Original Article

Comparison of early and delayed strategy for renal replacement therapy initiation for severe acute kidney injury with heart failure: a retrospective comparative cohort study

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Background: Determining the timing of renal replacement therapy (RRT) in patients with acute kidney injury (AKI) and heart failure (HF) can optimize the clinical management strategy. We compared the impact of "early" and "delayed" timing of RRT on the prognosis of patients with AKI and HF.

Methods: Clinical data from September 2012 to September 2022 were retrospectively analyzed. Patients with AKI complicated by HF and undergoing RRT in the intensive care unit (ICU) were enrolled. Patients with stage 3 AKI and fluid overload present (FOP) or who met the emergency indications for RRT were assigned to the delayed RRT group. Patients with stage 1 AKI or stage 2 AKI and without urgent indications for RRT and patients with stage 3 AKI without FOP and without urgent indications for RRT were enrolled in the Early RRT group. At 90-day follow-up after initiation of RRT, the mortality was compared between the two groups. Logistic regression analysis was performed to adjust for confounding factors affecting 90-day mortality.

Results: A total of 151 patients were enrolled, including 77 in the early RRT group and 74 in the delayed RRT group. For baseline characteristics, patients in the early RRT group had significantly lower acute physiology and chronic health evaluation-II (APACHE-II) score, sequential organ failure assessment (SOFA), serum creatinine (Scr) values and blood urea nitrogen (BUN) values on the day of ICU admission than those in the delayed RRT group (both P values <0.05), there were no significant differences in other baseline characteristics. The number of RRT-free days in the ICU was significantly longer in the early RRT group than in the delayed RRT group [1.69 (0.35–10.87) *vs.* 0.88 (0.20–4.55) days; P=0.046]. However, clinical outcomes (except for the number of RRT-free days) and complications showed no significant differences between these 2 groups (all P values >0.05). Multivariate binary logistic regression analysis showed early initiation of RRT was not an independent risk factor for increased 90-day mortality [odds ratio (OR): 0.671; 95% confidence interval (CI): 0.314–1.434; P=0.303].

Conclusions: Early initiation of RRT is not recommended to reduce mortality in AKI patients with HF.

Keywords: Acute kidney injury (AKI); heart failure (HF); fluid overload present (FOP); initiation of renal replacement therapy (RRT); timing of renal replacement therapy

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Introduction

Acute kidney injury (AKI) affects about 30% to 60% of critically ill patients and may eventually become chronic kidney disease (CKD) in some patients, increasing the mortality (1). In addition to treating the primary disease and optimizing the hemodynamics, renal replacement therapy (RRT) is also an effective strategy that has increasingly been adopted in clinical settings (2,3).

Clinical prediction models show that age, respiratory rate, mean arterial pressure, and severity score are all related to the clinical prognosis of patients undergoing RRT (4). The timing of RRT also deserves clinical attention. Early initiation of RRT will increase the cost of hospitalization and the risk of complications, and too late initiation will lead to delayed treatment. RRT should be started immediately when patients have a range of emergency indications, such as severe acidosis, electrolyte abnormalities, and fluid overload (FO) (5). However, when such emergency indications do not exist, whether and when RRT can be initiated in AKI patients remains controversial (6). Several recent randomized controlled trials on the timing of RRT initiation have yielded varying conclusions (7-11). While the ELAIN (7) study suggested that early initiation (within 8 hours of stage 2 AKI) of RRT could lower the mortality, other studies, including AKIKI (8), IDEAL-ICU (9), and STARRT-AKI (10), argued that early initiation of RRT did not improve long-term mortality. In addition, the latest AKIKI2 (11) study suggested that more delayed RRT is an independent risk factor for 60-day mortality in stage 3 AKI patients with persistent oliguria for more than 72 hours or blood ureanitrogen concentration (BUN) higher than 112 mg/dL. and the more delayed RRT was defined as the initiation of RRT was postponed until mandatory indication (noticeable hyperkalaemia or metabolic acidosis or pulmonary oedema) or until BUN concentration reached 140 mg/dL. In these studies (7-11), the "early" and "delayed" initiation of RRT was often defined according to the severity of AKI and/or the time from patient enrollment to the initiation of RRT. Different studies have different definitions of "early" and "delayed" initiation of RRT. For example, the criteria for "early" initiation in the IDEAL-ICU study were almost identical to the criteria for "delayed" initiation in the ELAIN study (within 12 hours of stage 3 AKI), and the different grouping criteria affected the assessment of prognosis.

Meanwhile, AKI is divided into many subphenotypes (12), and AKI with heart failure as one of the subphenotypes is more likely to experience FO (13), and delayed RRT in AKI patients with FO has been shown to increase mortality (14). Subgroup analysis of previous studies (7-11) did not investigate whether patients with heart failure complicated with AKI could benefit from early RRT. Our study combined AKI stage and the severity of heart failure to define the "early" and "delayed" initiation of RRT, and explored the relationship between the timing of RRT initiation and clinical prognosis in this subphenotype, the main objective was to provide evidence for clinical optimization of the timing of RRT initiation in AKI patients with HF. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-146/rc).

Highlight box

Key findings

- Early RRT cannot reduce mortality in patients with AKI and heart failure (HF).

What is known and what is new?

- More delayed RRT was associated with worse clinical outcomes.It is unclear whether HF patients can benefit from early RRT.
- Early RRT can increase the RRT-free days in the ICU in patients with AKI and HF.

What is the implication, and what should change now?

- Multicenter randomized controlled studies are needed to further investigate the timing of RRT in patients with HF.

Methods

Study design and data sources

In this single-center, retrospective cohort study, critically ill patients treated in the intensive care unit (ICU) of the Fourth Hospital of Hebei Medical University from September 2012 to September 2022 were enrolled. All data were retrieved from the clinical electronic medical record system of the center. Patients were followed up via telephone or electronic medical records; the maximum follow-up period was 90 days after RRT initiation. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the Fourth Hospital of Hebei Medical University (No. 2021KS042). Individual consent for this retrospective analysis was waived.

Table 1 Criteria for the classification of AKI (16)

Stage	Serum creatinine	Urine output
1	1.5 to 1.9 times baseline or ≥26.5 μmol/L increase	<0.5 mL/kg/h for 6–12 h
2	2.0 to 2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline or increase to ≥353.6 μmol/L or decreased eGFR to <35 mL/minute/1.73 m^2 in patients who started RRT or were younger than 18 years old	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy.

Inclusion and exclusion criteria

The inclusion criteria were as follows: patients diagnosed with AKI complicated by HF and who underwent RRT after admission to the ICU. The diagnosis of AKI was based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (15,16). AKI was diagnosed if patients had the following conditions: (I) serum creatinine (Scr) increased to ≥26.5 μmol/L within 48 hours; (II) Scr increased to ≥1.5 times the baseline value within one week; and (III) urine output was <0.5 mL/kg/h for >6 hours. The clinical stages of AKI were also based on the KDIGO guidelines (*Table 1*). If the baseline Scr value was not available, the estimated glomerular filtration rate (eGFR; 75 mL/min/1.73 m^2 by back calculation) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) equation (17). The formulas were as follows: eGFR (mL/min/1.73 m^2) = 186 × Scr – 1.154 × [age (years)] – 0.203 (for females) × 0.742 × 1.233 (for Chinese); and %FO = (total fluid intake – total fluid output) (L)/baseline body weight (kg) × 100% (18). The exclusion criteria were: aged <18 years; ICU length of stay (LoS) ≤24 hours; having received RRT within 1 week before admission to the ICU; with stage 4 or 5 CKD; with a previous history of kidney transplantation and/or nephrectomy; with AKI due to retrorenal obstruction; and lack of clinical data and/or loss of follow-up (*Figure 1*).

Variables and definitions

Patients with stage 3 AKI and fluid overload present (FOP) and/or meeting the emergency indications for RRT were assigned to the delayed RRT group, patients with stage 1 AKI or stage 2 AKI and without urgent indications for RRT and patients with stage 3 AKI without FOP and without urgent indications for RRT were enrolled in the Early RRT group. FOP is defined as the presence of pitting edema and/or positive fluid equilibrium with oxygenation index which is defined as arterial partial pressure of oxygen divided by the fraction of inspired oxygen [PaO_2/FiO_2 (P/F)] <200 mmHg (19). The diagnostic criteria for HF were based on left ventricular ejection fraction (LVEF) (20): LVEF ≤40% or LVEF >40% along with the evidence of elevated left ventricular (LV) filling pressure (e.g., elevated natriuretic peptide and noninvasive/invasive hemodynamic measurements). The emergency indications for RRT (13) included severe azotemia, refractory pulmonary edema with diuretic resistance, refractory hyperkalemia (potassium >6.5 mmol/L or rapidly elevated or with arrhythmias), and refractory metabolic acidosis (pH <7.2).

Study variables were: (I) general information on gender, age, body mass index (BMI), Acute Physiology And Chronic Health Evaluation-II (APACHE-II) score, Sequential Organ Failure Assessment (SOFA) score, diagnosis before admission to the ICU, and underlying diseases; (II) timing information, including the time of admission and discharge, transfer to/out of ICU, start and end of invasive mechanical ventilation (MV), and start and end of vasoactive drug use; (III) information on the first day of ICU admission and the day of RRT, including levels of organ support (invasive MV, use of vasopressors, use of inotropes, and mechanical circulation support); laboratory tests (blood routine tests, liver and renal function tests, blood gas analysis, troponin, myoglobin, etc.); and edema, cardiac output, fluid balance, and urine output; and (IV) clinical outcomes, including RRT-related complications, improvement of the disease conditions, deaths in the ICU, deaths within 28 days after RRT initiation, and deaths within 90 days after RRT initiation. Variables containing missing values of ≥10% were removed. If the missing values accounted for <10%, the medians or means were estimated to fill in the missing data.

Research outcomes

The primary outcomes were: (I) deaths in the ICU, deaths

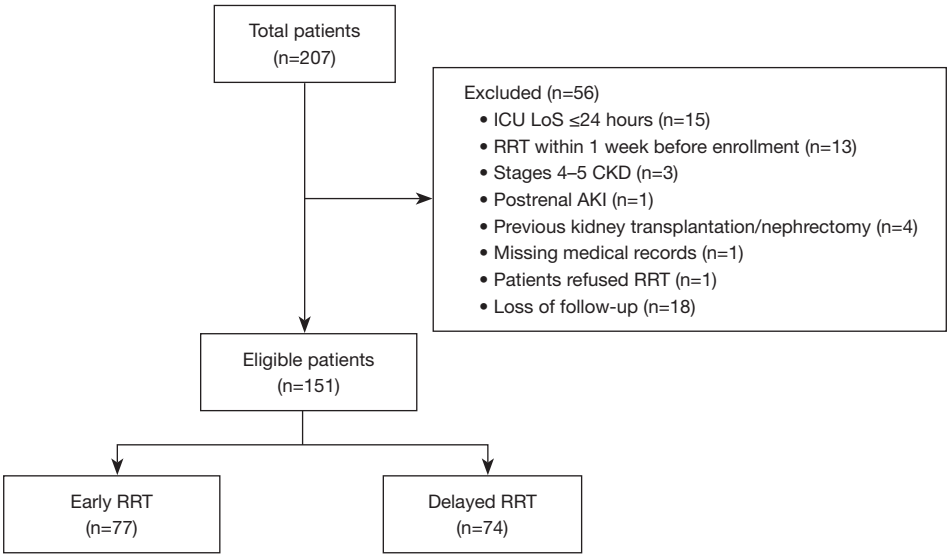

Figure 1 Flowchart of the total population. ICU, intensive care unit; LoS, length of stay; RRT, renal replacement therapy; CKD, chronic kidney disease; AKI, acute kidney injury.

within 28 days after RRT initiation, and deaths within 90 days after RRT initiation; and (II) total ICU expenditure, MV-free days in the ICU, RRT-free days in the ICU, and vasopressor/inotrope-free days in the ICU.

The secondary outcome was the incidence of RRT-related complications.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 (IBM Corp, Armonk, NY, USA) and the MedCalc 19.0.4 (MedCalc Software Ltd., Ostend, Belgium). Measurement data are presented as the mean ± standard deviation (SD) or the median (interquartile ranges). The normally distributed measurement data were analyzed using an independent samples *t*-test, and the non-normally distributed measurement data were analyzed using the Mann-Whiney rank sum test. Numerical data are presented using frequencies (rate) and compared with the chi-square test. Based on the real-world situation, the variables with significant statistical differences (P values <0.05) between these 2 groups at baseline were further analyzed using multivariate binary logistic regression analysis to correct the confounding factors affecting the 90-day mortality. If a covariate was very valuable in the prognostic evaluation of RRT patients, it was also included in the multivariate binary logistic regression analysis. And the number of included variables followed the principle of "10 × EPV (events per variable)" (21).

Results

Basic conditions

A total of 207 eligible patients were screened, among whom 56 were ruled out because they had an ICU LoS ≤24 hours (n=15), RRT within 1 week before enrollment (n=13), stages 4–5 CKD (n=3), postrenal AKI (n=1), previous kidney transplantation/nephrectomy (n=4), missing medical records (n=1), they refused RRT (n=1), or they were lost to follow-up (n=18). A total of 151 patients entered the final analysis, including 77 in the early RRT group and 74 in the delayed RRT group (*Figure 1*). Missing data were reported in several patients, including "body height" in 12 cases, "body weight" in 2 cases, and "cardiac output" in 14 cases. The variable brain natriuretic peptide (BNP)" was removed because either BNP or N-terminal pro-brain natriuretic peptide (NT-pro BNP) was measured in different patients. There were no significant differences in gender, age, BMI, underlying diseases, the main causes of HF, the proportion of MV on the day of ICU admission, the dose of vasoactive drugs, and the proportion of mechanical circulatory support [including extracorporeal membrane oxygenation (ECMO) and intra-aortic balloon pump (IABP); all P values >0.05]. Troponin, myoglobin, and baseline creatinine levels also

showed no significant differences (all P values >0.05). Patients in the early RRT group had significantly lower Scr values and BUN values on the day of ICU admission than those in the delayed RRT group (both P values <0.05). The APACHE-II score and the SOFA score on the first day of ICU admission were significantly lower in the early RRT group than in the delayed RRT group (both P values <0.01; *Table 2*). The median follow-up time was not significantly different between the early RRT group and the delayed RRT group [10.63 (2.28–88) *vs.* 16.7 (4.10–90) days; P=0.194; *Table 2*].

Timing of RRT initiation

There were no significant differences in the interval from AKI diagnosis to RRT initiation, RRT mode, and the prescription dose between these 2 groups. The proportion of vasoactive drugs/amiodarone, the dose of norepinephrine, and the proportion of patients treated with MV were not significantly different. There were also no significant differences in cardiac index, central venous pressure, blood lactate, and other hemodynamic parameters. The early RRT group had a significantly higher pH [7.37 (7.32–7.43) *vs.* 7.31 (7.18–7.39); P<0.01]. The delayed RRT group had fewer patients with stage 2 AKI and more patients with stage 3 AKI and had significantly higher Scr and BUN values and higher blood potassium and phosphorus levels accordingly (all P values <0.01). There were no significant differences in mean hourly urine output and fluid balance of 24 hours before RRT initiation, cumulative fluid balance from ICU admission to RRT initiation, mean cumulative fluid balance, and %FO between these 2 groups (all P values >0.05). The delayed RRT group had a lower oxygenation index and a higher incidence of peripheral edema (*Table 3*).

Clinical outcomes

The ICU mortality showed no significant difference between the early and delayed RRT groups (44% *vs.* 57%; P=0.122). The 28-day mortality (45% *vs.* 54%; P=0.291) and the 90-day mortality (56% *vs.* 65%, P=0.259) were also not significantly different (*Table 4*). The number of RRT-free days in the ICU was significantly longer in the early RRT group than in the delayed RRT group [1.69 (0.35–10.87) *vs.* 0.88 (0.20–4.55) days; P=0.046]. However, the duration of RRT, MV-free days in the ICU, vasopressor/inotrope-free days in the ICU, total hospital LoS, ICU LoS, and average daily ICU expenditure showed no significant differences between these 2 groups (all P values >0.05). The incidence of RRT-related adverse events was 66% and 59%, respectively, in these 2 groups (P=0.389). Low serum phosphorus was the most common complication, affecting 42% of patients in the early RRT group and 34% in the delayed RRT group (P=0.325). The incidence of heparin-induced thrombocytopenia (HIT), thrombosis, and coagulation dysfunction also showed no significant differences (all P values >0.05; *Table 4*).

Multivariate binary logistic regression analysis of 90-day mortality

In the multivariate binary logistic regression analysis, 3 variables, which were APACHE-II score on the first day of ICU (to avoid collinearity problems, SOFA score on the first day were removed), BUN on ICU admission, and blood phosphorus level before RRT initiation (all P values <0.05), were finally included. Previous studies (3,13) have demonstrated that the interval from AKI diagnosis to RRT initiation affected prognosis; therefore, this variable was included in the analysis, along with "early RRT initiation" (*Table 5*). Although Scr on ICU admission showed statistically significant differences (P value <0.01), it was a sub-variable in the APACHE-II score and SOFA score on the first day of ICU admission (*Table 2*). Some other variables were obtained at the time of RRT initiation, such as Scr, BUN, eGFR, P/F, peripheral pitting edema, PH, K^+, stage of AKI (all P values <0.05), the differences in these variables between the two groups were related to the grouping criteria we set (*Table 3*). Therefore, they were not included in the multivariate binary logistic regression analysis. The APACHE-II score of ICU admission was an independent risk factor for 90-day mortality [OR (95% CI): 1.079 (1.024–1.138); P=0.005], patients with higher BUN at ICU admission had lower 90-day mortality [OR (95% CI): 0.943 (0.910–0.978); P<0.01], and the blood phosphorus level before RRT initiation and interval from AKI diagnosis to RRT initiation were not independent risk factors for 90-day mortality (both P values >0.05). The strategy of early RRT initiation did not independently reduce the 90-day mortality [OR (95% CI): 0.671 (0.314–1.434); P=0.303; *Table 5*].

Discussion

There has long been debate about the "early" *vs.* "delayed" initiation of RRT. The AKIKI, IDEAL-ICU, and STARRT-

Table 2 Baseline characteristics of the patients

Variables	Total patients (n=151)	Early RRT (n=77)	Delayed RRT (n=74)	P value
Age (years)	68 [57–77]	65 [56–77]	69 [60–77]	0.343
Female gender	48 [32]	26 [34]	22 [30]	0.594
BMI (kg/m^2)	25.26 [22.27–27.36]	25.00 [22.21–27.35]	25.54 [24.49–27.76]	0.772
Comorbidity				
Hypertension	88 [58]	43 [56]	45 [61]	0.536
Diabetes	45 [30]	24 [31]	21 [28]	0.708
Cardiovascular diseases	53 [35]	26 [34]	27 [36]	0.726
Malignant tumor	34 [23]	16 [21]	18 [24]	0.602
COPD	8 [5]	2 [3]	6 [8]	0.131
CKD	10 [7]	4 [5]	6 [8]	0.472
Nephrotoxic drugs and/or contrast used within 1 week	55 [36]	28 [36]	27 [36]	0.590
Reason for heart failure				
Takotsubo cardiomyopathy	12 [8]	5 [6]	7 [9]	0.501
Cardiovascular surgery	40 [26]	22 [29]	18 [24]	0.554
Sepsis-induced cardiomyopathy	12 [8]	4 [5]	8 [11]	0.202
Acute myocardial infarction	42 [28]	23 [30]	19 [26]	0.565
Postresuscitation syndrome	24 [16]	12 [16]	12 [16]	0.915
Chronic heart failure	17 [11]	9 [12]	8 [11]	0.865
Others	4 [3]	2 [3]	2 [3]	0.968
APACHE-II score	22.47±7.80	20.83±7.01	24.18±8.25	<0.01
SOFA score	10.39±3.73	9.55±3.37	11.27±3.90	<0.01
MV	130 [86]	66 [86]	64 [86]	0.891
Vasopressor/inotrope	102 [68]	50 [65]	52 [70]	0.484
Baseline Scr (μmol/L)	78.00 [65.9–92.2]	78.00 [61.08–91.65]	75.35 [68.50–92.20]	0.545
Scr on ICU admission (μmol/L)	158.60 [119.08–254]	142.60 [114–220.58]	219.00 [139.5–315]	<0.01
BUN on ICU admission (mmol/L)	13.80 [9.1–20.99]	12.20 [8.91–18.03]	16.10 [9.50–23.70]	0.028
cTnI (μg/L)	1.58 [0.24–12.13]	1.56 [0.32–13.03]	1.59 [0.16–7.72]	0.582
Myo (μg/L)	1,081.75 [332–2,000]	995.00 [327.88–1,654.55]	1,148.60 [326.35–2,600.03]	0.442
ECMO	14 [9]	8 [10]	6 [8]	0.629
IABP	30 [20]	17 [22]	13 [18]	0.487
Median follow-up time (days)	14.70 [2.82–90]	10.63 [2.28–88]	16.70 [4.10–90]	0.194

Data are presented as median [interquartile ranges], n [%], or mean ± SD. RRT, renal replacement therapy; BMI, body mass index; COPD, chronic obstructive pulmonary diseases; CKD, chronic kidney disease; APACHE-II, acute physiology and chronic health evaluation-II; SOFA, sequential organ failure assessment; MV, mechanical ventilation; Scr, serum creatinine; ICU, intensive care unit; BUN, blood urea nitrogen; cTnI, cardiac troponin I; Myo, myohemoglobin; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

Table 3 Patient characteristics at the time of RRT initiation

Variables	Total patients	Early RRT (n=77)	Delayed RRT (n=74)	P value
Interval from AKI diagnosis to RRT initiation (days)	0.44 [0.18–1.67]	0.52 [0.21–1.76]	0.30 [0.14–1.48]	0.163
RRT dose (mL/kg/h)	35.29 [29.10–49.81]	35.29 [29.31–42.49]	35.34 [28.57–41.67]	0.538
RRT mode				
CVVH	94 [62]	49 [64]	45 [61]	0.720
CVVHD	8 [5]	6 [8]	2 [3]	0.163
CVVHDF	49 [32]	22 [29]	27 [36]	0.299
Scr (μmol/L)	221.70 [150.28–287.85]	184.00 [137–239.28]	254.30 [209–335.80]	<0.01
BUN (mmol/L)	16.30 [10.90–23.38]	14.20 [10.33–18.70]	18.95 [11.40–29.40]	<0.01
eGFR (mL/min/1.73 m^2)	32.34 [22.75–49.14]	38.08 [27.43–54.94]	26.49 [17.85–36.39]	<0.01
P/F (mmHg)	197.00 [133.66–294.13]	244.10 [156.85–344.78]	157.30 [105.50–228.50]	<0.01
Peripheral pitting edema	67 [44]	21 [27]	46 [62]	<0.01
UOmean (mL/h)	27.27 [9.21–65.45]	27.08 [12.72–64.06]	27.91 [3.75–66.04]	0.749
Fluid balance of 24 hours before RRT initiation (mL)	613.00 [91–1,352.5]	665.25 [128.5–1,062.8]	519.30 [53–1,777.2]	0.800
Cumulative fluid balance from ICU admission to RRT initiation (mL)	755.00 [164–2,167.48]	851.40 [269.83–2,113.95]	519.30 [53–2,198]	0.380
Mean cumulative fluid balance (mL/h)	58.64 [5.79–143.08]	56.26 [12.03–140.99]	64.58 [3.75–163.64]	0.967
%FO (%)	1.08 [0.22–3.11]	1.36 [0.34–3.08]	0.76 [0.05–3.14]	0.358
Dose of norepinephrine (μg/kg/min)	0.40 [0.1–1.0]	0.46 [0.05–1.00]	0.40 [0.10–1.00]	0.707
MV	124 [82]	63 [82]	61 [82]	0.922
Vasopressor/inotrope	100 [66]	50 [65]	50 [68]	0.732
Amiodarone	19 [13]	9 [12]	10 [14]	0.588
CI (L/min/m^2)	1.92 [1.56–2.35]	1.87 [1.52–2.33]	1.97 [1.61–2.45]	0.271
CVP (mmHg)	11 [8.13–14]	10 [8–13.5]	12 [10–15]	0.180
Lactate (mmol/L)	3.10 [1.73–7.0]	3.20 [1.8–6.3]	3.05 [1.5–9.2]	0.583
pH	7.34 [7.25–7.41]	7.37 [7.32–7.43]	7.31 [7.18–7.39]	<0.01
HCO_3^- (mmol/L)	19.64±5.85	20.16±5.47	19.12±6.17	0.277
K^+ (mmol/L)	4.43 [4.1–5.0]	4.30 [3.90–4.83]	4.70 [4.20–5.10]	<0.01
Serum phosphorus (mmol/L)	1.58 [1.17–2.29]	1.46 [1.01–1.92]	1.98 [1.32–2.54]	<0.01
Stage of AKI				
Stage 1	19 [13]	12 [16]	7 [9]	0.257
Stage 2	55 [36]	42 [55]	13 [18]	<0.01
Stage 3	77 [51]	23 [30]	54 [73]	<0.01

Data are presented as median [interquartile ranges], n [%], or mean ± SD. UOmean (mL/h) = cumulative urine output from ICU admission to RRT initiation/time from ICU admission to RRT initiation. Mean cumulative fluid balance (mL/h) = cumulative fluid balance from ICU admission to RRT initiation/time from ICU admission to RRT initiation. %FO (%) = [cumulative fluid balance (litre)/ICU admission weight] × 100%. RRT, renal replacement therapy; AKI, acute kidney injury; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; Scr, serum creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; P/F, PaO_2/FiO_2; ICU, intensive care unit; FO, fluid overload; MV, mechanical ventilation; CI, cardiac index; CVP, central venous pressure.

Table 4 Clinical outcomes and complications compared between the 2 groups

Variables	Total patients	Early RRT (n=77)	Delayed RRT (n=74)	P value
RRT duration (days)	4.53 [1.74–11.64]	4.22 [1.75–11.44]	4.89 [1.63–11.84]	0.876
RRT-free days of ICU (days)	1.07 [0.26–6.58]	1.69 [0.35–10.87]	0.88 [0.20–4.55]	0.046
MV-free days of ICU (days)	0 [0–5.2]	0 [0–6.30]	0 [0–3.68]	0.265
Pressor/inotrope-free days of ICU (days)	0.04 [0–5.94]	0.26 [0–7.35]	0.02 [0–3.46]	0.347
Hospital LoS (days)	20.95 [10.62–32.53]	19.55 [13.94–32.48]	23.03 [9.01–32.79]	0.933
ICU LoS (days)	9.69 [4.35–19.81]	11.85 [4.51–20.33]	8.93 [3.68–18.57]	0.419
Average daily cost of ICU stay ($)	1,919.01 [1,333.50–2,587.29]	1,814.27 [1,351.84–2,580.08]	1,988.45 [1,327.15–2,596.81]	0.647
ICU mortality	76 [50]	34 [44]	42 [57]	0.122
28-day mortality	75 [50]	35 [45]	40 [54]	0.291
90-day mortality	91 [60]	43 [56]	48 [65]	0.259
Complications potentially related to RRT	95 [63]	51 [66]	44 [59]	0.389
HIT	18 [12]	6 [8]	12 [16]	0.110
Thrombosis	27 [18]	16 [21]	11 [15]	0.345
Bleeding/coagulopathy	39 [26]	18 [23]	21 [28]	0.483
Hypophosphataemia	57 [38]	32 [42]	25 [34]	0.325

Data are presented as median [interquartile ranges] or n [%]. RRT, renal replacement therapy; ICU, intensive care unit; MV, mechanical ventilation; LoS, length of stay; HIT, heparin-induced thrombocytopenia.

Table 5 Multivariable analysis of risk factors for 90-day mortality

Variables	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
APACHE-II score	1.064 (1.015–1.114)	0.009	1.079 (1.024–1.138)	0.005
Interval from AKI diagnosis to RRT initiation (days)	1.029 (0.959–1.105)	0.422	1.049 (0.972–1.133)	0.222
Early RRT	0.685 (0.356–1.320)	0.258	0.671 (0.314–1.434)	0.303
Serum phosphorus before RRT initiation (mmol/L)	1.050 (0.808–1.365)	0.714	1.210 (0.728–2.011)	0.462
BUN on ICU admission (mmol/L)	0.961 (0.932-0.991)	0.010	0.943 (0.910–0.978)	<0.01

CI, confidence interval; APACHE-II, acute physiology and chronic health evaluation-II; AKI, acute kidney injury; RRT, renal replacement therapy; BUN, blood urea nitrogen; ICU, intensive care unit.

AKI studies suggested that early initiation of RRT did not improve mortality in AKI patients (8-10). However, the ELAIN (7) and AKIKI-2 (11) studies argued that delayed RRT initiation was harmful and RRT should be initiated as early as possible in stage 3 AKI patients with oliguria for more than 72 hours or blood urea nitrogen >112 mg/dL. Most patients in the ELAIN study (7) had undergone surgery, and 46.7% of them had received cardiac surgery, suggesting surgical patients may benefit from early RRT. A meta-analysis concluded that early initiation of RRT in patients admitted to the surgical ICU could reduce the risk of death, and the risk of eventual transition to long-term dialysis was even lower (22). In our study, the proportion of patients undergoing cardiac/macrovascular surgery was 26%, which was lower than that in the ELAIN study. There was no significant difference in the ICU mortality

and the 28-day and 90-day mortality after RRT initiation between the early RRT group and the delayed RRT group. This finding was consistent with the mainstream view that early RRT does not improve the long-term prognosis of patients. Thus, whether the proportion of surgical patients affects the timing of RRT initiation warrants further investigations. We also found that the number of RRT-free days in the ICU was significantly longer in the early RRT group than in the delayed RRT group [1.69 (0.35–10.87) *vs.* 0.88 (0.20–4.55) days; P=0.046]. This finding may be due to the difference in disease severity between these 2 groups. In addition, there was a statistically significant difference in the SOFA score on the day of admission to the ICU (9.55±3.37 *vs.* 11.27±3.90, P<0.01).

In addition to selecting the patient population, organ dysfunction should also be incorporated into the decision-making on RRT initiation (23). For instance, the tolerance of FO is poor in patients with acute respiratory distress syndrome (ARDS), for whom the emergency indications for RRT should also be kept in mind. In a single-center retrospective study of 155 patients undergoing RRT after cardiac surgery, the preemptive RRT group had a significantly lower in-hospital mortality (38.0% *vs.* 59.2%; P<0.01) and a shorter time for renal function recovery (24). Chousterman *et al.* (25) found that patients with craniocerebral trauma were prone to intracranial hypertension due to cerebral edema. They argued that delayed RRT should not be applied to these patients. Therefore, the timing of RRT initiation for different AKI "subphenotypes" was quite unique. HF patients have systemic and pulmonary congestion and poorly tolerate fluid therapy (20,26). The decreased renal perfusion due to decreased cardiac output and renal congestion can ultimately worsen renal function (27). Thus, it is clinically important to investigate HF patients as a "subphenotype" of AKI. Chronic HF initially manifests as increased central venous pressure and ventricular filling pressure, while congestion as a clinical symptom occurs relatively late (28). Jugular venous pressure <8 cmH_2O, absence of orthopnea, and absence of peripheral edema are the criteria for "free of congestion" in HF patients (29). Therefore, we took FO as one of the reference criteria for "early" or "delayed" RRT.

Two parameters can be used to assess fluid overload in patients: %FO and FOP. The concept of %FO was first proposed by pediatricians and is defined as the ratio of cumulative fluid balance to basal body weight (18). A %FO >10% is suggestive of the presence of FO. FO is characterized by fluid retention in multiple locations throughout the body, often due to impaired renal function and/or excessive fluid infusion. Studies found that %FO was associated with adverse outcomes, such as high mortality and a prolonged time for renal function recovery in critically ill patients (30,31). In our current study, some patients had clinical signs and symptoms suggestive of FO. However, because these patients received RRT within 24 hours after ICU admission and had restrictive fluid management, the median %FO was 1.36% in the early RRT group and 0.76% in the delayed RRT group, far less than 10%. Thus, we believe that the threshold of %FO >10% is not suitable for assessing whether there is FO in adults. The recent STARRT-AKI study (10) and AKIKI2 study (11) revealed a mean cumulative fluid balance between 1.5 and 3 L. It also illustrates that fluid overload is not a common phenomenon in patients with AKI today. Therefore, FOP was adopted in place of %FO to assess whether patients had FO (19).

Cardiorenal syndrome (CRS) is a series of complex disease conditions caused by the interaction of the heart and the kidneys (32). The requirement of RRT in patients with AKI and HF is due to the imbalance between kidney demand and reserve (33). So we used FOP combined with AKI stage for grouping. The furosemide stress test (FST) is thought to be useful in assessing renal reserve in AKI patients and predicting the risk of AKI progression and can be applied in deciding the timing of CRRT (34). However, diuretic resistance is common in HF patients, which may limit the role of FST in the timing of RRT initiation in AKI patients with HF (35). BMI can affect the clinical outcome of AKI patients, the hospital prognosis of AKI and AKI-RRT patients after cardiac surgery was best when their BMI was in the 24–28 kg/m^2 range (36). Another study of COVID-19 complicated with AKI suggested that patients undergoing RRT had higher BMI (37). However, we did not find a significant difference in BMI between the two groups in our study, and this area needs further exploration. Biomarkers have a role in determining when to initiate RRT in critically ill patients with AKI. Although some biomarkers have shown predictive ability for RRT in critically ill patients with AKI, the evidence is not strong enough to prove that they can be used routinely in clinical practice to guide the decision of when to initiate RRT (38). The RUBY study (39) found that urinary C-C motif chemokine ligand 14 (CCL14) had a strong ability to predict stage3 AKI lasting 72 hours or more. The area under the receiver operating characteristic (ROC) curve of CCL14 was 0.83, and higher concentration of CCL14 was associated with an increased risk of a composite endpoint

consisting of adverse events such as RRT initiation or death within 90 days, the CCL14 is expected to be used in clinical decision making in the future.

Our current study had several advantages. First, few previous clinical studies have explored the timing of RRT initiation in critically ill patients with HF complicated by AKI, and our current study filled this gap. Second, whether RRT should be initiated "early" or "delayed" was based on the combination of KDIGO classifications for AKI and FO instead of the KDIGO classifications or the time of ICU admission alone. Third, a more clinically feasible diagnostic criterion for FO was adopted that was more conducive to guiding future clinical practice. Fourth, the basal creatinine value was estimated using the modified MDRD-eGFR formula for a Chinese population, which was more suitable for the ethnic characteristics of the research participants.

However, our study had some limitations. First, as a single-center retrospective study, the sample size may need to be expanded further. A multi-center, large sample, prospective study and external verification is needed. Second, patients were enrolled over a wide time span, during which the advances in treatment concepts and techniques might have influenced patient outcomes. Third, only AKI patients who underwent RRT were included, while patients with severe AKI who avoided RRT through clinical treatments were not included, which might lead to selection bias. Fourth, the baseline levels were inconsistent among the participants, and the confounding factors could only be corrected by multivariate binary logistic regression. Finally, the clinical data on HF grading were incomplete and were not included in the analysis.

Conclusions

In patients with severe AKI and HF, early RRT can increase the RRT-free time in the ICU. However, it does not increase MV-free days, vasoactive drug-free days, or ICU expenditure. Furthermore, it cannot decrease the ICU mortality or the 28-day and 90-day mortality after RRT initiation.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-146/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-146/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the Fourth Hospital of Hebei Medical University (No. 2021KS042). Individual consent for this retrospective analysis was waived.

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