Review

# When to start renal replacement therapy in acute kidney injury: What are we waiting for?

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## ARTICLE INFO

## ABSTRACT

Acute kidney injury remains a serious condition with a high mortality risk. In the absence of any new drugs, renal replacement therapy (RRT) is the most important treatment option. Randomized controlled trials have concluded that in critically ill patients without an emergency indication for RRT, a watchful waiting strategy is safe; however, further delays in RRT did not seem to confer any benefit, rather was associated with potential harm. During this process, balancing the risks of complications due to an unnecessary intervention with the risk of not correcting a potentially life-threatening complication remains a challenge. Dynamic renal function assessment, especially dynamic assessment of renal demand-capacity matching, combined with renal biomarkers such as neutrophil gelatinase-associated lipocalin and furosemide stress test, is helpful to identify which patients and when the patients may benefit from RRT.

## Background

Acute kidney injury (AKI) is a common complication in patients admitted to the intensive care unit (ICU) and is associated with a high risk of death or major complications and a high level of resource use. Since its introduction in the ICU in the 1960s, renal replacement therapy (RRT) has proven to be a key breakthrough for the treatment of AKI, saving countless lives. However, when to initiate RRT in the absence of a potentially life-threatening complication directly related to renal failure remains a subject of debate. In particular, the Artificial Kidney Initiation for Kidney Injury (AKIKI) trial[1] and early *vs.* late initiation of RRT in critically ill patients with AKI (ELAIN)[2] study have shown that early RRT was not associated with survival benefits, rather it was associated with a greater occurrence of RRT-related complications. Several subsequent single-center, randomized control trials (RCTs), and meta-analyses have also confirmed that late RRT or the "watchful waiting" strategy is not only safe but can also reduce RRT-related complications.[1,3,4] However, further deferring might result in poor outcomes such as the occurrence of preventable complications and death. Therefore, the question remains what is the best strategy to delay RRT; in other words, what are we waiting for? This article attempts to briefly summarize the recent RRT trials regarding the "watchful waiting" strategy and provides a brief overview of how to execute it.

## Delayed RRT may Be Safe in AKI

Because RRT can rapidly correct life-threatening complications associated with AKI, such as severe hyperkalemia, metabolic acidosis, or pulmonary edema due to fluid overload, it is reasonable to hypothesize that early correction of AKI-related complications when renal function is reduced may improve the prognosis of patients with AKI if RRT is applied early.

The ELAIN study,[2] a single-center RCT published in 2016, demonstrated that early initiation of RRT in stage 2 AKI could significantly reduce the 90-day mortality and shorten RRT duration and length of hospital stay in patients with AKI after surgery (primarily cardiac surgery) compared with late initiation in stage 3 AKI. However, the concurrent AKIKI study,[1] instead of confirming an early benefit, found that delayed initiation of RRT ultimately allowed 49% of patients with severe AKI to avoid RRT, and early initiation resulted in an increased likelihood of hypophosphatemia and catheter-related bloodstream

infections. Subsequent large sample, multicenter RCT studies, including the Initiation of Dialysis Early versus Delayed in the Intensive Care Unit (IDEAL-ICU),[3] the Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI),[4] and AKIKI 2[5] also found similar results. In the delayed RRT initiation group, one-third to half of all patients with severe AKI eventually recovered their renal function spontaneously, thus avoiding RRT. Whereas in the early group, renal function recovery was delayed, although there was no significant difference in mortality. These findings suggest that for patients with severe AKI, it is safe to adopt the watchful waiting strategy which involves waiting for a conventional indication or recovery and delay the initiation of RRT as long as possible. Several recent meta-analyses have also confirmed the efficacy of this approach.[6–8] The underlying mechanism may lie in the prevalence of RRT-related side-effects.[1,3–5,9] Early initiation of RRT may better control metabolic abnormalities and other complications associated with increased mortality, such as fluid overloading. However, early application of RRT unnecessarily exposes patients to more iatrogenic complications such as hypotension, bleeding, infection, or hypothermia, with some being very severe. Biological incompatibility between patient blood and RRT membranes is another issue. Although the biocompatibility of RRT membranes has been greatly improved, studies have demonstrated that the so-called "biocompatible membranes" could lead to the formation of platelets–neutrophils microaggregates.[10] Therefore, the so-called "biocompatible membranes" are not really compatible, i.e., the RRT membrane is not an endothelium. In addition, RRT plays the role of promoting the regeneration of renal tubules.[11]

The kidneys of patients with severe AKI are more sensitive to these complications or issues, which may lead to further deterioration of renal function, called artificial kidney-induced kidney injury.[5,9] Gaudry et al.[5] further analyzed the data of the AKIKI trial and found that the urine volume of the early group was significantly lesser than that of the delayed group in the first 2 days after inclusion in the study, and this phenomenon still existed even after excluding patients who used diuretics, and the urine volume of these 2 days was independently related to the recovery of renal function. Benichou et al.[9] pointed out that the conservative treatment strategy, i.e., the delayed initiation of the RRT strategy, can reduce or avoid the occurrence of these complications, thus giving the kidney a chance to recover spontaneously. A recent meta-analysis that included 10 recent RCTs adds powerful evidence to this perspective.[8] The meta-analysis found that accelerated and standard RRT did not improve all-cause mortality and freedom from dialysis.[8] Moreover, about 90.8% (89.7% in the accelerated and 91.9% in the standard group) of survivors with severe AKI did not receive RRT because of the spontaneous recovery of their renal function.[8]

**What Do We Wait and See?**

Existing evidence shows that the longer the waiting time for delayed initiation of RRT, the higher the proportion of patients who do not need RRT. For example, the STARRT-AKI study,[4] the IDEAL-ICU study,[3] and the AKIKI[1] study delayed RRT by a mean of 25 h, 48 h, and 57 h, respectively, and the proportion of patients who eventually did not need RRT was 38.2%, 38%, and 49%, respectively.

However, it is important to note that delayed initiation may be detrimental, potentially increasing the incidence of preventable organ failure and death.[5] In the AKIKI and IDEAL-ICU studies, although patients in the delayed group who eventually did not receive RRT had the lowest mortality (37.1% and 29%, respectively), patients in the late initiation group who eventually required RRT had the highest mortality (61.8% and 58.4%, respectively). Of 41 patients in the IDEAL-ICU group who received RRT because of urgent indications, 28 died. Hence, delayed RRT initiation is not postponed indefinitely. In 2021, Gaudry et al.[5] completed a large-sample, multicenter RCT study – AKIKI 2 study – whose purpose was to verify whether the more-delay strategy of RRT initiation could lead to more RRT-free days and more benefits than the delay group in the AKIKI trial. In the AKIKI trial, indications to initiate RRT delayed were the conventional urgent indicators such as life-threatening metabolic complications or oliguria for more than 72 h or a blood urea nitrogen concentration >112 mg/dL. In AKIKI 2, the duration of oliguria was no longer an indication for RRT, and the concentration of blood urea nitrogen that mandated initiation was set to higher values.

However, although the more-delayed strategy results in fewer patients receiving RRT, it was not associated with more RRT-free days, which was the primary goal. Survival did not differ between groups, but a prespecified multivariable analysis revealed that the 60-day mortality was higher with the more-delayed strategy. These findings provide crucial information for future guidelines. It is critical to know to what extent RRT initiation can be delayed. This study provides arguments for answering this question.[5] What can we do until the new guidelines are published? In fact, during this waiting and observation period, we "wait" for the kidney function of some patients to recover spontaneously, so that RRT can be avoided. However, this kind of waiting does not mean doing nothing, rather it entails active monitoring for and resolution of pathogenic etiologies. The first is to treat the primary diseases, such as infection, heart failure, and shock. At the same time, the most important management is to optimize the hemodynamics of the kidney by implementation of a functional hemodynamic monitoring and optimization of perfusion pressure and volume. The nephroprotective measures comprise avoidance of nephrotoxic agents, close monitoring of renal function, avoidance of hyperglycemia, and avoidance of radiocontrast agents, which should be comprehensively implemented.[12]

Clinicians should not miss the optimum timing for RRT initiation owing to "waiting," which may lead to the aggravation of illness and poor outcomes in some patients.

It is true that we do not currently have reliable tools to predict the need for RRT in patients with severe AKI. Most studies on the timing of RRT initiation have used AKI severity grading to determine the early and delayed groups, and most results were consistent, in that, there was no significant difference in the impact of the two strategies on outcomes. The results suggested that AKI severity and complications are inadequate and imprecise in answering these questions, which made other studies on RRT timing urgent. Current evidence suggests that dynamic renal function, biomarkers, and machine-learning techniques can

guide decision-making tools to help with better clinical judgment.

### Dynamic assessment of renal function

Beyond urgent indications, there is currently insufficient evidence to determine which level of renal function requires RRT initiation. The recovery or deterioration of renal function is a dynamic process. Clinicians should observe and evaluate its change dynamically. If renal function continues to deteriorate progressively after treatment, it is likely that RRT should be initiated when any urgent indications appear. The new techniques for real-time online monitoring of glomerular filtration rate can monitor the changes of renal function in a timely manner and likely help to determine the timing of RRT initiation.[13]

### Assessment of kidney demand-capacity mismatch

In 2016, the Acute Dialysis Quality Initiative (ADQI) organization suggested that RRT should be initiated when the patient's demand for kidneys exceeds the capacity of the kidneys, rather than only the severity of AKI.[14] The so-called demand for the kidney is the work that needs to be performed by the kidneys, such as the regulation of water, electrolytes, acid-base balance, and removal of metabolites. When the body's demand for kidney function exceeds the ability of the kidney itself, even if the kidney's function has not reached the diagnostic criteria for severe AKI, RRT is needed to help the kidney carry out its functions such as hyperkalemia during hypercatabolism. This approach includes the assessment of severity of illness as well as AKI severity at given time points and provides a dynamic score that trends a patient's course. Clinicians can individualize treatment according to the trends in the mismatch score and identify which patients may be more or less likely to need and benefit from RRT. Clinicians may opt to initiate RRT if there is progressively increased demand and reduced kidney capacity or select the waiting approach in patients with improvement in illness severity and kidney function.

Thus far, the concept of demand-capacity and personalization of RRT initiation did not rely on the analysis of robust clinical data. Grolleau et al.[15] reported an interesting study that reflects varying degrees of kidney demand-capacity mismatch. They used data from the AKIKI[1] and IDEAL-ICU[3] to develop a multivariable logistic regression model for RRT initiation within 48 h after allocation to a delayed strategy. They then used interaction with spline terms in a Cox model to estimate treatment effects across the predicted risks of RRT initiation. They categorized patients (*n*=1107) by fifths of the risk predicted by their final model. In each fifth of risk, they compared the early *vs.* delayed strategy of RRT initiation on primary and secondary outcomes.

These results indicated that the only patients who might benefit from early RRT were those at high risk of poor prognosis but not the highest risk, known as tier four patients. Early initiation of RRT is harmful for patients who are not too severe, i.e., low-to-moderate risk patients, because they do not need RRT at all; on the other hand, early RRT may not be necessary even in particularly severe patients because the poor prognosis outweighs the potential benefit, or because early RRT may cause further damage by disrupting the weak intrinsic balance in these pa-

tients. The findings also suggest that AKI staging systems inaccurately reflect the timing of the underlying pathology.[16] The definition of the timing of late RRT needs to be refined.[5,17] Finally, it may be feasible to use risk models to decide the timing of RRT. Though the results from the risk-modeling methodology are consistent between the two trials, the results will require replication and refinement before they can be implemented in practice.[15,17] However, the risk-modeling methodology described in this article can help advance the precision medicine agenda, as it may be applicable to a wide variety of treatments in critical care.[15] It is important to reiterate that this matching assessment is also a dynamic course.

### Biomarkers

Serum creatinine and urine volume, as indicators of the diagnosis and severity of AKI, neither sensitive nor specific, and are not always representative of true kidney damage and therefore, ineffective in guiding treatment and predicting outcome in AKI patients, such as the timing of RRT initiation. Some AKI biomarkers have the theoretical potential to indicate the course of AKI, particularly the probability of persistent severe AKI and the likelihood for receipt of RRT. In 2020, the ADQI organization suggested that in combination with clinical practice, biomarker data can be used to screen patients who need RRT and select the best timing for RRT initiation.[18]

A recent meta-analysis including 13 different biomarkers and over 15,000 patients demonstrated that urine and blood neutrophil gelatinase-associated lipocalin (NGAL), serum creatinine, cystatin C, urinary interleukin-18, tissue inhibitor of metalloproteinases (TIMP)-2, and insulin-like growth factor binding protein (IGFBP)-7 showed some potential as biomarkers for prediction of RRT initiation in AKI.[19] A major limitation of biomarker studies evaluating the prediction of RRT is the fact that a gold standard for this point is missing. Two recent trials – ELAIN[2] and STARRT-AKI[4] – employed an NGAL threshold as an inclusion criterion. In the ELAIN trial, plasma NGAL >150 ng/mL, along with an AKI Kidney Disease: Improving Global Outcomes stage 2 was used as an inclusion criterion for early RRT, and AKI stage 3 was defined as delayed RRT.

NGAL was found to detect patients with progressively deteriorating AKI.[2] In the STARRT-AKI study, NGAL ≥400 ng/mL along with a two-fold increase in serum creatinine and oliguria was used to guide the early start of RRT. Other major limitations of biomarker studies were the lack of optimal cut-offs, optimal time points of the measurements, and confounding by underlying.[20]

Several other novel biomarkers were identified as promising prognostic markers in discriminating patients who benefit from RRT.

C-C motif chemokine ligand 14 (CCL-14) is a member of the chemokine family of small molecules. The RUBY study, a multicenter, international, prospective, observational study, found that CCL-14 has the ability to predict the development of persistent severe AKI (defined as stage 3 AKI for 72 h or the use of RRT or death after stage 3 AKI). The predictive ability was significantly greater than that of other biomarkers associated with AKI including urinary kidney injury molecule (KIM)-1, plasma cystatin C, and urinary NGAL.[21] Higher CCL-14 concentrations were also associated with an increased risk of the composite end-

point of RRT initiation or death within 90 days.[18] This ability was externally confirmed by Bagshaw et al.[22] using data from the SAPPHIRE study.

The soluble urokinase-type plasminogen activator receptor (suPAR) is a signaling glycoprotein with pleiotropic biological effects. Nusshag et al.[23] showed in a recently published study that the suPAR, together with the TIMP-2 and IGFBP-7, had the diagnostic ability to predict septic AKI requiring RRT. However, despite their higher nominal area under curve (AUC), no statistical improvement was seen compared with other surrogate parameters of glomerular filtration rate. However, the combination of suPAR and CysC resulted in a significantly improved diagnostic performance compared with standard urinary parameters and showed a trend toward superior performance compared with serum creatinine, CysC, and Sequential Organ Failure Assessment score.[23] Another very important problem in evaluating the further usefulness of biomarkers is the time points of the evaluation. suPAR was identified as a stable marker for predicting disease severity and the risk of death in ICU patients.[24] Nusshag et al.[23] also found that in contrast to [TIMP-2] × [IGFBP-7], baseline suPAR values could predict the future need for RRT with promising diagnostic accuracy. The highest suPAR concentrations were found in those septic patients who developed AKI and required RRT throughout the observation period.[25] The optimal suPAR cut-off value for predicting the need for RRT was 10.422 ng/mL with an AUC of 0.801 (sensitivity: 0.889; specificity: 0.636).[25]

### Furosemide stress test (FST)

The FST is a quick and easy method for the assessment of glomerular filtration and tubular damage.

Because of its low cost and availability, FST is often considered a functional test revealing the loss of tubular functional capacity or the severity of AKI. FST is usually performed by administering furosemide intravenously (1 mg/kg in furosemide-naive patients or 1.5 mg/kg in previous furosemide users), and a urine output of <200 mL in 2 h is defined as FST non-responsiveness.[26,27] The FST trial showed that 86% of patients who responded to FST could avoid RRT, while 75% of patients who did not respond eventually needed RRT.[26] Koyner et al.[27] compared the FST with eight of the most widely investigated AKI biomarkers and found that FST outperformed all other conventional AKI biomarkers in predicting the receipt of RRT and inpatient death. FST when combined with other biomarkers could improve the predictive ability only in those patients with increased biomarker levels (urinary NGAL >150 ng/mL, urinary TIMP-2 × IGFBP-7 >0.3).[27]

Of note, there were some differences between this FST study[27] and other studies in biomarkers,[25–27] which may explain the discrepancy in biochemical biomarker performance. In Koyner et al.'s study,[27] biomarkers were often measured 6–12 h after clinical evidence of AKI was determined, which means that at that time several patients had already progressed to stage 2. While the analyses from the Translational Research Investigating Biomarker Endpoints AKI,[28] SAKInet,[29] and Kashani[29] cohorts all excluded patients with stage 2 AKI at the time of biomarker measurement. Thus, it is not surprising that injury or structural biomarkers did not perform well in this FST protocol,[27] because the kinetics of these biomarkers are not suited for detection at the delayed stage in this established AKI population. In 2020, Chen et al.[30] conducted a meta-analysis evaluating FST as a predictive marker of AKI progression or RRT. Their meta-analysis showed that FST is a simple tool for the identification of AKI populations at high risk of RRT (the pooled sensitivity and specificity results of FST for RRT prediction were both 0.84, and the pooled diagnostic odds ratio [DOR] was 13.59) and was better in stages 1 and 2 AKI than stage 3 AKI. As a screen tool, FST can be easily conducted to discriminate between patients who can and cannot benefit from RRT and provide investigators and clinicians with resources and financial efficiency.[30]

Although the accuracy of these biomarkers in determining the timing of RRT is uncertain, it is believed that future studies will provide more evidence and answers to guide the initiation of RRT by using these biomarkers.

### Subgroups

The negative results of the primary endpoints of the existing studies may be masked by the high heterogeneity of disease progression, which cannot be accurately predicted by the stage of AKI at enrollment. Meta-analyses by Chen et al.[7] and Pan et al.[8] showed that only patients with AKI after surgery or patients with continuous RRT could benefit from early initiation. This may be because of the low degree of heterogeneity among the two groups. Pan et al.[8] further tried to explore the clinical impact of some other potential factors such as different study settings, disease severities, diabetic percentage, and dialysis discrepancy time <24 h. In their subgroup analyses, they found no survival differences between accelerated *vs.* standard RRT initiation after multivariate adjustment, as did sepsis.[8,31] Therefore, subgroups based on clinical phenotypes should not be used to decide RRT initiation. Of note, these results suggest that the use of subgroups alone to guide the timing of RRT initiation is still a type of group treatment and not accurate in the era of modern personalized medicine.

### Machine-learning techniques

Over the last few years, several groups have reported both electronic health record-based and non-electronic health record-based risk algorithms that can predict AKI and the need for RRT earlier than serum creatinine.[32–35] Saly et al.[34] used data from a previous randomized trial of AKI alerts (*n*=2241) to develop a time-updated prognostic model by using stepwise regression compared with other more advanced variable selection techniques (random forest model). These models predicted RRT with AUCs ranging from 0.82 to 0.89 and inpatient mortality from 0.80 to 0.90. Koyner et al.[35] developed a machine-learning risk assessment tool for the prediction of AKI across several hospital locations, including the emergency department, wards, and ICU. Their algorithm, which includes patient demographics, vitals, and laboratories as well as clinical interventions and diagnostics, can be used to identify patients at high risk for developing severe AKI or requiring RRT a median of 41 h earlier than using serum creatinine alone. Real-time implementation of such risk tools allows for better differentiation of patients headed toward severe AKI regardless of their baseline renal function and requires no additional AKI biomarker testing. In the future, these

research results need to be validated by more well-designed studies.[36]

## Conclusions

Early initiation of RRT may not only fail to bring survival benefits but also increase some RRT-associated adverse outcomes, especially aggravating or delaying the recovery of renal function, and even increasing the risk of death. It is safe to apply a delayed approach under the "watchful waiting" strategy (in the absence of life-threatening conditions such as severe hyperkalemia or pulmonary edema) during severe AKI, during which time clinicians "wait" for the kidney to recover or "wait" for the best time to start RRT in case it is too late. During this waiting process, dynamic renal function assessment, especially demand-ability matching of renal function, in conjunction with kidney injury biomarkers, especially NGAL and FST, can help identify which patients are likely to benefit from initiating RRT and when. Other methods such as machine-learning techniques can help identify the optimum RRT initiation time.

## Author Contributions

**Lixia Liu** had the idea for and designed the study, conducted a search of the scientific literature, and drafted as well as critically revised the report. **Zhenjie H**u had the idea for and designed the study, critically revised the report, supervised the study, and provided administrative, technical, and material support.

## Ethics Statement

Not applicable.

## Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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