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Original Article

ORIGINAL ARTICLE

Accelerated versus watchful waiting strategy of kidney replacement therapy for acute kidney injury: a systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Background. Critically ill patients with severe acute kidney injury (AKI) requiring kidney replacement therapy (KRT) have a grim prognosis. Recently, multiple studies focused on the impact of KRT initiation time [i.e., accelerated versus watchful waiting KRT initiation (WWS-KRT)] on patient outcomes. We aim to review the results of all related clinical trials.

Methods. In this systematic review, we searched all relevant randomized clinical trials from January 2000 to April 2021. We assessed the impacts of accelerated versus WWS-KRT on KRT dependence, KRT-free days, mortality and adverse events, including hypotension, infection, arrhythmia and bleeding. We rated the certainty of evidence according to Cochrane methods and the GRADE approach.

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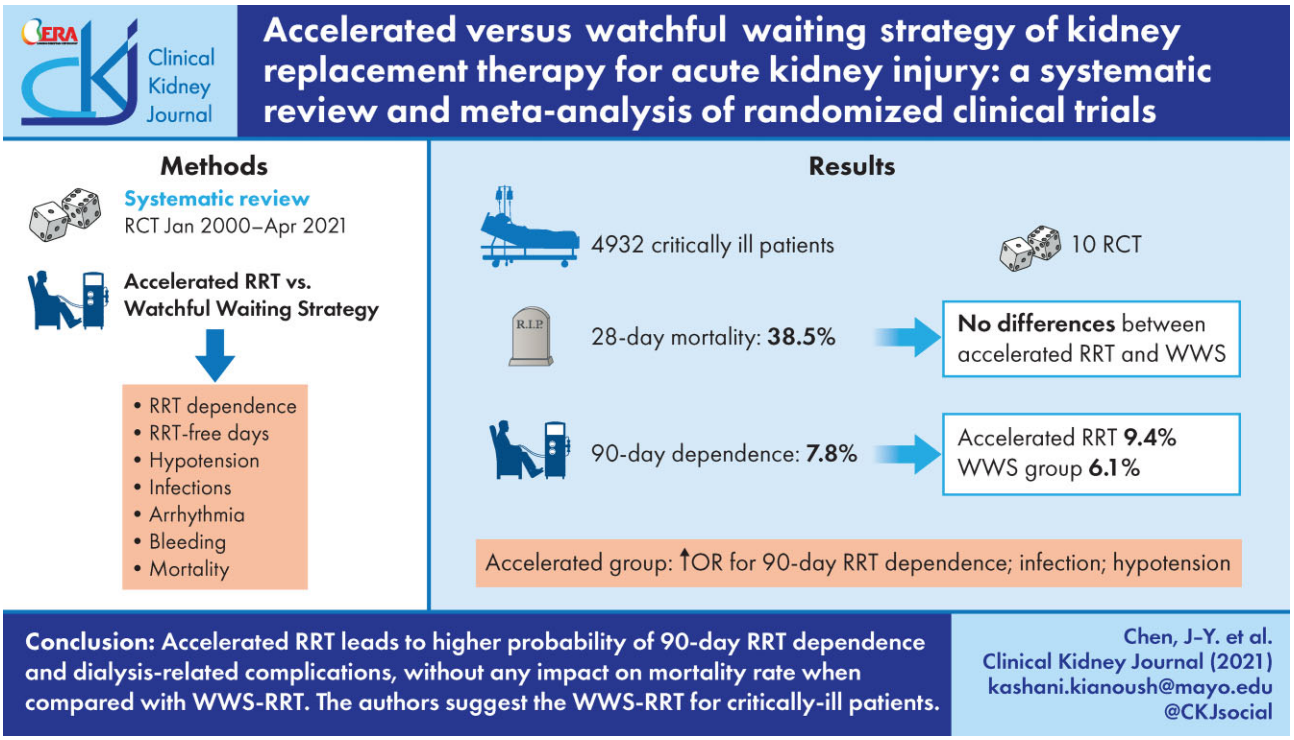
Results. A total of 4932 critically ill patients with AKI from 10 randomized clinical trials were included in this analysis. The overall 28-day mortality rate was 38.5%. The 28-day KRT-dependence rate was 13.0%. The overall incident of KRT in the accelerated group was 97.4% and 62.8% in the WWS-KRT group. KRT in the accelerated group started 36.7 h earlier than the WWS-KRT group. The two groups had similar risks of 28-day [pooled log odds ratio (OR) 1.001, $P = 0.982$] and 90-day (OR 0.999, $P = 0.991$) mortality rates. The accelerated group had a significantly higher risk of 90-day KRT dependence (OR 1.589, $P = 0.007$), hypotension (OR 1.687, $P < 0.001$) and infection (OR 1.38, $P = 0.04$) compared with the WWS-KRT group.

Conclusions. This meta-analysis revealed that accelerated KRT leads to a higher probability of 90-day KRT dependence and dialysis-related complications without any impact on mortality rate when compared with WWS-KRT. Therefore, we suggest the WWS-KRT strategy for critically ill patients.

GRAPHICAL ABSTRACT



Keywords: acute kidney injury, accelerated kidney replacement therapy, complication, kidney replacement therapy dependence, mortality, watchful waiting strategy

INTRODUCTION

Critically ill patients with acute kidney injury (AKI) have unfavorable prognoses. About 5–20% of intensive care unit (ICU) patients develop AKI and approximately 6% require kidney replacement therapy (KRT) during ICU admission [1]. Patients with severe AKI requiring KRT have higher mortality rates of 40–55% [2].

The timing of KRT initiation is one of the factors that could lead to changes in patient outcomes. Several studies compared the clinical benefit between accelerated and watchful waiting (WWS-KRT) strategies for the KRT initiation time. In these studies, the accelerated group received KRT as soon as moderate-to-severe AKI diagnosis was made. In contrast, in WWS-KRT groups, dialysis was initiated based on specific indications, including fluid overload, electrolyte imbalance and/or azotemia [3]. Each strategy has its pros and cons. The accelerated KRT initiation while it can prevent the development of AKI-associated complications, including fluid overload, acid–base and electrolyte imbalances, may also expose patients to increased risks of hemodynamic instability, anticoagulation-induced bleeding, dialysis-related infection and even inflammatory or oxidative stress. In comparison, WWS-KRT could not only limit the clinical abilities to prevent AKI-related complications, but may also provide more time for hemodynamic optimization before KRT, avoid harmful removal of nutrients, antibiotics and electrolytes, or prevent unnecessary KRT-associated complications [4].

Several recent randomized controlled trials (RCTs) indicate that the WWS-KRT strategy could allow AKI recovery without the need for KRT, without leading to a higher mortality rate compared with accelerated KRT initiation [5]. However, the impact of WWS-KRT on clinical prognoses and complications is still not entirely understood. Thus, we conducted this systematic review and meta-analysis to include all relevant RCTs.

MATERIALS AND METHODS

Search strategy and selection criteria

Two investigators (J.-Y.C.; C.-C.H.) searched the published RCTs in PubMed, Embase, Cochrane, Collaboration Central Register of Controlled Clinical Trials, Cochrane Systematic Reviews and Cnki.net (Supplementary data, Figure S1A and B) from January 2000 to April 2021 without any language limitation. A third investigator (V.-C.W.) resolved the disagreements between the other two investigators.

The meta-analysis was conducted according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement [6] and Cochrane methods [7]. The systematic review protocol was registered in PROSPERO [CRD42021240311] (Supplementary data).

Inclusion and exclusion methods

We included all RCTs that enrolled adult (≥18 years old) critically ill patients with AKI who did not receive KRT before enrollment. The included studies randomized participants into control and experimental groups to compare the accelerated and WWS-KRT strategies and assessed at least one of the following outcomes: KRT independence at hospital discharge, KRT-free days, and 28- and 90-day mortality rates. Clinical trials that included healthy human subjects or animals, pregnant women, or did not use controlled randomization were excluded. In addition, all letters, conference or case reports, and those that lacked data on mortality and/or the KRT initiation strategy were not included.

Reference lists of related studies, systematic reviews and meta-analyses were manually examined to identify any additional publications relevant to our analysis. Full-text papers were selected for quality assessment and data syntheses. We contacted the authors of the articles that we enrolled in our study to acquire additional details.

Data extraction

All the relevant data were extracted from the included studies by two investigators (J.-Y.C.; V.-C.W.). Each study characteristic including the sample size in both accelerated and WWS-KRT groups, population setting and site (i.e., single-center, multi-centers mixed population and sepsis population), location, average age, sex, comorbid conditions (i.e., hypertension, type 2 diabetes mellitus, heart failure and chronic kidney disease), the definition of accelerated KRT versus WWS-KRT and KRT modality were abstracted. We also recorded outcome-related variables, including AKI stage, urine output (mL/24 h), the time difference of KRT initiation between accelerated and WWS-KRT groups, study quality and baseline Sequential Organ Failure Assessment (SOFA) score and the primary outcomes.

Quality assessment

The Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess the risk of bias in the included randomized trials [8]. Any study with a total score of >7 was considered a high-quality study [9]. The evaluated domains included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. The studies were considered high-risk when ≥2 items rated as high risk of bias, low-risk when ≥5 items rated as low bias risk with ≤1 high-risk factor, and finally moderate risk study in all remaining situations.

Definition of accelerated versus WWS-KRT

WWS-KRT included patients who started KRT after the occurrence of azotemia, hyperkalemia, severe pulmonary edema, fluid overload refractory to diuretics or severe metabolic acidosis according to the designed protocol. Accelerated initiation was defined as relatively earlier versus later hemodialysis, according to each study definition.

Outcomes

The primary outcomes of this meta-analysis were 28- and 90-day mortality rates following the hospital discharge. The secondary outcomes included 28- and 90-day dialysis dependence, 28- and 90-day KRT-free days, hospital and ICU mortality rates, length of stay in ICU and hospital, 28-day mechanical ventilator-free (MV) and vasopressor-free days. The potential KRT-related adverse events were recorded, including hypotension, infection, arrhythmia and bleeding episodes.

Subgroup analysis

Subgroup analyses related to the mortality rates and 90-day KRT dependence were conducted based on the study population (surgery versus mixed/medical), disease severity with SOFA score at admission (>11 versus ≤11), the discrepancy in the interval between accelerated and standard initiation time (TD) (high TD >24-h versus low TD ≤24 h), patients from the single-center or multi-centers and sepsis prevalence.

Data synthesis and statistical analysis

We used a fixed-effects model to construct the cumulative Z curve. O'Brien-Fleming's α-spending–function is applied and converted to sequential boundaries, which were calculated assuming significance levels of 0.05 and a power of 90% [10]. We estimated the odds ratio (OR) and 95% confidence intervals (CIs) using the fixed model by the Mantel–Haenszel method. We chose a relative risk reduction of 20% for mortality and 90-day KRT dependence as it was compatible with ICU trials [11]. A relative risk reduction of 35% for 28-day KRT dependence was chosen to calculate the futility zone. When the cumulative Z curve across to the sequential boundaries or neutrality zones represented sufficient evidence to support or reject the anticipated intervention effect, we did not consider any further analyses.

Statistical heterogeneity was assessed by the Chi-squared test and the I^2 statistic with a $P < 0.05$ or $I^2 > 50\%$ as an indication of substantial heterogeneity. In the case of considerable heterogeneity ($I^2 > 50\%$ or $P < 0.05$), we performed a sensitivity analysis to detect each study's influence on the overall estimate by omitting one article at a time and used the pooled data on the remaining investigations. Funnel plots were conducted to examine potential publication bias. We also did the trial sequential analysis (TSA) to control type I and type II errors for 28-day mortality and 28-day KRT dependence [12].

We used Comprehensive Meta-Analysis (Version 3.3.070, 20 November, 2014) for all statistical analyses. TSA version 0.9.5.5 b (reviewed in November 2016) software was used to analyze the cumulative effect of randomized trials on mortality. A statistical significance was defined as P-values <0.05.

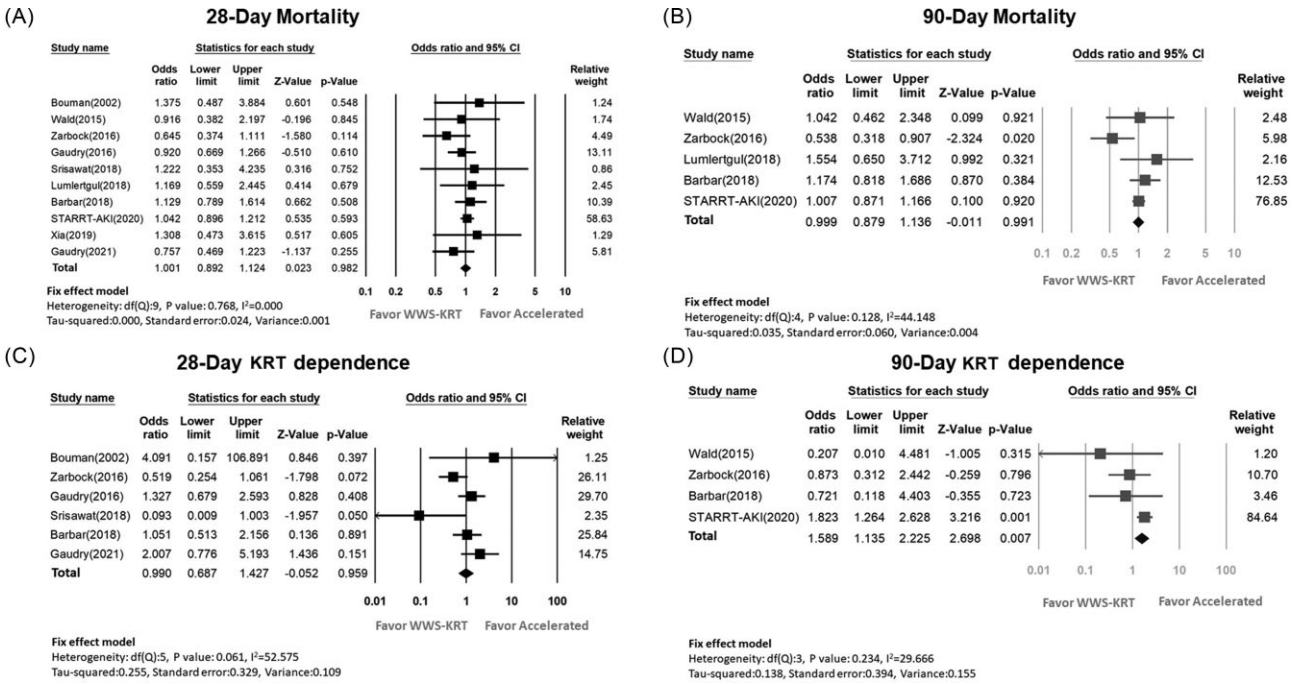


FIGURE 1: Forest plot showing the risk of (**A**) 28-day, (**B**) 90-day mortality, (**C**) 28-day KRT dependence and (**D**) 90-day KRT dependence between accelerated KRT and WWS-KRT initiation. KRT, kidney replacement therapy; WWS, watchful waiting strategy.

RESULTS

Study search outcomes and included patients

In this study, 28,301 studies were identified through database search, and after removing 13,208 duplicate articles and 14,002 non-relevant papers (Figure S1A 1A), the title and abstract of the remaining 1091 papers were screened. Following the exclusion of 1028 papers for eligibility criteria, 63 full texts were reviewed. Finally, 10 RCTs with 4932 critically ill patients with AKI who had complete data were selected for the final meta-analysis [13–22] (Table 1). Among the included patients, 2462 critically ill AKI patients received accelerated KRT, whereas 2470 patients were in the WWS-KRT group [13–22].

Heterogeneity and publication bias

The included studies were published from 2002 to 2021 (Supplementary data, Figure S2). All 10 [13–22] trials had low risk of bias for random sequence generation, blinding of outcome assessment and incomplete outcome data. Nine [13, 15–22] trials were low risk for allocation concealment and nine [13, 15–22] trials were low risk for selective reporting. Eight [13, 15–18, 20–22] trials had a low risk for other biases (Supplementary data, Figure S2). One study [14] was rated as a moderate risk study and the other nine [13, 15–22] trials were identified as low risk according to overall quality criteria (Table 2).

Mortality and KRT dependence

The average time for dialysis discrepancy between accelerated group and WWS-KRT group was 36.7 h. Both accelerated and WWS-KRT groups had a similar 28-day mortality rate of 38.5% with similar pooled log OR [fixed-effect log OR 1.001 (95% CI 0.892–1.124), $P = 0.98$]. The heterogeneity among included studies was low ($I^2 < 1\%$) (Figure 1A).

Following the randomization, the proportion of patients who received KRT was significantly higher in the accelerated group (2398 of 2462 patients, 97.4%) than in the WWS-KRT group (1550 of 2470 patients, 62.8%) ($P < 0.001$). KRT dependence in 28 days was assessed in 1,118 patients. The pooled ratio was 13%, i.e., 72 of 555 patients in the accelerated group and 73 of 563 patients in the WWS-KRT group. Additionally, the pooled 90-day KRT dependence among 2023 patients was 9.4% (96 of 1012 patients) in the accelerated group and 6.1% (62 of 1011 patients) in the WWS-KRT group. The pooled OR of 28-day KRT dependence was similar between the two groups, i.e., log OR 0.99 (95% CI 0.687–1.427, $P = 0.96$) with an I^2 value of 52.58%. The accelerated group had a higher risk of 90-day KRT dependence than the WWS-KRT group, i.e., log OR 1.589 (95% CI 1.135–2.225, $P = 0.007$) with an I^2 value of 29.67% (Figure 1C and D)

Funnel plots showed symmetrical distributions for 28-day mortality (Supplementary data, Figure S3A) and 28-day KRT dependence (Supplementary data, Figure S3b). For 28-day mortality and 28-day KRT dependence, the TSA indicated 3964 and 1713 to reach a stopping boundary of superiority, respectively. The Z-curve was parallel to the superior boundary of the accelerated KRT, in terms of no superiority to WWS-KRT, while it crossed the neutrality boundary after including all trials for 28-day mortality and 28-day KRT dependence (Figure 2A and B).

TSA revealed a total of 3964 patients for superiority or neutrality boundary for 28-day mortality. The Z curve was parallel to the accelerated group's superiority zone. This finding suggests accelerated KRT was not superior to the WWS-KRT. More importantly, it crossed the futility boundary for all trials (Figure 2A).

TSA also denoted that a diverse adjusted information size was 1713 patients and the cumulative Z curve reached the futility area for 28-day KRT dependence (Figure 2B). This

Table 1. Summary of the baseline characteristics of the included RCTs

Author	Patients (early/standard)	Population setting and site	Nation, continent	Mean age (years)	Male (%)	HTN/DM/HF/CKD (%)	Sepsis (%)	Definition of early	Definition of WWS	KRT modality
Barbar [13]	477 (239/238)	Multicenter Septic shock population	France (Europe)	69 ± 12.2	60.7	57.8/30.5/8.2/15.6	100	Within 12 h after the onset of the failure stage of RIFLE	Serum potassium ≥6.5 mmol/L; pH ≤7.15; severe pulmonary edema refractory to diuretics; no kidney function recovery after 48 h	IHD, CKRT
Xia [14]	60 (30/30)	Single-center Sepsis population	China	67.8 ± 14.7	50.0	NA	100	uNGAL >1310 ng/mL	One or more of the following criteria: Serum potassium >6.5 mmol/L), fluid overload (heart failure or pulmonary edema), severe metabolic acidosis (pH <7.20; HCO_3 ≤12 mmol/L)	CKRT
Zarbock [15]	231 (112/119)	Single-center Mixed population	Germany (Europe)	67 ± 13.1	63.2	81.8/19.5/41.6/40.7	32.5	Within 8 h of diagnosis of KDIGO stage 2	Within 12 h of diagnosis of KDIGO stage 3; or serum urea >100 mg/dL; serum potassium >6 mmol/L; serum magnesium >4 mmol/L; urine < 200 mL per 12 h or anuria; organ edema refractory to diuretics	CKRT
Srisawat [16]	40 (20/20)	Two-center Mixed population	Thailand (Asia)	66.8 ± 15.9	55.0	NA	72.5	AKI (any stage of RIFLE)	potassium >6.2 mmol/L; pH <7.2, severe pulmonary edema refractory to diuretics; persistent oliguria or anuria; serum urea >60 mg/dL	CKRT
Gaudry [17]	278 (137/141)	39 intensive care units	France (Europe)	65 ± 13	73.7	59.4/25.5/5.4/11.9	57.6	oliguria >72 h or BUN >112 mg/dL	Until mandatory indication (noticeable hyperkalemia or metabolic acidosis or pulmonary edema) or until BUN ≥ 140 mg/dL	Intermittent KRT, CKRT
Bouman [19]	71 (35/36)	Two-center Mixed population	Netherlands (Europe)	68.5 ± 11.6	59.2	NA	NA	Within 12 h if UOP <30 mL/h for 6 h; Ccr <20 mL/min	Plasma urea level of >40 mmol/L; potassium of >6.5 mmol/L or severe pulmonary edema	CKRT

Table 1. Continued.

Author	Patients (early/standard)	Population setting and site	Nation, continent	Mean age (years)	Male (%)	HTN/DM/HF/CKD (%)	Sepsis (%)	Definition of early	Definition of WWS	KRT modality
Wald [18]	100 (48/52)	Multicenter Mixed population	Canada (North America)	63.1 ± 12.8	72.0	53.0/39.0/11.0/NA	56.0	At least two of the following: 2-fold increase in serum creatinine from baseline; urine output <6 mL/kg in the preceding 12 h; whole-blood NGAL ≥400 ng/m	Serum potassium >6.2 mmol/L; serum bicarbonate <10 mmol/L, severe pulmonary edema; persistent AKI for >72 h	IHD, CKRT, SLED
Gaudry [20]	619 (311/308)	Multicenter Mixed population	France (Europe)	66.1 ± 13.9	65.4	53.0/26.3/9.0/9.7	79.8	KDIGO stage 3	Serum potassium >6 mmol/L; severe pulmonary edema refractory to diuretics; pH <7.15; serum urea >40 mmol/L; oliguria >72 h	IHD, CKRT
Lumlertgul [21]	118 (58/60)	Multicenter, Mixed population	Thailand (Asia)	67.1 ± 15.8	46.2	44.9/24.6/NA/NA	58.5	Furosemide stress test-nonresponsive Patients (UOP <200 mL in 2 h) (initiation within 6 h); AKI (any stage of KDIGO)	Serum urea >100 mg/dL; severe hyperkalemia (>6 mmol/L); severe metabolic acidosis (pH <715); severe pulmonary edema	CVVH
STARRT-AKI [22]	2927 (1465/1462)	Multicenter, Mixed population	Multiple countries (Asia, Europe, North America, Oceania, South America)	64.6 ± 14.9	68.0	55.9/30.7/13.9/43.9	57.7	Within 12 h of fulfilling eligibility: at least two of the following: 2-fold increase in serum Cr from baseline; UOP <6 mL/ kg in the preceding 12 h; whole blood NGAL >400 ng/mL	Until the development of one or more of the following criteria: a serum potassium level >6.0 mmol/L, a pH <7.20 or a serum bicarbonate <12 mmol/L, severe respiratory failure based on a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of <200 and clinical perception of volume overload, or persistent AKI for at least 72 h after randomization	IHD, CKRT

BUN, blood urea nitrogen; Ccr, creatinine clearance rate; CKD, chronic kidney disease; CKRT, continuous kidney replacement therapy; CVVH, continuous venovenous hemofiltration; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; IHD, intermittent hemodialysis; NA, not available; NGAL, neutrophil gelatinase-associated lipocalin; KRT, kidney replacement therapy; SLED, sustained low-efficiency dialysis; uNGAL, urinary neutrophil gelatinase-associated lipocalin; UOP, urine output; WWS, watchful waiting strategy.

Table 2. Summary of the outcome of the included RCTs

Author	AKI definition by stage/biomarker for AKI	HR/OR/RR (CI) for primary endpoint	Urine output (mL/24 h)	Time difference between early and WWS (h)	Study quality	SOFA score at the adminis-tration	Primary outcome
Bouman [19]	NA	NA	NA	34.8	High	10.4 ± 2.1	In-hospital mortality, in-ICU mortality, 28-day mortality
Barbar [13]	RIFLE-F	NA	NA	45	High	12.3 ± 2.9	90-day mortality
Xia [14]	KDIGO/ uNGAL ≥1310 ng/mL	NA	NA	72	Moderate	9.7 ± 3.3	28-day mortality
Zarbock [15]	KDIGO Stage 2pNGAL ≥150 ng/mL	0.66 (0.45–0.97)/–/–	358.7	20	High	15.8 ± 2.3	30-/60-/90-day mortality
Srisawat [16]	RIFLE-R/pNGAL ≥400 ng/mL	NA	NA	48	High	9.3 ± 3.6	28-day mortality
Gaudry [17]	KDIGO Stage 3	NA	NA	60	High	11 ± 3	The number of KRT-free days between randomization and day 28
Wald [18]	NA	NA	329.8	24	High	13 ± 2.8	In-hospital mortality; in-ICU mortality; 90-day mortality
Gaudry [20]	KDIGO Stage 3	1.02 (0.81–1.29)/–/–	NA	55	High	10.9 ± 3.1	60-/90-day mortality
Lumlertgul [21]	KDIGO Stage 1	0.96 (0.60–1.53)/–/–	551.1	19	High	12 ± 3.7	28-day mortality
STARRT-AKI [22]	KDIGO Stage 2/pNGAL >400 ng/mL	–/1.05 (0.90–1.23)/1.00(0.93–1.09)	464	NA	High	11.7 ± 3.6	90-day mortality

AKI, acute kidney injury; HR, hazard ratio; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcome; NA, not available; OR, odds ratio; pNGAL: plasma neutrophil gelatinase-associated lipocalin level; RIFLE-F, risk, injury, failure, loss of kidney function and end-stage kidney disease; RR, relative risk; SOFA, Sequential Organ Failure Assessment; uNGAL, urine neutrophil gelatinase-associated lipocalin level; WWS, watchful waiting strategy.

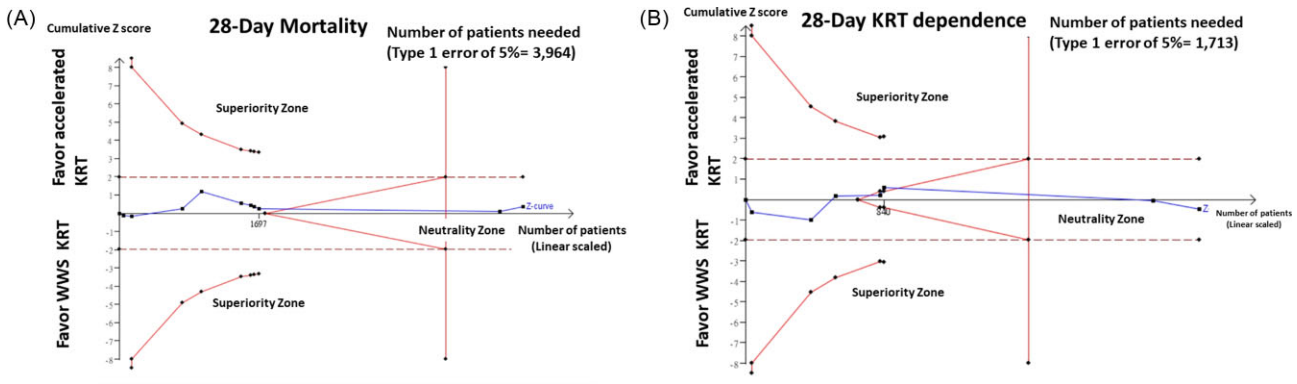


FIGURE 2: Trial sequential analysis of the low risk of bias in randomized studies comparing the impact on **(A)** 28-day mortality and **(B)** 28-day KRT dependence between accelerated KRT and WWS-KRT for critically ill patients with acute kidney injury. KRT, kidney replacement therapy; WWS, watchful and waiting strategy.

evidence suggests the enrolled number of patients was enough to reach an inference.

Adverse events

The hypotension incidence rate was 12.5% in the accelerated strategy and 8.0% in the WWS-KRT. According to the result, the accelerated KRT led to the increased hypotension episodes compared with the WWS-KRT, with log OR 1.687 (95% CI 1.354–2.102, $P < 0.001$) (Figure 3A).

In the accelerated KRT and WWS-KRT groups, the rates of KRT-related infection were 4.9% and 3.8%, respectively, reflecting a higher risk of infection in the accelerated KRT initiation group with log OR 1.38 (95% CI 1.018–1.872, $P = 0.04$) (Figure 3B).

The forest plot further denoted that there was no significant difference between the two groups regarding hospital

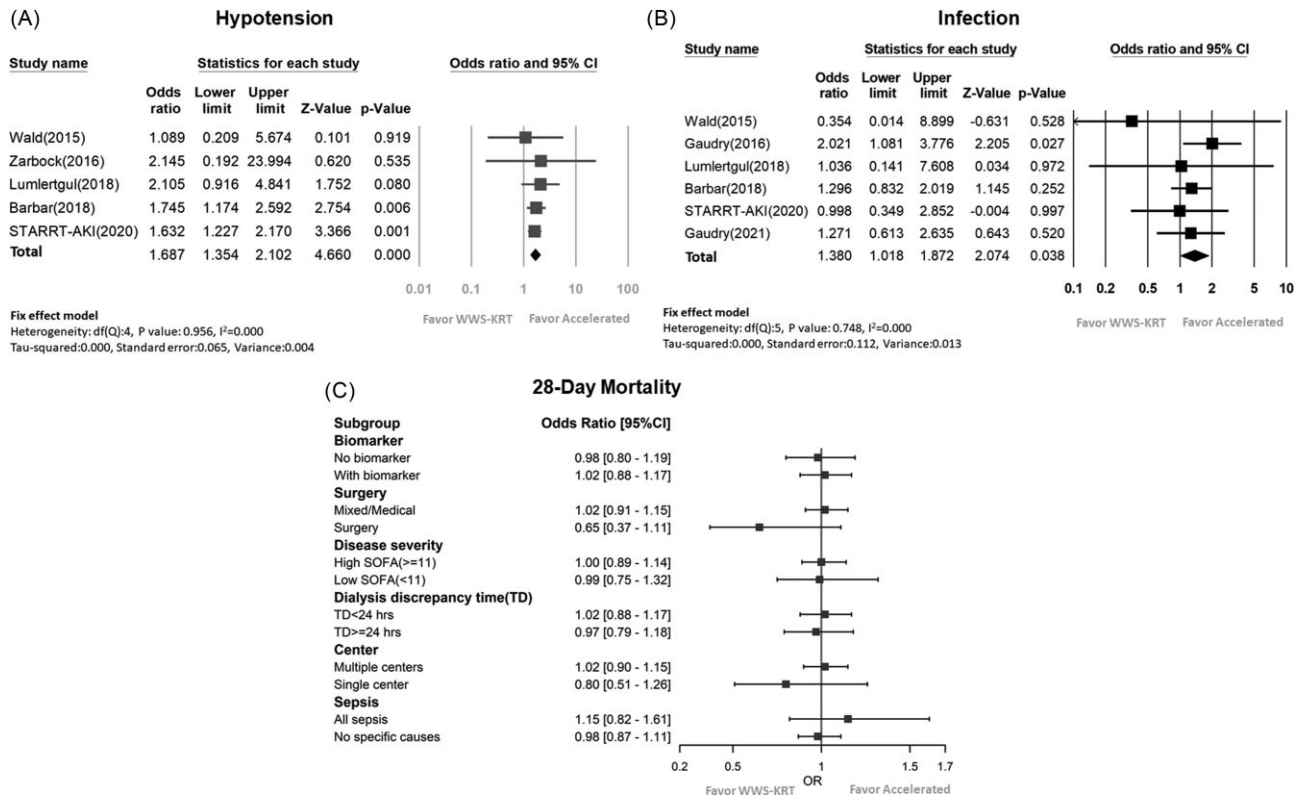


FIGURE 3: (A) Hypotension, (B) infection and (C) subgroup analysis for 28-day mortality, between accelerated KRT and WWS-KRT for critically ill patients with acute kidney injury. SOFA, Sequential Organ Failure Assessment; TD, time to dialysis discrepancy; WWS, watchful waiting strategy.

(Supplementary data, Figure S4) and ICU mortality (Supplementary data, Figure S5), ICU (Supplementary data, Figure S6) and hospital (Supplementary data, Figure S7) length of stay, arrhythmias (Supplementary data, Figure S8A), bleeding (Supplementary data, Figure S8B), 28-day (Supplementary data, Figure S9A) and 90-day KRT-free (Supplementary data, Figure S9B) 28-day KRT free days (Supplementary data, Figure S10A) 28-day MV-free days (Supplementary data, Figure S10B) and 28-day vasopressor-free days (Supplementary data, Figure S10C).

Subgroup analysis

Twenty-eight-day mortality between accelerated KRT and WWS-KRT groups did not differ in the subgroup analyses (Figure 3C).

Quality of evidence

Because of the risk of bias, the quality of evidence for 28-day mortality was moderate and the quality of 28-day KRT dependence was also moderate for high *I*-square value. In addition, the quality of 90-day mortality and 90-day KRT dependence was high (Supplementary data, Supplement 14).

Summary receiver operating characteristic curves based on serum urea

There were six articles reported with serum urea as one of the criteria for WWS-KRT. The summary receiver operating characteristic curves for 28-day mortality (Supplementary data, Figure S11A) and 28-day KRT dependence (Supplementary data, Figure S11B) showed low sensitivity and high false positivity.

DISCUSSION

We demonstrated that the WWS-KRT strategy in critically ill patients with AKI who require dialysis results in significant reductions in the need for KRT, risk of infection and hypotension. The WWS-KRT did not lead to a higher risk of 90-day mortality, ICU or hospital length of stay than the accelerated KRT.

To our knowledge, this is the most comprehensive systematic review that included the highest number of RCTs, including the recent two large studies [17, 22] with the largest number of included critically ill AKI patients.

Outside of the larger sample size, one of the differences between our study with the previously published meta-analysis [23] is the inclusion of cumulative Z curve analysis, which showed crossing the futility line after achieving the required information sample size. This confirms the robustness of indifference in mortality between the groups even after inclusion of the STARRT-AKI [22] and AKIKI-2 studies [17].

KRT is a life-saving intervention to correct the severe acid–base and electrolyte imbalances, remove uremic toxins and excess fluids, and eliminate the circulating cytokines among patients with a substantial decline in their kidney function in acute or chronic settings. To date, there is no established treatment for AKI; hence, KRT may be an inevitable strategy for critically ill patients with severe kidney function impairment. Accelerated KRT initiation is considered a modality to maintain fluid and electrolytes balance and acid–base homeostasis.

Additionally, it presumptively regulates inflammatory cytokine levels during inflammatory processes to avoid organ dysfunction [24]. However, earlier KRT may result in an increased risk of hemodynamic instability, bleeding, inflammatory or oxidative stress, and excessive removal of necessary prescription drugs, including antibiotics [25].

The medical management of patients with AKI to avoid AKI progression or its related complications is considered the primary approach [26]. KRT is often considered when medical management strategies fail to show any benefit. Diuretics can often prevent and correct fluid overload (i.e., in patients with acute lung injury or congestive heart failure). However, among patients with significant kidney dysfunction and diuretic-refractory oliguria, KRT may be necessary to limit the impact of overwhelming fluid overload [27]. In the sodium bicarbonate therapy for patients with severe metabolic acidemia in the intensive care unit (BICAR-ICU) trial, sodium bicarbonate supplement was found to improve survival among patients with AKI stages 2 and 3 associated with severe metabolic acidosis [28]. Severe hyperkalemia is considered a clinical emergency. Outside of temporizing measures, using diuretics or potassium binders are effective medical management choices for hyperkalemia [29]. Adequate hydration and possible vasopressor support are essential to address perfusion–consumption mismatch in the kidneys among AKI patients with azotemia [30]. In 'medically manageable AKI' patients, these strategies could mitigate the need for KRT initiation.

In the included studies, 97.4% of patients in the accelerated group received KRT, while only 62.8% of patients in the WWS-KRT group required KRT. We further showed that WWS could reduce KRT-related adverse events, such as infection and hypotension. Therefore, based on the current evidence, it is plausible to recommend that the delayed KRT be associated with improved outcomes and lower healthcare economic burden. KRT should be reserved for when conservative management strategies fail or time-sensitive life-threatening conditions are present.

We demonstrated that WWS-KRT does not lead to an increased risk of arrhythmia or bleeding, or lower 28-day MV-free days and 28-day vasopressor-free days. On the contrary, the accelerated KRT group had a higher risk of hypotension hemodynamic instability [31] and infection [32].

Based on the Acute Disease Quality Initiative XVII recommendations [33] and Kidney Disease: Improving Global Outcome (KDIGO) guidelines [34], acute KRT would be reconsidered when metabolic and fluid status demands exceed total kidney capacity. However, based on our systematic review, WWS should be considered for patients in equipoise as it may decrease the need for KRT.

Strengths and limitations

Our study has some strengths. First, we only included RCTs to reduce selection bias, which led to a relatively homogeneous population. We used standard Cochrane protocols and had the largest cumulative RCTs study sample size to date. One of the differences that our study has compared with previous reports is the inclusion of the two recently published RCTs [17, 22], which were not included in the prior meta-analysis. This accounts for the differences in our results from those of earlier systematic reviews [9, 35–37]. Second, we included trials with lower AKI severity, which showed accelerated KRT probably does not benefit patients as the Z curve crossed the neutrality line. Such analysis would increase the generalizability of our findings.

There are some limitations in this study that should be addressed. First, we did not find differences in the rate of all-cause mortality. This notion was likely due to a relatively high heterogeneity in disease progression that led to inaccurate prediction of death by the AKI severity at the time of inclusion. Second, older studies did not clearly use the standard AKI definitions [e.g., RIFLE (risk, injury, failure, loss of kidney function and end-stage kidney disease), KDIGO] [18, 19]. Third, the definition of accelerated versus WWS-KRT was not homogeneous in the enrolled studies. However, after adjusting the time to dialysis, a similar risk of mortality with these two strategies was noted. Fourth, we could not ascertain the reason for the observed improved KRT independence among patients in the WWS-KRT group.

CONCLUSIONS

Accelerated KRT for critically ill patients with advanced AKI did not improve survival compared with the WWS-KRT group. At the same time, WWS-KRT resulted in a lower incidence of 90-day KRT dependence, hypotension and infection. We also showed that when AKI biomarkers guide WWS-KRT, it could lead to a lower 90-day KRT-dependence. Therefore, among critically ill patients with medically manageable AKI, the WWS-KRT strategy should be considered.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHORS' CONTRIBUTIONS

V.-C.W. chaired the group, conceived and designed the study, performed the statistical analysis, and contributed to data collection, data interpretation and critical revision of the manuscript. J.-Y.C., Y.-Y.C. and H.-C.P. conducted a literature search, performed statistical analysis and wrote the manuscript. C.-C.S. and C.-T.H. performed a literature search, wrote the manuscript and performed a critical revision of the manuscript. T.-M.H., C.-C.H. and T.-W.H. performed a literature search and summary. Y.-T.H. registered the PROSPERO. K.K. and V.-C.W. wrote the manuscript

and performed a critical review of the manuscript. All authors contributed to subsequent drafts and examined the article.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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