REVIEW ARTICLE

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

Zhikang Ye, MPharm[1]
Ying Wang, MPharm[1]
Long Ge, PhD[2]
Gordon H. Guyatt, MD[1,3]
David Collister, MD[4,5]
Waleed Alhazzani, MD[1,3]
Sean M. Bagshaw, MD[6]
Emilie P. Belley-Cote, MD[1,3]
Fang Fang, MD[1]
Liangying Hou, MSc[2]
Philipp Kolb, MBA[7]
Francois Lamontagne, MD[8,9]
Simon Oczkowski, MD[1,3]
Lonnie Pyne, MD[1,3]
Christian Rabbat, MD[1,3]
Matt Scaum, RN[10]
Borna Tadayon Najafabadi, MSc[1]
Wimonchat Tangamornsuksan, PharmD PhD[1]
Ron Wald, MD[11]
Qi Wang, MSc[1]
Michael Walsh, MD[1,3,12]
Liang Yao, MSc[1]
Linan Zeng, PhD[1,13]
Abdullah Mohammed Algarni, MBBS[14]
Rachel J. Couban, MA, MISt[15]
Paul Elias Alexander, PhD[1]
Bram Rochwerg, MD[1,3]

OBJECTIVES: To compare different modalities of renal replacement therapy in critically ill adults with acute kidney injury.

DATA SOURCES: We searched Medline, PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception to 25 May, 2020. We included randomized controlled trials comparing the efficacy and safety of different renal replacement therapy modalities in critically ill patients with acute kidney injury.

STUDY SELECTION: Ten reviewers (working in pairs) independently screened studies for eligibility, extracted data, and assessed risk of bias.

DATA EXTRACTION: We performed random-effects frequentist network meta-analyses and used the Grading of Recommendations, Assessment, Development, and Evaluation approach to assess certainty of evidence. The primary analysis was a four-node analysis: continuous renal replacement therapy, intermittent hemodialysis, slow efficiency extended dialysis, and peritoneal dialysis. The secondary analysis subdivided these four nodes into nine nodes including continuous veno-venous hemofiltration, continuous veno-venous hemodialysis, continuous veno-venous hemodiafiltration, continuous arterio-venous hemodiafiltration, intermittent hemodialysis, intermittent hemodialysis with hemofiltration, slow efficiency extended dialysis, slow efficiency extended dialysis with hemofiltration, and peritoneal dialysis. We set the minimal important difference threshold for mortality as 2.5% (relative difference, 0.04).

DATA SYNTHESIS: Thirty randomized controlled trials (n = 3,774 patients) proved eligible. There may be no difference in mortality between continuous renal replacement therapy and intermittent hemodialysis (relative risk, 1.04; 95% CI, 0.93–1.18; low certainty), whereas continuous renal replacement therapy demonstrated a possible increase in mortality compared with slow efficiency extended dialysis (relative risk, 1.06; 95% CI, 0.85–1.33; low certainty) and peritoneal dialysis (relative risk, 1.16; 95% CI, 0.92–1.49; low certainty). Continuous renal replacement therapy may increase renal recovery compared with intermittent hemodialysis (relative risk, 1.15; 95% CI, 0.91–1.45; low certainty), whereas both continuous renal replacement therapy and intermittent hemodialysis may be worse for renal recovery compared with slow efficiency extended dialysis and peritoneal dialysis (low certainty). Peritoneal dialysis was probably associated with the shortest duration of renal support and length of ICU stay compared with other interventions (low certainty for most comparisons). Slow efficiency extended dialysis may be associated with shortest

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length of hospital stay (low or moderate certainty for all comparisons) and days of mechanical ventilation (low certainty for all comparisons) compared with other interventions. There was no difference between continuous renal replacement therapy and intermittent hemodialysis in terms of hypotension (relative risk, 0.92; 95% CI, 0.72–1.16; moderate certainty) or other complications of therapy, but an increased risk of hypotension and bleeding was seen with both modalities compared with peritoneal dialysis (low or moderate certainty). Complications of slow efficiency extended dialysis were not sufficiently reported to inform comparisons.

CONCLUSIONS: The results of this network meta-analysis suggest there is no difference in mortality between continuous renal replacement therapy and intermittent hemodialysis although continuous renal replacement therapy may increases renal recovery compared with intermittent hemodialysis. Slow efficiency extended dialysis with hemofiltration may be the most effective intervention at reducing mortality. Peritoneal dialysis is associated with good efficacy, and the least number of complications however may not be practical in all settings. Importantly, all conclusions are based on very low to moderate certainty evidence, limited by imprecision. At the very least, ICU clinicians should feel comfortable that the differences between continuous renal replacement therapy, intermittent hemodialysis, slow efficiency extended dialysis, and, where clinically appropriate, peritoneal dialysis are likely small, and any of these modalities is a reasonable option to employ in critically ill patients.

KEY WORDS: continuous renal replacement therapy; critically ill; intermittent hemodialysis; network meta-analysis; renal replacement therapy

The prevalence of acute kidney injury (AKI) in critically ill patients is high, and some of these patients will require renal replacement therapy (RRT) while in the ICU (1). Two large multicenter cohort studies have shown that approximately 5% of ICU patients require RRT (2, 3), and once requiring RRT, overall hospital-based mortality is around 40–45% (4, 5).

There are a number of RRT modalities and controversy exist regarding which is best for critically ill patients. Although many centers use continuous RRT (CRRT) in this setting, the largest randomized controlled trials (RCTs) failed to demonstrate a difference between CRRT and intermittent hemodialysis (IHD), even in patients who are hemodynamically unstable and treated with vasopressors (6). Previous systematic reviews and meta-analyses have compared the clinical efficacy and safety of CRRT, IHD, or sustained low efficiency dialysis (SLED) in critically ill patients (7, 8); however, these analyses were limited to head-to-head pairwise comparisons. Network meta-analysis (NMA) has the advantage of simultaneously considering multiple comparisons within the same analytic model, including both direct and indirect evidence.

We conducted a systematic review and NMA comparing the efficacy and safety of different modalities of RRT in critically ill patients with AKI.

METHODS

We registered the protocol for this systematic review in PROSPERO (CRD42020149006). We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (9).

Search Strategy

We developed our literature search in collaboration with a research librarian. The search included Medline, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception to May 25, 2020, and a PubMed search for studies not yet indexed or not found in Medline. We tailored the search strategy to each database (**ESM 1**, http://links.lww.com/CCX/A586). We also searched conference abstracts for the last 2 years from three major critical care conferences: Society of Critical Care Medicine, European Society of Intensive Care Medicine, and American Thoracic Society. We reviewed reference lists of all included studies and relevant systematic reviews for additional references.

Study Selection

Ten reviewers (working in five pairs) screened titles and abstracts independently and in duplicate in a first stage and then reviewed the full texts of potentially eligible studies in a second stage to determine the final eligible studies. We resolved disagreements by discussion or by referring to a third reviewer if necessary.

We included RCTs that compared the efficacy and safety of different modalities of RRT in adult critically ill patients with AKI. We did not limit the modalities of RRT. We included studies reporting the following outcomes: mortality, renal recovery rate, renal support duration (d), length of ICU stay (d), length of hospital stay (d), duration of mechanical ventilation (d), RRT-free days, and treatment complications (hypotension, bleeding, and catheter infection). We used the individual study definition for renal recovery rate which most commonly defined this as independence from RRT. We defined renal support duration as the period of time from the initiation of RRT to the time when RRT was no longer administered.

Data Extraction

The same 10 reviewers performed data abstraction independently and in duplicate. We resolved any inconsistencies in abstraction through discussion. We extracted the following items: study characteristics (year of publication, country, and sample size), population characteristics (age, proportion of males, proportion of surgery, proportion of oliguria, proportion of sepsis), illness severity (Acute Physiology and Chronic Health Evaluation II, Simplified Acute Physiology Score II, multiple organ dysfunction syndrome, or Sequential Organ Failure Assessment, and proportion of patients receiving invasive mechanical ventilation or vasopressor support), description of interventions and comparators (anticoagulation, mode, filter/dialyzer, dialysate, blood flow, and dose), outcomes, and corresponding definitions.

Risk of Bias Assessment

Two reviewers independently assessed the risk of bias for each individual study using a modified Cochrane Collaboration tool (10) that includes assessment of sequence generation, allocation sequence concealment, blinding, missing outcome data, and other bias. We assessed blinding in five groups: blind to patients, healthcare providers, data collectors, outcome assessors, and data analysts. If the rate of missing data of one study was more than 5%, we judged this study as high risk of bias for this domain. The category of "other bias" included early trial discontinuation. We judged each criterion as low, probably low, high, or probably high risk of bias.

Data Analysis

For mortality, if multiple time points were reported, we included hospital mortality or the closest to 30-days. For renal recovery rate, we preferentially included both survivors and nonsurvivors if reported; if not, we used renal recovery in survivors only.

We performed two categories of analysis. The primary analysis was a four-node analysis categorizing the modalities of RRT into CRRT, IHD, SLED, and peritoneal dialysis (PD). The secondary analysis subdivided these four nodes into nine nodes including continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), continuous veno-venous hemodiafiltration (CVVHDF), continuous aterio-venous hemodiafiltration (CAVHDF), IHD, IHD with hemofiltration (IHDF), SLED, SLED with hemofiltration (SLEDF), and PD. Although CAVHDF is no longer used in most clinical settings, we retained these data as it contributed to the network and informed indirect comparisons that were still relevant.

We performed a series of conventional meta-analyses using a DerSimonian-Laird random-effects model in R Version 3.4.3 (R Core Team, Vienna, Austria) for all direct comparisons in which at least two studies were available examining the outcome of interest. We assessed between-study heterogeneity in treatment effects using visual inspection of forest plots, the I^2 statistic, and the chi-square test (11). We reported pooled effect estimates using relative risk (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, both with 95% CIs.

We conducted frequentist random-effects NMA (12) to assess the relative effect of all interventions simultaneously using the *netmeta* package of R Version 3.4.3 (R Core Team). We assumed a common heterogeneity variable for all treatment comparisons (13). We assessed the transitivity (similarity) assumption by comparing the distribution of the population, the intervention, and the methodological characteristics of the studies across treatment comparisons. To assess coherence (inconsistency between the direct and indirect estimates), we fitted both a consistency and an inconsistency model for each outcome and assessed global incoherence for the entire network for each outcome under the assumption of a full design-by-treatment interaction random-effects model (14) and then local incoherence for each comparison using the

node-splitting model (15). We calculated the ranking of treatment as P-score (frequentist analogue of the surface under the cumulative ranking curve [SUCRA]) for each treatment (16). We assessed small-study effects with a comparison-adjusted funnel plot of treatment estimates for each outcome (17).

We conducted network meta-regression using the proportion of patients being administered vasopressors as the independent variable to explore the impact of degree of shock on effect of different RRT modalities. We also conducted network meta-regression using the proportion of patients with sepsis (according to individual study criteria) and the proportion of patients who were surgical (again according to individual study criteria) as the independent variables to explore the effect of these variables on RRT modality. We limited network meta-regression analyses to mortality and renal recovery rate as the other outcomes had insufficient data. Although we had planned to perform meta-regression for risk of bias, there proved insufficient studies judged to be at low risk of bias to allow for this analysis. We considered a post hoc meta-regression analysis based on RRT dose, but heterogeneity in how dose was reported between studies did not allow for this. At the request of peer reviewers, we conducted two additional post hoc meta-regression analysis, one based on year of publication (as a continuous variable), and the other based on income level of the country in which the trial was performed (high- vs low-/middle-income countries—based on World Bank data). We judged credibility in subgroup findings using the Instrument for assessing the Credibility of Effect Modification Analyses tool (18).

Certainty of Evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence (19–22). We started by rating the certainty of evidence for direct comparisons (23–27) assessing domains related to individual study risk of bias, inconsistency, indirectness, and publication bias. Next, we rated indirect comparison in which ratings started from the lowest rating of the direct comparisons that contributed to the most-dominant first-order loop informing the indirect comparison. We rated down further if there were concerns related to intransitivity. Assuming coherence between the direct and indirect estimate, we started with the higher of the direct and indirect estimates for the certainty of the network estimate, assuming this was the dominant contributor to the network estimate. We then assessed for imprecision in the network estimate (having not applied imprecision to the direct or indirect estimates). If incoherence was present, we used the estimate—direct or indirect—with the higher certainty of evidence as the best estimate or used the network estimate if the ratings for direct and indirect estimates were the same. We used statements of GRADE guidance in this article—"probably" is used for moderate certainty and "may" for low certainty (28).

For imprecision rating, the minimal important difference (MID) boundary and large effect boundary were discussed, and consensus was reached by the review authors which include critical care medicine and nephrology experts. We set the MID threshold and large effect boundary for mortality as 2.5% (relative difference, 0.04) and 15% (relative difference, 0.27), respectively, and the MID threshold and large effect boundary for renal recovery rate as 3.25% (relative difference, 0.09) and 20% (relative difference, 0.57), respectively. We set the MID threshold for all continuous outcomes at 1 day. We set all MID thresholds based on what was perceived to be important to patients. In keeping with updated GRADE guidance, if the CI crossed either side of the MID threshold, we rated down once for imprecision; if the CI crossed both sides of large effect boundary, we rated down twice for imprecision.

To help with interpretation of the results and draw useful conclusions from the NMA, we used minimally contextualized approach to group interventions of secondary analyses in categories based on estimates of effect, the certainty of the evidence, and the rankings (29).

RESULTS

Description of Included Studies

We identified 6,047 citations with our search. After title and abstract screening, we reviewed 211 full text and included 30 eligible RCTs (**Fig. 1**).

These 30 trials were published from 1998 to 2018 and enrolled 3,774 patients, with sample sizes ranging from 20 to 407. Only one study reported CAVHDF (30), and this study only reported on and contributed to the outcome of hypotension. For the four-node

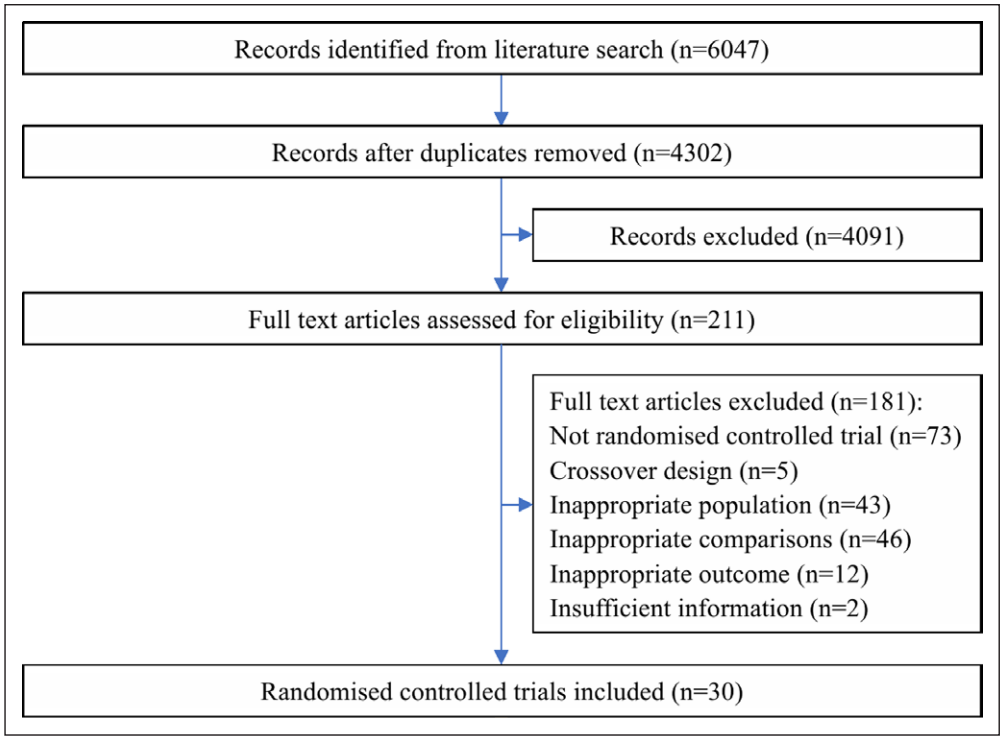

Figure 1. Flow chart for the systematic review.

analysis, the most common comparison was between CRRT and IHD (10 trials) enrolling 1,582 patients, followed by CRRT versus SLED (5 trials) enrolling 463 patients. For the nine-node analysis, the most common comparisons were CVVH versus CVVHD (4 trials with 227 patients) and CVVH versus IHD (4 trials with 700 patients); CVVH versus IHD was the comparison included most patients followed by CVVHDF versus IHD (3 trials with 650 patients). **ESM 2** (http://links.lww.com/CCX/A587) presents study characteristics.

Risk of bias

ESM 3 (http://links.lww.com/CCX/A588) summarizes the risk of bias assessment for each RCT. Only one study blinded patients to treatment allocation while another study blinded outcome assessors. Many of the included studies did not include description of adequate allocation sequence concealment (56.7%).

Outcomes

ESM 4 (http://links.lww.com/CCX/A589) presents network plots for each outcome. **ESM 5** (http://links.lww.com/CCX/A590) presents ranking of interventions for each outcome.

Mortality

The primary four-node analysis for mortality included 19 studies (4, 27–44) examining 2576 patients. CRRT may be no different from IHD in terms of effect on mortality (RR, 1.04; 95% CI, 0.93–1.18; low certainty) (**Table 1**) and demonstrated a possible increase in mortality compared with SLED (RR, 1.06; 95% CI, 0.85–1.33) (Table 1) and PD (RR, 1.16; 95% CI, 0.92–1.49) (Table 1) although certainty in evidence for both comparisons is low, and conclusions are limited by important imprecision (CIs do not exclude possibility of benefit). There may be no important difference between IHD and SLED (RR, 1.02; 95% CI, 0.79–1.31; low certainty) (Table 1). PD may reduce mortality compared with SLED (RR, 0.91; 95% CI, 0.75–1.11; low certainty) (Table 1).

The secondary analysis for mortality included eight interventions and 27 trials (4, 27–42, 44–53) with 3,399 patients (**Table 1** of **ESM 6**, http://links.lww.com/CCX/A591). Among the comparisons with high or moderate certainty evidence relative to CVVHDF, IHD was in the intermediate category, and CVVH was the least effective (**Fig. 2**). Among the comparisons with low or very low certainty evidence relative to CVVHDF, SLEDF may be the most effective in reducing mortality, and the other modalities may be in the intermediate category (Fig. 2).

Network meta-regression failed to demonstrate a credible subgroup effect on mortality based on percent of patients on vasopressors, those with sepsis, those designated surgical patients, or based on year of study publication in either the primary or secondary analysis. Income level of the country in which the trial was performed demonstrated a potential subgroup effect in primary analysis; however, the credibility of this effect was judged to be very low given the post hoc nature of the analysis, the small number of studies contributing,

TABLE 1.
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 = continuous renal replacement therapy, IHD = intermittent hemodialysis, NA = not applicable, PD = peritoneal dialysis, SLED = sustained low efficiency dialysis.
[a]Rated down for risk of bias.
[b]Rated down for inconsistency.
[c]Rated down for imprecision.

and the lack of a clearly defined a priori hypothesis (**ESM 7**, http://links.lww.com/CCX/A592) (18).

Renal Recovery Rate

Most studies defined renal recovery as independence from RRT, whereas three studies (31–33) defined it using specific serum creatinine criteria, and one study (34) used glomerular filtration rate criteria. The primary analysis for renal recovery rate included four interventions and 15 trials (4, 27–31, 35–41, 43, 44) with 2,072 patients. The results suggested that CRRT may increases renal recovery compared with IHD (RR, 1.15; 95% CI, 0.91–1.45; low certainty and limited by imprecision) (**Table 2**), whereas both CRRT and IHD may be worse for renal recovery compared with SLED (CRRT vs SLED: 0.88; 95% CI, 0.65–1.19 and IHD vs SLED: 0.77; 95% CI, 0.53–1.12) (Table 2, both comparisons based on low certainty of evidence and limited by imprecision) and PD (CRRT vs PD: 0.87; 95% CI, 0.60–1.27 and IHD vs PD: 0.76; 95% CI, 0.49–1.18, both comparisons based on low certainty of evidence and limited by imprecision) (Table 2). There may be no important difference between PD and SLED (1.02; 95% CI, 0.68–1.51; low certainty) (Table 2).

The secondary analysis for renal recovery rate included eight interventions and 18 trials [4, 27–31, 35–41, 44, 46, 51–53) with 2,602 patients (**Table 2** of ESM 6, http://links.lww.com/CCX/A591). Among the comparisons with high or moderate certainty evidence relative to CVVHDF, PD was most effective at improving renal recovery rate, whereas IHD was in the less effective category (Fig. 2). Other modalities may be in the less effective category with low or very low certainty evidence (Fig. 2).

Similar to mortality, network meta-regression suggested that vasopressor use, sepsis, surgery, and year of publication do not contribute to important subgroup effects in terms of renal recovery rate in either the primary or secondary analysis. Income level of the country in which the trial was performed demonstrated a potential subgroup effect in primary analysis; however, the credibility of this effect was judged to be very low given the post hoc nature of the analysis, the small number of studies contributing, and the lack of a clearly defined a priori hypothesis (ESM 7, http://links.lww.com/CCX/A592) (18).

A

	Mortality RR (95% CI)	Renal recovery rate RR (95% CI)	Renal support duration (d) MD (95% CI)	Length of ICU stay (d) MD (95% CI)	Length of hospital stay (d) MD (95% CI)	RRT free days MD (95% CI)	Hypotension RR (95% CI)	Bleeding events RR (95% CI)
CVVH	1.39 (1.10 to 1.75)	1.08 (0.70 to 1.66)	-2.15 (-8.38 to 4.07)	3.04 (-0.69 to 6.78)	4.13 (-7.36 to 15.62)	-1.00 (-3.20 to 1.20)	0.75 (0.31 to 1.84)	0.33 (0.05 to 2.15)
CVVHD	0.94 (0.69 to 1.26)	1.05 (0.52 to 2.10)	-2.65 (-9.18 to 3.88)	-0.01 (-12.33 to 12.32)	-0.87 (-20.59 to 18.84)	NA	NA	NA
IHD	0.95 (0.77 to 1.18)	0.90 (0.63 to 1.28)	0.58 (-2.24 to 3.39)	1.77 (-1.96 to 5.51)	0.64 (-9.33 to 10.62)	0.10 (-3.09 to 3.29)	1.00 (0.67 to 1.52)	1.02 (0.49 to 2.13)
IHDF	0.98 (0.64 to 1.49)	0.97 (0.46 to 2.04)	2.23 (-4.13 to 8.59)	NA	NA	-5.40 (0.75 to -11.55)	0.81 (0.44 to 1.49)	0.80 (0.18 to 3.57)
PD	0.89 (0.66 to 1.20)	1.69 (1.15 to 2.50)	-3.01 (-3.67 to -2.35)	-10.00 (-11.68 to -8.32)	NA	NA	0.36 (0.17 to 0.76)	0.27 (0.10 to 0.73)
SLED	0.97 (0.71 to 1.33)	0.87 (0.50 to 1.52)	-2.44 (-8.90 to 4.03)	2.83 (0.04 to 5.62)	NA	NA	2.00 (0.18 to 20.00)	NA
SLEDF	0.58 (0.34 to 0.97)	1.47 (0.87 to 2.50)	NA	-4.95 (-9.15 to -0.75)	-6.58 (-14.09 to 0.93)	NA	NA	NA
CVVHDF (ref)	-(Intermediate mortality rate)	- (Lower renal recovery rate)	- (Longer renal support duration)	- (Longest length of ICU stay)	- (All in the same category)	- (Shorter RRT free days)	- (Higher hypotension rate)	- (Higher bleeding events rate)

B

High or moderate certainty evidence	**Category 2:** Lowest mortality rate, Shortest length of ICU stay	**Category 1:** Intermediate mortality rate, Higher renal recovery rate, Shorter renal support duration, Intermediate length of ICU stay, Longer RRT free days, Lower hypotension rate, Lower bleeding events rate	**Category 0:** Highest mortality rate, Lower renal recovery rate, Longer renal support duration, Longest length of ICU stay, Shorter RRT free days, Higher hypotension rate, Higher bleeding events rate
Low or very low certainty evidence	**Category 2:** May be lowest mortality rate, May be shortest length of ICU stay	**Category 1:** May be intermediate mortality rate, May be higher renal recovery rate, May be shorter renal support duration, May be intermediate length of ICU stay, May be longer RRT free days, May be lower hypotension rate, May be lower bleeding events rate	**Category 0:** May be highest mortality rate, May be lower renal recovery rate, May be longer renal support duration, May be longest length of ICU stay, May be shorter RRT free days, May be higher hypotension rate, May be higher bleeding events rate

Figure 2. Network meta-analysis results sorted based on Grading of Recommendations, Assessment, Development, and Evaluation certainty of evidence for the comparisons of renal replacement therapy (RRT) modalities versus continuous veno-venous hemodiafiltration (CVVHDF) for secondary analyses. CVVH = continuous veno-venous hemofiltration, CVVHD = continuous veno-venous hemodialysis, IHD = intermittent hemodialysis, IHDF = IHD with hemofiltration, MD = mean difference, NA = not applicable, PD = peritoneal dialysis, ref = reference, RR = relative risk, SLED = slow efficiency extended dialysis, SLEDF = SLED with hemofiltration.

Renal Support Duration

The primary analysis for duration of renal support included four interventions and six trials (6, 35–39) with 1,229 patients. IHD may lead to increased duration of renal support compared with SLED (MD, 1.44 d; –3.00 to 5.89 d; low certainty) (**Table 3** of ESM 6, http://links.lww.com/CCX/A591), whereas there is likely no

TABLE 2.
Primary Analysis for 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 = continuous renal replacement therapy, IHD = intermittent hemodialysis, NA = not applicable, PD = peritoneal dialysis, RRR = renal recovery rate, SLED = slow efficiency extended dialysis.
[a]Rated down for inconsistency.
[b]Rated down for risk of bias.
[c]Rated down for imprecision.

important difference between CRRT and IHD (moderate certainty) or CRRT and SLED (low certainty). Compared with PD, CRRT, IHD, and SLED (low to moderate certainty) may increase the duration of renal support.

The secondary analysis for duration of renal support included seven interventions and nine trials (6, 36–43) with 1,613 patients (**Table 4** of ESM 6, http://links.lww.com/CCX/A591). Among the comparisons with high or moderate certainty evidence relative to CVVHDF, PD was most effective at reducing the duration of renal support (Fig. 2). Among the comparisons with low or very low certainty evidence, CVVH, CVVHD, and IHD may be in the category of shorter duration of renal support, whereas IHDF and SLED may be in the category of longer duration of renal support (Fig. 2).

Length of ICU, Hospital Stay, Days of Mechanical Ventilation, and RRT-Free Days

The primary analysis for length of ICU stay included four interventions and 11 trials (6, 31, 32, 34, 35, 37, 38, 44–47) with 1,785 patients. Compared with SLED, CRRT (MD, 1.78 d; –2.31 to 5.87 d; low certainty) (**Table 5** of ESM 6, http://links.lww.com/CCX/A591) and IHD (MD, 3.14 d; –2.40 to 8.68 d; low certainty) (Table 5 of ESM 6, http://links.lww.com/CCX/A591) may increase ICU length of stay. CRRT may reduce length of ICU stay compared with IHD (MD, –1.36 d; –5.09 to 2.38 d; low certainty) (Table 5 of ESM 6, http://links.lww.com/CCX/A591). Compared with PD, CRRT, IHD, and SLED may increase length of ICU stay (low to moderate certainty).

The secondary analysis for length of ICU stay included seven interventions and 12 trials (4, 27–29, 31, 35, 36, 40–42, 49, 51) with 2,024 patients (**Table 6** of ESM 6, http://links.lww.com/CCX/A591). Among the comparisons with high or moderate certainty evidence relative to CVVHDF, PD was most effective at reducing ICU length of stay, SLEDF was in the category of intermediate length of ICU stay, and CVVH and IHD were least effective at reducing ICU length of stay (Fig. 2). Among the comparisons with low or very low certainty evidence, CVVHD and SLED may be least effective at reducing ICU length of stay (Fig. 2).

Few studies reported length of hospital stay and days of mechanical ventilation. In the primary analyses, SLED may be associated with the shortest length of hospital stay (**Table 7** of ESM 6, http://links.lww.com/CCX/A591) and days of mechanical ventilation (**Table 9** of ESM 6, http://links.lww.com/CCX/A591) compared with other interventions (low to moderate certainty). **Tables 8** and **10** of ESM 6 (http://links.lww.com/CCX/A591) present secondary analysis for length of hospital stay and RRT-free days.

Safety

The primary analysis for hypotension included four interventions and five trials (6, 35, 39, 45, 48) with 719 patients. CRRT and IHD probably increase the risk of hypotension compared with PD (CRRT vs PD: 2.74; 95% CI, 1.45–5.18 and IHD vs PD: 3.00; 95% CI, 1.52–5.91; moderate certainty) (**Table 11** of ESM 6, http://links.lww.com/CCX/A591). There may be no important difference in other comparisons (low or moderate certainty) (Table 11 of ESM 6, http://links.lww.com/CCX/A591) including CRRT versus IHD (moderate certainty). The secondary analysis for hypotension comparing six interventions included six trials (6, 35, 39, 42, 45, 48) with 992 patients (**Table 12** of ESM 6, http://links.lww.com/CCX/A591). Among the comparisons with high or moderate certainty evidence relative to CVVHDF, PD was more effective in terms of avoiding hypotension (Fig. 2). Among the comparisons with low or very low certainty evidence, CVVH, IHD, IHDF, and SLED may be in the category associated with the higher rates of hypotension (Fig. 2).

The primary analysis for bleeding included three interventions and four trials (6, 32, 35, 49) with 674 patients. There may be no difference in bleeding between CRRT, IHD, and PD (low and moderate certainty) (**Table 13** of ESM 6, http://links.lww.com/CCX/A591). The secondary analysis for bleeding included five interventions and six trials (6, 32, 35, 42, 49, 50) with 1,153 patients (**Table 14** of ESM 6, http://links.lww.com/CCX/A591). Among the comparisons with high or moderate certainty evidence relative to CVVHDF, PD was more effective at avoiding bleeding, whereas CVVH and IHD were in the category of higher bleeding risk (Fig. 2). Among the studies with low or very low certainty evidence, IHDF may be in the category of higher risk of bleeding (Fig. 2).

For catheter infection, there was probably no important difference between interventions (moderate certainty) (**Table 15** of ESM 6, http://links.lww.com/CCX/A591).

DISCUSSION

This systematic review and NMA assessed different modalities of RRT in critically ill patients with AKI. We found no difference in mortality between CRRT and IHD. Although SLED may be associated with decreased mortality compared with CRRT, this conclusion was limited by imprecision and resultant low certainty evidence. SLEDF may be the most effective in reducing mortality with low certainty evidence. CRRT was found to may increase renal recovery compared with IHD; however, both CRRT and IHD may be worse for renal recovery compared with SLED and PD, again with all conclusions limited by imprecision and low certainty evidence. PD was probably associated with a shorter duration of renal support and length of ICU stay compared with the other interventions, whereas SLED may be associated with shorter length of hospital stay and days of mechanical ventilation. Safety outcomes were more sporadically reported among included trials; however, CRRT and IHD likely increase the risk of hypotension and bleeding compared with PD. There was no credible subgroup effect based on percent of patients requiring vasopressors, percent with sepsis, percent that were surgical as opposed to medical ICU patients, year of study publication, or income level of the country in which the study was performed.

Strengths and Limitations of Study

Strengths of this review include a comprehensive search to identify eligible trials; independent and duplicate study selection, data extraction, and risk of bias assessment; and application of the GRADE approach to rate the certainty of evidence. We explicitly and a priori set the MID threshold and a large effect boundary for imprecision ratings using a minimally contextualized framework. These thresholds were set in discussion with experts in critical care medicine and nephrology. In order to consider all relevant comparisons while maximizing precision, we conducted primary analyses using grouped nodes (comparing CRRT, IHD, SLED, or PD) and secondary analyses using less grouped

nodes (comparing CVVH, CVVHD, CVVHDF, CAVHDF, IHD, IHDF, SLED, SLEDF, or PD). Finally, to effectively interpret the results and draw conclusions from the NMA, we grouped interventions in categories based on estimates of effect, the certainty of the evidence, and the rankings.

There are also several limitations. First, some studies (although a minority) only reported rate of renal recovery in survivors rather than all those randomized, and as such, there may be issues with competing events between renal recovery and death. Second, the number of included trials and patients was insufficient for some planned secondary and subgroup analyses. This same limitation led to imprecision for a number of comparisons leading to a number of outcomes with only low or very low certainty evidence. Most trials had high risk of bias due to blinding, which further rated down the certainty of evidence. Third, there is important clinical heterogeneity between trials when it comes to the years they were performed (acknowledging temporal trends in care), geographical location, resource availability (high- vs low-/middle-income countries), severity of illness, intensity, prescription and dose of RRT, and use of cointerventions. This clinical heterogeneity, in addition to RRT modality, may have contributed to differences that were seen. Reassuringly, this clinical heterogeneity did not translate into important statistical heterogeneity or inconsistency for most comparisons or outcomes of interest, and our meta-regression analysis did not identify any credible subgroup effects based on the clinical variables assessed. Fourth, this analysis assumes decisions around RRT modality are an all-or-none phenomenon, whereas in many clinical settings, different modes are used interchangeably, even in the same patient, as clinical status changes. Last, the generalizability of these results would be subject to institutional comfort in providing these different modes of RRT in the ICU setting.

Relation to Prior Work

Compared with previous conventional pairwise meta-analysis (7, 8), the indirect evidence of this NMA provided more granular evidence on the efficacy and safety of RRT in critically ill patients with AKI. By considering multiple comparisons in the same analysis, this systematic review included more trials and more patients than previous reviews. We also used the GRADE framework to rate the certainty of evidence for each comparison and grouped interventions in categories based on estimates of effect, the certainty of the evidence, and the rankings, which was not been done in earlier systematic reviews. Although previous conventional pairwise meta-analyses (7, 8) demonstrated no difference in mortality or renal recovery rate between modalities, our review suggested that CRRT may increase mortality compared with SLED and PD, and both CRRT and IHD may be worse for renal recovery compared with SLED and PD.

At least three recently published clinical practice guidelines have recommended CRRT for hemodynamically unstable patients, and CRRT or IHD for hemodynamically stable patients (51–53); however, our results did not support credible subgroup effect based on vasopressor requirement. These recommendations may require reassessment in the context of our results which suggest CRRT, IHD, or SLED would be reasonable options for any ICU patient whether on vasopressors or not.

Implications of Study

In most resource-rich countries, the RRT modality used to support AKI in the ICU is predominantly CRRT with IHD reserved for mostly hemodynamically stable patients. However, there is variability across centers depending on who is responsible for the provision of RRT (ICU vs nephrology), reimbursement policies, and clinician preference. SLED is used infrequently in select centers, sometimes as a substitute for CRRT and other times as an intermediate between CRRT and IHD, but is limited by its added dialysis nursing time (54). PD is not typically used due to concerns regarding its ability to provide adequate ultrafiltration in patients that are volume overloaded, its ability to provide adequate clearance in hypercatabolic patients, the risk of peritonitis, absolute and relative contraindications (intra-abdominal surgery, obesity, hernias), and most importantly the lack of infrastructure and experience in many centers required for a successful acute PD program (e.g., PD catheter insertion, nephrology and PD nurse expertise, protocols, individualized therapy, trouble-shooting PD catheter malfunction, and leaks) (55, 56).

In low-/middle-income countries, these considerations may be different. Our results suggest that PD, a less costly option for RRT, is at least no different than CRRT and IHD when it comes to mortality and may be better in terms of renal recovery and duration of renal

support. Due to the resource considerations, many critical care centers in low and middle income countries have developed an institutional comfort with providing PD in the ICU, and the results of this analysis support this approach. Whether there could be utility and cost-savings associated with resource-rich countries considering PD in critically ill patients remains to be seen as there are many barriers to its uptake including acceptability and feasibility. Specific issues with PD include clinician/hospital reimbursement, catheter insertion, and diseases that limit the ability to perform PD (liver disease, coagulopathy, etc). Less than 20% if participants in RCTs comparing PD with IHD (49, 57) had volume overload as an indication for the initiation of RRT, and although sepsis was common, not many patients in these trials had significant metabolic issues including hyperkalemia and acidosis. Other RRT modalities may be more suitable for "sicker" patients although frequent short PD exchanges can manage many of these complications (56). With the recent use of acute PD in coronavirus disease 2019 associated AKI due to the saturation of traditional RRT modalities (58, 59), acute PD may be more feasible than previously thought.

This NMA suggests that there may be no benefit with CRRT over any other RRT modality, even in patients with sepsis or those treated with vasopressors, although these conclusions are based on low certainty evidence. Given that CRRT is potentially more costly than other RRT modalities (60), IHD or SLED may be preferable if otherwise available. The findings that SLED (and SLEDF) may decrease mortality, improve renal recovery, decrease ICU length of stay, and at least it is not inferior to CRRT or IHD (although again based on low certainty evidence and limited by imprecision) suggest there could be a role to consider this modality more frequently depending on institution-specific practicalities.

CONCLUSIONS

The results of this NMA suggest there is likely no difference in mortality between CRRT and IHD although CRRT may increases renal recovery compared with IHD. SLED, especially with hemofiltration, may be the most effective intervention at reducing mortality. PD is associated with good efficacy, and the least number of complications however may not be practical in all settings. Importantly, all conclusions are based on very low to moderate certainty evidence, limited by imprecision. At the very least, ICU clinicians should feel comfortable that the differences between CRRT, IHD, SLED, and where clinically appropriate, PD, are likely small, and any of these modalities is a reasonable option to employ in critically ill patients. Given the low certainty, further data are required examining differences between RRT modes, when delivered at similar doses, and among specific ICU populations.

1 *Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada.*

2 *Evidence Based Social Science Research Center, School of Public Health, Lanzhou University, Lanzhou, China.*

3 *Department of Medicine, McMaster University, Hamilton, ON, Canada.*

4 *Division of Nephrology, University of Manitoba, Winnipeg, MB, Canada.*

5 *Chronic Disease Innovation Center, Seven Oaks General Hospital, Winnipeg, MB, Canada.*

6 *Department of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta and Alberta Health Services, Edmonton, AB, Canada.*

7 *Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada.*

8 *Université de Sherbrooke, Sherbrooke, QC, Canada.*

9 *Centre de recherche du CHU de Sherbrooke, Sherbrooke, QC, Canada.*

10 *Hamilton Health Sciences, Hamilton, ON, Canada.*

11 *Division of Nephrology, St. Michael's Hospital, Toronto, ON, Canada.*

12 *Population Health Research Institute, Hamilton Health Sciences/McMaster University, Hamilton, ON, Canada.*

13 *Department of Pharmacy/Evidence-based Pharmacy Center, West China Second University Hospital, Sichuan University, Sichuan, China.*

14 *Family medicine department, Aseer Centeral Hospital, Abha, Saudi Arabia.*

15 *DeGroote Institute for Pain Research and Care, McMaster University, Hamilton, ON, Canada.*

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For information regarding this article, E-mail: rochwerg@mcmaster.ca

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