Fellow NETWORK
@ssfarouk



CRRT DOSE

- The KDIGO clinical practice guideline for acute kidney injury (AKI) recommends**“delivering an effluent volume of 20 to 25 mL/kg/h for CRRT in (AKI)**

CRRT DOSE:

prescribed dose is not always *delivered* due to CRRT interruptions due to procedures, clotting, replacement of filters, and tubing changes. Therefore, the guidelines also recommend frequent evaluation and "assessment of the actual delivered dose in order to adjust the prescription

To Summarize

- CRRT Dose
  = Delivered effluent volume of 20-25ml/kg/hr
  = Prescribed effluent volume of 25-30ml/kg/hr

- Filtration fraction during CRRT must be < 30%

KDIGO recommends "to increase effluent dosing by 25% to ensure delivery of the target dose"

High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study):

prospective, randomized, open, multicenter clinical trial conducted at 18 intensive care units

140 critically ill patients with septic shock and AKI for less than 24 h

HVHF at 70 mL/kg/h or standard-volume hemofiltration 35 mL/kg/h

No reduction of 28-day mortality or contributes to early improvements in hemodynamic profile or organ function

Dosing and initiation timing COVID-19

- CRRT dosing for COVID-19 patients :same guidelines as non-COVID-19 patients
- Recommendation for
- pre-dilution filter : 25-30 mL/kg/h
- post- dilution :20-25 mL/kg/h
- high volume hemofiltration (remove inflammatory mediators, usually in severe sepsis) :> 35 mL/kg/h

CRRT Dosing:

High-dose CRRT vs
standard-dose CRRT

Pediatric Continuous Renal Replacement Therapy (PCRRT) registry workgroup suggests high flow CVVHDF at 50 ml/kg/h for 12 h followed by step down CVVHDF at a dose of 25–30 ml/kg/h

HYPOTHESIS AND THEORY ARTICLE

Front. Pediatr., 03 July 2020 | https://doi.org/10.3389/fped.2020.00413

HV-CRRT EFFECTS PCT, TNF-α, IL-4, IL-6, IL-8 AND IL-10 LEVELS IN PANCREATITIS,LIU et al: DOI: 10.3892/etm.2017.4843

Used for more than one patient
⇩ filter clotting
More effective in clearance of inflammatory cytokines

Not confer a benefit over Standard CRRT
Consumption of replacement fluid

Serum IL-6 and IL-1-ra with sequential organ failure assessment scores in septic patients receiving high-volume hemofiltration and continuous venovenous hemofiltration https://doi.org/10.1111/j.1440-1797.2006.00600.x

High-volume hemofiltration at 6L/h may seem to successfully remove some inflammatory cytokines in septic patients. The improvement in the SOFA scores at day 7 promises benefit of continuous renal replacement therapy in septic patients, but after 20 days this effect may be lost

OPTIMAL CATHETER LOCATION

- The optimal site for catheter insertion is uncertain
- Avoid subclavian dialysis catheters (risks of subclavian vein stenosis, disability for direct hemostasis in the event of hemorrhage)
- KDIGO guidelines recommend:

1. Right internal jugular vein
2. Femoral veins
3. left internal jugular vein
4. Subclavian vein
5. External jugular veins may be used when other veins are not usable

Dominant side to preserve the contralateral side for future dialysis access

Hemodialysis catheter:

- Temporary HD catheter
- Length of catheter: important foe sufficient BFR and less clotting

❖RIJ: 15-20 cm

❖Left IJ: 20-24 CM

❖Femoral: 24-30 cm

- Subclavian: 20cm

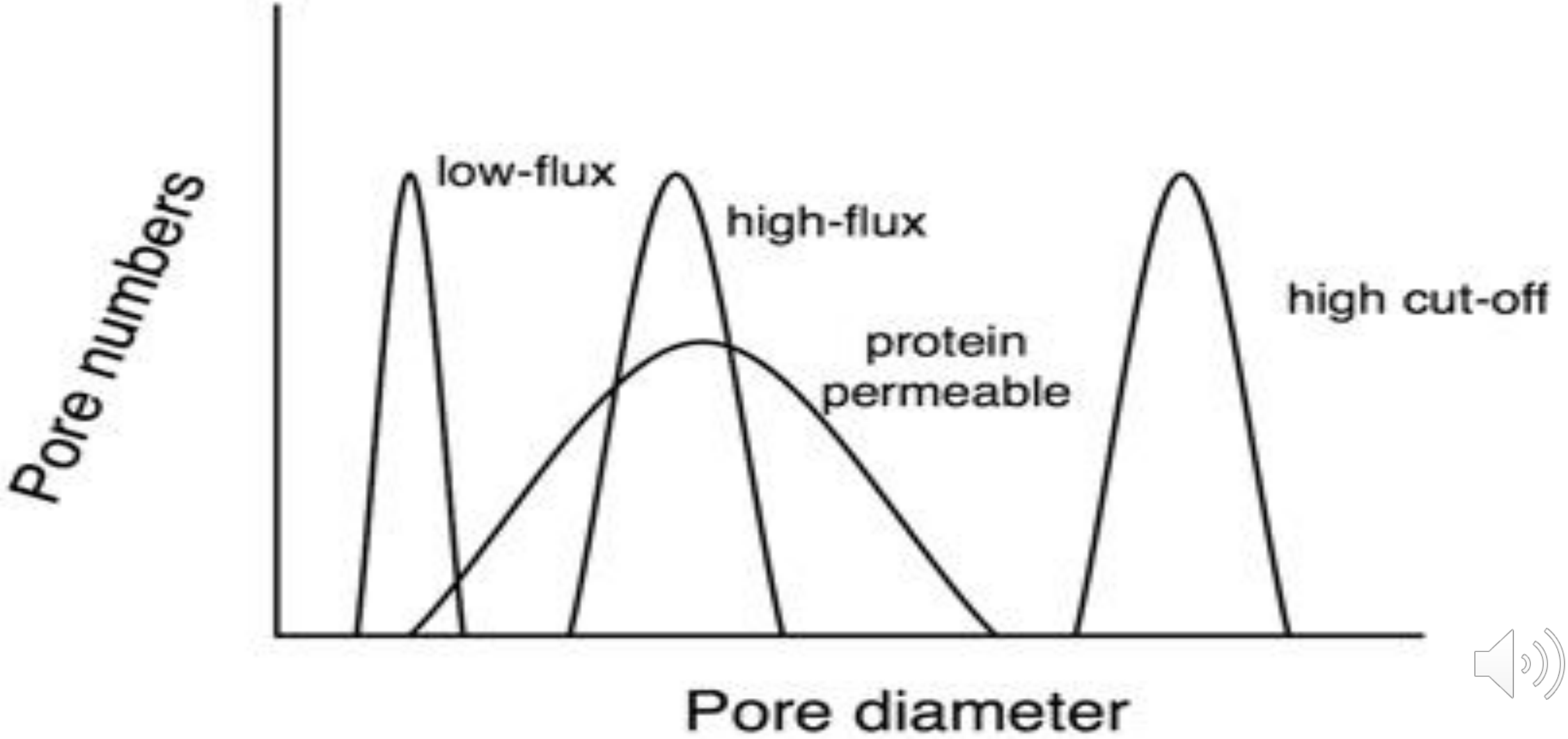
- Location:

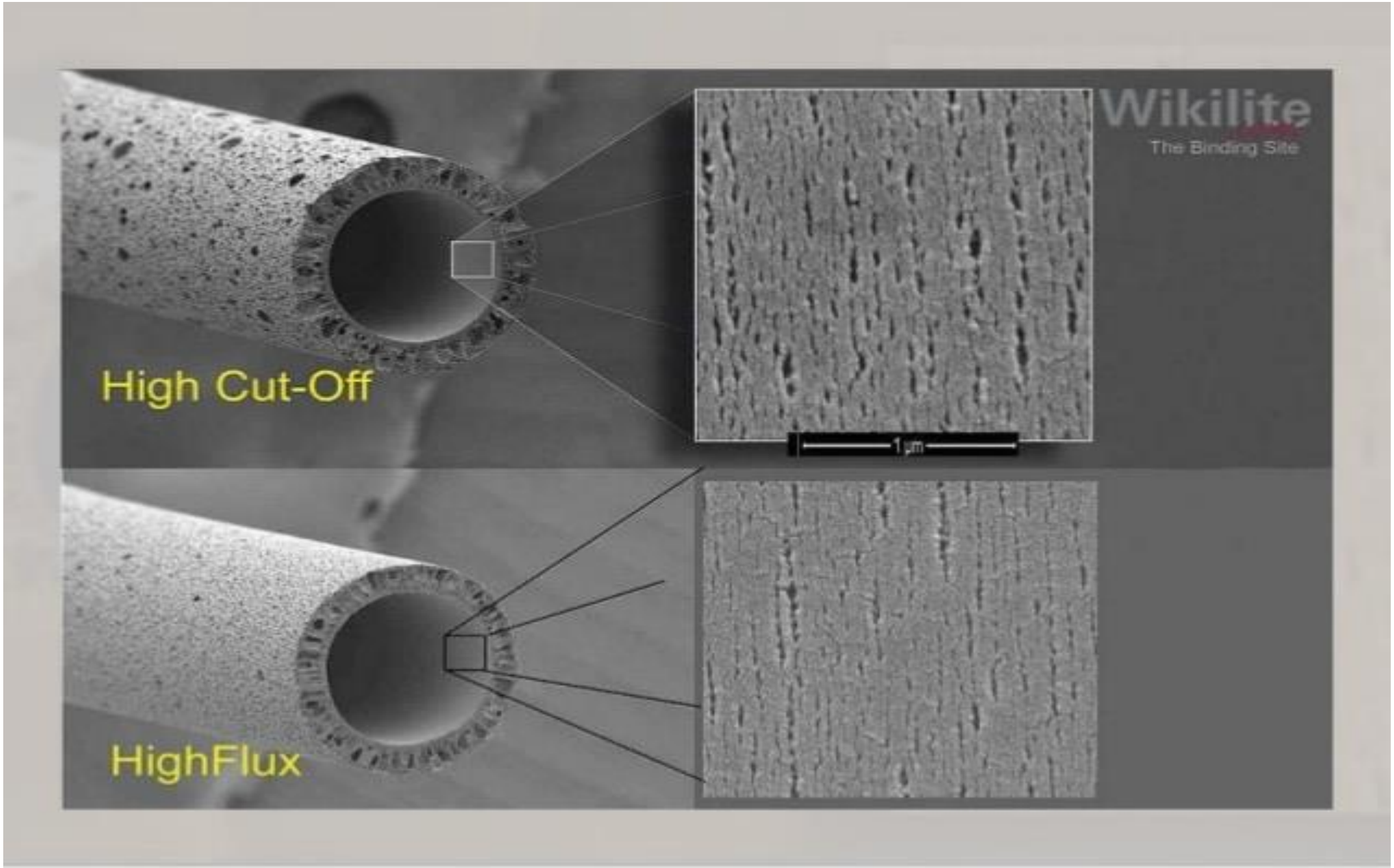
❖ Right IJ Preferred especially for prone position

FILTER MEMBRANES

- **low-flux membranes** , cut-off of approximately 5 kDa and low water permeability
- **high-flux membranes** ,high hydraulic permeability, more efficient ultrafiltration ,clearance of larger solutes
- standard membrane for hemofiltration , cut-off 30-35 kDa, clearance of small to middle molecules
- **super permeable (super high-flux) membranes** ,cut-off 40-100 kDa ,larger molecules(such as cytokines, immunoglobulins and myoglobin, that could be theoretically beneficial in the treatment of sepsis and rhabdomyolysis) ,increased albumin loss, and clinical or survival benefit has not yet been established

FILTER MEMBRANES




Wikilite
The Binding Site
High Cut-Off
1 µm
HighFlux

In general, the size of the molecule and the degree of protein binding determines the degree to which the substance can be removed (smaller, nonprotein bound substances are easiest to remove).

Classification	Molecule	Molecular weight (Daltons)
Small (<500 Da)	Sodium	23
	Magnesium	24
	Phosphorus	31
	Potassium	35
	Calcium	40
	Urea	60
	Phosphate	80
	Creatinine	113
	Uric acid	168
	Glucose	180
	Gentamycin	470
Middle (500 – 15 000 Da)	Vitamin B12	1355
	Vancomycin	1488
	Endothelin	4238
	Endotoxin fragments	1000 – 15 000
	Cytokines	15 000 – 30 000
Large (>15 000 Da)	Inulin	5200
	Beta-2 microglobulin	11 800
	Myoglobin	17 000
	Albumin	55 000-60 000
	Globulin	150 000

Cytokine removal

- Molecular sizes of most cytokines :8 -60 kDa
- cutoff points of standard hemofiltration membranes :10 and 30 kD need of more targeted membrane characteristics to achieve greater levels of cytokine removal
- high cutoff (HCO) filters: 60 and 150 kDa and better removal of cytokines ex vivo

FILTER MEMBRANES

- In preclinical and pilot clinical studies, RRT using these filters appeared to allow earlier reduction of noradrenaline doses in septic membranes in sepsis

A Double-Blind Randomized Controlled Trial of High Cutoff Versus Standard Hemofiltration in Critically Ill Patients With Acute Kidney Injury (2018)

76 patients: Vasopressor-dependent patients in acute kidney injury who were admitted to the ICU

CVVH-high cutoff vs CVVH-standard

The median hours of norepinephrine-free time at day 7 : 32 VS 56 hours
no significant difference in time to cessation of norepinephrine , hemofiltration and filter life and Serum albumin

- **Conclusions:** In critically ill patients with AKI, CVVH-high cutoff did not reduce the duration of vasopressor support or mortality or change albumin levels compared with CVVH-standard

Cytokine removal In COVID-19

- Direct hemoperfusion using a neutro-macroporous sorbent
- CKRT with hollow fibrer filters with adsorptive properties
- high-dose CKRT with medium cut-off (MCO) or high cut-off (HCO) membranes

Compare HCO membranes, MCO membranes

- MCO Membranes:
- More uniformity in pore size

- Effective and selective removal of middle molecules such as myoglobin (17 kDa), IL-6 (21 kDa) and IL-10 (18 kDa)

- Minimizing albumin loss

https://doi.org/10.1038/ s41581-020-0284-7

Major Renal Replacement Techniques

Intermittent

IHD
Intermittent haemodialysis

IUF
Isolated Ultrafiltration

Hybrid

SLEDD
Sustained (or slow) low efficiency daily dialysis

SLEDD-F
Sustained (or slow) low efficiency daily dialysis with filtration

Continuous

CVVH
Continuous veno-venous haemofiltration

CVVHD
Continuous veno-venous haemodialysis

CVVHDF
Continuous veno-venous haemodiafiltration

SCUF
Slow continuous ultrafiltration

IHD versus CRRT

- Availability
- experience of the team
- cost
- hemodynamic stability of the patient
- need for anticoagulation
- indication for renal replacement therapy

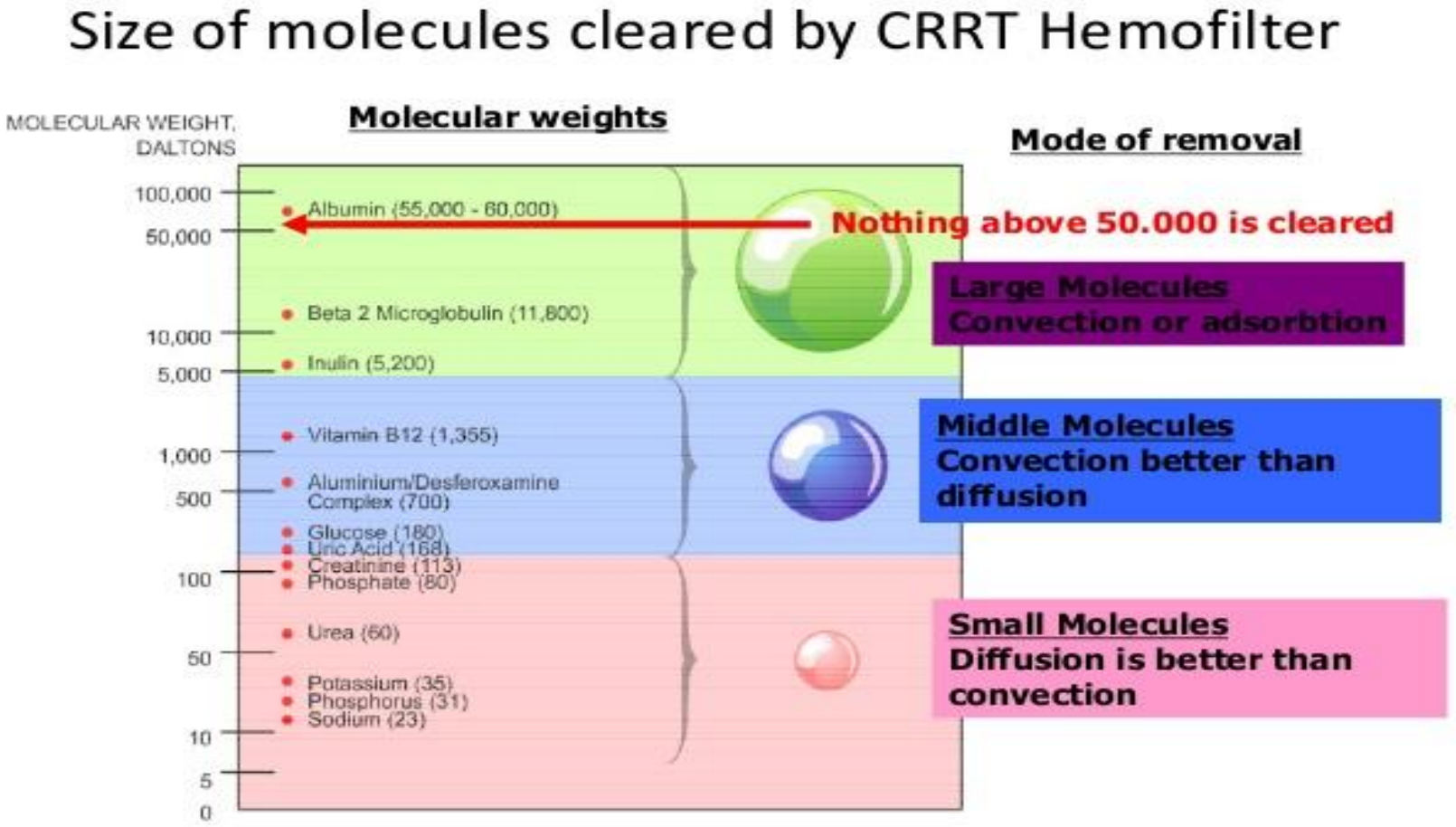
Advantageous OF CRRT

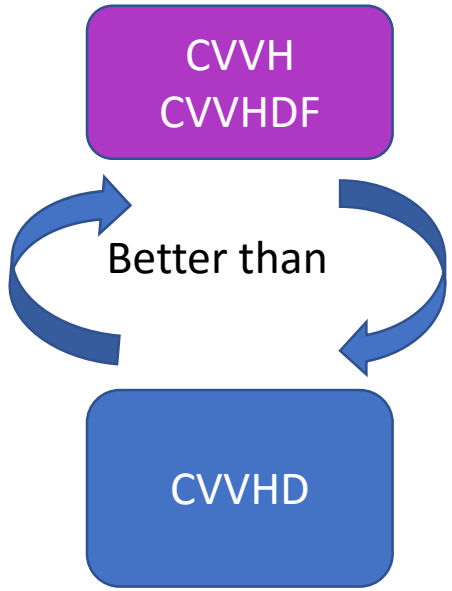
- Superior management of volume overload
- more consistent net salt and water removal in hemodynamically unstable patients
- Enhanced clearance of inflammatory mediators
- Better preservation of cerebral perfusion in patients with acute brain injury and fulminant hepatic failure

CRRT

- Use continuous and intermittent RRT as complementary therapies in AKI patients. (Not Graded)
- 5.6.2: We suggest using CRRT, rather than standard intermittent RRT, for **hemodynamically unstable patients** (2B)
- 5.6.3: We suggest using CRRT, rather than intermittent RRT, for AKI patients **with acute brain injury or other causes of increased intracranial pressure or generalized brain edema** (2B)

CRRT Modality





Renal replacement therapy modality in critically ill patients with acute kidney injury – A network meta-analysis of randomized controlled trials

Journal of Critical Care
, August 2021, Pages 82-90

meta-analysis ,Twenty-three studies
compare the efficacy and safety of various RRT modalities: CRRT, IHD, hybrid RRT, and PD

primary outcomes were renal recovery and short-term mortality

No difference in the renal recovery
No difference in short-term mortality among the four RRT modalities
Similar effects on the incidence of infectious complications
PD :less fluid removal volume and lower incidence of hypotension

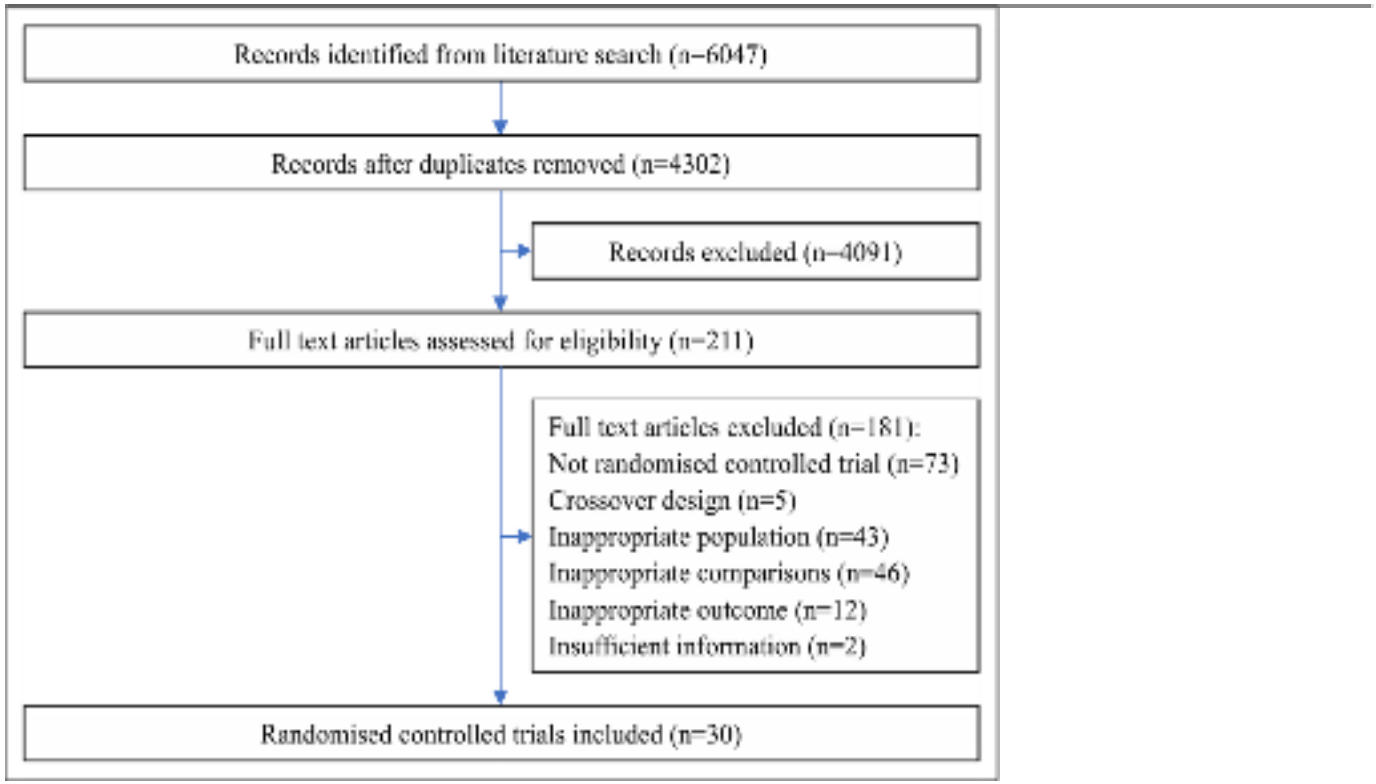
Renal replacement therapy modality in critically ill patients with acute kidney injury – A network meta-analysis of randomized controlled trials

Conclusions

No superiority of one particular RRT modality over another in terms of renal recovery and short-term mortality in critically ill patients with AKI

PD exhibited worse fluid removal and better safety in the prevention of hypotension than the extracorporeal modalities

Comparing Renal Replacement Therapy Modalities in Critically Ill Patients With Acute Kidney Injury: A Systematic Review and Network Meta-Analysis



www.ccejournal.org
May 2021

Primary Analysis Results for Mortality

Comparison	Direct Estimate (95% CI); Certainty of Evidence	Indirect Estimate (95% CI); Certainty of Evidence	Network Estimate (95% CI); Certainty of Evidence[a]	Plain Text Summary
CRRT vs IHD	1.04 (0.93–1.18); moderate[a]; 9 studies	NA	1.04 (0.93–1.18); low[a,c]	There may be no important difference
CRRT vs PD	1.08 (0.76–1.49); low[a,b]; 3 studies	1.28 (0.90–1.82); moderate[a]	1.16 (0.92–1.49); low[a,c]	CRRT may increase mortality compared with PD
CRRT vs SLED	1.12 (0.85–1.47); moderate[a]; 5 studies	0.94 (0.63–1.41); low[a,b]	1.06 (0.85–1.33); low[a,c]	CRRT may increase mortality compared with SLED
IHD vs PD	NA	1.12 (0.85–1.46); low[a,b]	1.12 (0.85–1.46); very low[a,b,c]	Whether there is an important difference or not is very uncertain
IHD vs SLED	NA	1.02 (0.79–1.31); moderate[a]	1.02 (0.79–1.31); low[a,c]	There may be no important difference
PD vs SLED	0.88 (0.71–1.10); moderate[a]; 2 studies	1.05 (0.68–1.62); low[a,b]	0.91 (0.75–1.11); low[a,c]	PD may reduce mortality compared with SLED

CRRT may be no different from IHD in terms of effect on mortality possible increase in mortality compared with SLED and PD (evidence for both comparisons is low)

No important difference between IHD and SLED

PD may reduce mortality compared with SLED

Renal Recovery Rate

Comparison	Direct Estimate (95% CI); Certainty of Evidence	Indirect Estimate (95% CI); Certainty of Evidence	Network Estimate (95% CI); Certainty of Evidence[a]	Plain Text Summary
CRRT vs IHD	1.15 (0.91–1.44); moderate[b]; 7 studies	NA	1.15 (0.91–1.45); low[b,c]	CRRT may increase RRR compared with IHD
CRRT vs PD	0.97 (0.60–1.55); moderate[a]; 2 studies	0.71 (0.38–1.35); moderate[a]	0.87 (0.60–1.27); low[a,c]	CRRT may reduce RRR compared with PD
CRRT vs SLED	0.84 (0.60–1.16); moderate[a]; 4 studies	1.13 (0.55–2.34); moderate[a]	0.88 (0.65–1.19); low[a,c]	CRRT may reduce RRR compared with SLED
IHD vs PD	NA	0.76 (0.49–1.18); moderate[a]	0.76 (0.49–1.18); low[a,c]	IHD may reduce RRR compared with PD
IHD vs SLED	NA	0.77 (0.53–1.12); moderate[a]	0.77 (0.53–1.12); low[a,c]	IHD may reduce RRR compared with SLED
PD vs SLED	1.18 (0.68–2.04); moderate[b]; 2 studies	0.87 (0.49–1.54); moderate[a]	1.02 (0.68–1.51); low[b,c]	There may be no important difference

CRRT may increases renal recovery compared with IHD , both CRRT and IHD may be worse for renal recovery compared with SLED no important difference between PD and SLED

CONCLUSION:

- CRRT may **increase mortality** compared with SLED and PD
- CRRT and IHD may be worse for **renal recovery** compared with SLED and PD
- CRRT, IHD, or SLED would be reasonable options for any ICU patient whether on vasopressors or not

RRT in covid-19 associated AKI

➢ **CRRT**

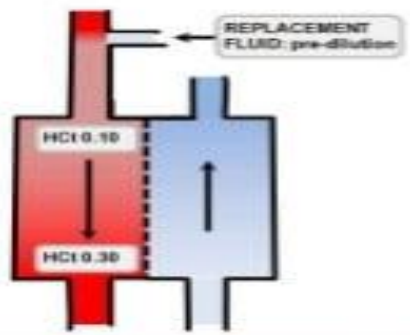
- Best modality in sepsis and unstable patients(KDIGO 2012)
- Recommended by the American Society of Nephrology (ASN)(Because of hemodynamic instability and minimization of nursing staff exposure)

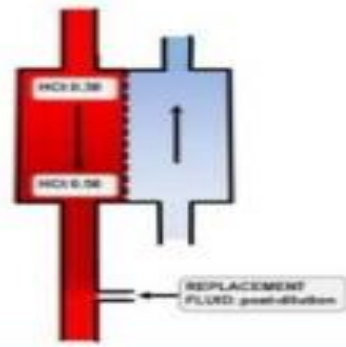
➢**PIRRT**(Prolong intermittent renal replacement); SLED,….

- If CRRT is not available
- No data for comparison between CRRT and SLED in COVID-19

➢**PD**

J Clin Med Res. 2020;12(5):276



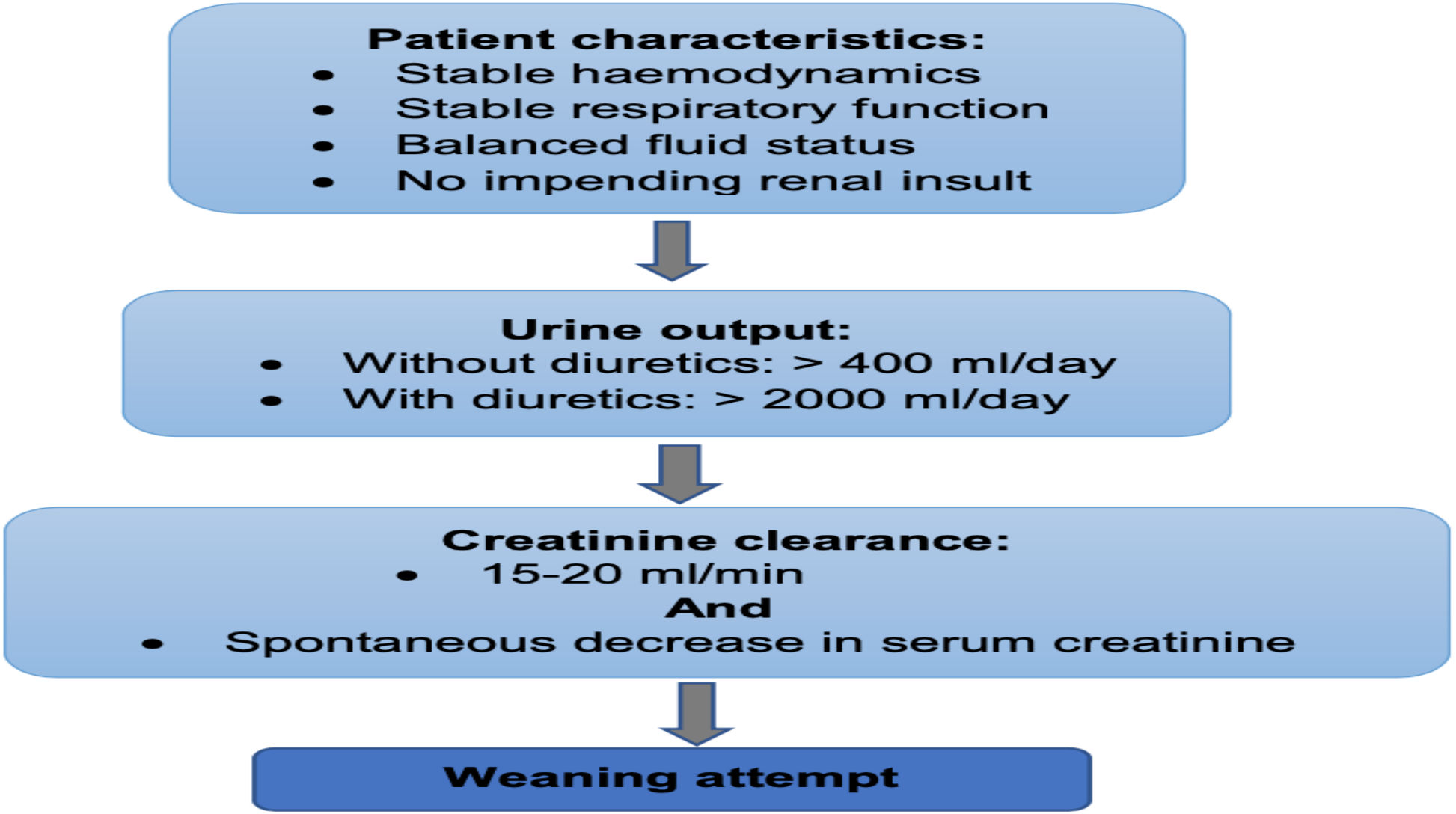


Pre-dilution	Post-dilution
Low risk of clotting	High risk of clotting

No clinical study has definitively addressed when pre- or post-dilution HF should be used, so this decision is largely a matter of local experience and preference.

Ronco et al. Critical Care (2015) 19:146

Stop CRRT:


Patient characteristics:
Stable haemodynamics
Stable respiratory function
Balanced fluid status
No impending renal insult
Urine output:
Without diuretics: > 400 ml/day
With diuretics: > 2000 ml/day
Creatinine clearance:
15-20 ml/min
And
Spontaneous decrease in serum creatinine
Weaning attempt

Dose of Therapeutic Agents

- Therapeutic drug monitoring is important
- β-lactams, glycopeptides, and aminoglycoside readily pass across RRT membranes and Require dose adjustment (especially high volume hemofiltration)

Therapeutic options for patients with kidney disease

- Patients with estimated glomerular filtration rate (eGRF) < 30 represent a large proportion of the patients who become critically ill from COVID-19
- Antiviral agents :Nucleoside analogs,HIV protease inhibitor ; Lopinavir/ritonavir
- Monoclonal antibodies :Adalimumab ,Tocilizumab , Bevacizumab
- Pirfenidone
- Leflunomide,….

Remdesivir

- Nucleoside analogs
- limited water solubility
- IV dose of 200 mg once followed by 100 mg daily for a total of 5–10 days in adults and children ≥40 kg
- Elimination of Remdesivir and its active metabolite :renal predominant (74%)
- Potential accumulation of Remdesivir and its sulfobutylether-*β*-cyclodextrin (SBECD) carrier in kidney disease

JASN July 2020, 31 (7) 1384-1386; DOI:https://doi.org/10.1681/ASN.2020050589

Remdesivir

- **CYCLODEXTRIN CARRIER(**found in IV voriconazole):
- Filtered solely by the glomerulus
- Each 100 mg of remdesivir powder contains 3 g cyclodextrin
- Maximum recommended dose of 250 mg/kg/day
- Both dialysis and CRRT remove cyclodextrin
- The patient is on CRRT or is expected to begin it, the risk of cyclodextrin accumulation is low
- Patients at highest risk of cyclodextrin accumulation are those who have pre-existing advanced chronic kidney disease and no plan for dialysis

Remdesivir

The FDA has stated that patients with eGFR < 30 should not receive remdesivir unless the potential benefit outweighs the potential risk

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

Not demonstrate an increased risk of renal adverse events

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 12, 2019 VOL. 381 NO. 24

A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics

Renal adverse events were not reported when remdesivir was used in a clinical trial for Ebola

limited duration of treatment (5–10 days)

on a case-by-case basis, this medication could be used in patients with kidney failure

low concentration of SBECD carrier

The best initial candidates to receive remdesivir:
Without underlying liver disease who are expected to undergo continuous or intermittent dialysis
or
Transient AKI

JASN 31: 1384–1386, 2020. doi: https://doi.org/10.1681/ASN.20200

Others drug:

	Covid status	Dosage according to GFR	Renal adverse event
Ribavirin	phase2	Need	Not reported ;hyperuricemia due to hemolytic anemia
Lopinavir/ritonavir	Phase 4	Normal dosage regardless of hemodialysis schedule	Reversible AKI
Tenofovir	phase4	Need	AKI; RTAProximal;hyperkalemia
pirfenidone	Phase3	Not available	Not reported
Adalimumab	phase4	Normal dosage	Autoimmune GN(MN,IgA,Lupus,ANCA vasculitis);granulomatous AIN
Tocilizumab	phase4	Normal dosage	Not reported
IVIg	phase3	After HD	AKI; osmotic nephrosis

Kidney International (2020) 97, 1297–1302


Thank You