How to Cite:
Obaida, Z. A., & Zahra, A. N. (2024). Outcome of early versus late CRRT in critically ill patients with acute kidney injury. *International Journal of Health Sciences*, *8*(S1), 1461–1467. https://doi.org/10.53730/ijhs.v8nS1.15288

Outcome of early versus late CRRT in critically ill patients with acute kidney injury

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***Abstract*---**AKI is a common but serious complication in acutely unwell patients and results in high morbidity and mortality. This review considers the issue of the effects of early versus late initiation of CRRT on patient outcomes. Early CRRT may be defined as inception shortly after the diagnosis of AKI has been established, especially in the case of signs related to fluid overload or severe electrolyte disturbances. Early CRRT would offer potential benefits like an improved survival rate, complications avoided as regards pulmonary edema and cardiac failure, better nutritional support, and a reduced need for more intensive renal replacement support later. On the other hand, late CRRT is performed in clinical practice when more severe AKI manifestations have occurred, which are usually associated with higher mortality and complications due to fluid overload and metabolic disturbances. Key studies referred to report worse outcomes for late initiation, considering higher multi-organ failure and prolongation of the length of stay in the ICU. Most observational studies report better outcomes with early CRRT, while randomized controlled trials exhibit variable results, with some finding no clinically significant difference in mortality between the timing of early and delayed initiation. Variability in the definition of AKI, timing of RRT, and heterogeneity in the patient population studied fuel the ongoing debate. The general impression is that early initiation of CRRT is superior to its late initiation in critically ill patients with AKI. Ideally, such patients are followed continuously by a clinician who may intervene early to maximize survival and recovery, taking into consideration the risk of subjecting the patient to unnecessary exposure to renal replacement modalities. Larger studies are still needed regarding more specific recommendations on the optimal timing of CRTT in these fragile patients.

***Keywords*---**Acute kidney injury, Early continuous renal replacement therapy, Late continuous renal replacement therapy.

Introduction

Acute kidney injury (AKI) is a common yet potentially fatal complication of illnesses among 1% of the community-based population, 8–15% of hospitalized patients, and up to 50% of critically ill patients admitted to the intensive care unit (ICU). AKI carries an increased risk of morbidity and mortality and adds to the healthcare cost, even in mild temporary form. The timing of Continuous Renal Replacement Therapy (CRRT) in critically ill patients with Acute Kidney Injury (AKI) can significantly influence outcomes. Here's an overview of the outcomes associated with early versus late initiation of CRRT[1]

Early CRRT

Definition: Early CRRT is typically initiated soon after the diagnosis of AKI, particularly when patients exhibit signs of fluid overload, severe electrolyte imbalances, or impending complications.[2]

Potential Benefits:

1. **Improved Survival Rates:** Early initiation may be associated with lower mortality rates in critically ill patients.
2. **Prevention of Complications:** It can help prevent complications related to fluid overload, such as pulmonary edema and cardiac failure.
3. **Better Nutritional Support:** Early CRRT may allow for better nutritional support, as it can help control uremic symptoms and maintain a more stable metabolic state.
4. **Reduced Need for Dialysis Later:** Early intervention may decrease the likelihood of needing more intensive renal support later.

Key Studies:

- Some studies suggest that early CRRT can lead to improved outcomes in terms of survival and recovery of kidney function, particularly in septic patients.[3]

Late CRRT

Definition: Late CRRT is initiated after the patient has developed more severe manifestations of AKI, often when complications have already occurred.[4]

Potential Risks:

1. **Increased Mortality Rates:** Delaying CRRT can be associated with higher mortality rates, particularly in severe cases of AKI.
2. **Greater Complications:** Patients may experience more complications related to fluid overload, electrolyte disturbances, and metabolic imbalances.
3. **Deterioration of Overall Condition:** Late initiation may correlate with worsening organ dysfunction and longer ICU stays.

Key Findings:

- Studies indicate that late initiation of CRRT is generally linked to poorer outcomes, including higher rates of multi-organ failure.[5]

Summary of Key Points

1. **Timing Matters:** Early CRRT is often associated with improved outcomes, while late initiation can lead to worse mortality and complications.
2. **Patient Selection:** The decision to initiate CRRT should consider the individual patient's condition, hemodynamics, and the underlying cause of AKI.
3. **Clinical Guidelines:** Current guidelines often recommend considering CRRT early in the course of AKI in critically ill patients, especially those with specific indications like severe fluid overload or metabolic derangements.

Although renal replacement therapy (RRT) remains the primary supportive management strategy for patients with severe AKI, it could also be associated with complications and adverse events. Despite improvements in RRT technology, it is still not clear whether the outcome of patients with AKI who require RRT has improved over the years. Earlier initiation of RRT may provide better control of fluid and electrolyte balance, superior acid-base homeostasis, removal of uremic waste, and prevention of subsequent complications attributable to AKI.[6]

Furthermore, earlier RRT could potentially limit kidney-specific and remote organ injuries due to fluid overload, electrolyte imbalance, and systemic inflammation. However, earlier RRT may also expose the patients to increased risks of hemodynamic instability, anticoagulation-induced bleeding, blood-stream infection, and even inflammatory or oxidative stress induced by the bio-incompatibility of the dialyzer membranes. In comparison, later initiation of RRT may allow more time for hemodynamic optimization prior to RRT, and it may avoid the need for RRT and its associated complications.[7]

In recent decades, the timing of RRT initiation has been evaluated in different population types (e.g., surgical or medical patients). Variability in the definitions of AKI and RRT timing has resulted in contradicting conclusions among the various studies. Similarly, previous systematic analyses regarding the optimal timing of RRT initiation were unable to draw definitive conclusions owing to the scarcity of large-scale randomized controlled trials (RCTs), non-standardized triggers for RRT initiation, and heterogeneities of population and study design. In summary, while the observational studies tended to show more beneficial effects for earlier RRT, clinical trials were unable to replicate these findings.[8]

Recently, two large RCTs showed contradictory results and attracted considerable attention from both clinicians and researchers. The first was a multicenter RCT by the AKIKI study group, which showed no significant differences in 60-day mortality between early and delayed RRT groups. Another was the ELAIN trial, a single-center RCT that showed significant benefits in terms of 90-day mortality, renal function recovery, and hospital length of stay (LOS) among patients in the early RRT group.[9]

Acute kidney injury (AKI) is a clinical syndrome defined as a sudden decrease in renal function. AKI occurs in up to 50% of intensive care unit (ICU) patients and is associated with prolonged ICU and hospital stay, development of chronic kidney disease (CKD), and increased short and long-term mortality. Renal

replacement therapy (RRT) initiation in critically ill patients with life-threatening complications of AKI (e.g. pulmonary edema, hyperkalemia, or refractory metabolic acidosis) is unanimously accepted. However, in the absence of clearly urgent indications, the ideal timing for initiating RRT is still uncertain.[9]

Early initiation of RRT may improve fluid and electrolyte balance, remove uremic toxins, and prevent other AKI-associated complications. However, many patients spontaneously recover from AKI with no need for RRT. Thus, a pre-emptive strategy may occasionally expose the patient unnecessarily to dialysis-related complications such as hypotension, infection, arrhythmia, or bleeding. Those patients could benefit from conventional or late initiation, where RRT is only started when a life-threatening complication emerges.[10]

Various observational studies and small-randomized controlled trials (RCTs) suggest early RRT initiation may improve survival, consistent with the ELAIN (Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury) trial's findings —a large single-center RCT focused on the topic. Other RCTs [Initiation of Dialysis Early Versus Delayed in Intensive Care Unit (IDEAL-ICU) or Artificial Kidney Initiation in Kidney Injury (AKIKI)] have failed to demonstrate significant differences in survival between early and delayed RRT initiation strategies.[11]

Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI), published in 2020, is the largest-to-date multinational RCT assessing RRT timing—it suggested that an accelerated RRT strategy is not associated with a lower risk of death at 90 days. Given the conflicting evidence available and to guide future clinical practice, the authors decided to conduct an updated meta-analysis comparing the impact on mortality, recovery of renal function (RRF), and RRT-associated complication rates of early versus late RRT initiation strategies in critically ill adult patients presenting with AKI.[12]

Finally, one must also acknowledge that despite the lack of evidence favoring early RRT initiation, protracted delays in RRT may also pose harm to critically ill patients with AKI. This was recently reinforced by the AKIKI 2 trial which compared a delayed and a more-delayed strategy for RRT initiation in this population. Patients were randomly assigned to one of the two strategies if they developed a blood urea nitrogen (BUN) concentration between 112 and 140 mg/dL (40–50 mmol/L) and/or oliguria for more than three consecutive days. In the delayed group, RRT was started within 12 h after randomization, whereas in the more delayed group, RRT was postponed until an urgent indication emerged or BUN exceeded 140 mg/dL (50 mmol/L). RRT-free days did not differ between the strategies. However, a pre-specified multivariable analysis revealed higher 60-day mortality in the more-delayed group. According to the experts' opinion, this finding is potentially related to the effects of prolonged untreated AKI, exaggerated non-renal organ dysfunction, and modified recovery from critical illness.[13]

Acute kidney injury (AKI) is a common complication in critically ill patients and is associated with substantial morbidity and mortality. Severe AKI may be associated with up to 60% hospital mortality. Over the years, renal replacement

therapy (RRT) has emerged as the mainstay of the treatment for AKI. Intermittent hemodialysis (IHD), peritoneal dialysis (PD), and continuous renal replacement therapy (CRRT) are various modalities to conduct RRT. Early initiation of RRT helps in the removal of uremic toxins, allows fluid and electrolyte balance, and prevents life-threatening complications such as metabolic encephalopathy, hyperkalemia, andpulmonary edema.[8]

The timing of initiation of RRT for better patient outcomes is still debatable with conflicting data from randomized controlled trials. Two meta-analyses concluded that early RRT improves survival in critically ill patients. However, "early" initiation of RRT in critical illness complicated by AKI does not improve patient survival or confer reductions in intensive care unit (ICU) or hospital length of stay (LOS). This meta-analysis included both RCTs and cohort studies. Moreover, after the publication of this meta-analysis, two large studies have been published. We conducted an updated systematic review including RCTs and Quasi-RCTs (no observational studies) to support or refute the earlier evidence on the initiation of early versus late RRT.[14]

Acute kidney injury (AKI) is a frequent complication in patients hospitalized in the intensive care unit (ICU) and is associated with high mortality. Renal replacement therapy (RRT) is the cornerstone of the management of AKI, although it could also be associated with complications and adverse events. There is, however, an ongoing debate concerning when to initiate it. Earlier initiation of RRT may help with fluid and electrolyte balance, removal of uremic toxins, and the prevention of complications (e.g., metabolic encephalopathy and gastric hemorrhage). However, early initiation of RRT may unnecessarily expose a subset of patients who spontaneously recover renal function to potential harm.[15]

Despite the physiologic rationale, randomized controlled trials (RCTs) examining the ideal time for initiation of renal replacement therapy for AKI remains controversial. Early initiation of RRT is not associated with lower mortality rates; however, those studies have been limited by inconsistency, imprecision, and the risk of publication bias. Since these reviews, several large RCTs on the topic have been published. Given the conflicting evidence of RCTs and the limitations of the previous meta-analyses, we conducted an updated systematic review and meta-analysis to investigate the effect on mortality of the timing of the initiation of RRT in patients with AKI.[11]

Conclusion

In summary, early CRRT is generally favorable compared to late initiation in critically ill patients with AKI. Clinicians should closely monitor these patients and consider early intervention to optimize outcomes.[9]

Declarations:

Consent for publication

Not applicable.

Availability of data and materials:
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests
The authors declare that they have no competing interests.

Funding:
None.

Author contributions:
Zaineb Abdulameer Obaida and Ahmed Najah Zahra shared the study idea, collection and analysis of data, and finalizing the results.

Acknowledgements:
Not applicable.

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