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Comparison between Watchful Waiting Strategy and Early Initiation of Renal Replacement Therapy in The Critically Ill Acute Kidney Injury

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Abstract
Background: The timing of "renal replacement therapy" (RRT) in patients with "acute kidney injury" (AKI) has been greatly debated among nephrologists. Some prefer the initial regimen; rapidly correct metabolic disturbances and fluid overload, while others prefer the delayed approach to avoid possible RRT complications.
Objective: To compare the outcomes of early versus delayed RRT in intensive care unit (ICU) patients diagnosed with stage 3 AKI.
Patients and methods: In this prospective study, 104 ICU patients with stage 3 AKI diagnoses were enrolled and then randomly assigned to two groups; Group A included patients who received RRT within 24 hours of AKI diagnosis, and Group B included other patients who had RRT after 24 hours.
Results: Sepsis/septic shock was the most common etiology of AKI in both groups. Other causes included major surgery, hypovolemic/hemorrhagic shock, and cardiogenic shock. The two groups showed comparable needs for vasopressor support and mechanical ventilation. Nonetheless, the duration of RRT, mechanical ventilation, ICU stay, and hospitalization decreased significantly in the early group. In-hospital mortality increased significantly with the delayed approach (65.38% vs. 42.3% in the early group) ($p = 0.034$). Discharge creatinine in the survived cases was lower in the early group (2.01 vs. 2.77 in delayed cases – $p < 0.001$).
Conclusion: Early RRT is associated with better outcomes compared to the delayed one in patients with stage 3 AKI. Therefore, early RRT is recommended in such cases to improve patient outcomes.
Keywords: Acute kidney injury; Renal replacement therapy; Early vs. delayed.

INTRODUCTION

In intensive care units (ICUs) around the world, "Acute kidney injury" (AKI) is a commonly encountered medical problem that may occur in 20 – 70% of the admitted patients. Not only does it yield longer hospitalization periods and more financial costs, but it also carries a high mortality risk [1].

Some AKI patients may require "renal replacement therapy" (RRT) when they develop life-threatening complications like hyperkalemia, pulmonary edema, or marked acid-base disturbance. However, RRT may be commenced for some AKI before the development of these serious complications [2].

There is a great debate among nephrologists and ICU physicians regarding the timing of RRT. With no clear consensus published, the timing of RRT is widely variable in the literature, which differs according to institutional treatment protocols, resource settings, and empiricism [3].

Some studies have recommended early AKI in such cases, even if there is a mild rise in serum creatinine. That opinion is supported by the significant beneficial impact of RRT on patient outcomes. Early RRT enables the physician to control acid-base imbalance, electrolyte disorders, and fluid overload more rapidly and properly. However, when the early strategy is implemented, the patient may develop RRT-related adverse events (like hemodynamic instability, infection, and access-related complications) [4].

With the lack of international and Egyptian studies evaluating the potential benefits of early RRT in ICU patients diagnosed with AKI, the goal of the current study was to compare the effects of early versus late RRT on AKI outcomes in patients who were critically ill.

PATIENTS AND METHODS

This prospective randomized trial was created for ICU patients who suffered from AKI while they were being admitted to Benha University Hospitals and the National Institute of Urology and Nephrology. The study was carried out from April 2023 to September 2023 over six months. The needed sample size was determined using the "G power" program (version 3.1.9.7) with a type II error of 0.2 and a significance threshold of 0.05. For each research group, a minimum sample size of 52 patients was necessary (total patients = 104).

We included adult patients who were admitted to either of the previous hospitals' ICUs during the previously mentioned period and developed AKI stage 3, based on the "Acute Kidney Injury Network" (AKIN) classification [5]. We excluded patients who had stage 1 or 2, developed AKI on to pre-existing chronic kidney disease, had less than one-day ICU stay, and had urgent indications for RRT (like pH< 7.2, pulmonary edema, and refractory hyperkalemia).

All patients were adequately assessed via detailed history-taking and clinical examination. Laboratory assessment focused on renal function tests, arterial blood gas (ABG) analysis, serum electrolytes, and urinalysis. Moreover, the following scores were

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assessed for all patients on ICU admission: the "Glasgow Coma Scale" (GCS) [6], "Acute Physiology and Chronic Health Evaluation II" (APACHE II) score [7], and "Simplified Acute Physiology Score III" (SAPS III) [8].

One hundred four patients were enrolled, and the "closed envelop method" was used to divide them into two groups. Group A (n = 52) included patients who had RRT within 24 hours after AKI diagnosis, while Group B (n = 52) included the remaining patients who had RRT after 24 hours. RRT was performed using the "Fresenius Medical Care 4008s" machine with a micro-undulated filter.

"Conventional intermittent hemodialysis" was performed for most patients except for patients requiring vasopressor drugs, who received "sustained low-efficiency dialysis" (SLED) or "continuous venovenous hemodialysis" (CVVHD). The conventional technique was performed over four hours with a 300-ml/minute blood flow rate and a 600-ml/minute dialysate flow rate. The previous two flow rates were 200 and 300 ml/minute, respectively, for the SLED, which was performed over six hours. Regarding the CVVHD, blood flow was kept at 150 – 300 ml/minute, whereas the dialysate flow rate was 1500 ml/minute. Some patients received different RRT modalities according to their hemodynamic profile during their ICU stay.

After stabilization of their general condition and discontinuation of RRT, the patients were transferred to the internal ward, and serum creatinine was monitored. The last reading before discharge was recorded in both groups.

Study outcomes:

The main outcome of the present study was the in-hospital mortality rate, whereas other outcomes included the need for mechanical ventilation and its duration, the length of ICU and hospital stays, the duration of RRT, and discharge creatinine levels.

Ethical considerations:

The study was done after being accepted by the Research Ethics Committee, Benha University (Approval code: MS 25-4-2023). All patients (or their first-degree relatives) provided written informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy, and the explanation of the benefits of each therapeutic modality. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Using the SPSS program (version 26 for Windows), the parameters that were gathered were analyzed between the two groups. Qualitative data were presented as frequency and percentage. Quantitative data were presented as mean ± standard deviation (SD), or as median and interquartile range (IQR). We applied either of the three statistical tests: Chi-square, Student-t, or Mann-Whitney tests (to compare percentages, means, and medians, respectively). Any obtained p-value less than 0.05 was considered statistically significant.

RESULTS

There was no discernible difference between the two research groups regarding age, gender, BMI, and comorbidities (Table 1).

Table (1): Basic demographic data of the studied patients.

	Group A (n = 52)	**Group B (n = 52)**	**P-value**
Age (years)	49.40 ± 12.54	50.60 ± 12.42	0.627
Gender			
-Male	38 (73.08%)	35 (67.31%)	0.520
-Female	14 (26.92%)	17 (32.69%)	
BMI (kg/m^2)	27.87 ± 4.47	28.15 ± 4.59	0.758
Comorbidities			
-Hypertension	33 (63.46%)	35 (67.31%)	0.680
-Diabetes mellitus	28 (53.85%)	25 (48.08%)	0.556
-Ischemic heart disease	8 (15.38%)	8 (15.38%)	1
-Heart failure	7 (13.46%)	5 (9.62%)	0.539
-Chronic liver disease	3 (5.77%)	2 (3.85%)	0.647

BMI: body mass index, data are presented as mean ± SD or as frequency (Percentage).

Regarding the contributing factors of AKI, sepsis/septic shock were the most common etiologies (Table 2).

Table (2): Etiology of AKI in the studied groups.

	Group A (n = 52)	Group B (n = 52)	P-value
Contributing factors for AKI			
-Sepsis/septic shock	29 (55.77%)	31 (59.62%)	
-Major surgery	10 (19.23%)	11 (21.15%)	
-Hypovolemic/hemorrhagic shock	10 (19.23%)	8 (15.38%)	0.911
-Cardiogenic shock	3 (5.77%)	2 (3.85%)	

AKI: acute kidney injury, Data are presented as frequency (Percentage)

The next table (Table 3) displays the patient's vital signs at the time of admission; there was no discernible difference between the two groups.

Table (3): Vital signs of patients on admission.

	Group A (n = 52)	Group B (n = 52)	P-value
Systolic blood pressure (mmHg)	84.81 ± 8.69	85.29 ± 6.96	0.756
Diastolic blood pressure (mmHg)	55.96 ± 9.13	55.48 ± 6.59	0.759
Heart rate (bpm)	114.35 ± 14.18	116.60 ± 12.78	0.397
Temperature (°C)	37.78 ± 0.88	37.73 ± 0.79	0.726

Bpm: beat per minute, Data are presented as mean ± SD.

Table (4) illustrates pre-RRT laboratory values in the two study groups, which were statistically comparable between the two groups.

Table (4): Laboratory criteria of the studied groups on admission.

	Group A (n = 52)	Group B (n = 52)	P-value
Hemoglobin (gm/dl)	10.02 ± 1.31	9.95 ± 1.43	0.797
Leukocytic count (× 109/L)	13.15 (4.2 – 22.7)	13.95 (4.7 – 21.8)	0.792
Platelets (x103/ml)	178 (82 – 299)	172 (80 – 299)	0.594
Urea (mg/dl)	147.13 ± 29.06	145.40 ± 28.15	0.758
Creatinine (mg/dl)	4.44 ± 0.86	4.57 ± 0.97	0.490
Potassium (mEq/L)	4.43 ± 0.64	4.41 ± 0.53	0.855
pH	7.29 ± 0.03	7.30 ± 0.03	0.158
HCO_3^- (mEq/L)	19.92 ± 2.74	20.84 ± 2.20	0.164

Data are presented as mean ± SD or as median (Interquartile range).

There were no discernible variations between the two groups' pre-RRT severity scores (Table 5).

Table (5): Severity scores of the studied groups.

	Group A (n = 52)	Group B (n = 52)	P-value
GCS	11 (7 – 14)	11 (7 – 14)	0.791
APACHE II	28 (18 – 36)	25 (18 – 36)	0.247
SPAS III	70 (59 – 85)	73 (60 – 85)	0.241

Data are presented as median (Interquartile range), GCS: Glasgow Coma Scale, APACHE II: Acute Physiology and Chronic Health Evaluation II, SAPS III: Simplified Acute Physiology Score III.

In Groups A and B regarding mechanical ventilation, there was no discernible difference between the two groups. Other outcomes showed a significant improvement in Group A (early RTT) compared to Group B. The duration of RRT, mechanical ventilation, ICU stay, and hospitalization decreased significantly in the former group. Additionally, a significant decline in mortality rate was noted in the same group. In the survived cases, discharge creatine levels had significantly lower values in Group A than in Group B (Table 6).

Table (6): Study outcomes of the studied groups.

	Group A (n = 52)	Group B (n = 52)	P-value
Need for mechanical ventilation	42 (80.77%)	43 (82.69%)	0.800
Need for vasopressors	47 (90.38%)	45 (86.54%)	0.539
Duration of mechanical ventilation (days)	4 (1 – 7)	6 (2 – 12)	0.001 *
Duration of ICU stay (days)	16 (8 – 30)	26 (15 – 40)	< 0.001*
Duration of hospitalization (days)	22 (14 – 35)	30 (18 – 45)	< 0.001*
Time on RRT (days)	6 (3 – 9)	8 (4 – 15)	< 0.001*
Mortality	22 (42.3%)	34 (65.38%)	0.034 *
Discharge creatinine (mg/dl)	2.01 ± 0.27	2.77 ± 0.41	< 0.001*

Data are presented as frequency (Percentage), as median (Interquartile range), or as mean ± SD, ICU: intensive care unit, RRT: Renal Replacement Therapy, *: Significant.

DISCUSSION

The purpose of the current study was to assess the impact of RRT timing on AKI outcomes in patients who were critically ill and admitted to the ICU. The timing of RRT initiation differed among previous studies. Some authors used serum urea [9], while others used the time elapsed since ICU admission [10] to define early versus late RRT. Additional research defined early versus late RRT based on the AKI stage [11].

In our study, we defined early versus late RRT based on the time of diagnosis (early = intervention within 24 hours of AKI diagnosis, and late = after 24 hours of diagnosis). Additionally, we included a homogenous patient population who were diagnosed with stage 3 according to the AKIN classification, and we did not start RRT until the patients had reached that stage.

We restricted our inclusion criteria to AKI patients who had stage 3, as we believe that is more practical, according to our center protocol. Patients with AKI do not necessarily need RRT or progress to stage 3. Nonetheless, most patients with stage 3 will require RRT. The reader should notice that most of our pre-RRT parameters expressed no significant difference between the two groups. That should decrease the bias risk. Additionally, it indicates our proper randomization technique. All of the previously mentioned points are in favor of our research. Our patients' mean ages were 49.4 and 50.6 years in Groups A and B, respectively, and that is near to the reported ages in the study conducted by **Elhawy *et al.*** (54.6 years in the early group and 56.2 years in the late group) [12]. However, **Gaudry *et al.*** reported older ages (64.8 and 67.4 years in the early and delayed groups, respectively) [13].

We noticed an increased male gender prevalence in both study groups, and that is similar to **Combes *et al.***, who reported that men represented 79% of early cases and 80% of late cases [14].

Multiple factors could explain the association between male gender and AKI, including higher prevalence of risk factors (like hypertension, cardiovascular disease, and diabetes) [15], occupational and lifestyle factors (smoking, alcoholism, and occupation exposure to nephrotoxic agents) [16,17], and hormonal differences (estrogen has protective effects on the kidneys) [18].

Our findings revealed elevated serum creatinine in both study groups, and that is in accordance with previous reports, which confirmed the rise of that parameter in association with AKI, as the kidney is unable to excrete it after its formation from the metabolism of creatine [19].

We noticed a significant rise in serum urea in both study groups, and that could be explained by the insufficiency of the diseased kidneys to excrete urea (resulting from the hepatic breakdown of proteins) [20].

Our findings revealed that the mean serum potassium levels were within the normal reference range. **Gaudry and his colleagues** reported that serum potassium had mean values of 4.4 ± 0.7 and 4.4 ± 0.7 mg/dl in the early and delayed groups, respectively [13]. In AKI, serum potassium levels can fluctuate. Although potassium levels can rise in certain situations, increasing serum potassium in AKI is not necessarily usual. The underlying cause of AKI, the severity of renal injury, and the efficiency of compensatory mechanisms can affect changes in serum potassium levels [21].

Our pH findings revealed a tendency towards acidosis in both groups. Several factors could explain the previous findings, including impaired acid excretion, retention of waste products with acidic properties like creatinine, loss of urinary buffering capacity, decreased bicarbonate absorption, and lactic acidosis [22]. The previous facts could explain the incidence of metabolic acidosis in AKI and

consequently explain the decline in serum bicarbonate levels encountered in our study.

In the current study, vasopressor therapy was required for 90.38% of Group A and 86.54% of Group B. Another study reported that vasopressor therapy was needed in 68.8% and 72% of cases in the early and delayed groups, respectively [22]. The need for vasopressor therapy in AKI patients could be attributed to the presence of hypotension, septic shock (as a cause of AKI), or support during RRT [23].

In our study, mechanical ventilation was needed for most patients in both study groups. Other authors reported the same need in 75.3% and 78.5% of their early and late cases, respectively [22]. The need for mechanical ventilation in such cases could be explained by several factors, including pulmonary edema, acid-base disturbances, and associated organ dysfunction [24].

Our findings revealed a significant decline in the duration of mechanical ventilation in the early group. In line with our findings, **Elhawy *et al.*** found that early RRT was linked to a reduction in the length of mechanical ventilation; the early group's mean value was 12.8 ± 9.4 days, whereas the delayed group's mean value was 18.9 ± 9.4 days (p = 0.031) [12].

We noted a significant shortening in the duration of ICU stay in association with the early approach. **Wald *et al.*** reported similar findings [25]. Although **Elhawy and his colleagues** reported more prolonged ICU stay in association with the delayed approach (25.4 ± 10.9 vs. 19.4 ± 11.5 days in the early group), that difference turned out to be insignificant in the statistical analysis (p = 0.092) [12].

The early strategy in the current trial was linked to a notable reduction in the length of hospital stay, and that coincides with **Gaudry *et al.***, who reported that RRT was associated with a shorter hospitalization period compared to the delayed approach (29.6 vs. 32.7 days, respectively) [3].

Our results showed that the early group's RRT duration significantly decreased. **Elhawy *et al.*** agreed with our findings, as the duration of RRT showed a significant shortening in the early group (6.7 ± 4.9 vs. 9.7 ± 6.1 days in the delayed group – p = 0.41) [12].

Contrarily, **Combes and his associates** reported a significant prolongation in RRT in association with the early approach (median = five vs. two days in the delayed group – p < 0.001) [14]. The results of the previous study do not support delaying the start of dialysis treatment until a potentially fatal uremic complication has occurred; patients who require dialysis can be identified early through careful clinical and laboratory surveillance [26].

Our findings revealed a significant decline in serum creatinine on discharge of the survived cases, and that decline was more evident in Group A (2.01 vs. 2.77 mg/dl in Group B). **Barbar *et al.*** reported that the mean level of creatinine at discharge was 1.46 in the early group, which was lower than the delayed group (1.61 mg/dl) [27].

According to our research, the early RRT strategy was associated with a noteworthy decrease in the in-hospital mortality rate (42.3% vs. 65.38% in the delayed group – p = 0.034). Our incidence of mortality lies within the reported range of mortality for AKI, which ranges between 20% and 60% in the current literature [28,29].

In agreement with our findings, another study reported a significant increase in mortality rate in association with the delayed approach (81.7% vs. 51.2% in the early group – p = 0.002) [12]. Furthermore, **Shiao *et al.*** found that the mortality rate for early dialysis was 43.1%, considerably lower than that of the delayed group (74.5%) (p = 0.002) [11].

On the other hand, **Gaudry *et al.*** did not detect any significant difference between early and delayed RRT regarding 28-day mortality, which was 41.6% and 43.5% in the previous groups, respectively (p = 0.79) [13]. In addition, **Combes and his associates** reported the same one-month mortality rate in both early and delayed groups, which was 36% [14]. Differences in patient comorbidities, etiology of AKI, and level of care between nephrological centers could explain the heterogenicity among studies regarding mortality rates.

Although our study handled a unique nephrological perspective, it has some limitations. It included a relatively small sample size. We should have also assessed how the timing of RRT affected the incidence of chronic renal disease. The forthcoming research should adequately address the earlier shortcomings.

CONCLUSION

Early RRT is associated with better outcomes compared to the delayed one in patients with stage 3 AKI. That was manifested in the decreased duration of dialysis, mechanical ventilation, ICU stay, and hospital stay, in addition to the better survival rate and improvement of kidney function.

Conflicts of interest: Nil.
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