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Accessibility
The impact of “early” versus “late” initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis

Benjamin T. Wierstra1, Sameer Kadri2, Soha Alomar2, Ximena Burbano2, Glen W. Barrisford2 and Raymond L. C. Kao2,3*

Abstract

Background: The optimal timing of initiating renal replacement therapy (RRT) in critical illness complicated by acute kidney injury (AKI) is not clearly established. Trials completed on this topic have been marked by contradictory findings as well as quality and heterogeneity issues. Our goal was to perform a synthesis of the evidence regarding the impact of “early” versus “late” RRT in critically ill patients with AKI, focusing on the highest-quality research on this topic.

Methods: A literature search using the PubMed and Embase databases was completed to identify studies involving critically ill adult patients with AKI who received hemodialysis according to “early” versus “late”/“standard” criteria. The highest-quality studies were selected for meta-analysis. The primary outcome of interest was mortality at 1 month (composite of 28- and 30-day mortality). Secondary outcomes evaluated included intensive care unit (ICU) and hospital length of stay (LOS).

Results: Thirty-six studies (seven randomized controlled trials, ten prospective cohorts, and nineteen retrospective cohorts) were identified for detailed evaluation. Nine studies involving 1042 patients were considered to be of high quality and were included for quantitative analysis. No survival advantage was found with “early” RRT among high-quality studies with an OR of 0.665 (95% CI 0.384–1.153, p = 0.146). Subgroup analysis by reason for ICU admission (surgical/medical) or definition of “early” (time/biochemical) showed no evidence of survival advantage. No significant differences were observed in ICU or hospital LOS among high-quality studies.

Conclusions: Our conclusion based on this evidence synthesis is that “early” initiation of RRT in critical illness complicated by AKI does not improve patient survival or confer reductions in ICU or hospital LOS.

Keywords: Meta-analysis, Intensive care units (ICUs), Acute kidney injury (AKI), Renal replacement therapy (RRT), Early, Late

Background

Acute kidney injury (AKI) is a medical complication associated with significant morbidity and mortality in critically ill patients [1–3]. AKI is common in critical illness, and severe AKI is associated with up to 60% hospital mortality [4]. Renal replacement therapy (RRT) within the intensive care unit (ICU) is conducted as either intermittent hemodialysis or continuous renal replacement therapy (CRRT). Traditional indications for RRT require the development of overt clinical manifestations of renal insufficiency, such as acidosis, electrolyte disturbances (most notably hyperkalemia), uremic complications (encephalopathy or pericarditis), and volume overload unresponsive to aggressive medical management. In spite of research and increasing clinical experience with dialysis, the optimal time to initiate RRT in the course of critical illness complicated by AKI is unclear.

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The notion of “early” RRT is to initiate dialysis therapy before nitrogenous and other metabolic products accumulate to the degree where they become relatively resistant to therapy [5, 6]. Despite the intuitive rationale for “early” RRT, there is limited evidence to guide clinicians on the optimal time to initiate RRT in critical illness. Neither standard clinical parameters nor research into novel clinical biomarkers has emerged to clearly define an ideal time or clinical picture where the initiation of RRT optimizes patient outcomes. Earlier initiation of RRT must be balanced with potential patient harm associated with RRTs. Protocolling use of hemofiltration for 96 h in patients with septic shock admitted to an ICU regardless of their renal function suggests that “early” RRT can be associated with negative patient outcomes [7]. As a result, research into “early” RRT includes multiple definitions of early that reflect a potpourri of time factors, biochemical markers, and clinical parameters in an attempt to balance the risks of initiating RRT with the benefits expected from supporting renal function during critical illness.

The authors of two earlier meta-analyses pooled available data on this topic to suggest that “early” RRT improves survival in critical illness. Seabra et al. [8] identified 23 studies (5 randomized controlled trials [RCTs]/quasi-RCTs, 1 prospective study, and 17 retrospective cohort studies) and concluded that “early” initiation of RRT was associated with 28% mortality risk reduction (relative risk [RR] 0.72, 95% CI 0.64–0.82, p < 0.001). Karvellas et al. [9] identified 15 studies (2 RCTs, 4 prospective studies, and 9 retrospective cohort studies) and reached similar conclusions, reporting a significant improvement in 28-day mortality with “early” RRT (OR 0.45, 95% CI 0.28–0.72, p < 0.001). However, the overall findings were not congruent with the subgroup analysis of randomized trials (RR 0.64, 95% CI 0.4–1.05, p = 0.08), where there was a signal that “early” RRT was not associated with a significant survival advantage. This has diminished clinical confidence in the conclusions reached by the earlier meta-analyses, and consequently “early” RRT in critical illness remains a controversial therapeutic intervention.

Since 2012, additional studies have been published that do not support the conclusions of the previous meta-analyses, and this has further diminished the confidence in the previous conclusions that suggested a survival benefit in critical illness associated with “early” RRT. We conducted a systematic review and evidence synthesis to investigate whether “early” versus “late” initiation of RRT in critically ill patients with AKI improves patient survival and selected secondary outcomes for potential signals to suggest that “early” RRT may reduce patient morbidity or enhance illness recovery. Our goal was to identify the highest-quality studies on this topic and use a pooled meta-analysis of these studies to inform our conclusions.

**Methods**

**Search strategy**

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10] (see Additional file 1: Figure S1 for PRISMA checklist). Our null hypothesis was that “early” initiation of RRT does not improve patient survival in critical care patients with AKI. This systematic review was not registered, and a protocol does not exist. The PubMed and Embase databases were searched to identify published articles following four broad themes: AKI, RRT, time of initiation, and critical illness (see Additional file 2: Table S1 for search terms). SK is a National Institutes of Health (NIH) physician and requested the NIH librarian to provide oversight for the search strategy. Our search was limited to English-language-only, full-text primary research publications (including abstracts with full text availability) reporting findings of clinical trials and observational studies (cohort and case-control design) published between January 1985 and November 2015. Studies before 1985 were not actively sought, owing to a low likelihood of relevance to modern RRTs and critical care practices.

**Study selection**

References were screened and excluded if they were small case reports or observational studies (fewer than 10 subjects), were not focused on critically ill adult patients, did not report mortality data, involved basic science data, or did not clearly distinguish between “early” and “late” groups. This task was divided among the authors. A second evaluation led by the senior author (RLCK) was conducted to evaluate study quality. Studies were designated as being of “high quality” or “low quality.” Studies were assigned a “low-quality” rating if there was no illness severity assessment between cohorts or at the time of randomization (n = 8), significant differences (p < 0.05) between cohort groups (n = 7) at baseline, incomplete basic demographic data at baseline (n = 6) to exclude baseline differences, or a Newcastle-Ottawa Quality Assessment (NOQA) Scale [11] for cohort studies rating less than 7 (n = 6). The senior author (RLCK) was the arbiter in cases of disagreement. Only high-quality studies were included in quantitative meta-analysis of the primary and secondary outcomes.

**Primary and secondary outcomes**

The primary outcome of interest was mortality at 1 month (pooling outcomes for mortality at 28 or 30 days, depending on what was reported by the primary authors). In addition to mortality, we analyzed selected secondary
Table 1 Trial Summary Table by Study Type (n=36)

| Author, Year | Study Design | Country | Duration | Exclusion | Patient Population | Patients (n) | Age (mean) yrs | Illness Severity Score | Early RRT Criteria | Late RRT Criteria | Study Quality | Primary Outcome |
|--------------|--------------|---------|----------|-----------|-------------------|-------------|---------------|-----------------------|-------------------|-----------------|--------------|-----------------|
| Bouman, 2002 [12] | RCT, two-center study | Netherlands | May 1998 - Mar 2000 | Pre-existing renal disease | Multisystem | 106 | 70 | 36 | EHV: SOFA 10.3; APACHE2=23.5; ELV: SOFA 10.1; APACHE2=21.7; LLV: SOFA 10.6; APACHE2=23.6 | TIME: Early < 12 h (200ml); Early Low Vol < 12 h (100-150ml) | TIME: Late > 12h | HIGH | 28 d mortality: EHV/ELV/LLV died; \( p=0.8 \) |
| Durraz, 2003 [13] | RCT | Turkey | Sept 1999 - Aug 2001 | Age<18, chronic dialysis | Post Cardiac Surgery | 24 | 21 | 23 | | | | LOW | Hospital mortality: Early 1/21 (4.8%) died, Late 7/23 (30.4%) died; \( p=0.048 \); Favors Early |
| Sugahara, 2004 [14] | RCT | Japan | Jan 1995 - Dec 1997 | Pregnancy, BMI > 30, Mental disorder, Cancer, Early recovery of urine output >30ml/kg/hr prior to RRT | Multisystem | 28 | 14 | 14 | Early: SOFA 11.6; SAPS2 54.3; Late: APACHE2=19; Late: SOFA 10.4; SAPS2 52.4 | TIME: Protocolized RRT × 96hrs w/ diagnosis of ‘sepsis’. Mean time to RRT start 18d±0.9 post op | | HIGH | 14 d mortality: Early 2/14 died (14%), Late 12/14 died (86%); \( p=0.01 \); Favors Early |
| Payen, 2009 [7] | RCT, multicenter | France | Jan 1997 - Jan 2000 | Age<18, chronic dialysis, pregnant, morbid state, prior immunosuppressive therapy | Multisystem | 76 | 37 | 39 | | | | HIGH | Early 20/37 (54%) died, Late 17/37 (44%) died; \( p=0.49 \) |
| Jamal, 2013 [15] | RCT, single center | India | April 2010 - July 2012 | Required urgent dialysis at time of randomization | Multisystem | 208 | 102 | 106 | Early: SOFA 7.3; Late: SOFA 8.2 | BIOCHEM: Cr > 618 μmol/L | | HIGH | Mortality: Early 27/102 (20%) died, Late 13/106 (12%); \( p=0.2 \) |
| Combes, 2015 [16] | RCT, multicenter | USA | 2009-2012 | <18, Pregnant, Chronic RRT, Weight >120kg, SAPS II>90 (i.e. moribund) | Post Cardiac Surgery | 224 | 112 | 112 | Early: SOFA 11.5; SAPS2=54; Late: SOFA 12.0; SAPS2=55.1 | TIME: RRT initiated <24hrs and continued for min of 48hrs; Mean time to randomization 12hrs | | HIGH | Mortality: Early 40/112 (36%) died, Late 40/112 (36%) died; \( p=1.0 \) |
| Wald, 2015 [17] | RCT, multicenter | Canada | May 2012 - Nov 2013 | Intoxication requiring RRT, Limited resuscitation directives, RRT within the previous 2 months, RPGN, Obstructive uropathy, > 48hrs to doubling time of Cr | Multisystem | 100 | 48 | 52 | Early: SOFA 13.3; Late: SOFA 12.8 | TIME: Time from randomization < 12h; Mean time to RRT = 9.7hrs | | HIGH | Mortality: Early 16/48 (33%) died, Late 19/52 died; \( p=0.74 \) |
**Table 1** Trial Summary Table by Study Type (n=36) (Continued)

| Study | Type | Multicentre | Patient Characteristics | Study Period | Study Design | Follow-up | Criteria | Mortality | p-Value | Follow-up | Criteria | Mortality | p-Value |
|-------|------|-------------|--------------------------|--------------|-------------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|
| Liu, 2006 [18] | Prospective | Observational | Multi | Feb 1999 - Aug 2001 | Multi-system | 243 | 122 | 121 | Early: 54 | Late: 58 | NR | Anemia defined by BUN<76mg/dL | Anemia defined by BUN<76mg/dL | LOW | NOQA=6 | 28 d mortality: Early 43/120 (33%) died vs Late 50/121 (41%) | P=0.09 | Favor Early |
| Iyem, 2009 [19] | Prospective | Observational | Multi | May 2004 - April 2007 | Post-cardiac surgery | 185 | 95 | 90 | Early: 64 | Late: 62 | NR | TIME: Evidence of 10% increase in BUN, low urine output (<0.5ml/kg/h) triggering RRT started <48hrs | TIME > 48hrs to start of RRT for similar markers of renal failure managed medically for minimum 48hrs | LOW | NOQA=7 | In hosp mortality: Early 5/95(5%) died, Late 6/90(7%) died | NS |
| Bagshaw, 2009 [20] | Prospective | Observational | Multi | Sept 2000 - Dec 2001 | Pre-existing chronic RRT, drug toxicity, age <12 | 1227 | 959 | 268 | Early: 60 | Delayed: 63, Late: 64, p=0.003 | Early: SOFA 10.9 | SAPS2=53.5 | Delayed: SOFA 11.1, SAPS2=46 | Late: SOFA 10.7, SAPS2=43.1, p=0.04 | Early: RRT started for anemia (linea >30mmol/L, or low urine output x 12h <33 (n=780), Delayed RRT started 2-5d (n=174) from ICU admission | RRT started >5d from ICU admission | LOW | NOQA=7 | Hosp mortality: Early 462/785(59%) died, Delayed 108/174(62%) died, Late 155/268(72%) died, p=0.0011 Favor Early |
| Shiao, 2009 [21] | Prospective | Observational | Multi | Jan 2002 - Dec 2005 | Prior dialysis, without surgery, or surgery did not involve abdominal cavity. History of renal transplant | 98 | 51 | 47 | Early: 65 | Late: 68 | Major | Abdominal surgery | BIOM: RIFLE criteria: RISK & INJURY; BIOCHEM: RRT initiated for RIFLE: BIOCHEM: RIFLE criteria: RISK or pre-RISK criteria | TIME >24hrs from ICU admission | RFLE criteria INJURY or FAILURE criteria | [Mean Time to RRT from ICU admission = 7.3d] | HIGH | NOQA=7 | Hosp mortality: Early 22/151(14.3%), Late135/477(28%) | p=0.0028 Favor Early |
| Sabater, 2009 [22] | Prospective | Observational | Single | Dec 2001- Feb 2005 | Pre-existing renal disease (Cr<1.5mg/dl), reduced kidney size on ultrasound | 148 | 44 | 104 | All patients mean = 66 | NR | Multisystem | APACHE2=18, Late: APACHE2=18.8 | BIOM: RIFLE criteria: RISK or pre-RISK criteria | Time to RRT started 2-5d post ICU admission | RFLE criteria INJURY or FAILURE criteria | Mean Time to RRT from ICU admission = 8.4d | LOW | NOQA=7 | Mortality: Early 21/44 died, Late 66/104 died, P=0.047 Favor Early |
| Elistor, 2010 [23] | Prospective | Observational | Multi | 2001-2005 | Pre-existing renal disease (Cr<1.5mg/dl), reduced kidney size on ultrasound | 1303 | 653 | 650 | Early: 64, Late: 67 | Early: SOFA 9.9 | SAPS2=25.2 | Delayed: SOFA 8.5, SAPS2=6.2, p=0.001 | BIOM: Unspecified SHARF scoring criteria w/anemia Cr > 2mg/dL | Conservative approach = No RRT | | | LOW | NOQA=5 | Mortality: Early 378/653 (58%) died, Late 280/650 (43%) died, p=0.001 Favor Late |
| Vaira, 2012 [24] | Prospective | Observational | Multi | Sep 2011 - Feb 2012 | Sepsis, Cardiogenic Shock | 261 | NR | NR | NR | Survivors: SAPS2=47, Non-survivors: SAPS2=66 | TIME: Time >24hrs from ICU admit | Time > 24hrs from ICU admit | | | LOW | NOQA=5 | OR for late 2.69 (1.07-6.73, p=0.035) Favor Late |
| Perez, 2012 [25] | Prospective | Observational | Single | Dec 2001 - Feb 2005 | Sepsis | 244 | 135 | 109 | Early: 62, Late: 62 | Early: SOFA 12, Late: SOFA 11 | BIOM: RIFLE criteria: RISK or pre-RISK criteria | Time >24hrs from ICU admit | Time > 24hrs from ICU admit | | | LOW | NOQA=5 | 90 d mortality: Early 71/135(53%) died, Late 78/100(78%) died, p=0.003 Favor Early |
| Lim, 2014 [26] | Single Centre | Prospective Cohort | Single | Dec 2010 - April 2013 | Chronic dialysis patients, Dialysis initiated prior to ICU admission | 140 | 84 | 56 | Early: 60, Late: 64 | Early: SOFA 7, Late: SOFA 11, p=0.001 | BIOM: AKIN stage 1 or 2 AND compelling indication or AKIN stage 3 (Cr>1540umol/L or Cr >300% | Traditional indications K<6mmol/L, Urea ≥30mmol/L, pH<7.25, Bicarb | | | LOW | NOQA=6 | Hosp mortality: Early 36/84(43%) died, Late 37/56(66%) died |
### Table 1  Trial Summary Table by Study Type (n=36) (Continued)

| Study Group         | Countries | Study Period                  | Median Age | Median APACHE | Median SOFA | Median ISS | TRIAGE: AKI diagnosis to randomization < 17.6 hrs | Time from AKI diagnosis to randomization > 17.6 hrs | P  | Favors | Pooled mortality | Hosp mortality | Hosp mortality | Hosp mortality | Hosp mortality |
|---------------------|-----------|-------------------------------|------------|---------------|-------------|-----------|---------------------------------------------------|-------------------------------------------------|-----|--------|-----------------|---------------|---------------|---------------|---------------|
| POST-DIALYSIS (PDED) |           |                               |            |               |             |           |                                                   |                                                  |     |        |                 |               |               |               |               |
| PROSPECTIVE         |           |                               |            |               |             |           |                                                   |                                                  |     |        |                 |               |               |               |               |
| Retrospective Trials|           |                               |            |               |             |           |                                                   |                                                  |     |        |                 |               |               |               |               |
| Demirkic et al.     | Turkey    | Mar 1992 - Sep 2001           | NR         | NR            | NR          | NR        |                                                   |                                                  |     |        |                 |               |               |               |               |
| Elahi et al.        | UK        | Jan 2002 - Jan 2003           | Post cardiac surgery | 64 | 36 | 28 | Early 69 | Late 68 | SR | BUN < 60 mg/dL. AND Other, Blood loss, Cardiac surgery, Uremia, Mean RRT start post admission day 10; p<0.0001 |                                                    |     |        |                 |               |               |               |               |
| Wu et al.           | Taiwan    | July 2002 - Jan 2005          | Hepatorenal syndrome from cirrhosis, liver transplant, cardiopulmonary resuscitation | 80 | 54 | 26 | Early 55 | Late 63 | p=0.003 | BUN < 80 mg/dL. AND Other, Blood loss, Cardiac surgery, Uremia, Mean RRT start post admission day 88 |                                                    |     |        |                 |               |               |               |               |
| Andrade et al.      | Brazil    | 2002-2003                     |         |               |             |           |                                                   |                                                  |     |        |                 |               |               |               |               |
| Manche et al.       | Malta     | 1905-2006                     | NR         | Post Cardio Surgery | 71 | 56 | 15 | Early 66 | Late 63 | BUN < 0.5 mg/Kg/hr refractory to med mgt; Mean RRT start post-op |                                                   |     |        |                 |               |               |               |               |
| Lundy et al.        | US        | Nov 2005 - Aug 2007           | Preexisting renal disease, burn size of less than 40% Non-thermal injury, lithium toxicity | 57 | 29 | 28 | Early 27 | Late 38 | P=0.06 | BUN > 60 mg/dL. AND Other, Blood loss, Cardiac surgery, Uremia, Mean RRT start post admission day 10 |                                                    |     |        |                 |               |               |               |               |
| Study Type | Retrospective cohort | Country | Year Range | Study Type | Inclusion Criteria | Exclusion Criteria | Outcomes |
|-----------|----------------------|---------|------------|------------|--------------------|-------------------|----------|
| **Case 1** | Retrospective cohort | Taiwan | Jan 2002 - Oct 2004 | Age > 18, ICU stay < 2 days, RRT < 2 days | Sepsis, Multisystem | 460 | 370 192 178 Early 64, Late 66 | Time from ARO to RRT < 6 days |
| **Case 2** | Retrospective cohort | USA | Jan 1999 - Feb 2006 | Renal transplant, Pre-morbid ESRD on dialysis, RRT < 48h, insufficient data | Sepsis + AKI | 230 NR NR All patients mean = 66 NR | Time from ARO to RRT < 6 days |
| **Case 3** | Retrospective cohort | China | Apr 2004 - Mar 2009 | Patients readmitted post discharge, Discharged against medical advice, Death < 48h | Post cardiac surgery | 24 34 58 Early 64, Late 62 | Time from urine output <0.5ml/kg/h & Time to RRT > 12h post oliguria; Mean oliguria to start of RRT 21.3hrs |
| **Case 4** | Retrospective cohort | Taiwan | Jan 2002 - Apr 2009 | Dialysis before surgery, ESRD | Surgical | 212 436 648 Early 62, Late 66, P=0.000 | Time: Time to development of traditional RRT indications < 3d; Mean time to start of RRT 1.4days |
| **Case 5** | Retrospective cohort | South Korea | Apr 2009 - Oct 2010 | Liver cirrhosis, Pre-existing chronic disease | Sepsis | 19 36 55 Early 63, Late 62 | Time: Time to RRT > 24hrs; Mean time to RRT= 42.3hrs |
| **Case 6** | Retrospective cohort | France | Jan 2008 - Dec 2010 | Early transfer to another unit | Multisystem | 43 67 110 Early 62, Late 66 | Time: Time from RIFLE > RRT > 16hrs; Mean time to RRT= 64hrs |
| **Case 7** | Retrospective cohort | Japan | Jan 2009 - Feb 2013 | Age > 18, RRT for ESRD | Sepsis, Cardiogenic shock | 137 52 189 Early 74, Late 73 | Time: Time to RIFLE ‘Injury/Failure’ = 11.66 (1.26-107.9); Mean time to RRT=12.5hrs |
| **Case 8** | Retrospective cohort | China | Jan 2008 - Jun 2011 | Age > 18, Chronic dialysis, RRT prior to ICU | Sepsis | 89 31 120 Early 74, Late 73 | Time: Time to RIFLE ‘Injury/Failure’ > 24hrs; Mean time to RRT= 42.3hrs |
| **Case 9** | Retrospective cohort | Nov 2009 - Dec 2011 | Age < 12, Chronic renal disease, Terminal illness | Sepsis - AKIN 1 | 26 23 49 Early 48, Control 54 | Time: Time to RIFLE ‘Injury/Failure’ > 24hrs; Mean time to RRT= 42.3hrs |

**Table 1: Trial Summary Table by Study Type (n=36) (Continued)**
| Study Type | Year | Country | Study Group | Time from Anuria to RRT | Mortality | Notes |
|------------|------|---------|-------------|------------------------|----------|-------|
| Sepsis - AKIN 3 | 2007-2011 | Lithuania | No RRT (Control) | 28 d mortality: Early 31/46 (67%) died, Control 11/13 (85%) died; NS | 71% (early) vs 91% (late) | Patients refused CRRT for “personal reasons” |
| Sepsis - AKIN 3 | 2007-2011 | Lithuania | Early SOFA 10, APACHE2=21.8; Control SOFA 11.2, APACHE2=20.5 | No RRT (Control) | 71% (early) vs 91% (late); p=0.028; Favors Early | Time from anuria to RRT < 12hrs |
| Lithium | 2007-2011 | Lithuania | Early SOFA 10, APACHE2=21.8; Control SOFA 11.2, APACHE2=20.5 | No RRT (Control) | 71% (early) vs 91% (late); p=0.028; Favors Early | Time from anuria to RRT > 12hrs |

**Total** | 2841 | 1434 | 1177 | 28 d mortality: Early 714/1434 (50%) died, Control 732/1177 (62.2%); n=19 | 50% (early) vs 62.2% (late); p=0.003; Favors no RRT |

**Notes:**
- AKI: Acute Kidney Injury
- AKIN: Acute Kidney Injury Network
- APACHE: Acute Physiology and Chronic Health Evaluation
- CRF: Chronic Renal Failure
- CRRT: Chronic Renal Replacement Therapy
- eGFR: Estimated Glomerular Filtration Rate
- EHV: Early High Volume
- ELV: Early Low Volume
- ESRD: End-Stage Renal Disease
- ICU: Intensive Care Unit
- LTV: Late Low Volume
- NOQA: Newcastle-Ottawa Quality Assessment
- NR: Not Reported
- NSARF: National Taiwan University Hospital-Surgical ICU-Acute Renal Failure database
- RRT: Renal Replacement Therapy
- RPGN: Rapidly Progressive Glomerulonephritis
- SAPS2: Sequential Acute Physiology Score
- SHARF: Stuivenberg Hospital Acute Renal Failure Score
- SOFA: Sequential Organ Failure Assessment
- UOP: Urine Output

**References:**
- 44 | Gaudry, 2014 | France | Jan 2004 - Nov 2011 | Age<18, limitation in medical therapy, death<24hrs, chronic renal insufficiency, RRT prior to ICU, kidney transplant, lithium toxicity, multiple myeloma | Early: 65; Late 65 | Early: SOFA 9, SAPS2=60; Control: SOFA 8, SAPS2=55; P=0.001 |
- 45 | Serpytis, 2014 | Lithuania | 2007-2011 | All patients mean = 72 NR | Early 59; Control 55 | Early SOFA 10, APACHE2=21.8; Control SOFA 11.2, APACHE2=20.5 |

**Legend:**
- AKI: Acute Kidney Injury
- AKIN: Acute Kidney Injury Network
- APACHE: Acute Physiology and Chronic Health Evaluation
- CR: Creatinine
- CRF: Chronic Renal Failure
- CRRT: Chronic Renal Replacement Therapy
- eGFR: Estimated Glomerular Filtration Rate
- EHV: Early High Volume
- ELV: Early Low Volume
- ESRD: End-Stage Renal Disease
- ICU: Intensive Care Unit
- LLV: Late Low Volume
- NOQA: Newcastle-Ottawa Quality Assessment
- NR: Not Reported
- NSARF: National Taiwan University Hospital-Surgical ICU-Acute Renal Failure database
- RRT: Renal Replacement Therapy
- RPGN: Rapidly Progressive Glomerulonephritis
- SAPS2: Sequential Acute Physiology Score
- SHARF: Stuivenberg Hospital Acute Renal Failure Score
- SOFA: Sequential Organ Failure Assessment
- UOP: Urine Output
outcomes, including ICU length of stay (LOS) and hospital LOS. Secondary outcomes were not consistently reported for all studies, and only studies with applicable data were included in our pooled analysis. Weighted means were calculated as a product of the number of patients and mean duration to reach a total and represented as a total of patient-days per study. These values were summed and divided by the total number of patients from all included studies to reach weighted mean duration of LOS for both hospital and ICU LOS metrics. A similar process was used to derive the mean weighted illness severity scores. Other potentially relevant secondary outcomes, including mechanical ventilation requirements, vasopressor requirements, and renal recovery rates, were considered, but these variables were inconsistently reported and commonalities could not be reached among the heterogeneous parameters that were available.

Definition of “early” versus “late”

“Early” was defined on the basis of criteria used by the original authors in their respective studies. We accepted a broad definition of early based on biochemical markers according to RIFLE classifications (risk, injury, failure, loss of function, and end-stage kidney disease), Acute Kidney Injury Network (AKIN) stages, or time-based cutoffs (e.g., within a defined time from ICU admission or development of a biochemical “start time”). Accepting a broad definition of early was intended to optimize the potential for identifying an effect associated with “early” RRT. A limitation of this approach is that “early” according to one study investigator might be considered “late” by another study investigator. “Late” RRT criteria involved either usual practice or expectant care (i.e., no RRT initiated). “Usual practice” generally involved implementing RRT following the development of classic RRT indications unresponsive to medical management.

Statistical analysis

The quality of cohort trials was assessed using the NOQA Scale (range from 0 to 9, with 9 indicating the highest quality) [11]. The NOQA Scale for cohort studies assesses the domains of population selection, comparability of cohorts, and outcome assessment. A meta-analysis was conducted using the high-quality studies to calculate the pooled OR for mortality at 1 month. A random effects model was used because of the significant heterogeneity between studies on this topic. A random effects model is indicated when study populations differ in ways that could impact the results. Heterogeneity was assessed on the basis of the Q value and I² and τ² statistics. A p value less than 0.05 was considered statistically significant. All analyses were performed using Comprehensive Meta-Analysis version 3.3.070 software (www.meta-analysis.com; Biostat, Englewood, NJ, USA).

Results

The systematic literature search yielded 2405 references that were subsequently refined to 36 studies eligible for inclusion in this meta-analysis (see Additional file 3: Figure S2 for article selection breakdown). These references included 7 RCTs [7, 12–17], 10 prospective cohort studies [18–27], and 19 retrospective cohort studies [28–46]. Only nine studies met our criteria for high quality [7, 12, 14–17, 21, 35, 40]. A summary of the fundamental characteristics of all evaluated studies is provided in Table 1.

Primary outcome

The observed pooled crude mortality rates varied significantly between the high- and low-quality studies. Among the high-quality studies, the pooled “early” RRT group mortality rate was 34.6 % (192 of 555) compared with 40.2 % (196 of 487) in the pooled “late” RRT group. The low-quality studies demonstrated a pooled “early” RRT group mortality rate of 51.3 % (1871 of 3645) compared with 54.3 % (1486 of 2737) in the “late” RRT groups. The most frequently reported measurement of illness severity in the studies we analyzed was the Sequential Organ Failure Assessment (SOFA) score. The SOFA score has been correlated with critical care patient outcomes [47, 48], but it is not as robust as other scoring systems validated in predicting survival (e.g., Acute Physiology and Chronic Health Evaluation II [APACHE2] or Simplified Acute Physiology Score II [SAPS2]) [49]. The mean weighted SOFA scores in the high-quality studies were 10.2 and 10.4 in the “early” and “late” groups, respectively. SOFA scores were reported for 78 % of patients in the high-quality studies. Among the high-quality studies, the SOFA score appeared to correspond with an APACHE2 score of approximately 20 or a SAPS2 score of approximately 53 when these additional illness severity metrics were reported by the principal investigators. Unfortunately, more detailed quantitative evaluation of illness severity using APACHE2 or SAPS2 scores was not possible, owing to heterogeneous reporting methods between investigators and a lack of sufficient data. SOFA scores were reported for 65 % of the patients in the studies assigned low-quality ratings. The mean weighted SOFA scores in the “early” and “late” groups among the low-quality studies were comparable to those for the high-quality studies at 10.0 and 9.2, respectively. No further comments can be made regarding illness severity scores among the low-quality studies, owing to lack of homogenous and sufficient data. Illness severity scores for all studies are summarized in Table 1.

Pooled analysis of the high-quality studies (n = 9) indicates no mortality benefit with “early” versus “late” RRT, with an OR of 0.665 (95 % CI 0.384–1.153, p = 0.146) (Fig. 1). The bulk of the data in support of “early” RRT
rests in the pooled low-quality studies ($n = 27$), with an OR of 0.471 (95% CI 0.343–0.649, $p < 0.001$) (Fig. 2). Similarly to authors of previous meta-analyses, we found very high heterogeneity among studies on this topic. Heterogeneity was highest among the low-quality studies, reflected by a $Q$ value of 163.8, $I^2$ value of 84%, and $\tau^2 = 0.495$ ($p < 0.001$). Among the high-quality studies, there continued to be statistically significant heterogeneity, with a $Q$ value of 29.1, $I^2$ value of 72.5%, and $\tau^2 = 0.481$ ($p < 0.001$). Subgroup analysis of the high-quality studies according to ICU admission type and surgical [14, 16, 21] versus mixed medical admissions [7, 12, 15, 35, 40] demonstrated no significant subgroup mortality benefits associated with “early” RRT (see Additional file 4: Figure S3a and b for forest plots by ICU admission type). Subgroup analysis among the high-quality studies was also conducted using the definition of early according to time criteria (hours or days) versus biochemical parameters (i.e., rising creatinine, uremia, oliguria) (see Additional file 5: Figure S4a and b for forest plots by biochemical or time definition of early). There were no significant effects observed in pooled mortality trends in studies that defined early by time criteria rather than on the basis of biochemical parameters.

Secondary outcomes

The secondary outcomes analyzed included ICU LOS and hospital LOS. Five of the nine high-quality studies reported ICU LOS data [12, 16, 17, 35, 40]. The mean weighted ICU LOS in the “early” group was 9.4 days ($n = 351$), compared with 10.8 days ($n = 281$) in the “late” group. None of the studies reported a significant finding with respect to ICU LOS and “early” RRT. Pooled analysis for ICU LOS also demonstrated no significant change in ICU LOS associated with “early” RRT, with a standard difference in the means of $−0.035$ (95% CI $−0.196$ to 0.127, $p = 0.674$) using a fixed effects model ($Q = 0.598$, $p = 0.963$) (Fig. 3). Hospital LOS was reported in five of nine high-quality studies [12, 16, 17, 21, 40]. The mean weighted hospital LOS in the “early” group was 19.3 days ($n = 317$), compared with 17.1 days ($n = 266$) in the “late” group. The pooled hospital LOS data do not reveal any significant difference in hospital LOS using a fixed effects
model with a standard difference in the means of 0.040 (95% CI −0.125 to 0.204, $p = 0.638$) (Fig. 4).

### Discussion

Despite several studies having been conducted on this topic over the last 30 years, a clear answer regarding the optimal timing of RRT in critical illness remains elusive. Our analysis does not confirm the conclusions of previous meta-analyses on this topic. Four studies [12, 14, 21, 35] in the high-quality group were previously included in the meta-analysis by Karvellas et al. [9], and only one study [12] was included in the meta-analysis by Seabra et al. [8]. The addition of four recently published studies [15–17, 40] and one high-quality study that was not previously included in meta-analysis [7] accounts for our results that differ from those of earlier authors. Our conclusions build on the concerns raised by both earlier meta-analyses that the results of cohort trials in favor of “early” RRT were not reproduced in methodologically more rigorous study designs (i.e., RCTs). In our further analysis we did not identify critical illness patient subgroups for whom “early” RRT might be more beneficial. Similarly, how one defines early (according to time or on the basis of biochemical characteristics) does not identify a survival advantage associated with “early” RRT compared with usual care. The optimal timing for initiation of RRT is not clarified on the basis of research evaluated to date.

The strength of our present analysis rests on our extensive literature search and strict classification according to study quality to limit risk of type I hypothesis testing error. Prior meta-analyses relied heavily on retrospective cohort study data that possessed incomplete preintervention data or preexisting significant differences in groups which predisposed the investigators to identify a survival difference attributed to “early” RRT that may have been accounted for by the preintervention population differences. We identified differences in the crude mortality rates between the high- and low-quality studies that are incompletely explained. The crude mortality rate differences may be explained by factors that are not adequately controlled for between the groups before the intervention of “early” versus “late” RRT (e.g., unreported regional institutional differences, variation in intensive care resources, institutional setting variability [academic versus community], or natural history variability of the diseases precipitating critical illness). In cohort trials, a difference in preintervention study groups indicates a

| Model | Study name | Statistics for each study | Std diff in means | Lower limit | Upper limit | p-Value |
|-------|------------|---------------------------|-----------------|-------------|-------------|---------|
|       |            |                           |                  |             |             |         |
| Fixed |            |                           | -0.035           | -0.196      | 0.127       | 0.674   |
| Random|            |                           | -0.035           | -0.196      | 0.127       | 0.674   |

Fig. 3 Forest plot of pooled analysis of standard difference of the means for intensive care unit length of stay ($n = 5$)

| Model | Study name | Statistics for each study | Std diff in means | Lower limit | Upper limit | p-Value |
|-------|------------|---------------------------|-----------------|-------------|-------------|---------|
| Fixed |            |                           | -0.035           | -0.196      | 0.127       | 0.674   |
| Random|            |                           | -0.035           | -0.196      | 0.127       | 0.674   |

Fig. 4 Forest plot of pooled analysis of standard difference of the means for hospital length of stay ($n = 5$)
critical methodological flaw that precludes deriving conclusions from their results. This is referred to as a type I error in hypothesis testing and may falsely attribute differences in outcomes to the study variable rather than the differences between cohorts that existed before analysis. Among high-quality studies, there was no survival advantage to “early” RRT with an OR of 0.665 ($p = 0.146$). Any inclusion of the low-quality study data would significantly pull the conclusion in favor of “early” RRT, which would represent fulfillment of a type I statistical hypothesis error. The strength of our work is that we vigorously guarded against this possibility.

Subgroup analysis of the high-quality studies did not reveal a survival benefit associated with either a surgical or medical critical care patient population. This conclusion remained the same regardless of whether early was defined by time or on the basis of biochemical parameters. Our secondary outcome analysis was limited by inconsistent and incomplete data reported across studies. Limited pooled analysis of the available data suggested that there was no significant effect on either ICU or hospital LOS associated with “early” RRT. Incomplete data does not permit us to evaluate additional secondary outcomes of interest (such as requirement for mechanical ventilation or rates of renal recovery) that might also be clinically relevant considerations factored into the decision to initiate RRT in critical illness.

By limiting our analysis to studies meeting high-quality criteria, we dismissed a large volume of research on this topic. A critique of our work is that we discarded studies for methodological shortcomings that others may feel should have been included. Most studies ($n = 21$) in the low-quality group were excluded for incomplete cohort data or significant preintervention differences between cohort groups. The decision to exclude these trials is less controversial than our decision to exclude cohort trials for an NOQA Scale rating less than 7 ($n = 6$). This is potentially controversial because the NOQA Scale has received criticism regarding its validity and applicability in meta-analysis cohort trial quality assessment [50]. The NOQA Scale has received positive endorsement from some authors [11], but detailed psychometric properties have not been published in peer-reviewed journals to date. Furthermore, our selection of an NOQA Scale rating less than 7 to identify low quality is arbitrary. Our rationale for selecting this cutoff was that it necessitates that at least one of the three NOQA Scale domains be seriously compromised, and we felt that this represented a significant bias predisposing the study results to committing a type I error pattern. Seabra et al. [8] attempted to assign a quality score to trials ($0 = $ lowest quality to $5 = $ best quality) to evaluate this domain, but their methodology for score assignment was obscure and was not able to be replicated or directly compared with our methods. In qualitative comparison, the study assigned their top score [12] was included in our quantitative analysis; however, their second highest quality study [13] was excluded due to lack of reported illness severity scores between groups. Including studies with methodological errors does not advance scientific understanding of this topic and has contributed to the discordant findings on it.

Early studies on this topic were small and may have overestimated an effect size associated with “early” RRT based on the small size of the study populations. An example of this problem is the Sugahara et al. study [14], where 14-day mortality within the “early” group was 14 % (2 of 14), compared with 86 % (12 of 14) in the “late” group ($p < 0.01$). While this study was included in our quantitative analysis, the magnitude of the mortality benefit reported in this trial associated with “early” RRT has not been reproduced by subsequent investigators, for reasons that are not clear. In our review of the ongoing trials on this topic registered with the NIH (www.clinical Trials.gov), we identified three trials [51–53] that may add to knowledge in this area. The methodology of all three active RCTs is roughly similar, with patients randomized from a point in time triggered by the development of biochemical renal injury reflected by a RIFLE grade of “failure” (at least one of rise in creatinine by minimum of 300 %, oliguria less than 0.3 ml/kg/h for 12 h, or anuria lasting more than 12 h). From this biochemical entry point, patients will be randomized to immediate initiation of RRT (goal time to RRT less than 12 h) or standard care (RRT initiated after failure of medical management to temporize metabolic derangements or volume overload). These study designs are similar to the design used by Wald et al. [17], included in our analysis, that was able to separate an “early” group to mean time to RRT of 9.2 h and a “late” RRT group with a mean time to RRT of 32 h after biochemical inclusion criteria were met. Wald et al. [17] did not identify a significant difference in mortality rates between their two groups ($p = 0.74$). These studies in process will add to the quantity of patients evaluated in this manner and will build on the availability of high-quality data on this topic. By clearly defining routine biochemical criteria associated with acute renal injury, they provide a practical method of renal injury assessment that can be determined by intensivists and nephrologists considering RRT.

Conclusions

The results of our meta-analysis contradict the findings reported by previous authors [8, 9], and we conclude that “early” initiation of RRT in critically ill patients with AKI does not improve survival. This conclusion is derived from the pooled high-quality trial data and excludes data from cohort trials where there were methodological shortcomings that predisposed them to find an effect
misattributed to the intervention. Pooled analysis of secondary outcomes did not demonstrate a statistical reduction in ICU or hospital LOS. Additional well-designed RCTs will provide greater confidence in these conclusions as optimal patient care practices progress in critical care. Clinical triggers for the initiation of RRT to optimize patient outcomes have not been clearly identified by current research. Meanwhile, intensivists and nephrologists are encouraged to refrain from lowering their clinical thresholds for implementing RRT in critical care patients with acute renal injury.

Key messages

- High-quality trial data do not demonstrate improved survival using an “early” RRT approach in critical illness complicated by AKI.
- Lower-quality trial data demonstrate significantly higher mortality rates and form the basis for the bulk of support for “early” AKI.
- The optimal time to initiate RRT in critical illness remains undefined.
- A conservative approach to initiating RRT in critical illness is supported.

Additional files

| Additional file 1: Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. (PDF 51 kb) |
| Additional file 2: Table S1. Search terms used during literature review. (DOCX 15 kb) |
| Additional file 3: Figure S2. Article selection process. (PDF 86 kb) |
| Additional file 4: Figure S3. a Mortality forest plot of subgroup analysis of high-quality studies according to post-surgical ICU admission type (n = 3). b Mortality forest plot of subgroup analysis of high-quality studies according to medical ICU admission type (n = 6). (ZIP 120 kb) |
| Additional file 5: Figure S4. a Mortality forest plot of subgroup analysis of high-quality studies based on the definition of “early” according to time criteria (hours or days) (n = 4). b Mortality forest plot of subgroup analysis of high-quality studies based on the definition of “early” according to biochemical parameters (i.e., rising creatinine, uremia, oliguria) (n = 5). (ZIP 121 kb) |

Abbreviations

AKI: acute kidney injury; AKIN: Acute Kidney Injury Network; AMA: against medical advice; APACHE2: Acute Physiology and Chronic Health Evaluation II; ARDS: acute respiratory distress syndrome; BUN: blood urea nitrogen; CKD: chronic kidney disease; Cr: creatinine; CRF: chronic renal failure; CRRT: continuous renal replacement therapy; eGFR: early high volume hemofiltration; ELV: early low volume hemofiltration; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; ICU: intensive care unit; ISS: illness severity score; LTV: late low volume hemofiltration; LOS: length of stay; NIH: National Institutes of Health; NOQA: Newcastle-Ottawa Quality Assessment; NR: not reported; NS: not significant; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: randomized controlled trial; RIFLE: risk, injury, failure, loss of function, and end-stage kidney disease; RPGN: rapidly progressive glomerulonephritis; RR: relative risk; RRT: renal replacement therapy; SAPS2: Simplified Acute Physiology Score II; Sharpe: Stuivenberg Hospital Acute Renal Failure score below; SOFA: Sequential Organ Failure Assessment; sRIFLE: simple criteria for risk injury failure loss of function and end-stage kidney disease; UOP: urine output; NR: not reported.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

BTW performed the literature search, reviewed studies for inclusion, performed the pooled data analysis using CMA software, and wrote the manuscript. RLCK acted as chair for article review and inclusion, reviewed studies for inclusion, provided senior oversight during manuscript development, and was primary editor of the manuscript during revisions. SK provided oversight for the literature search with the NIH librarian, reviewed studies for inclusion, and contributed to manuscript review. SA, XB, and GWB reviewed studies for inclusion and contributed to manuscript review. All authors contributed to and also read and approved the final version of the manuscript submitted for publication.

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