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SYSTEMATIC REVIEW

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Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis

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Abstract *Purpose:* Choice of renal replacement therapy (RRT) modality may affect renal recovery after acute kidney injury (AKI). We sought to compare the rate of dialysis dependence among severe AKI survivors according to the choice of initial renal replacement therapy (RRT) modality applied [continuous (CRRT) or intermittent (IRRT)]. *Methods:* Systematic searches of peer-reviewed publications in MEDLINE and EMBASE were performed (last update July 2012). All studies published after 2000 reporting dialysis dependence among survivors from severe AKI requiring RRT were included. Data on follow-up duration, sex, age, chronic kidney disease, illness severity score, vasopressors, and mechanical ventilation were extracted when available. Results were pooled using a random-effects model. *Results:* We identified 23 studies: seven randomized controlled trials (RCTs) and 16 observational studies involving 472 and 3,499 survivors, respectively. Pooled analyses of RCTs showed no difference in the rate of dialysis dependence among survivors (relative risk, RR 1.15 [95 % confidence interval (CI) 0.78–1.68], $I^2 = 0$ %). However, pooled analyses of observational studies suggested a higher rate of dialysis dependence among survivors who initially received IRRT as compared with CRRT (RR 1.99 [95 % CI 1.53–2.59], $I^2 = 42$ %). These findings were consistent with adjusted analyses (performed in 7/16 studies), which found a higher rate of dialysis dependence in IRRT-treated patients [odds ratio (OR) 2.2–25 (5 studies)] or no difference (2 studies). *Conclusions:* Among AKI survivors, initial treatment with IRRT might be associated with higher rates of dialysis dependence than CRRT. However, this finding largely relies on data from observational trials, potentially subject to allocation bias, hence further high-quality studies are necessary.

Keywords Hemofiltration · Hemodialysis · Continuous renal replacement therapy · Acute kidney injury · Intensive care unit · Meta-analysis

Background

Acute kidney injury (AKI) is common in critically ill patients and associated with high mortality and morbidity [1]. When AKI is severe, renal replacement therapy (RRT) is often required while disease-specific treatments are applied. RRT is typically provided in two modalities: continuous (CRRT) or intermittent (IRRT). Both modalities achieve a satisfactory degree of metabolic control, and to date, despite numerous observational studies, randomized controlled trials (RCTs) [2–9], and meta-analyses [2, 10–12], neither modality has been found superior in terms of mortality. In contrast, only few studies have specifically focused on the effects of CRRT and IRRT on renal recovery and dialysis dependence among survivors. This question, however, is important because chronic hemodialysis is a major burden for patients, their families, and healthcare systems, and is associated with higher long-term mortality [13–16].

A Cochrane systematic review [10] sought to compare IRRT with CRRT in many aspects including the rate of dialysis dependence. However, only three small, randomized controlled studies [8, 9, 17] were included in this part of the review, and the multiple observational studies reporting renal recovery after RRT were not included.

Accordingly, we sought to systematically review the current literature and to analyze all data on dialysis dependence among critically ill patients who survived an episode of AKI requiring acute RRT. We used intention-to-treat analysis to test the hypothesis that patients assigned to initially receive IRRT might have higher rates of dialysis dependence compared with those assigned to initially receive CRRT.

Methods

We performed this systematic review using the guidelines proposed by the Cochrane Collaboration in the *Cochrane Handbook for Systematic Reviews of Interventions* (http://www.cochrane-handbook.org).

Study selection criteria

Participants

This review focuses on survivors of critical illness who received RRT for AKI.

Interventions

For the purpose of the review, we use the term "IRRT" to describe intermittent hemodialysis, intermittent hemofiltration, and slow low-efficiency dialysis (SLED). As SLED is substantially different from other intermittent techniques, sensitivity analyses were performed excluding studies reporting data on such modality.

We use the term "CRRT" to describe continuous hemofiltration and/or continuous hemodialysis and/or continuous hemodiafiltration, all intended to run on a continuous basis (24 h/day).

For patients who received both modalities (crossover), we classified patients according to the initial modality administered whenever such data were available (intention-to-treat principle).

Comparators

We compared outcomes according to the initial RRT modality applied on an intention-to-treat basis.

Types of outcome measures

The primary outcome was dialysis dependence among survivors. We assessed dialysis dependence as the need for any form of RRT at the end of the follow-up period.

Types of studies

We included all RCTs and observational studies in English language reporting data on dialysis dependence after RRT for AKI between 2000 and 2012. We excluded reviews, commentaries, and editorials.

Search methods for identification of studies

Study selection

We searched MEDLINE and EMBASE via the OvidSP portal. The keywords/MESH headings used are presented in the ESM Appendix. Two independent investigators (A.G.S. and N.J.G.) carried out the initial search and subsequent study selection. After title screening, we evaluated abstracts for relevance and identified as included, excluded or requiring further assessment. At this stage, if a paper required further assessment, we contacted the study lead investigator by e-mail and/or telephone with a request for further information. We then reviewed the bibliography of selected publications. We corresponded with the authors when missing data were identified. We updated the search in July 2012. All studies that reported data on dialysis dependence after RRT for AKI were included.

For the purpose of meta-analysis we included all studies where simultaneous data on IRRT and CRRT

treatment were obtained. Studies in which all patients received a single modality (IRRT or CRRT) or RCTs not comparing IRRT with CRRT were analyzed and presented separately as sensitivity analyses.

Data extraction

Data extraction was performed by A.G.S. and confirmed independently by N.J.G. For each study, we recorded the year of publication, the type of study (RCT or observational), and the number of centers involved. We obtained the total number of RRT patients included in each study, and determined how many survived the acute illness and how many were dialysis dependent at the end of the study follow-up. In addition, we collected the following variables when available: duration of follow-up, sex, age, chronic kidney disease (CKD), illness severity score [Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III or Simplified Acute Physiology Score (SAPS) II], and use of vasopressors and mechanical ventilation when available. We obtained all results for the whole cohorts and recorded them separately according to RRT modality.

Synthesis of results/statistical analysis

Assessment of risk of bias

We examined RCTs for adequate allocation concealment, randomization process, and balance of baseline characteristics. We assessed study methodology using the Jadad scale [18]. As blinding is virtually impossible when comparing RRT modalities, a score of 3 was considered satisfactory.

For observational trials, we recorded the rule for allocation to either RRT modality to assess allocation bias. Similarly, we extracted data on sex, age, CKD, illness severity score, vasopressors, and mechanical ventilation where available, as all these variables are susceptible to confound the association between choice of RRT modality and dialysis dependence. We recorded the presence of adjusted analyses for dialysis dependence as well as their results. Finally, we assessed selective reporting according to the rate of loss to follow-up.

Data synthesis

We analyzed data using Review Manager version 5.1.4 (The Cochrane Collaboration, Oxford, UK) and Stata release 12.0 (StataCorp, College Station, TX). Due to expected heterogeneity between study protocols, populations, and interventions, we decided a priori to combine results using a random-effects model for all analyses [19].

For dichotomous outcomes, we used relative risk (RR) with 95 % confidence interval (CI) to pool the results.

To enable study comparison, we transformed illness severity scores (SAPS II and APACHE III) into the equivalent APACHE II score, using previously described methodology [20].

We quantified statistical heterogeneity for pooled results using the chi-square and I^2 statistics. We estimated publication bias with a funnel plot.

Stratification

We stratified pooled analyses according to study design (RCT versus observational). We further stratified observational studies according to duration of follow-up, inclusion or exclusion of patients with CKD, and number of centers for the purpose of sensitivity analyses.

We considered RCTs not designed to compare IRRT with CRRT as equivalent to observational studies.

In addition, we separately analyzed studies where RRT was limited to a single modality (only IRRT or CRRT) as direct comparison was not possible. For such comparison, we calculated a pooled OR with 95 % CI (details of calculation presented in ESM Appendix).

Results

The study selection process is presented in Fig. 1. We identified 383 eligible studies for abstract review. Of these, 146 were selected for full-text search. Finally, 50 studies presented data on dialysis dependence after RRT and were included in this systematic review. Of those, 23 presented outcome data for both modalities (IRRT and CRRT) and were included in the meta-analysis; 7 were randomized controlled trials [8, 9, 17, 21–24] and 16 were observational studies [25–41], including a total of 3,971 patients who survived an episode of AKI requiring RRT [2,255 (CRRT) and 1,716 (IRRT)].

In the other 27 studies (2,536 survivors), a single initial RRT modality was applied to all patients. This modality was IRRT in 11 of these studies (644 survivors) [42–52] and CRRT in 16 (1,892 survivors) [53–68].

Study description, patient demographics, and risk of bias evaluation

Randomized controlled trials

The seven RCTs included in this review are presented in the ESM Appendix. Altogether, these studies report dialysis dependence data for a total of 472 AKI survivors (1,160 patients enrolled). Of those, 240 received IRRT as

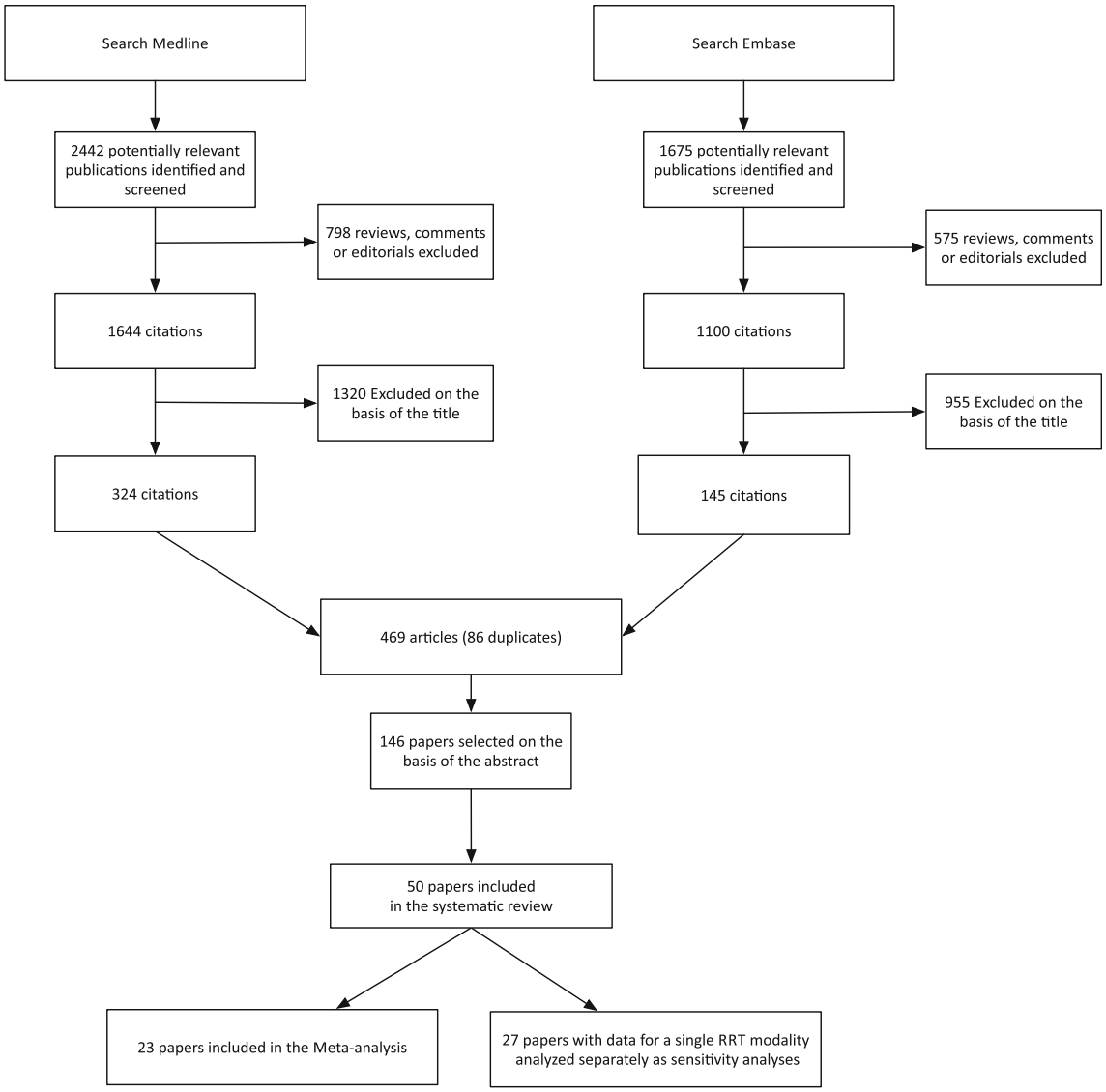

Fig. 1 Study selection (CONSORT diagram)

an initial modality and 232 CRRT. Four of these were single-center studies, and three were multicenter studies.

Although all studies compared IRRT with CRRT, significant heterogeneity between designs was present. In particular, the IRRT arm consisted of slow low-efficiency dialysis (SLED) for two studies [21, 22] as opposed to intermittent hemodialysis for the other five. Hemodynamically unstable patients were excluded in one study [17], while only those with multiple organ dysfunction syndrome were included in another [24]. In addition, imbalances in baseline characteristics between the two groups were present in 3/7 studies, and crossover from allocated modality occurred in 5/7 studies (involving more than 15 % of the patients in 3 of these studies). Studies were all powered to demonstrate a difference in mortality but not in renal recovery to dialysis independence. Finally, four of the studies were graded as "poor quality" (Jadad score 1–2) and three as "satisfactory" (Jadad score 3).

Observational studies

The 16 observational studies included in this review reported data on dialysis dependence in 3,505 AKI survivors (7,158 patients enrolled). Of these, 1,481 received IRRT as an initial modality and 2,024 CRRT. Their baseline characteristics are presented in Table 1.

As presented in the ESM Appendix, modality allocation was likely to be biased in most (14/16) studies as the

Table 1 Observational studies: RRT modality-specific patient characteristics

Author [Ref.]	Follow-up	RRT modality	*N*	Mortality (%)	Males (%)	Age (years)	APACHE II equivalent	CKD (%)	Mechanical ventilation (%)	Vasopressors (%)	% Survivors dialysis dependent
Andrikos [25]	28 days	CRRT	79	58.2	57.0	66.7	–	8.8	–	–	15.2
		IRRT	12	66.7	83.3	71.2	–	33.3	–	–	25.0
Bagshaw [26]	90 days	CRRT	130	58.5	–	–	–	–	–	–	22.2
		IRRT	110	61.8	–	–	–	–	–	–	35.7
Bell [27]	90 days	CRRT	1911	50.6	65.6	–	–	0.0	–	–	8.3
		IRRT	291	45.7	71.5	–	–	0.0	–	–	16.5
Cartin-Ceba [28]	90 days	CRRT	415	44.8	–	–	–	0.0	–	–	11.3
		IRRT	650	14.6	–	–	–	0.0	–	–	46.1
Chang [29]	90 days	CRRT	53	79.2	79.2	52.0	33.2	–	–	–	9.1
		IRRT	95	53.7	73.7	45.0	21.4	–	–	–	9.1
Lin [34]	90 days	CRRT	242	65.7	–	–	–	–	–	100.0	12.0
		IRRT	100	46.0	–	–	–	–	–	–	20.4
Khanal [41]	90 days	CRRT	32	50.0	59.4	58.3	–	34.0	–	78.0	12.5
		SLED	106	47.2	60.4	57.5	–	45.3	–	77.4	8.9
		IRRT	8	37.5	62.5	70.0	–	75.0	–	62.5	14.3
Swartz [38]	90 days	CRRT	200	68.0	59.0	55.0	26.7	0.0	86.0	80.0	14.3
		IRRT	183	39.9	59.6	60.3	20.0	0.0	27.9	24.0	30.0
Jacka [33]	Hdisch	CRRT	65	62.1	69.2	54.7	25.1	0.0	100.0	62.0	20.0
		IRRT	28	50.0	60.7	62.6	23.5	0.0	100.0	36.0	64.3
Lins [35]	Hdisch	CRRT	26	84.6	–	–	–	0.0	–	–	25.0
		IRRT	74	50.0	–	–	–	0.0	–	–	24.3
Park [37]	Hdisch	CRRT	37	75.7	48.6	61.2	22.4	21.6	100.0	–	14.3
		IRRT	121	31.4	56.4	59.9	19.6	43.0	66.9	–	44.6
Uchino [39]	Hdisch	CRRT	1006	64.2	65.8	66.0	26.1	28.1	84.4	78.8	14.4
		IRRT	212	48.1	60.8	62.0	25.4	37.3	61.8	50.5	33.6
Waldrop [40]	Hdisch	CRRT	30	53.3	–	52.7	25.4	–	–	–	42.9
		IRRT	27	55.6	–	55.2	26.0	–	–	–	58.3
Elseviers [30]	Hdisch	CRRT	275	64.4	60.4	62.8	24.4	0.0	78.9	–	13.3
		IRRT	375	53.3	65.3	65.1	25.1	0.0	59.2	–	21.1
Garcia-Fernandes [31]	Hdisch	CRRT	173	68.2	61.8	68.4	–	55.5	–	85.0	0.0
		IRRT	30	46.7	43.3	67.0	–	56.7	–	63.3	0.0
Gonwa [32]	1 year	CRRT	50	50.0	–	–	–	0.0	–	–	16.0
		IRRT	12	50.0	–	–	–	0.0	–	–	16.7
Pooled value		**CRRT**	–	–	–	–	**26.0**	**10.5**	**85.2**	**81.9**	–
		IRRT	–	–	–	–	**23.3**	**7.9**	**55.8**	**40.1**	–

RRT renal replacement therapy, *CRRT* continuous RRT, *IRRT* intermittent RRT, *CKD* chronic kidney disease, *Hdisch* hospital discharge
Bold characters represent pooled values per RRT modality

reasons for choice of RRT modality were not described (13 studies) or CRRT was preferentially applied to patients on inotropic or vasopressor drug support. This risk was considered low in two studies where a before–after study design was applied [40, 41].

When specific baseline characteristics were reported according to RRT modality, IRRT patients had lower illness severity scores in 6/8 studies. They required vasopressors (pooled percentage from six studies: 40.1 % for IRRT versus 81.9 % for CRRT, $p < 0.0001$) or mechanical ventilation less frequently (pooled percentage from five studies 55.8 % for IRRT versus 85.2 % for CRRT, $p < 0.0001$). Finally, the pooled percentage of patients with CKD was lower among IRRT patients (7.9 % for IRRT versus 10.5 %, $p = 0.04$). Adjusted analyses taking these confounders into account were performed in seven studies.

Additional studies providing no direct comparison

An additional 27 studies that did not provide direct comparison between IRRT and CRRT were analyzed. Of those, 11 studies reported dialysis dependence data for 644 AKI survivors initially treated with IRRT and 16 in 1,892 survivors initially treated with CRRT.

Patient characteristics per RRT modality are presented in the ESM Appendix. On pooled average, IRRT survivors were younger (57.8 versus 63.5 years old) and had lower APACHE II score (26.8 versus 28.7), and a smaller percentage had pre-existing CKD (5.8 versus 19.4 %) or required mechanical ventilation (77.6 versus 78.9 %). However, a larger percentage of IRRT patients required vasopressors (74 versus 67.6 %).

Finally, the duration of follow-up was shorter in "IRRT studies" [28 days (in 5/11) or until hospital

discharge (in 5/11)] as compared with "CRRT studies" [90 days (in 5/16) or until hospital discharge (in 9/19)].

Renal recovery according to dialysis modality

Overall

When all studies comparing CRRT with IRRT were pooled (Fig. 2), IRRT was associated with a higher risk for dialysis dependence compared with CRRT (RR 1.73 [1.35–2.20]). There was evidence for moderate heterogeneity (chi square $p = 0.02$ and $I^2 = 44$ %).

Randomized controlled trials

Within RCTs (Fig. 2), there was no statistically significant difference in the risk of hemodialysis (HD) dependence between IRRT and CRRT (RR 1.15 [95 % CI 0.78–1.68]). There was no evidence for heterogeneity (chi square $p = 0.78$, $I^2 = 0$ %). Similar results were obtained when the two "SLED" studies were excluded from analysis (RR 1.18 [0.79–1.75], $I^2 = 0$ %) (ESM Appendix). When only studies of "satisfactory" quality according to the Jadad scale were included the RR was 1.48 [0.82–2.66] ($I^2 = 0$ %).

Observational studies

Within observational studies (Fig. 2), IRRT was associated with a 1.99 relative risk of dialysis dependence compared with CRRT (95 % CI 1.53–2.59). There was evidence for moderate heterogeneity (chi square $p = 0.04$ and $I^2 = 42$ %).

This association remained when studies were pooled according to exclusion or inclusion of patients with pre-existing CKD (Fig. 3), follow-up duration (hospital discharge or 90 days), and number of centers involved in the study (additional figures in ESM Appendix).

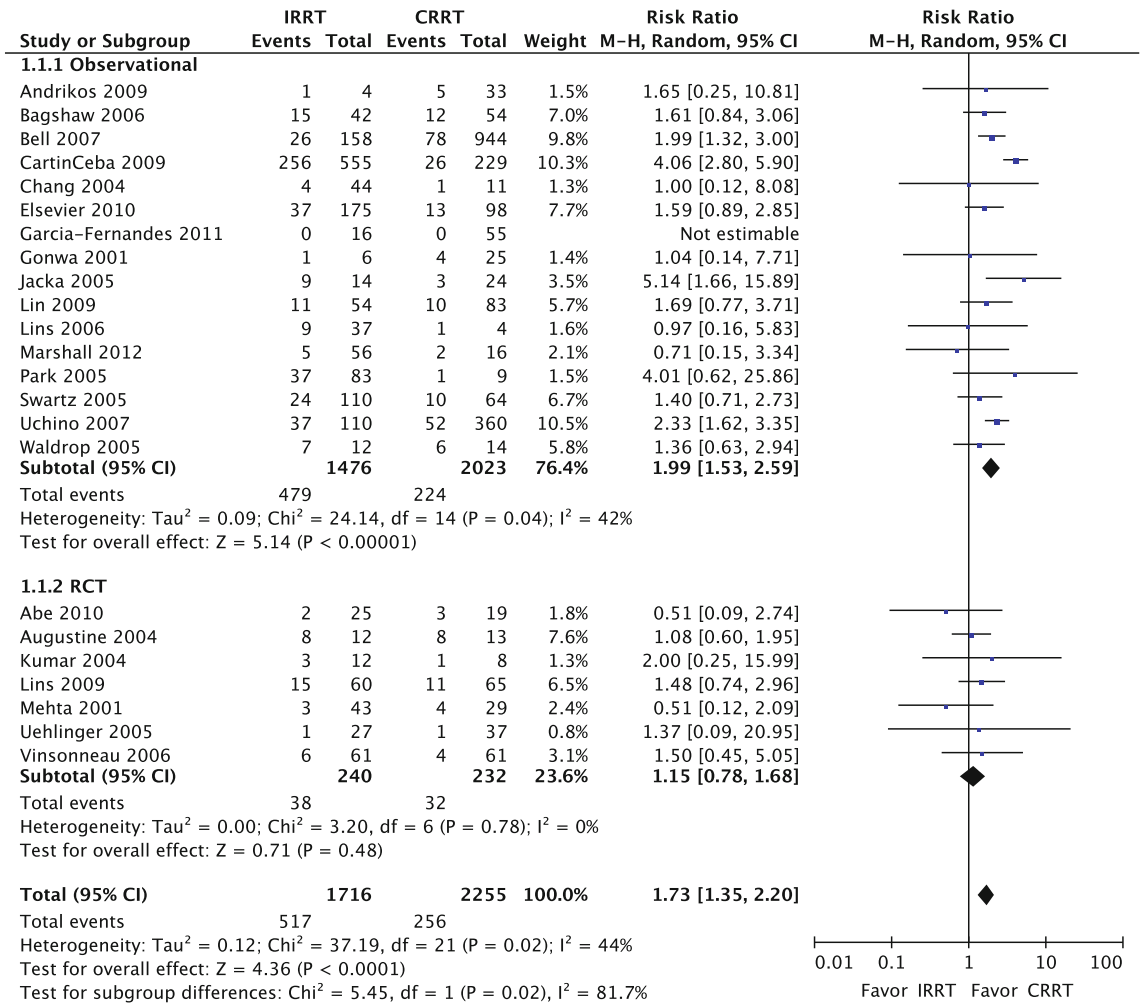

Fig. 2 Forest plot for dialysis dependence among survivors. Stratified by study design. *M–H* Mantel–Haenszel

When adjusted analyses were performed (7/16), the odds ratios for a higher rate of dialysis dependence in IRRT patients ranged from 2.2 to 25 (5 studies) or no difference was found (2 studies).

Additional studies providing no direct comparison

When all dialysis dependence data from studies providing no direct comparison were pooled, IRRT was associated with a higher OR for dialysis dependence (OR 2.30 [95 CI % 1.79–2.96]).

Discussion

Key findings

We performed a systematic review of the literature and identified 50 original studies reporting data on the rate of dialysis dependence among more than 6500 survivors who received RRT for AKI. We found that patients who received IRRT as an initial RRT modality for AKI had a 1.7 times increased risk of remaining dialysis dependent as compared with those who initially received CRRT.

This finding was consistent across subgroups but did not reach statistical significance amongst RCTs. These RCTs, however, were relatively small and of only moderate quality, and did not all include hemodynamically unstable patients. Allocation bias was present in observational trials, with IRRT appearing to be preferentially allocated to patients with lesser illness severity and some degree of chronic kidney disease. Similar findings were present when studies reporting outcomes of a single modality were analyzed.

Comparison with previous studies

To date, observational studies, RCTs [2–9], and meta-analyses [2, 10–12] have failed to demonstrate any survival advantage for IRRT or CRRT in AKI.

Two meta-analyses [11, 69] included renal recovery as an outcome and did not find a difference between IRRT and CRRT. Both of these studies restricted their analyses to RCTs, with similar results to those in the RCT section of this study. However, the limited number of patients and the poor quality of these studies limit the precision of the estimate and the robustness of the findings. Moreover, such a comparison of only 240 versus 232 RCT patients with a rate of dialysis dependence of 15.8 % in the IRRT group would only have a 51 % power to detect even a one-third decrease in relative risk. The present review includes data from observational studies. Such studies, although subject to bias, involve a large number of patients and might be more likely to accurately represent the natural history of an episode of severe AKI.

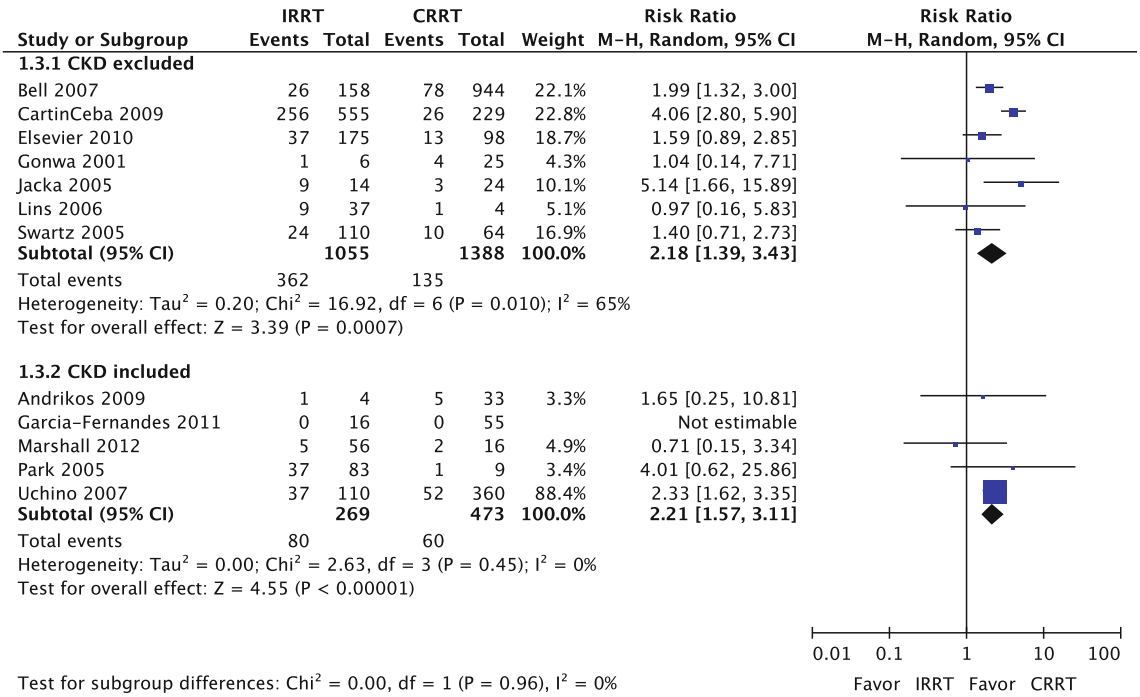

Fig. 3 Forest plot for dialysis dependence among survivors among observational trials. Stratified by inclusion or exclusion of patients with chronic kidney disease (CKD). *M–H* Mantel–Haenszel

The association between IRRT and increased dialysis dependence is physiologically plausible. Several animal models [70–72] have shown that renal blood flow autoregulation is lost in AKI. Therefore, any hypotension is likely to decrease renal blood flow and compromise glomerular filtration rate (GFR). Indeed, hemodynamic changes induced by IRRT [73–75] are clinically important [12, 76–81]. Moreover, renal biopsies taken in patients receiving IRRT reveal areas of tubular necrosis consistent with fresh tubular damage [82]. No such concerns have been reported in relation to CRRT [83–86].

Clinical implications and future studies

Trials in critically ill patients with AKI have targeted mortality as the primary outcome [55, 73]. However, for survivors, limiting disabilities and maximizing quality of life are of major importance [87, 88]. Dialysis dependence negatively impacts quality of life [89] and is financially burdensome [13–15]. Thus, future studies or comparative trials of RRT modality should focus on dialysis dependence as a major outcome of interest.

Strengths and limitations

To the best of our knowledge, this study is the first to systematically assess the effect of RRT modality on dialysis dependence among patients who survived an episode of AKI requiring RRT. It included data from more than 6,500 patients, 50 studies, and 31 countries, from both large observational studies and randomized controlled studies, and all types of adult critically ill who survived an episode of AKI requiring RRT.

However, this study has several important limitations. First, as we report an association, no inferences of causality can be made. Second, this association is largely dependent upon observational studies and might have been affected by allocation bias. However, factors susceptible to confound the association that were recorded do not support this assertion. In particular, when direct comparative data were available, patients allocated to IRRT had lower levels of illness severity and required mechanical ventilation and vasopressors less frequently. Of even greater relevance, our findings were consistent between studies that did or did not exclude patients with pre-existing CKD, an important risk factor for nonrecovery. This finding makes the possible impact of CKD on nonrecovery among IRRT patients an implausible explanation for our observations. Finally, when adjusted analyses were performed, IRRT was found to be associated with a greater risk of dialysis dependence in all but two studies.

Third, we focused on AKI survivors because dialysis dependence at time of death is rarely reported. We therefore can only report on conditional, not absolute, dialysis dependence. However, the benefit of recovery to dialysis dependence followed by death within 90 days of treatment initiation is low.

Fourth, CRRT may increase the risk of death. Thus, those patients who might have remained dialysis dependent, had they survived, simply died and were therefore not counted. However, there is no convincing evidence in the literature to suggest an association between the choice of RRT modality and mortality after correction for confounders such as illness severity, and need for vasopressors and mechanical ventilation [2, 10–12].

We used the intention-to-treat principle. However, in most studies, patients crossed between modalities or often such data were not reported. Thus, we cannot study the possibility of a dose effect on nonrecovery. However, the fact that many patients were exposed to IRRT only for a part of their overall RRT time implies that our intention-to-treat analysis would logically underestimate the nonrecovery risk of IRRT.

Finally, studies utilizing SLED as an RRT modality have been considered as IRRT. However, as SLED is a hybrid technology combining properties from both IRRT and CRRT, we have presented results including and excluding such studies. These emerging technologies might have a role in future clinical practice, but further studies are required.

Conclusions

Currently available randomized controlled trials do not allow a definitive conclusion on whether choice of initial RRT modality is associated with greater renal recovery rates. Analysis of observational trials suggests that initial support with IRRT might be associated with a higher rate of RRT dependence amongst survivors who received RRT for AKI. As these studies might be associated with allocation bias and given the human and public health implications of these findings, large studies focusing on renal recovery after AKI according to choice of RRT are needed to fully understand the effects of initial modality choice on subsequent dialysis dependence.

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Conflicts of interest Drs. Bellomo and Bagshaw have acted as occasional paid consultant for Gambro Pty ltd over the last five years. All other authors stated that they had no conflicts of interest to declare.

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