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 (RCT) and 16 observational studies involving 472 and 3499 survivors, respectively. Pooled analyses of RCTs showed no difference in the rate of dialysis dependence among survivors (RR 1.15 [95% 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 [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.

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 (RCT)[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 health care 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).

Studies selection criteria

Participants

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

Interventions

For the purpose of the review, we used 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 used the term "CRRT" to describe continuous hemofiltration and/or continuous hemodialysis and/or continuous hemodiafiltration all intended to run on a continuous basis (24 hours/day).

For patients that received both modalities (cross-over), 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 RCT 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.

<u>Search methods for identification of studies</u>

Studies selection

We searched MEDLINE and Embase via the OvidSP portal. The keywords / MESH headings used are presented in the Appendix. Two independent investigators (AS and NG) 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, which 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 RCT not comparing IRRT to CRRT were analysed and presented separately as sensitivity analyses.

Data extraction

Data extraction was performed by AS and confirmed independently by NG. 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, 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 (APACHE II, APACHE III or SAPS II), use of vasopressors and mechanical ventilation when available. We obtained all results for the whole cohorts and recorded them separately according to RRT modality.

<u>Synthesis of results / Statistical analysis</u>

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 analysed data using Review Manager version 5.1.4 (The Cochrane Collaboration, Oxford, England) and Stata release 12.0 (StataCorp, CollegeStation, Texas). Due to expected heterogeneity between study protocols, populations and interventions, we decided *a priori* to combine results using a random-effect 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 the duration of the 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 analysed 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 Appendix).

RESULTS

The study selection process is presented in Figure 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 observational studies [25-41] including a total of 3971 patients who survived an episode of AKI requiring RRT (2255 (CRRT) and 1716 (IRRT)).

In the other 27 studies (2536 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 (1892 survivors) [53-68].

Studies description, patients demographics and risk of bias evaluation

Randomized controlled trials

The seven RCTs included in this review are presented in the appendix. Altogether, these studies report dialysis dependence data for a total of 472 AKI survivors (1160 patients enrolled). Of those, 240 received IRRT as an initial modality and 232 CRRT. Four of these were single-center studies and three multi-center 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 cross-over 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 3505 AKI survivors (7158 patients enrolled). Of these, 1481 received IRRT as an initial modality and 2024 CRRT. Their baseline characteristics are presented in Table 1.

As presented in the appendix, modality allocation was likely to be biased in most (14/16 studies) as the reasons for choice of RRT modality was 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 [41, 69].

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 6 studies: 40.1% for IRRT versus 81.9% for CRRT, $p<0.0001$) or mechanical ventilation less frequently (pooled percentage from 5 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 7 studies.

Additional studies providing no direct comparison

An additional 27 studies, which did not provide direct comparison between IRRT and CRRT were analysed. Of those, 11 studies reported dialysis dependence data for 644 AKI survivors initially treated with IRRT and 16 in 1892 survivors initially treated with CRRT.

Patients' characteristics per RRT modality are presented in the appendix. On pooled average, IRRT survivors were younger (57.8 vs 63.5 year old), had lower APACHE II score (26.8 vs 28.7), a smaller percentage had pre-existing CKD (5.8 vs 19.4%) or required mechanical ventilation (77.6 vs 78.9%). However, a larger percentage of IRRT patients required vasopressors (74 vs 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 (Figure 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 (Figure 2), there was no statistically significant difference in the risk of 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%) (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 (Figure 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 (Figure 3), follow-up duration (hospital discharge or 90 days), and number of centers involved in the study (additional figures in appendix).

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, 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 analysed.

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, 70] have included renal recovery as an outcome and did not find a difference between IRRT and CRRT. Both 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 limits the precision of the estimate and the robustness of the findings. Moreover, such a comparison of only 240 vs. 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.

The association between IRRT and increased dialysis dependence is physiologically plausible. Several animal models [71-73] have shown that renal blood flow autoregulation is lost in AKI. Therefore, any hypotension is likely to decrease renal blood flow and compromise GFR. Indeed, the hemodynamic changes induced by IRRT,[74-76] and clinically important.[12, 77-82]. Moreover, renal biopsies taken in patients receiving IRRT reveal areas of tubular necrosis consistent with fresh tubular damage.[83] No such concerns have been reported in relation to CRRT [84-87].

Clinical implications and future studies

Trials in critically ill patients with AKI have targeted mortality as the primary outcome.[55, 74] However, for survivors, limiting disabilities and maximizing quality of life is of major importance [88, 89]. Dialysis dependence negatively impacts quality of life [90] 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 6500 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 non-recovery. This finding makes the possible impact of CKD on non-recovery 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, 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 non-recovery. However, given 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 non-recovery risk of IRRT.

Finally, studies utilising SLED as an RRT modality have been considered as IRRT. However, as SLED is a hydrid technology combining properties from both IRRT and CRRT, we have presented results including and excluding such studies. These emerging technologies might have 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 INTERESTS:

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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Table 1 Observational studies: RRT modality specific patients characteristics

Author / year	Follow-up	RRT modality	N	Mortality	Males	Age	APACHE II equivalent	CKD	Mechanical ventilation	Vasopressors	% Survivors dialysis dependent
Andrikos (2009)	28d	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 (2006)	90d	CRRT	130	58.5%							22.2%
		IRRT	110	61.8%							35.7%
Bell (2007)	90d	CRRT	1911	50.6%	65.6%	.		0.0%			8.3%
		IRRT	291	45.7%	71.5%	.		0.0%			16.5%
CartinCeba (2009)	90d	CRRT	415	44.8%				0.0%			11.3%
		IRRT	650	14.6%				0.0%			46.1%
Chang (2004)	90d	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 (2009)	90d	CRRT	242	65.7%						100.0%	12.0%
		IRRT	100	46.0%						.	20.4%
Khanal (2012)	90d	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 (2005)	90d	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 (2005)	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 (2006)	Hdisch	CRRT	26	84.6%				0.0%			25.0%
		IRRT	74	50.0%				0.0%			24.3%
Park (2005)	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 (2007)	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 (2005)	Hdisch	CRRT	30	53.3%	.	52.7	25.4				42.9%
		IRRT	27	55.6%	.	55.2	26.0				58.3%
Elsevier (2010)	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-	Hdisc	CRRT	173	68.2%	61.8	68.	.	55.5		85.0%	0.0%

Fernandes (2011)	h				%	4		%			
		IRRT	30	46.7%	43.3 %	67. 0	.	56.7 %		63.3%	0.0%
Gonwa (2001)	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 and IRRT Intermittent RRT, CKD: Chronic Kidney Disease, Hdisch: hospital discharge

Figure 1 Study selection (CONSORT Diagram)

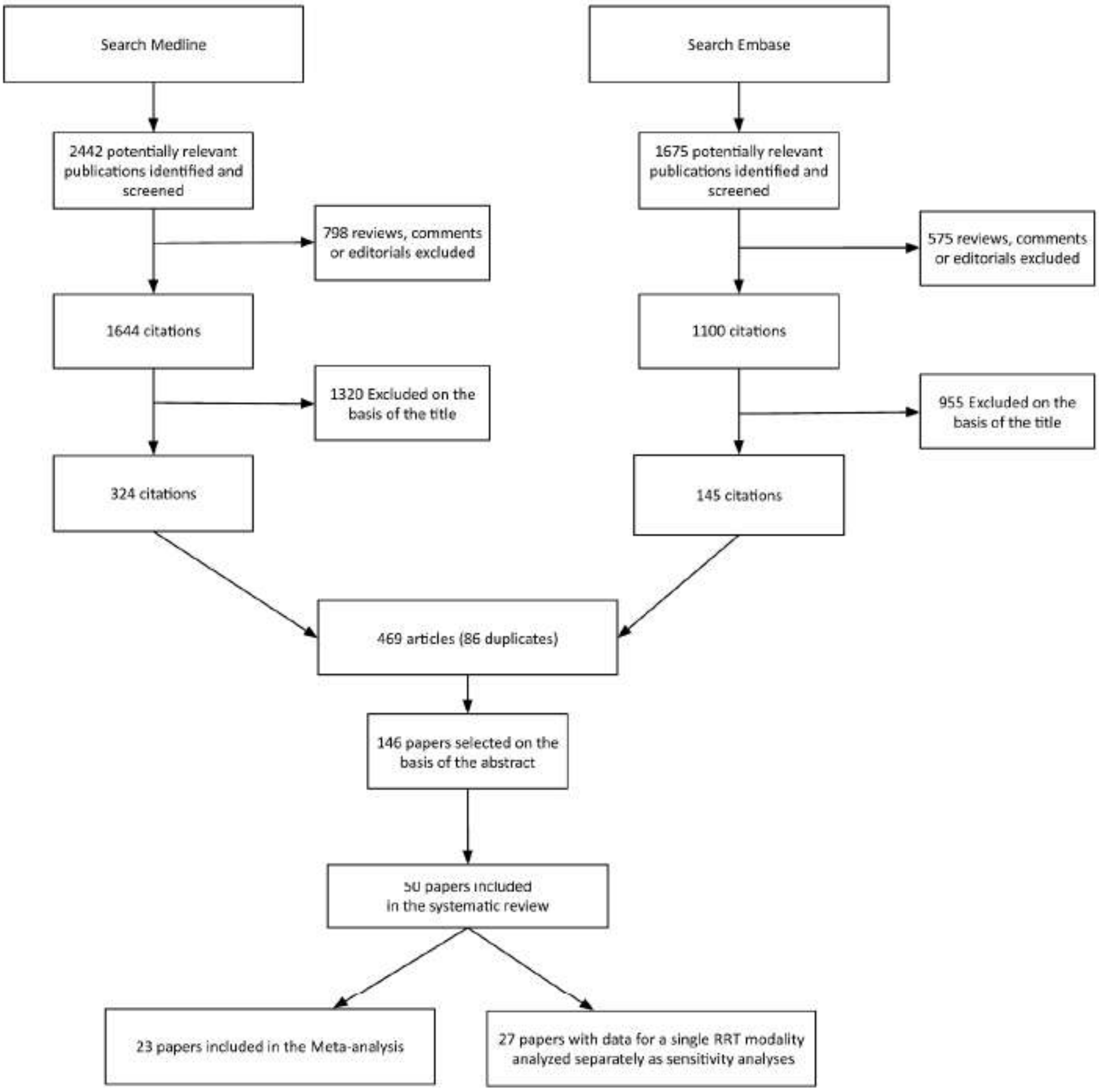

Figure 1: Study selection (CONSORT Diagram)
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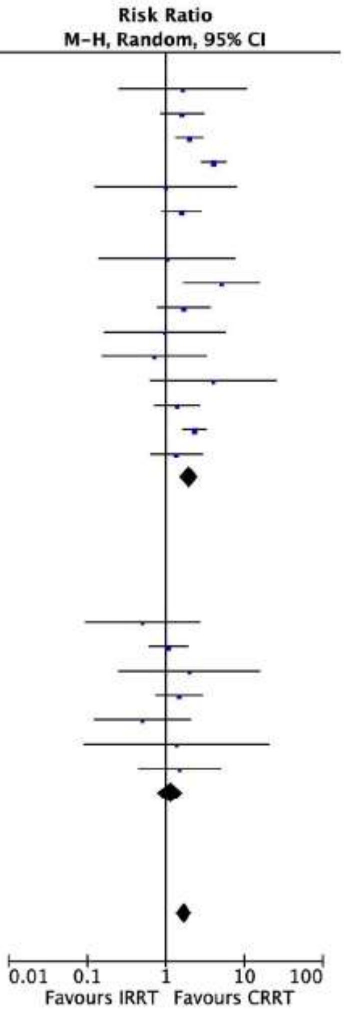
Figure 2 Forest plot for dialysis dependence among survivors. Stratified by study design. M-H: Mantel-Haenszel

Study or Subgroup	IRRT Events	IRRT Total	CRRT Events	CRRT Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Observational						
Andrikos 2009	1	4	5	33	1.5%	1.65 [0.25, 10.81]
Bagshaw 2006	15	42	12	54	7.0%	1.61 [0.84, 3.06]
Bell 2007	26	158	78	944	9.8%	1.99 [1.32, 3.00]
CartinCeba 2009	256	555	26	229	10.3%	4.06 [2.80, 5.90]
Chang 2004	4	44	1	11	1.3%	1.00 [0.12, 8.08]
Elsevier 2010	37	175	13	98	7.7%	1.59 [0.89, 2.85]
Garcia-Fernandes 2011	0	16	0	55		Not estimable
Gonwa 2001	1	6	4	25	1.4%	1.04 [0.14, 7.71]
Jacka 2005	9	14	3	24	3.5%	5.14 [1.66, 15.89]
Lin 2009	11	54	10	83	5.7%	1.69 [0.77, 3.71]
Lins 2006	9	37	1	4	1.6%	0.97 [0.16, 5.83]
Marshall 2012	5	56	2	16	2.1%	0.71 [0.15, 3.34]
Park 2005	37	83	1	9	1.5%	4.01 [0.62, 25.86]
Swartz 2005	24	110	10	64	6.7%	1.40 [0.71, 2.73]
Uchino 2007	37	110	52	360	10.5%	2.33 [1.62, 3.35]
Waldrop 2005	7	12	6	14	5.8%	1.36 [0.63, 2.94]
Subtotal (95% CI)		**1476**		**2023**	**76.4%**	**1.99 [1.53, 2.59]**
Total events	479		224			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 24.14$, df = 14 (P = 0.04); $I^2 = 42\%$						
Test for overall effect: Z = 5.14 (P < 0.00001)						
1.1.2 RCT						
Abe 2010	2	25	3	19	1.8%	0.51 [0.09, 2.74]
Augustine 2004	8	12	8	13	7.6%	1.08 [0.60, 1.95]
Kumar 2004	3	12	1	8	1.3%	2.00 [0.25, 15.99]
Lins 2009	15	60	11	65	6.5%	1.48 [0.74, 2.96]
Mehta 2001	3	43	4	29	2.4%	0.51 [0.12, 2.09]
Uehlinger 2005	1	27	1	37	0.8%	1.37 [0.09, 20.95]
Vinsonneau 2006	6	61	4	61	3.1%	1.50 [0.45, 5.05]
Subtotal (95% CI)		**240**		**232**	**23.6%**	**1.15 [0.78, 1.68]**
Total events	38		32			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.20$, df = 6 (P = 0.78); $I^2 = 0\%$						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**1716**		**2255**	**100.0%**	**1.73 [1.35, 2.20]**
Total events	517		256			
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 37.19$, df = 21 (P = 0.02); $I^2 = 44\%$						
Test for overall effect: Z = 4.36 (P < 0.0001)						
Test for subgroup differences: $Chi^2 = 5.45$, df = 1 (P = 0.02), $I^2 = 81.7\%$						



Forest plot for dialysis dependence among survivors. Stratified by study design
M-H: Mantel-Haenszel

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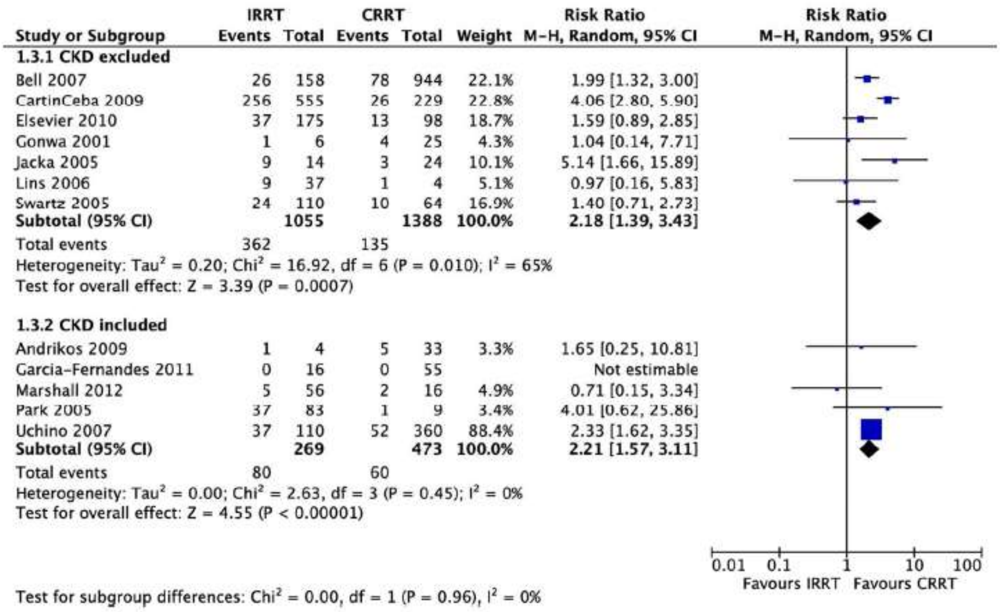
Figure 3 Forest plot for dialysis dependence among survivors among observational trials. Stratified by inclusion or exclusion of patients with chronic kidney disease (CKD). M-H: Mantel-Haenszel



Study or Subgroup	IRRT Events	IRRT Total	CRRT Events	CRRT Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 CKD excluded						
Bell 2007	26	158	78	944	22.1%	1.99 [1.32, 3.00]
CartinCeba 2009	256	555	26	229	22.8%	4.06 [2.80, 5.90]
Elsevier 2010	37	175	13	98	18.7%	1.59 [0.89, 2.85]
Gonwa 2001	1	6	4	25	4.3%	1.04 [0.14, 7.71]
Jacka 2005	9	14	3	24	10.1%	5.14 [1.66, 15.89]
Lins 2006	9	37	1	4	5.1%	0.97 [0.16, 5.83]
Swartz 2005	24	110	10	64	16.9%	1.40 [0.71, 2.73]
Subtotal (95% CI)		**1055**		**1388**	**100.0%**	**2.18 [1.39, 3.43]**
Total events	362		135			
Heterogeneity: Tau² = 0.20; Chi² = 16.92, df = 6 (P = 0.010); I² = 65%						
Test for overall effect: Z = 3.39 (P = 0.0007)						
1.3.2 CKD included						
Andrikos 2009	1	4	5	33	3.3%	1.65 [0.25, 10.81]
Garcia-Fernandes 2011	0	16	0	55		Not estimable
Marshall 2012	5	56	2	16	4.9%	0.71 [0.15, 3.34]
Park 2005	37	83	1	9	3.4%	4.01 [0.62, 25.86]
Uchino 2007	37	110	52	360	88.4%	2.33 [1.62, 3.35]
Subtotal (95% CI)		**269**		**473**	**100.0%**	**2.21 [1.57, 3.11]**
Total events	80		60			
Heterogeneity: Tau² = 0.00; Chi² = 2.63, df = 3 (P = 0.45); I² = 0%						
Test for overall effect: Z = 4.55 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%						

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

118x72mm (300 x 300 DPI)

APPENDIX

Table 1: Keywords / MESH headings used for the search strategy

Hemodiafiltration OR Hemofiltration OR Intermittent hemodialysis OR Dialysis OR Renal replacement therapy	Acute renal failure OR Acute renal insufficiency OR Acute kidney injury OR Anuria OR Oliguria
AND	

Table 2: Pooled Odds ratio calculation for studies reporting data on a single RRT modality

	Dialysis dependent	Not Dialysis dependent	Total
IRRT	120	524	644
CRRT	171	1721	1892

Odds Ratio for dialysis dependence (IRRT compared with CRRT) and 95% CI: **2.30 [1.79 - 2.96]**

Table 3: RCTs quality evaluation

	ITT analyses	Adequate Allocation Concealment	Lost to Follow-up	Random described	Blinding	Renal recovery a priori defined	Stand crit for RRT initiation	Appr sample size / power calculation	Balance of baseline charact	Crossover from prim allocation	Funding source	Groups	Jadad Score	*Potential issues limiting validity of results*
Uehlinger	Yes	Yes	No	Yes	No	Yes	No	No	No	0%	Public	IHD vs CVVHDF	3	*Terminated early (difficult to guarantee that no patient escaped randomization)*
Abe	Yes	Unclear	No	No	No	Yes	Yes	No	Yes	0%	Unclear	CVVHDF vs S-HDF	1	*IRRT=SLED*
Augustine	Yes	Unclear	No	Yes	No	Yes	No	Unclear	Yes	37.50%	Unclear	IHD vd CVVHD	1	*Randomization within 24 hrs of initial dialysis treatment*
Lins	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	7.20%	Unclear	Daily IRRT vs CRRT	3	*54% of patients excluded for NON medical reasons: lack of time, technical computer problems,* ***dialysis modlity not availabl,*** *SHARF parameters not available). 37% excluded because of* ***hemodynamic instability***
Kumar	Unclear	No	No	Yes	No	Yes	No	No	No	7.50%	Unclear	Continuous HD vs Extended HD	1	*IRRT=SLED*
Mehta	Yes	Yes	No	Yes	No	Yes	No	No	No	19.30%	Public	CRRT vs IHD	2	*20.8% pot eligible patients excluded because of hemodynamic criteria (MAP needs to be >70 with or without inotropes in last 8 hours)*
Vinsonneau	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	17.70%	Public	CVVHDF vs IHD	3	*Only most severe patients (SAPS II>37)*

ITT: Intention to Treat Analyses, RRT: renal replacement therapy, IHD: intermittent hemodialysis, CVVHDF: continuous veno-venous hemodiafiltration, S-HDF: Slow Hemodiafiltration, CVVHD: continuous veno-venous hemodialysis, IRRT: intermittent renal replacement therapy, CRRT: continuous renal replacement therapy, SLED: Slow low efficiency dialysis, SAPS: simplified acute physiology score

Table 4: Observational studies quality evaluation

	Cohort description / Inclusion criteria	Exclusion criteria	% ICU patients	Cross-over rate	Funding source	Allocation bias	Adjusted analysis?*	Selective reporting bias
Andrikos	Adults with AKI admitted to ICU in Greece (Sept to Dec 2005)	None	100%	NR	NR	Unclear [1]	No	Unclear [a]
Bagshaw	Adults resident of the Calgary region requiring RRT and discharged alive 1999 to 2002	None	100%	31%	Public	Unclear [1]	No association	Low risk
Bell	All adult admitted to a swedish ICU and presenting AKI requiring RRT between 1995 and 2004	ESRD or lacking information on diagnosis	100%	1.7%	NR	Unclear [1]	Yes: 2.19 (1.4-3.5)	Low risk
CertinCeba	Adults critically ill adm 2003 to 2006 with RIFLE F or req RRT in one centre in USA (four ICUs)	ESRD, Kidney Tx, adm < 12hrs	100%	NR	Public	Unclear [1]	Yes: 5.5 [3.4 - 9.1]	Low risk
Chang	ICU patients requiring RRT between 1999 and 2001 in one center in Seoul	none	100%	12.2%	NR	Unclear [2]	No	Low risk
Elseviers	Adults consecutively admitted to the ICU with a serum creatinine >2mg/dl.	Pre-existing CKD	100%	NR	NR	Unclear [1]	No	Low risk
Garcia-F.	Adult who underwent heart surgery and survived >48h after surgery in 24 spanish hospitals in 2007	Peri-operative RRT or minor cardiac surgery	100%	NR	NR	Unclear [1]	No	Low risk
Gonwa	Liver transplant who underwent pre or post-operative RRT between 1996 and 1999 in one USA center	Incomplete data and combined liver Kidney Transplantation	NR	NR	NR	Unclear [1]	No	Unclear [a]
Jacka	AKI requiring RRT in the year 2000 in one center in USA	Chronic HD, RRT for intoxication	100%	NR	NR	Unclear [6]	Yes : 25 [2.4 - 250]	Low risk
Lin	All Surgical ICU patients with post op AKI requiring RRT in ICU between 2002 and 2006	Renal Transplantation, RRT started before surgery and ESRD	100%	NR	Public	High risk [3]	Yes: 2.0 (1.2-3.2)	Low risk
Lins	Hospital survivors after AKI (Creat>177) from 8 centers in Belgium	Pre-existing CKD,	100%	NR	NR	Unclear [1]	No	Low risk
Khanal	Adult ICU patients from 3 centers (NZ, Australia and Italy) during introduction of SLED (1995 to 2005)	None	100%	NR	Public	Low risk [4]	No	Unclear [a]
Park	ICU adults with AKI requiring RRT between 2001 and 2003 in one USA center	CKD, renal Transplant, prior Epo, refused blood transfusions, RRT not for AKI, NFR	100%	15.5%	NR	Unclear [1]	No	Low risk
Swartz	Patients receiving RRT between 1999 and 2001 in USA center	Pre-existing CKD, ESRF, RRT not for AKI	80%	19.0%	Public	Unclear [5]	No association	Low risk
Uchino	ICU patients treated with RRT in 54 centers (23 countries)	ESRF, RRT not for AKI	100%	16.6%	Public	High risk [1]	Yes: 3.3 (1.84-6.0)	Low risk
Waldrop	ICU patients requiring RRT from 1999 to 2002 (cases, CRRT) and 1997 to 1999 (controls: IHD) in one USA center	None	100%	Yes	NR	Low risk [4]	No	Unclear [a]

ICU: Intensive care unit, AKI: Acute kidney injury, RRT: Renal replacement therapy, RIFLE: Risk Injury Failure Loss and End-Stage Renal Failure, USA: United States of America, NZ: New Zealand, IHD: intermittent Hemo-dialysis, ESRD: End-Stage Renal Failure, CKD: chronic kidney disease, NFR: Not for resuscitation, NR: Not reported

Footnotes:

1	Allocation to RRT modality not described
2	Allocation by attending nephrologist
3	CRRT applied if inotrope score>15 otherwise IHD
4	Before and after design
5	By primary service and the nephrology consultation service
6	By the attending intensivist
*	Odds ratio or HR for HD dependence for IRRT as compared with CRRT if available
a	Lost to follow-up not reported

Table 4 : Dialysis dependence and patients descriptions for studies that did report outcome data for a single modality

	author	year	N	survivors	males	mean age	APACHE II eq	ckd	mv	vasopr	time	SLED	Nb dialysis dependent	% survivors	Weight
CRRT	Boussekey	2008	19	10	78.9%	70.4	32.3	0.0%	100.0%	100.0%	28d	0	0	0.0%	0.5%
	Beitland	2010	40	26	85.7%	.	23.3	0.0%	.	72.5%	90d	0	0	0.0%	1.0%
	Bellomo	2009	1464	810	64.7%	64.5	30.2	20.9%	73.9%	71.8%	90d	0	45	5.6%	35.6%
	Ng	2012	259	88	62.2%	63.9	.	4.6%	.	.	90d	0	13	15.1%	6.3%
	Saudan	2006	206	95	61.2%	63.5	25.0	33.0%	.	.	90d	0	4	4.2%	5.0%
	Van der Voort	2009	71	47	60.6%	69	24.0	0.0%	100.0%	.	90d	0	2	4.3%	1.7%
	Oudemans-Van Straaten	2009	200	101	68.0%	73	28.0	.	90.0%	.	90d	0	8	7.9%	4.9%
	Bouman	2002	106	61	61.3%	68.3	22.9	0.0%	100.0%	.	Hdisch	0	1	1.6%	2.6%
	Chung	2008	18	8	100.0%	26	34.0	0.0%	.	61.0%	Hdisch	0	0	0.0%	0.4%
	Kowalik	2011	107	33	63.6%	65.3	.	.	.	.	Hdisch	0	8	24.2%	2.6%
	Lines	2011	821	279	58.0%	59	29.0	.	.	.	Hdisch	0	18	6.5%	19.9%
	Luckraz	2010	92	53	67.4%	68	.	.	.	.	Hdisch	0	2	3.7%	2.2%
	Soubrier	2006	197	55	64.5%	66	28.6	10.6%	84.8%	64.0%	Hdisch	0	7	12.7%	4.8%
	Tolwani	2007	200	76	58.0%	60	26.0	47.5%	77.5%	59.0%	Hdisch	0	19	25.0%	4.9%
	Vats	2011	230	118	61.3%	66	.	.	.	48.8%	Hdisch	0	34	28.8%	5.6%
	Hussain	2009	86	32	55.8%	59	.	.	.	.	Longer	0	9	28.1%	2.1%
Pooled	**N=16**		**4116**	**1892**	**62.8%**	**63.7**	**28.7**	**19.4%**	**78.9%**	**67.6%**			**171**	**9.0%**	100.0%
IRRT	Albright	2000	66	49	54.5%	.	21.0	0.0%	.		28d	0	20	40.8%	6.0%
	Bahar	2005	168	34	74.4%	56.4	.	3.0%	.	80.4%	28d	0	13	38.2%	15.2%
	Faulhaber-Walter	2009	156	91	63.5%	51.5	30.3	0.0%	.	72.4%	28d	1	35	38.5%	14.1%
	Gabriel	2008	60	28	66.6%	62.5	24.1	0.0%	75.0%	63.3%	28d	0	7	24.1%	5.4%
	Kumpers	2010	109	68	61.5%	51	34.0	0.0%	.	.	28d	1	20	29.7%	9.9%
	Holt	2008	21	13	66.7%	46.5	28.0	0.0%	100.0%	100.0%	60 days	1	1	7.7%	1.9%
	Franzen	2010	39	25	61.5%	66	20.1	46.2%	53.8%	69.2%	Hdisch	0	5	20.0%	3.5%
	Iyem	2009	185	174	63.2%	63.4	.	0.0%	.	.	Hdisch	0	3	1.7%	16.7%
	Ponikvar	2001	72	14	76.4%	61.7	22.1	0.0%	86.1%	66.7%	Hdisch	0	1	7.1%	6.5%
	Schiffl	2002	146	96	54.8%	60	25.2	0.0%	.	.	Hdisch	0	0	0.0%	13.2%
	Al-Malki	2009	83	52	.	.	.	50.0%	.	.	Hdisch	0	15	28.8%	7.5%
Pooled	**N=11**		**1105**	**644**	**59.5%**	**57.8**	**26.8**	**5.8%**	**77.6%**	**74.0%**			**120**	**18.6%**	100.0%

Odds Ratio (IRRT compared with CRRT) **HDD in survivors:** **2.30 [1.79 -2.96]**

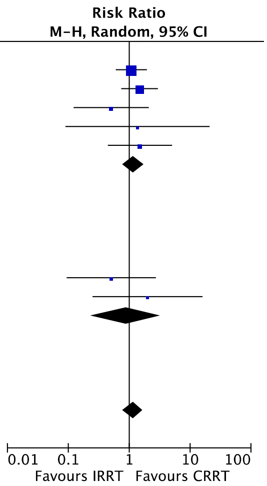
CKD: chronic kidney disease, MV mechanical ventilation, vasopr: vasopressors, SLED: Slow Low Efficiency Dialysis, IHD: Intermittent Hemodialysis, RCT: Randomized controlled trial, CRRT: Continuous renal replacement therapy, IRRT, Intermittent renal replacement therapy Hdisch: hospital discharge, CVVH: Continous veno-venous Hemofiltration, CVVHDF: continuous veno-venous hemodiafiltration, AKI: acute kidney injury, PD: peritoneal dialysis

FIGURES:

Additional Figure 1: Forest plot for dialysis dependence among survivors within RCTs. Stratified by type of IRRT (Intermittent Hemodialysis IHD) versus Slow Low-Efficiency Dialysis (SLED))

M-H: Mantel-Haenszel

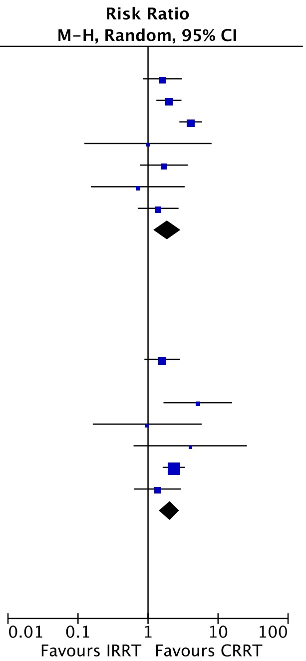
Study or Subgroup	IRRT Events	IRRT Total	CRRT Events	CRRT Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 IHD						
Augustine 2004	8	12	8	13	42.3%	1.08 [0.60, 1.95]
Lins 2009	15	60	11	65	30.2%	1.48 [0.74, 2.96]
Mehta 2001	3	43	4	29	7.2%	0.51 [0.12, 2.09]
Uehlinger 2005	1	27	1	37	2.0%	1.37 [0.09, 20.95]
Vinsonneau 2006	6	61	4	61	9.9%	1.50 [0.45, 5.05]
Subtotal (95% CI)		**203**		**205**	**91.5%**	**1.18 [0.79, 1.75]**
Total events	33		28			
Heterogeneity: Tau² = 0.00; Chi² = 2.02, df = 4 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
1.7.2 SLED						
Abe 2010	2	25	3	19	5.1%	0.51 [0.09, 2.74]
Kumar 2004	3	12	1	8	3.4%	2.00 [0.25, 15.99]
Subtotal (95% CI)		**37**		**27**	**8.5%**	**0.88 [0.23, 3.27]**
Total events	5		4			
Heterogeneity: Tau² = 0.01; Chi² = 1.01, df = 1 (P = 0.31); I² = 1%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Total (95% CI)		**240**		**232**	**100.0%**	**1.15 [0.78, 1.68]**
Total events	38		32			
Heterogeneity: Tau² = 0.00; Chi² = 3.20, df = 6 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%						



Additional Figure 2: Forest plot for dialysis dependence among survivors. Stratified by follow-up duration (observational studies only)

M-H: Mantel-Haenszel

Study or Subgroup	IRRT Events	IRRT Total	CRRT Events	CRRT Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 90 days						
Bagshaw 2006	15	42	12	54	16.7%	1.61 [0.84, 3.06]
Bell 2007	26	158	78	944	21.2%	1.99 [1.32, 3.00]
CartinCeba 2009	256	555	26	229	21.9%	4.06 [2.80, 5.90]
Chang 2004	4	44	1	11	3.8%	1.00 [0.12, 8.08]
Lin 2009	11	54	10	83	14.2%	1.69 [0.77, 3.71]
Marshall 2012	5	56	2	16	6.2%	0.71 [0.15, 3.34]
Swartz 2005	24	110	10	64	16.2%	1.40 [0.71, 2.73]
Subtotal (95% CI)		**1019**		**1401**	**100.0%**	**1.89 [1.22, 2.94]**
Total events	341		139			
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 17.15$, df = 6 (P = 0.009); $I^2 = 65\%$						
Test for overall effect: Z = 2.85 (P = 0.004)						
1.2.2 Hospital discharge						
Elsevier 2010	37	175	13	98	24.7%	1.59 [0.89, 2.85]
Garcia-Fernandes 2011	0	16	0	55		Not estimable
Jacka 2005	9	14	3	24	8.1%	5.14 [1.66, 15.89]
Lins 2006	9	37	1	4	3.4%	0.97 [0.16, 5.83]
Park 2005	37	83	1	9	3.1%	4.01 [0.62, 25.86]
Uchino 2007	37	110	52	360	45.0%	2.33 [1.62, 3.35]
Waldrop 2005	7	12	6	14	15.8%	1.36 [0.63, 2.94]
Subtotal (95% CI)		**447**		**564**	**100.0%**	**2.05 [1.47, 2.87]**
Total events	136		76			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 6.00$, df = 5 (P = 0.31); $I^2 = 17\%$						
Test for overall effect: Z = 4.20 (P < 0.0001)						

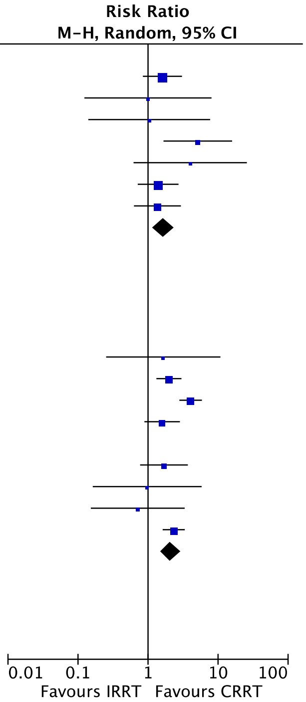


Test for subgroup differences: $Chi^2 = 0.08$, df = 1 (P = 0.78), $I^2 = 0\%$

Figure 3: Forest plot for dialysis dependence among survivors. Stratified by number of centres (observational studies only)

M-H: Mantel-Haenszel

Study or Subgroup	IRRT Events	IRRT Total	CRRT Events	CRRT Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Single center studies						
Bagshaw 2006	15	42	12	54	30.7%	1.61 [0.84, 3.06]
Chang 2004	4	44	1	11	2.9%	1.00 [0.12, 8.08]
Gonwa 2001	1	6	4	25	3.2%	1.04 [0.14, 7.71]
Jacka 2005	9	14	3	24	10.0%	5.14 [1.66, 15.89]
Park 2005	37	83	1	9	3.7%	4.01 [0.62, 25.86]
Swartz 2005	24	110	10	64	28.3%	1.40 [0.71, 2.73]
Waldrop 2005	7	12	6	14	21.4%	1.36 [0.63, 2.94]
Subtotal (95% CI)		**311**		**201**	**100.0%**	**1.68 [1.18, 2.40]**
Total events	97		37			
Heterogeneity: $Tau^2 = 0.00; Chi^2 = 5.77, df = 6 (P = 0.45); I^2 = 0\%$						
Test for overall effect: Z = 2.87 (P = 0.004)						
1.4.2 Multicentric studies						
Andrikos 2009	1	4	5	33	3.0%	1.65 [0.25, 10.81]
Bell 2007	26	158	78	944	20.1%	1.99 [1.32, 3.00]
CartinCeba 2009	256	555	26	229	21.2%	4.06 [2.80, 5.90]
Elsevier 2010	37	175	13	98	15.6%	1.59 [0.89, 2.85]
Garcia-Fernandes 2011	0	16	0	55		Not estimable
Lin 2009	11	54	10	83	11.4%	1.69 [0.77, 3.71]
Lins 2006	9	37	1	4	3.2%	0.97 [0.16, 5.83]
Marshall 2012	5	56	2	16	4.2%	0.71 [0.15, 3.34]
Uchino 2007	37	110	52	360	21.4%	2.33 [1.62, 3.35]
Subtotal (95% CI)		**1165**		**1822**	**100.0%**	**2.11 [1.50, 2.98]**
Total events	382		187			
Heterogeneity: $Tau^2 = 0.11; Chi^2 = 15.42, df = 7 (P = 0.03); I^2 = 55\%$						
Test for overall effect: Z = 4.29 (P < 0.0001)						



Test for subgroup differences: $Chi^2 = 0.81, df = 1 (P = 0.37), I^2 = 0\%$

Additional Figure 4: Funnel Plot