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# The Timing of Continuous Renal Replacement Therapy Initiation in Sepsis-associated Acute Kidney Injury in the Intensive Care Unit: the CRTSAKI study (Continuous RRT Timing in Sepsis-associated AKI in ICU): study protocol for a multicenter, randomized controlled trial



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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-040718 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 20-May-2020 |
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| Keywords: | Acute renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY, INFECTIOUS DISEASES, INTENSIVE & CRITICAL CARE |
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Title page

# The Timing of Continuous Renal Replacement Therapy Initiation in Sepsis-associated Acute Kidney Injury in the Intensive Care Unit: the CRTSAKI study (Continuous RRT Timing in Sepsis-associated AKI in ICU): study protocol for a multicenter, randomized controlled trial

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Word count: 3,936 words

## ABSTRACT

**Introduction:** Acute kidney injury (AKI) is one of the most common organs dysfunction in sepsis, and increases the risk of unfavorable outcomes. Renal replacement therapies (RRT) is the predominant treatment for sepsis-associated AKI (SAKI). However, no adequate prospective randomized study has addressed whether initiating RRT earlier will attenuate renal injury and improve the outcome of sepsis to date. The objective of the trial is to compare early with delayed strategy on the outcomes of patients with SAKI in intensive care unit (ICU).

**Methods and analysis:** This is a large-scale, multicenter, randomized controlled trial about SAKI. In total, 460 patients with sepsis and evidence of AKI stage 2 of KDIGO will be recruited and equally randomized into the early group and the delayed group at 1:1 ratio. In the early group, continuous RRT (CRRT) will started immediately after randomization. In the delay group, CRRT will initiated if at least one of the following criteria was met: stage 3 of KDIGO, severe hyperkalemia, pulmonary edema, blood urea nitrogen (BUN) level higher than 112 mg/dl after randomization. The primary outcome is overall survival in a 90-day follow-up period (90-day all-cause mortality). Other endpoints include 28-day mortality, 60-day mortality, recovery rate of renal function by day 28 and day 90, ICU and hospital length of stay, the numbers

of CRRT-free days, mechanical ventilation-free days and vasopressor-free days, the rate of complications potentially related to CRRT, CRRT-related cost, and concentrations of inflammatory mediators in serum.

**Ethics and dissemination:** The trial has been approved by the Clinical Research and Application Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical University (2017-31-ks-01). Participants will be screened and enrolled from ICU patients with SAKI by clinicians, with no public advertisement for recruitment. Results will be disseminated in research journals and through conference presentations.

**Trial registration:** NCT03175328.

## ARTICLE SUMMARY

### Strengths and limitations of this study

- CRTSAKI study is one of the very few large-scale, multicenter, prospective, two-arm randomized controlled trial designed to compare early with delayed initiation of CRRT on the outcomes of patients with SAKI in ICU.
- All participants will be enrolled at KDIGO stage 2 AKI and receive CRRT within 8 hours after randomization in the early group.
- Positive results will help clinician choose appropriate timing to initiate CRRT and improve outcomes of SAKI.
- A risk of “unnecessary” CRRT and the rate of complications potentially

related to CRRT might be increase in the early group.

- A limitation of the study is its single-blind design, which would yield bias, although blind evaluation is adopted to minimize bias.

## INTRODUCTION

As a life-threatening syndrome with organ dysfunction caused by infection, sepsis continues to be a major global concern because of its increasing incidence and high mortalityc[1-2]. As far as we know, sepsis is a leading cause of acute kidney injury (AKI) in intensive care unit (ICU). In turn, as an independent risk factor, AKI increases mortality of sepsis. It is reported that the mortality of sepsis-associated AKI (SAKI) is from 30 to 60 %[3-6]. Undoubtedly, RRT is an important method for AKI. But the optimal timing of initiation of RRT remains controversial. Several studies have tried to provide an answer to this dilemma. A meta-analysis from Karvellas CJ et al.[7] in 2011 demonstrated that earlier initiation of RRT may have a significant improvement in 28-day mortality. While several meta-analyses in recent years[8-10] suggested that early initiation of RRT didn't provide an advantage on improving survival, but was associated with a significant reduction in hospital length of stay (LOS). However, the strength of the conclusion was weakened by the heterogeneous definition of "early" or "late" in these studies. Two high quality RCTs published in 2016 also reported contradictory results. The ELAIN study[11] showed that early initiation of RRT significantly reduced 90-day mortality. Here "early RRT" was initiated at stage 2 of Kidney Disease

Improving Global Outcomes (KDIGO) classification, and “delayed RRT” was initiated at stage 3 of KDIGO classification or if absolute indications for RRT were present. The AKIKI study[12] found no significant difference in 60-day mortality between an early and a delayed strategy for the initiation of RRT. In this study, all patients were required to have KDIGO stage 3 AKI. “Early” meant initiating RRT within 6 hours after randomization, and “delayed” meant initiating RRT if the absolute indications for RRT were present or if oliguria or anuria lasted for more than 72 hours after randomization. In addition to differences in population, it is hard to exclude that the differences in outcomes of these two studies are caused by differences in timing of RRT initiation. When compared to non-septic AKI, patients with SAKI are generally sicker, greater aberrations in hemodynamics and laboratory parameters, higher need for mechanical ventilation and vasoactive drug therapy, have longer duration of stay in both ICU and hospital[13-14] . The pathophysiology of SAKI is complex and remains only partially understood. Animal studies revealed that at the early stage of SAKI mainly involves functional changes, minimal structural kidney lesions[15]. In the past, it was believed that renal hypoperfusion was the major contributor of SAKI. Recently, our understanding has been improved on this topic. Inflammatory damage was thought to be the key pathophysiologic process. TLRs recognize PAMPs and DAMPs, trigger inflammation and tissue injury, induce microvascular thrombus formation, vascular permeability and interstitial edema, impair renal microcirculatory disturbance, cause renal

venous congestion, lower the glomerular filtration rate (GFR) at last[16-17]. It is reported that a correlation was observed between the concentrations of circulating inflammatory cytokines and mortality in patients with septic shock[18-20]. In an observational study, Sood MM et al.[3] found that early reversible AKI was associated with improved survival in sepsis. Therefore, it is hypothesis that adequate removal of inflammatory mediators from the circulation, avoiding fluid overload to reduce renal venous congestion and interstitial edema, may provide a potential therapy for this devastating condition. It is demonstrated that early continuous RRT (CRRT) not only can stabilized the internal environment, but also can remove inflammatory mediators[21]. Thus, it is supposed that an early strategy may control excessive inflammation as early as possible, which can reduce kidney injury and benefit to improve survival. A systematic review and meta-analysis in 2019[22], which recruited 5 trails including 900 patients with SAKI, suggests that earlier initiation is not associated with survival improvement. However, the finding should be interpreted with caution. In fact, three of them supported that early initiation of CRRT could improve 28-day mortality, but the sample size was small[23-25]. Among these 5 studies, one study was the multicenter IDEAL-ICU study, which included 488 patients from 29 mixed medical and surgical ICUs. RRT was initiated within 12 hours following the diagnosis of RIFLE failure (RIFLE-F) AKI (equivalent to KDIGO stage 3) in the early group, and 48 hours after diagnosis of RIFLE-F AKI or if the absolute indications for RRT were present

in the delayed group. It is shown that there is no difference between the two strategies. However, 41 patients (17 %) in the delayed group needed emergency RRT. Of note, mortality in this subgroup increased significantly (68 %)[26].

To the best of our knowledge, only one such large randomized controlled study focusing on timing of RRT in patients with SAKI has been published. More studies are needed to clarify this issue. Moreover, considering the characteristics of SAKI, the “early strategy” in AKIKI study and IDEAL-ICU study may still be too late. Therefore, we propose another multicenter RCT on the impacts of mortality of the timing of CRRT initiation in patients with SAKI.

## METHODS AND ANALYSIS

### Study design, setting and patient population

The CRTSAKI study is a prospective, open-label, two-arm, multicenter, randomized, controlled study. All patients admitted to the ICUs of participating centers will be considered as potential candidates for the study. Once the patient is diagnosis of SAKI stage 2, he/she should be screened for eligibility by the physicians within 2 h. When the patient fulfills the criterion of recruitment, written informed consent should be obtained from the patient or a responsible surrogate before randomized.

The study will be conducted in 13 ICUs in Guangdong, China. Patient enrolment, intervention and follow-up are performed at the Second Affiliated Hospital of

Guangzhou Medical University, Dongguan People's Hospital, Guangdong Provincial People's Hospital, Guangdong No.2 Provincial People's Hospital, Guangzhou Red Cross Hospital, Huizhou Municipal Central Hospital, Guangzhou Panyu Central Hospital, the Six Affiliated Hospital of Guangzhou Medical University (Qingyuan People's Hospital), Shenzhen People's Hospital, Yue Bei People's Hospital, People's Hospital of Yangjiang, Zhongshan City People's Hospital and Sun Yat-sen Memorial Hospital in China. The study is expected to last for 2.5 years. Recruitment of participants has started in August 2019.

**Inclusion criteria**

1. Age between 18 and 90 years.
2. Patients admitted into ICU with Sepsis (sepsis-3)[1] compatible with the diagnosis of AKI at stage 2 of KDIGO classification.

- Sepsis-3: an increase in the SOFA score of 2 points or more caused by a dysregulated host response to infection.
- > 2 folds increase of SCr level compared to the baseline value and/or urine output (UO) < 0.5 ml/kg/h for 12 h.

3. Informed consent provided by the patient or person with decisional responsibility.

**Exclusion criteria**

1. Presence of one of the emergent CRRT conditions before randomization:

- Hyperkalemia > 6.0 mmol/L or > 5.5 mmol/L persisting despite medical treatment.
- Acute pulmonary edema due to fluid overload responsible for severe hypoxemia requiring oxygen flow rate > 5 L/min to maintain a percutaneous oxygen saturation ($SpO_2$) > 95% or a fraction of inspiration oxygen ($FiO_2$) > 50% in patients already on invasive or non-invasive mechanical ventilation and despite diuretic therapy.
- Blood urea nitrogen (BUN) > 112 mg/dl (40 mmol/L).

2. Pre-existing severe chronic renal failure [estimated glomerular filtration rate (eGFR) < 30 ml/min].
3. Previous renal replacement therapy.
4. Prior kidney transplant.
5. AKI caused by permanent postrenal obstruction or surgical lesion of renal vessel.
6. Pregnancy
7. Hepatorenal syndrome.
8. Acquired immune deficiency syndrome (AIDS)
9. Patient for whom survival to 90 days is unlikely due to end-stage diseases.
10. Patient is moribund with expected death within 24 h
11. Patient included in another interventional clinical trial

## Study definitions

### *Sepsis and septic shock*

Sepsis is defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[1] as a life-threatening syndrome with organ dysfunction caused by infection. For clinical diagnosis, patients can be identified by an increase in the SOFA score of 2 points or more caused by a dysregulated host response to infection. Septic shock, a subset of sepsis, can be identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater and serum lactate greater than 2 mmol/L despite of resuscitation.

### *Acute renal failure*

AKI will be defined and classified according to the KDIGO classification (table 1). AKI is identified by at least one of the following:

- An increase in SCr by ≥ 26.5 μmol/L within 48 h.
- An increase in SCr to ≥ 1.5 times baseline within the previous 7 days.
- Urine volume ≤ 0.5 ml/kg/h for 6 h.

**Table 1. KDIGO stage criteria for AKI**

| Stage | SCr | UO |
|---|---|---|
| 1 | 1.5-1.9 times baseline or ≥ 26.5 μmol/L increase | < 0.5 ml/kg/h for 6-12 h |
| 2 | 2.0-2.9 times baseline | < 0.5 ml/kg/h for ≥ 12 h |

| | | |
|---|---|---|
| 3 | ≥ 3 times baseline<br>or ≥ 353.6 μmol/L increase<br>or initiation of RRT<br>or in patients < 18 years a decrease in eGFR < 35 ml/min/1.73 $m^2$ | < 0.3 ml/kg/h for ≥24 h or anuria ≥ 12 h |

*Recovery of renal function*

Recovery of renal function will be classified as complete recovery, partial recovery or no recovery.

- Complete recovery of renal function will be defined as a SCr elevates ≤ 44.2 μmol/L compared to the baseline.
- Partial recovery will be defined as a SCr elevates > 44.2 μmol/L compared to the baseline, but not depending on dialysis.
- No recovery of renal function will be defined as patients who remained dialysis-dependent at time of death or study completion.

**Study intervention**

The study flow chart is detailed in Figure 1.

*Early CRRT group*

Patients randomized to the early CRRT group will initiate CRRT as fast as possible. A maximum of 8 h is allowed between randomization and the actual initiation of CRRT. The timing of initiation and cessation, the data of CRRT

are recorded by nurses.

*Delayed CRRT group*

Patients randomized to the delayed CRRT group will be observed closely. SCr will be measured at least 1 time/12 h until renal function recovery or one of the following criteria is met:

1. AKI develops to stage 3 of KDIGO classification [≥ 3 times baseline SCr level or SCr concentration > 353.6 μmol/L, and/or urine output < 0.3 ml/kg/h for more than 24 h or anuria (urine output < 100 ml) for more than 12 h ].
2. Presence of one of the emergent CRRT conditions after randomization:
   - Hyperkalemia > 6.0 mmol/L.
   - Acute pulmonary edema.
   - BUN > 112 mg/dl (40 mmol/L).

CRRT will be initiated when one of the above criteria is met. A maximum of 8 h is allowed between the appearance of indication and the actual initiation of CRRT. If the renal function of patients is recovery in the delayed group, initiation of CRRT can be avoided. The indication and timing of initiation and cessation, the data of CRRT are recorded by nurses.

*Modality of CRRT*

In order to keep uniformity of therapy between early and delayed CRRT group, identical settings of CRRT will be used in both groups. All patients undergoing CRRT will be treated using continuous veno-venous hemofiltration

(CVVH) or continuous veno-venous hemodiafiltration (CVVHDF). The rate of blood flow is recommended for 100-200 ml/min. The effluent flow will be prescribed based on the patient's body weight at the time of randomization and will be 20-25 ml/kg/h. The choice of vascular access, the strategy of anticoagulation is left to the investigator's discretion. Once CRRT is initiated, treatment is recommended to maintain at least 24 h. The membranes should be changed at least 72 h. In the absence of criteria for CRRT cessation or "intermittent", the interval of CRRT interruption should not be more than 24 h.

*Cessation or alternation of CRRT*

- "Intermittent" CRRT

If urine output ≥ 500 ml/24h without diuretics or ≥ 1000 ml/24h with diuretics, the interval of CRRT interruption is left to the investigator's discretion.

- Cessation of CRRT

CRRT will be discontinued if urine output is ≥ 1000 ml/24h without diuretics or ≥ 2000 ml/24h with diuretics, and creatinine clearance is > 20 ml/min.

- Alternation of CRRT

If cessation criteria are not fulfilled until the patient leaves ICU, CRRT can be changed to other RRT modality [i.e, intermittent hemodialysis (IHD), peritoneal dialysis (PD), prolonged intermittent RRT (PIRRT)].

**Additional treatments**

Management of sepsis and septic shock will follow the international guidelines

of Surviving Sepsis Campaign 2016 and 2018[27-28]. The patient's primary physicians will determine the management of other comorbidities. The dose of all medications will be adjusted for renal function and CRRT.

### Primary objective

The primary study endpoint is overall mortality measured from the date of randomization (D0) until death or day 90. For patients who were discharged alive from ICU, information on the primary endpoint will be acquired by a telephone call.

### Secondary and other objectives

The secondary endpoints include: (1) 28-day, 60-day and 1-year all-cause mortality; (2) recovery rate of renal function by day 28 and day 90; (3) ICU and hospital length of stay (LOS); (4) the percentage of receipt of CRRT at least once in the delayed group; (5) the number of days alive without CRRT, mechanical ventilation and vasopressor (the numbers of CRRT-free days, mechanical ventilation-free days and vasopressor-free days, between D0 and up to D90); (6) the Sequential Organ Failure Assessment (SOFA) score at day 0, 1, 3, 7, 14 and day 28; (7) impacts on other organ functions (heart, lung, liver); (8) the rate of complications potentially related to CRRT, including: (a) major bleeding associated with anticoagulants (defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial,

intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells) [29], (b) thrombosis of a large venous axis diagnosed by Doppler ultrasound, (c) catheter-related bloodstream infection (CRBSI)[30], (d) thrombocytopenia (< 100 × $10^9$ platelets/$mm^3$), (e) hypothermia (defined as a core body temperature of less than 35 ℃ or need electric blanket to keep warm), (f) hemodynamic instability due to CRRT and requiring the introduction or increase of vasopressor, (g) pulmonary edema during CRRT, (h) hyperkalemia (defined as serum potassium concentration > 6.5 mmol/L), (i) hypokalemia (defined as serum potassium concentration < 3.0 mmol/L), (j) new onset of serious arrhythmia during CRRT (including atrial fibrillation, ventricular tachycardia, ventricular fibrillation and torsades de pointes).

Other endpoints include: (1) cost analysis of CRRT; (2) duration between randomization to CRRT initiation; (3) duration between appearance of at least one of the criteria that initiated CRRT in the delayed group and actual initiation.

Add-on study: (1) new biomarkers of AKI; (2) concentrations of inflammatory mediators in serum will be analyzed between two groups [such as interleukin (IL)-1, IL-6 and tumor necrosis factor-alpha (TNF-α)].

### Sample size

The primary endpoint in this study is to compare the effect of early and delayed CRRT strategy on overall survival at day 90 in patients with SAKI. Our primary hypothesis is that the early CRRT strategy might beneficial to patients with SAKI. According to IDEAL-ICU study, the expected mortality of patients with SAKI in the delayed group may be estimated around 55%. Considering that the timing setting of CRRT in this study is similar to ELAIN study, a reduction in mortality of 15% in the early group (55% mortality in the delayed CRRT group versus 40% in the early CRRT group) can be expected. Differences between two groups will be detected with a power of 85% at a bilateral alpha risk of 0.05. Considering that in China, some patients will give up treatment and request discharged from hospital due to economic reason or customs, the rate of non-evaluable cases is expected to be 15% for the worst. Hence, a total of 460 patients (230 per group) are required. Power calculations were performed using the PASS 14.0 software.

### Randomization and blinding

Eligible patients are consecutively randomly assigned to either early group or delayed group in a 1:1 ratio. This allocation is achieved using a centralized, secure, computer-generated, web-response system accessible from each study center. The randomization is balanced by blocks of variable and undisclosed size, and stratified according to center. The block size is 6. The

randomization day is study day zero (D0). Because this is an interventional study, blinding is not possible for physicians, nurses and patients. However, the analysis will be blinded to allocation of groups.

### Data collection and follow-up

Each investigator from the 13 participating ICUs was trained to the protocol, electronic random system and data collection in the electronic Case Record Form (eCRF) before trial initiation. The electronic random system and eCRF are developed with Guangzhou Baofeng Pharmaceutical technology co. LTD, managed and closed by the Clinical Research center of the Second Affiliated of Guangzhou Medical University (China). It is a centralized, secure, web-response system accessible from each study center.

Flowchart of patient follow-up was shown in table 2. Demographic data and medical history, including nephrotoxic agents (i.e. contrast agent, aminoglycoside antibiotics, tacrolimus, amphotericin B, hydroxyethyl starch, vancomycin) use nearly 1 week will be collected. Details data including reasons for ICU admission, cause of SAKI, acute physiology and chronic health evaluation II (APACHEII) score, dates of hospital and ICU admission will be recorded. Details of mechanical ventilation, vasopressor, CRRT, diuretics, urine output, fluid balance will be documented daily. SOFA scores will be evaluated at baseline, D1, 3, 7, 14, 28. Blood will be collected at baseline, D1, D3, D7 and D14. Results of laboratory tests including white

blood cell count and differentials in peripheral circulation, serum electrolyte levels, serum glucose level, urea and creatinine concentration, liver and myocardial enzyme concentrations, arterial blood gas analysis, procalcitonin and lactate will be recorded. Biomarkers of AKI and inflammatory factors (i.e. IL-1β, IL-6, TNF-α, CRP) are planned to be tested.

During CRRT intervention, details of initiation, cessation, setting parameters, complications will be collected. SCr and urine output will be monitored daily to ensure whether criteria for CRRT discontinuation is present. All recruited patients will be followed to determine adverse events, renal function recovery and mortality until death or at 28, 60 90 days after randomization.

**Table 2. Flowchart of patient follow-up**

| | screening | D0 inclusion | Study period | Death/D90 |
|---|---|---|---|---|
| **Baseline information** | | | | |
| Demographic data and history | √ | √ | | |
| Inclusion and exclusion criteria | √ | | | |
| written informed consent | √ | | | |
| Vital signs | | √ | | |
| APCHEII/SOFA | | √ | √D1, 3, 7, 14, 28 | |
| **Efficacy observation** | | | | |

| | | | | |
|---|---|---|---|---|
| Mechanical ventilation | | √ | √ | |
| Treatment with vesopressor | | √ | √ | |
| CRRT initiation and application | | √ | √ | |
| UO and diuretic application | | √ | √ | |
| Renal function recovery | | | √ D28 | √ |
| UCG and ECG | | | √ D1, D14 | |
| Laboratory tests | √ | √ | √ D1, 3, 7, 14 | |
| Biomarkers and inflammatory factors | | √ | √ D1, 3, 7 | |
| **Safety observation** | | | | |
| Complications of CRRT | | √ | √ | |
| Adverse event | | √ | √ | |
| **Additional observation** | | | | |
| Total cost of CRRT | | | | √ |
| ICU and hospital LOS | | | | √ |
| Alive or dead status | | | √ D28, 60 | √ |



**Statistical analysis**

Data will be double checked by the clinical research team, and the data base is managed and closed by the Clinical Research center of the Second Affiliated of Guangzhou Medical University (China)。

For each group, quantitative variables with normal distribution will be described as mean and standard deviation. Quantitative variables with skewed distribution will be described as median (*M*) and inter-quartile range (IQR, 25$^{th}$ percentile to 75$^{th}$ percentile). Qualitative variables will be described as frequency and percentage.

The primary endpoint (all-cause mortality at 90 days) will be performed according to the intent-to-treat (ITT) principle. This dataset includes all trial subjects enrolled into the trial and randomized. Additional sensitivity analyses will be performed according to the per-protocol (PP) principle. This dataset includes all trial subjects who were treated according to protocol and reached a defined endpoint in the trial. The effect of early versus delayed initiation of CRRT on all-cause 90 days mortality will be performed using chi-squared test, with secondary analysis by the Kaplan-Meier method, comparison using a (two-sided) stratified log rank test (global significance level 5%, power 80%). Safety will be analyzed by the frequency of complications related to CRRT in both treatment groups and comparing rates using chi-square or Fisher's exact test, with an alpha risk set at 0.05.

Statistical analyses of the pre-specified secondary endpoints will be performed with descriptive and inductive statistical methods. Categorical variables will be compared using the chi-square or Fisher's exact test, as appropriate. Continuous variables will be compared using Student's *t* test or the Mann-Whitney test, as appropriate.

The primary efficacy analysis provides confirmative evidence. Further analyses will be regarded explorative (hypothesis generating) and will be interpreted accordingly. All point estimates of parameters of interest will be supplemented by 95% confidence intervals. Type I error enhancement due to multiple significance testing will be accounted for if applicable.

Statistical analyses will be performed according to the principles of the ICH-guideline E9 “Statistical Principles for Clinical Trials” using SAS version 9.4, or R software version 3.6.3 or later.

### Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. The results will be available to the public if necessary.

## ETHICS AND DISSEMINATION

The study protocol has been approved by the Clinical Research and Application Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical University (version 2.0, registration number: 2017-31-ks-01; date of approval: 29 October 2018). Participants will be screened and enrolled from ICU patients with SAKI by clinicians, with no public advertisement for recruitment. When the patient fulfills the criterion of recruitment, written informed consent should be obtained from the patient or a

responsible surrogate before randomized. All information from the participants will be kept private and will not be provided to any company or institution. Results will be disseminated in research journals and through conference presentations.

## DISCUSSION

Sepsis is the leading cause of AKI in the ICU, which often manifests as part of the multiple organ dysfunction syndrome (MODS). AKI during sepsis is an independent contributor to mortality. Early reversible AKI was associated with improved survival in sepsis[3]. It is reported that there is no acute tubular necrosis and only intracellular and metabolic modifications are observed in the early phases of SAKI[17]. Therefore, it is supposed that an early strategy which can reduce kidney injury may benefit to improve survival. Unfortunately, there are currently no pharmacological treatments available to SAKI therapy. CRRT is considered to be the most effective therapy to SAKI when the renal function becomes insufficient to maintain internal environmental stability. However, when to start CRRT remains a particularly challenging question during SAKI in critical ill patients. In 2018, IDEAL-ICU study shown that there is no difference between the two strategies. However, 41 patients (17 %) in the delayed group needed emergency RRT and have higher mortality[26]. On the one hand, Barbar et al.[31] thought it is unacceptable to expose 30% of patients to the potential risks of an extracorporeal support

technique if they do not actually need it. On the other hand, others argued that although there may be a risk of "unnecessary" RRT, there could be an even greater risk associated with not providing it. To the best of our knowledge, only one such large randomized controlled study focusing on timing of RRT in patients with SAKI has been published. Therefore, more studies are needed to clarify this issue.

Look at the previous studies on RRT timing of AKI, not only the conclusions were different, the definitions of "early" or "late" were different. In ELAIN study[11], "early RRT" was initiated at stage 2 of KDIGO classification. In AKIKI study[12], all patients were required to have KDIGO stage 3 AKI. "Early" meant initiating RRT within 6 hours after randomization. In IDEAL-ICU study, "early" meant initiating RRT within 12 hours following the diagnosis of RIFLE-F AKI (equivalent to KDIGO stage 3). Considering that the patients with SAKI are generally sicker than the patients with non-SAKI, the "early strategy" in AKIKI study and IDEAL-ICU study may still be too late. It might be preferred to initiate RRT at an earlier stage which was similar to that in ELAIN study. Therefore, we chose all patients with KDIGO stage 2 AKI. CRRT was initiated within 8 hours after randomization in the early group, and 8 hours after AKI developing to stage 3 of KDIGO classification or presence of one of the emergent CRRT conditions after randomization.

We hypothesize that initiating CRRT early enough may attenuate renal injury from systemic inflammation, acidemia, uremia and fluid overload in sepsis

patients. If this study confirms our hypothesis, it may help to improve mortality for patients with SAKI. Negative result will also encourage us to pay a deeper attention to details underlines insightful information: is there a way to better predict which patients are likely to require RRT and which patients have a high likelihood of spontaneous recovery?



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**Contributors** Xu-ming Xiong, Zhen-hui Zhang, Wei-yan Chen and Li-hua Cai designed the trial. Xu-ming Xiong obtained funding for the trial. Wei-yan Chen and Li-hua Cai drafted the manuscript. Xu-ming Xiong and Zhen-hui Zhang provided a critical revision of the manuscript. All authors discussed and help to improve the protocol, read and approved the final manuscript.

**Funding** This study was funded by a Grant from Guangzhou Medical University (B195001009).

**Competing interests** None declared.

**Patient and public involvement** Not required.

**Patient consent for publication** Not required.

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## Figure legend:

**Figure 1. Flow chart of the trial.** SAKI, sepsis-associated acute kidney injury; AKI, acute

kidney injury; KDIGO, Kidney Disease: Improving Global Outcome; CRRT, continuous renal replacement therapy; D90, day 90.

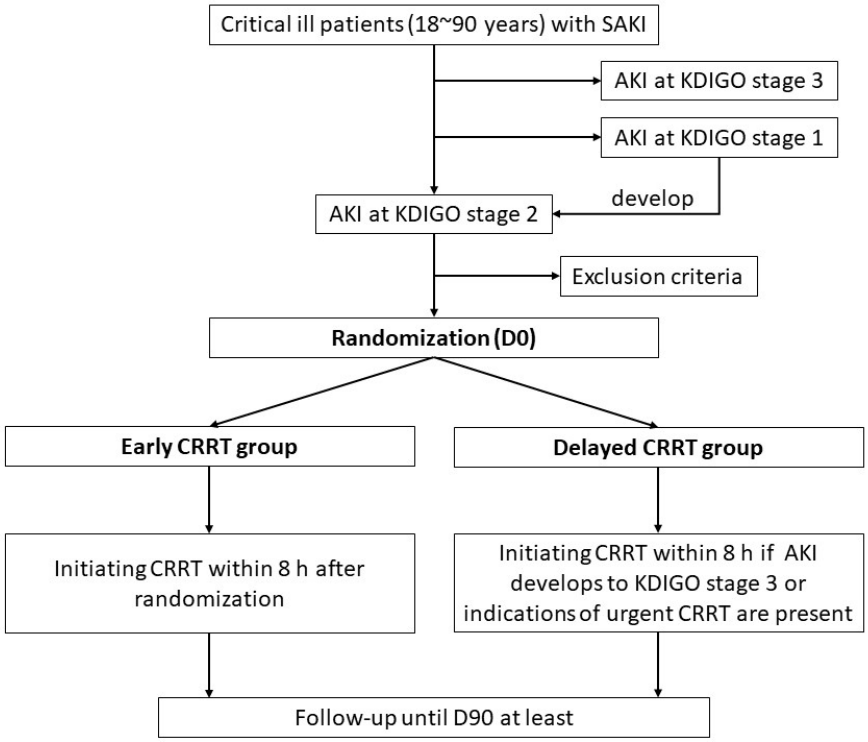


Figure 1. Flow chart of the trial. SAKI, sepsis-associated acute kidney injury; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcome; CRRT, continuous renal replacement therapy; D90, day 90.

254x190mm (96 x 96 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |

| | | | |
|---|---|---|---|
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | N/A |
| Protocol version | #3 | Date and version identifier | 19 |
| Funding | #4 | Sources and types of financial, material, and other support | 21-22 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 1, 21 |
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | N/A |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | N/A |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and | 16-17 |

| | | | |
|---|---|---|---|
| | | other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | |
| **Introduction** | | | |
| Background and rationale | #6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4-7 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 7 |
| Objectives | #7 | Specific objectives or hypotheses | 7, 13-14 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 7 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7-8 |

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|---|---|---|---|
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 8-9 |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 11 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | 12 |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | N/A |
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 13 |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 13-14 |

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| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 16-17 |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 14-15 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 14-15 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 15 |
| Allocation concealment mechanism | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 15 |

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| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 15 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 15 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 15 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 16 |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be | 16 |

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| | | collected for participants who discontinue or deviate from intervention protocols | |
| Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 16 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 17-18 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 18 |
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 17-18 |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the | 17 |

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| | | protocol. Alternatively, an explanation of why a DMC is not needed | |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 13-14, 18 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 17 |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 19 |
| Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) | N/A |

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|---|---|---|---|
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 19 |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 16 |
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | N/A |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 16 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 13 |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 19 |

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| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | 19 |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 19 |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | 19 |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | 16-17 |

BMJ Open

# The Timing of Continuous Renal Replacement Therapy Initiation in Sepsis-associated Acute Kidney Injury in the Intensive Care Unit: the CRTSAKI study (Continuous RRT Timing in Sepsis-associated AKI in ICU): study protocol for a multicenter, randomized controlled trial



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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-040718.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 05-Dec-2020 |





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| Complete List of Authors: | Chen, Wei-yan; Guangzhou Medical University Second Affiliated Hospital, Intensive Care Unit<br>Cai, Li-hua; Dongguan People's Hospital, Critical Care Medicine<br>Zhang, Zhen-hui; Guangzhou Medical University Second Affiliated Hospital, Intensive Care Unit<br>Tao, Li-li; Guangzhou Medical University Second Affiliated Hospital, Intensive Care Unit<br>Wen, Yi-chao; Guangzhou Medical University Second Affiliated Hospital, Intensive Care Unit<br>Li, Zhi-bo; Guangzhou Medical University Second Affiliated Hospital, Intensive Care Unit<br>Li, Li; Yue Bei People's Hospital, Critical Care Medicine<br>Ling, Yun; Huizhou Municipal Central Hospital, Critical Care Medicine<br>Li, Jian-wei; Zhongshan City People's Hospital, Critical Care Medicine<br>Xing, Rui; Guangdong No.2 Provincial People's Hospital, Intensive Care Unit<br>Liu, Xue-yan; Shenzhen People's Hospital, Intensive Care Unit<br>Lin, Zhuan-di; Guangzhou Panyu Central Hospital, Intensive Care Unit<br>Deng, Zhe-tong; Guangzhou Red Cross Hospital, Critical Care Medicine<br>Wang, Shou-hong; Guangdong Academy of Medical Sciences, Critical Care Medicine<br>Lin, Qin-han; The Sixth Affiliated Hospital of Guangzhou Medical University, Critical Care Medicine<br>Zhou, Dun-rong; People's Hospital of Yangjiang, Intensive Care Unit<br>He, Zhi-jie; Sun Yat-Sen University Sun Yat-Sen Memorial Hospital, Critical Medicine<br>Xiong, Xu-ming; Guangzhou Medical University Second Affiliated Hospital, Intensive Care Unit |
| Primary Subject Heading: | Intensive care |
| Secondary Subject Heading: | Renal medicine |
| Keywords: | Acute renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY, INFECTIOUS DISEASES, INTENSIVE & CRITICAL CARE |

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**Title page**

# The Timing of Continuous Renal Replacement Therapy Initiation in Sepsis-associated Acute Kidney Injury in the Intensive Care Unit: the CRTSAKI study (Continuous RRT Timing in Sepsis-associated AKI in ICU): study protocol for a multicenter, randomized controlled trial

Wei-yan Chen[1#], Li-hua Cai[2#], Zhen-hui Zhang[1], Li-li Tao[1], Yi-chao Wen[1], Zhi-bo Li[1], Li Li[3], Yun Ling[4], Jian-wei Li[5], Rui Xing[6], Xue-yan Liu[7], Zhuan-di Lin[8], Zhe-tong Deng[9], Shou-hong Wang[10], Qin-han Lin[11], Dun-rong Zhou[12], Zhi-jie He[13], Xu-ming Xiong[1*]

[#] This author contributed equally to the work.

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Word count: 4,087 words

**ABSTRACT**

**Introduction:** Acute kidney injury (AKI) is one of the most common organs dysfunction in sepsis, and increases the risk of unfavorable outcomes. Renal replacement therapy (RRT) is the predominant treatment for sepsis-associated AKI

(SAKI). However, no adequate prospective randomized study has addressed whether initiating RRT earlier will attenuate renal injury and improve the outcome of sepsis to date. The objective of the trial is to compare early with delayed strategy on the outcomes of patients with SAKI in intensive care unit (ICU).

**Methods and analysis:** This is a large-scale, multicenter, randomized controlled trial about SAKI. In total, 460 patients with sepsis and evidence of AKI stage 2 of KDIGO will be recruited and equally randomized into the early group and the delayed group at 1:1 ratio. In the early group, continuous RRT (CRRT) will started immediately after randomization. In the delay group, CRRT will initiated if at least one of the following criteria was met: stage 3 of KDIGO, severe hyperkalemia, pulmonary edema, blood urea nitrogen (BUN) level higher than 112 mg/dl after randomization. The primary outcome is overall survival in a 90-day follow-up period (90-day all-cause mortality). Other endpoints include 28-day, 60-day and 1-year mortality, recovery rate of renal function by day 28 and 90, ICU and hospital length of stay, the numbers of CRRT-free days, mechanical ventilation-free days and vasopressor-free days, the rate of complications potentially related to CRRT, CRRT-related cost, and concentrations of inflammatory mediators in serum.

**Ethics and dissemination:** The trial has been approved by the Clinical Research and Application Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical University (2017-31-ks-01). Participants will be screened and enrolled from ICU patients with SAKI by clinicians, with no public advertisement for recruitment. Results will be disseminated in research journals and through conference presentations.

**Trial registration:** NCT03175328.

## ARTICLE SUMMARY

### Strengths and limitations of this study

- CRTSAKI study is one of the very few large-scale, multicenter, prospective, two-arm randomized controlled trial designed to compare early with delayed initiation of CRRT on the outcomes of patients with SAKI in ICU.
- All participants will be enrolled at KDIGO stage 2 AKI and receive CRRT within 8 hours after randomization in the early group.
- Positive results will help clinician choose appropriate timing to initiate CRRT and improve outcomes of SAKI.
- A risk of "unnecessary" CRRT and the rate of complications potentially related to CRRT might be increase in the early group.
- A limitation of the study is its single-blind design, which would yield bias, although blind evaluation is adopted to minimize bias.

## INTRODUCTION

As a life-threatening syndrome with organ dysfunction caused by infection, sepsis continues to be a major global concern because of its increasing incidence and high mortality[1-2]. As far as we know, sepsis is a leading cause of acute kidney injury (AKI) in intensive care unit (ICU). In turn, as an independent risk factor, AKI increases

mortality of sepsis. It is reported that the mortality of sepsis-associated AKI (SAKI) is from 30 to 60 %[3-6].

Undoubtedly, renal replacement therapy (RRT) is an important method for AKI. But the optimal timing of RRT initiation remains controversial. Several studies have tried to provide an answer to this dilemma. A meta-analysis from Karvellas CJ et al.[7] in 2011 demonstrated that earlier initiation of RRT may have a significant improvement in 28-day mortality. While several meta-analyses in recent years[8-10] suggested that early initiation of RRT didn't provide an advantage on improving survival, but was associated with a significant reduction in hospital length of stay (LOS). However, the strength of the conclusion was weakened by the heterogeneous definition of "early" or "late" in these studies. Two high quality RCTs published in 2016 also reported contradictory results. The ELAIN study[11] showed that early initiation of RRT significantly reduced 90-day mortality. Here "early RRT" was initiated at stage 2 of Kidney Disease Improving Global Outcomes (KDIGO) classification, and "delayed RRT" was initiated at stage 3 of KDIGO classification or if absolute indications for RRT were present. The AKIKI study[12] found no significant difference in 60-day mortality between an early and a delayed strategy for the initiation of RRT. In this study, all patients were required to have KDIGO stage 3 AKI. "Early" meant initiating RRT within 6 hours after randomization, and "delayed" meant initiating RRT if the absolute indications for RRT were present or if oliguria or anuria lasted for more than 72 hours after randomization. Another large RCT (STARRT-AKI) published in this year, which included 3019 patients with a 2-fold increase in serum creatinine (SCr), demonstrated that an accelerated renal-replacement strategy was not associated with a lower risk of death at 90 days than a standard strategy. In this study, the timing of RRT initiation in the accelerated-strategy group was comparable to that of the ELAIN study, while the timing of RRT initiation in the standard-strategy group was comparable to that of the AKIKI study[13]. In addition to differences in population, it is hard to exclude that the differences in outcomes of these studies are caused by differences in timing of RRT initiation.

When compared to non-septic AKI, patients with SAKI are generally sicker, greater aberrations in hemodynamics and laboratory parameters, higher need for mechanical ventilation and vasoactive drug therapy, have longer duration of stay in both ICU and hospital[14-15] . The pathophysiology of SAKI is complex and remains only partially understood. Animal studies revealed that at the early stage SAKI mainly involves functional changes, minimal structural kidney lesions[16]. In the past, it was believed that renal hypoperfusion was the major contributor of SAKI. Recently, our

understanding has been improved on this topic. Inflammatory damage was thought to be the key pathophysiologic process. Toll-like receptors (TLRs) recognize pathogen-associated molecular pattern (PAMPs) and damage-associated molecular pattern (DAMPs), trigger inflammation and tissue injury, induce microvascular thrombus formation, vascular permeability and interstitial edema, impair renal microcirculatory disturbance, cause renal venous congestion, lower the glomerular filtration rate (GFR) at last[17-18]. It is reported that a correlation was observed between the concentrations of circulating inflammatory cytokines and mortality in patients with septic shock[19-21]. In an observational study, Sood MM et al.[3] found that early reversible AKI was associated with improved survival in sepsis. Therefore, it is hypothesis that adequate removal of inflammatory mediators from the circulation, avoiding fluid overload to reduce renal venous congestion and interstitial edema, may provide a potential therapy for this devastating condition. It is demonstrated that early continuous RRT (CRRT) not only can stabilized the internal environment, but also can remove inflammatory mediators[22]. Thus, it is supposed that an early strategy may control excessive inflammation as early as possible, which can reduce kidney injury and benefit to improve survival. A systematic review and meta-analysis in 2019[23], which included 5 trials including 900 patients with SAKI, suggests that earlier initiation is not associated with survival improvement. However, the finding should be interpreted with caution. In fact, three of them supported that early initiation of CRRT could improve 28-day mortality, but the sample size was small[24-26]. Among these 5 studies, one study was the multicenter RCT (IDEAL-ICU), which included 488 patients from 29 mixed medical and surgical ICUs. RRT was initiated within 12 hours following the diagnosis of RIFLE failure (RIFLE-F) AKI (equivalent to KDIGO stage 3) in the early group, and 48 hours after diagnosis of RIFLE-F AKI or if the absolute indications for RRT were present in the delayed group. It is shown that there is no difference between the two strategies. However, 41 patients (17 %) in the delayed group needed emergency RRT. Of note, mortality in this subgroup increased significantly (68 %)[27].

To the best of our knowledge, only one such large randomized controlled study focusing on timing of RRT in patients with SAKI has been published[27]. More studies are needed to clarify this issue. Moreover, considering the characteristics of SAKI, the "early strategy" in AKIKI study and IDEAL-ICU study may still be too late. Therefore, we propose another multicenter RCT on the impacts of mortality of the timing of CRRT initiation in patients with SAKI.

## METHODS AND ANALYSIS

### Study design, setting and patient population

The CRTSAKI study is a prospective, open-label, two-arm, multicenter, randomized, controlled study. All patients admitted to the ICUs of participating centers will be considered as potential candidates for the study. Once the patient is diagnosed of SAKI stage 2, he/she should be screened for eligibility by the physicians within 2 h. When the patient fulfills the criterion of recruitment, written informed consent (online supplementary file 1) should be obtained from the patient or a responsible surrogate before randomized.

The study will be conducted in 13 ICUs in Guangdong, China. Patient enrolment, intervention and follow-up are performed at the Second Affiliated Hospital of Guangzhou Medical University, Dongguan People's Hospital, Guangdong Provincial People's Hospital, Guangdong No.2 Provincial People's Hospital, Guangzhou Red Cross Hospital, Huizhou Municipal Central Hospital, Guangzhou Panyu Central Hospital, the Six Affiliated Hospital of Guangzhou Medical University (Qingyuan People's Hospital), Shenzhen People's Hospital, Yue Bei People's Hospital, People's Hospital of Yangjiang, Zhongshan City People's Hospital and Sun Yat-sen Memorial Hospital in China. The study is expected to last for 4.0 years. Recruitment of participants has started in August 2019.

### Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. The results will be available to the public if necessary.

### Inclusion criteria

1. Age between 18 and 90 years.
2. Patients admitted into ICU with Sepsis (sepsis-3)[1] compatible with the diagnosis of AKI at stage 2 of KDIGO classification.

- Sepsis-3: an increase in the SOFA score of 2 points or more caused by a dysregulated host response to infection.
- > 2 folds increase of SCr level compared to the baseline value and/or urine output (UO) < 0.5 ml/kg/h for 12 h.

3. Informed consent provided by the patient or person with decisional responsibility.

### Exclusion criteria

1. Presence of one of the emergent CRRT conditions before randomization:

- Hyperkalemia > 6.0 mmol/L or > 5.5 mmol/L persisting despite medical treatment.
- Acute pulmonary edema due to fluid overload responsible for severe hypoxemia requiring oxygen flow rate > 5 L/min to maintain a percutaneous oxygen saturation ($SpO_2$) > 95% or a fraction of inspiration oxygen ($FiO_2$) > 50% in patients already on invasive or non-invasive mechanical ventilation and despite diuretic therapy.

- Blood urea nitrogen (BUN) > 112 mg/dl (40 mmol/L).

2. Pre-existing severe chronic renal failure [estimated glomerular filtration rate (eGFR) < 30 ml/min].
3. Previous renal replacement therapy.
4. Prior kidney transplant.
5. AKI caused by permanent postrenal obstruction or surgical lesion of renal vessel.
6. Pregnancy
7. Hepatorenal syndrome.
8. Acquired immune deficiency syndrome (AIDS)
9. Patient for whom survival to 90 days is unlikely due to end-stage diseases.
10. Patient is moribund with expected death within 24 h
11. Patient included in another interventional clinical trial

**Study definitions**

***Sepsis and septic shock***

Sepsis is defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[1] as a life-threatening syndrome with organ dysfunction caused by infection. For clinical diagnosis, patients can be identified by an increase in the SOFA score of 2 points or more caused by a dysregulated host response to infection. Septic shock, a subset of sepsis, can be identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater and serum lactate greater than 2 mmol/L despite of resuscitation.

***Acute kidney injury***

AKI will be defined and classified according to the KDIGO classification (table 1). AKI is identified by at least one of the following:

- An increase in SCr by ≥ 0.3 mg/dl (26.5 μmol/L) within 48 h.
- An increase in SCr to ≥ 1.5 times baseline within the previous 7 days.
- Urine volume ≤ 0.5 ml/kg/h for 6 h.

**Table 1. KDIGO stage criteria for AKI**

| Stage | SCr | UO |
|---|---|---|
| 1 | 1.5-1.9 times baseline[a] or ≥ 0.3 mg/dl (26.5 μmol/L) increase | < 0.5 ml/kg/h for 6-12 h |
| 2 | 2.0-2.9 times baseline | < 0.5 ml/kg/h for ≥ 12 h |
| 3 | ≥ 3 times baseline or ≥ 4.0 mg/dl (353.6 μmol/L) increase or initiation of RRT or in patients < 18 years a decrease in eGFR < 35 ml/min/1.73 $m^2$ | < 0.3 ml/kg/h for ≥24 h or anuria ≥ 12 h |

[a] If the patient presents with AKI without a reliable baseline SCr on record, baseline SCr can be estimated using the Modification of Diet in Renal Disease (MDRD) Study equation[28]

***Recovery of renal function***

Recovery of renal function will be classified as complete recovery, partial recovery or no recovery.

- Complete recovery of renal function will be defined as a SCr elevates ≤ 0.5 mg/dl (44.2 μmol/L) compared to the baseline.
- Partial recovery will be defined as a SCr elevates > 0.5mg/dl (44.2 μmol/L) compared to the baseline, but not depending on dialysis.
- No recovery of renal function will be defined as patients who remained dialysis-dependent at time of death or study completion.

**Study intervention**

The study flow chart is detailed in Figure 1.

***Early CRRT group***

Patients randomized to the early CRRT group will initiate CRRT as fast as possible. A maximum of 8 h is allowed between randomization and the actual initiation of CRRT. The initiation and cessation time, the data of CRRT are recorded by nurses.

***Delayed CRRT group***

Patients randomized to the delayed CRRT group will be observed closely. SCr will be measured at least 1 time/12 h until renal function recovery or one of the following criteria is met:

1. AKI develops to stage 3 of KDIGO classification [≥ 3 times baseline SCr level or SCr concentration > 4.0 mg/dl (353.6 μmol/L), and/or urine output < 0.3 ml/kg/h for more than 24 h or anuria (urine output < 100 ml) for more than 12 h ].
2. Presence of one of the emergent CRRT conditions after randomization:
   - Hyperkalemia > 6.0 mmol/L.
   - Acute pulmonary edema.
   - BUN > 112 mg/dl (40 mmol/L).

CRRT will be initiated when one of the above criteria is met. A maximum of 8 h is allowed between the appearance of indication and the actual initiation of CRRT. If the renal function of patients is recovery in the delayed group, initiation of CRRT can be avoided. The indication and time of initiation and cessation, the data of CRRT are recorded by nurses.

***Modality of CRRT***

In order to keep uniformity of therapy between early and delayed CRRT group, identical settings of CRRT will be used in both groups. All patients undergoing CRRT will be treated using continuous veno-venous hemofiltration (CVVH) or continuous veno-venous hemodiafiltration (CVVHDF). The rate of blood flow is recommended for 100-200 ml/min. The effluent flow will be prescribed based on the patient's body weight at the time of randomization and will be 20-25 ml/kg/h. The choice of vascular access, the strategy of anticoagulation is left to the investigator's discretion. Once CRRT is initiated, treatment is recommended to maintain at least 24 h. The membranes should be changed at least 72 h. In the absence of criteria for CRRT cessation or "intermittent", the interval of CRRT interruption should not be more than 24 h.

***Cessation or alternation of CRRT***

- "Intermittent" CRRT

If urine output ≥ 500 ml/24h without diuretics or ≥ 1000 ml/24h with diuretics, the interval of CRRT interruption is left to the investigator's discretion.

- Cessation of CRRT

CRRT will be discontinued if urine output is ≥ 1000 ml/24h without diuretics or ≥ 2000 ml/24h with diuretics, and creatinine clearance is > 20 ml/min.

- Alternation of CRRT

If cessation criteria are not fulfilled until the patient leaves ICU, CRRT can be changed to other RRT modality [i.e., intermittent hemodialysis (IHD), peritoneal dialysis (PD), prolonged intermittent RRT (PIRRT)].

**Additional treatments**

Management of sepsis and septic shock will follow the international guidelines of Surviving Sepsis Campaign 2016 and 2018[29-30]. The patient's primary physicians will determine the management of other comorbidities. The dose of all medications will be adjusted for renal function and CRRT.

**Primary objective**

The primary study endpoint is overall mortality measured from the date of randomization (D0) until death or day 90. For patients who were discharged alive from ICU, information on the primary endpoint will be acquired by a telephone call.

**Secondary and other objectives**

The secondary endpoints include: (1) 28-day, 60-day and 1-year all-cause mortality; (2) recovery rate of renal function by day 28 and day 90; (3) ICU and hospital length of stay (LOS); (4) the percentage of receipt of CRRT at least once in the delayed group; (5) the number of days alive without CRRT, mechanical ventilation and vasopressor (the numbers of CRRT-free days, mechanical ventilation-free days and vasopressor-free days, between D0 and up to D90); (6) the Sequential Organ Failure Assessment (SOFA) score at day 0, 1, 3, 7, 14 and day 28; (7) impacts on other organ functions (heart, lung, liver); (8) the rate of complications potentially related to CRRT, including: (a) major bleeding associated with anticoagulants (defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells) [31], (b) thrombosis of a large venous axis diagnosed by Doppler ultrasound, (c) catheter-related bloodstream infection (CRBSI)[32], (d) thrombocytopenia (< 100 × $10^9$ platelets/$mm^3$), (e) hypothermia (defined as a core body temperature of less than 35 ℃ or need electric blanket to keep warm), (f) hemodynamic instability due to

CRRT and requiring the introduction or increase of vasopressor, (g) pulmonary edema during CRRT, (h) hyperkalemia (defined as serum potassium concentration > 6.5 mmol/L), (i) hypokalemia (defined as serum potassium concentration < 3.0 mmol/L), (j) new onset of serious arrhythmia during CRRT (including atrial fibrillation, ventricular tachycardia, ventricular fibrillation and torsades de pointes).
Other endpoints include: (1) cost analysis of CRRT; (2) duration between randomization to CRRT initiation; (3) duration between appearance of at least one of the criteria that initiated CRRT in the delayed group and actual initiation.
Add-on study: (1) new biomarkers of AKI [such as angiotensinogen, neutrophil gelatinase associated lipocalin (NGAL)]; (2) concentrations of inflammatory mediators in serum will be analyzed between two groups [such as interleukin (IL)-1, IL-6 and tumor necrosis factor-alpha (TNF-α)].

**Sample size**

The primary endpoint in this study is to compare the effect of early and delayed CRRT strategy on overall survival at day 90 in patients with SAKI. Our primary hypothesis is that the early CRRT strategy might beneficial to patients with SAKI. According to IDEAL-ICU study, the expected mortality of patients with SAKI in the delayed group may be estimated around 55%. Considering that the timing setting of CRRT in this study is similar to ELAIN study, a reduction in mortality of 15% in the early group (55% mortality in the delayed CRRT group versus 40% in the early CRRT group) can be expected. Differences between two groups will be detected with a power of 85% at a bilateral alpha risk of 0.05. Considering that in China, some patients will give up treatment and request discharged from hospital due to economic reason or customs, the rate of non-evaluable cases is expected to be 15% for the worst. Hence, a total of 460 patients (230 per group) are required. Power calculations were performed using the PASS 14.0 software.

**Randomization and blinding**

Eligible patients are consecutively randomly assigned to either early group or delayed group in a 1:1 ratio. This allocation is achieved using a centralized, secure, computer-generated, web-response system accessible from each study center. The randomization is balanced by blocks of variable and undisclosed size, and stratified according to center. The block size is 6. The randomization day is study day zero (D0). Because this is an interventional study, blinding is not possible for physicians, nurses and patients. However, the analysis will be blinded to allocation of groups.

**Data collection and follow-up**

Each investigator from the 13 participating ICUs was trained to the protocol, electronic random system and data collection in the electronic Case Record Form (eCRF) before trial initiation. The electronic random system and eCRF are developed with Guangzhou Baofeng Pharmaceutical technology co. LTD, managed and closed by the Clinical Research center of the Second Affiliated of Guangzhou Medical University (China). It is a centralized, secure, web-response system accessible from

each study center.

Flowchart of patient follow-up was shown in table 2. Demographic data and medical history, including nephrotoxic agents (i.e. contrast agent, aminoglycoside antibiotics, tacrolimus, amphotericin B, hydroxyethyl starch, vancomycin) use nearly 1 week will be collected. Details data including reasons for ICU admission, cause of SAKI, acute physiology and chronic health evaluation II (APACHEII) score, dates of hospital and ICU admission will be recorded. Details of mechanical ventilation, vasopressor, CRRT, diuretics, urine output, fluid balance will be documented daily. SOFA scores will be evaluated at baseline, D1, 3, 7, 14, 28. Blood will be collected at baseline, D1, D3, D7 and D14. Results of laboratory tests including white blood cell count and differentials in peripheral circulation, serum electrolyte levels, serum glucose level, urea and creatinine concentration, liver and myocardial enzyme concentrations, arterial blood gas analysis, procalcitonin and lactate will be recorded. Biomarkers of AKI (i.e. angiotensinogen and NGAL) and inflammatory factors (i.e. IL-1β, IL-6, TNF-α, CRP) are planned to be tested at D0, D1, D3 and D7.

During CRRT intervention, details of initiation, cessation, setting parameters, complications will be collected. Serum creatinine and urine output will be monitored daily to ensure whether criteria for CRRT discontinuation is present. All recruited patients will be followed to determine adverse events, renal function recovery and mortality until death or at 28, 60, 90 days and 1 year after randomization.

**Table 2. Flowchart of patient follow-up**

| | screening | D0 inclusion | Study period | Death/D90 |
|---|---|---|---|---|
| **Baseline information** | | | | |
| Demographic data and history | √ | √ | | |
| Inclusion and exclusion criteria | √ | | | |
| written informed consent | √ | | | |
| Vital signs | | √ | | |
| APCHEII/SOFA | | √ | √D1, 3, 7, 14, 28 | |
| **Efficacy observation** | | | | |
| Mechanical ventilation | | √ | √ | |
| Treatment with vesopressor | | √ | √ | |
| CRRT initiation and application | | √ | √ | |
| UO and diuretic application | | √ | √ | |
| Renal function recovery | | | √D28 | √ |
| UCG and ECG | | | √D1, D14 | |
| Laboratory tests | √ | √ | √D1, 3, 7, 14 | |
| Biomarkers and inflammatory factors | | √ | √D1, 3, 7 | |
| **Safety observation** | | | | |

| | | | |
|---|---|---|---|
| Complications of CRRT | √ | √ | |
| Adverse event | √ | √ | |
| **Additional observation** | | | |
| Total cost of CRRT | | | √ |
| ICU and hospital LOS | | | √ |
| Alive or dead status | | √D28, 60 | √ |

**Statistical analysis**

Data will be double checked by the clinical research team, and the data base is managed and closed by the Clinical Research center of the Second Affiliated of Guangzhou Medical University (China)。

For each group, quantitative variables with normal distribution will be described as mean and standard deviation. Quantitative variables with skewed distribution will be described as median (*M*) and inter-quartile range (IQR, 25$^{th}$ percentile to 75$^{th}$ percentile). Qualitative variables will be described as frequency and percentage.

The primary endpoint (all-cause mortality at 90 days) will be performed according to the intent-to-treat (ITT) principle. This dataset includes all trial subjects enrolled into the trial and randomized. Additional sensitivity analyses will be performed according to the per-protocol (PP) principle. This dataset includes all trial subjects who were treated according to protocol and reached a defined endpoint in the trial. The effect of early versus delayed initiation of CRRT on all-cause 90 days mortality will be performed using chi-squared test, with secondary analysis by the Kaplan-Meier method, comparison using a (two-sided) stratified log rank test (global significance level 5%, power 80%).

Safety will be analyzed by the frequency of complications related to CRRT in both treatment groups and comparing rates using chi-square or Fisher's exact test, with an alpha risk set at 0.05.

Statistical analyses of the pre-specified secondary endpoints will be performed with descriptive and inductive statistical methods. Categorical variables will be compared using the chi-square or Fisher's exact test, as appropriate. Continuous variables will be compared using Student's *t* test or the Mann-Whitney test, as appropriate.

The primary efficacy analysis provides confirmative evidence. Further analyses will be regarded explorative (hypothesis generating) and will be interpreted accordingly. All point estimates of parameters of interest will be supplemented by 95% confidence intervals. Type I error enhancement due to multiple significance testing will be accounted for if applicable.

Statistical analyses will be performed according to the principles of the ICH-guideline E9 "Statistical Principles for Clinical Trials" using SAS version 9.4, or R software version 3.6.3 or later.

## ETHICS AND DISSEMINATION

The study protocol has been approved by the Clinical Research and Application Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical

University (version 2.0, registration number: 2017-31-ks-01; date of approval: 29 October 2018). Participants will be screened and enrolled from ICU patients with SAKI by clinicians, with no public advertisement for recruitment. When the patient fulfills the criterion of recruitment, written informed consent (online supplementary file 1) should be obtained from the patient or a responsible surrogate before randomized. All information from the participants will be kept private and will not be provided to any company or institution. Results will be disseminated in research journals and through conference presentations.

## DISCUSSION

Sepsis is the leading cause of AKI in the ICU, which often manifests as part of the multiple organ dysfunction syndrome (MODS). AKI is an independent contributor to mortality in sepsis. Early reversible AKI was associated with improved survival[3]. It is reported that there is no acute tubular necrosis and only intracellular and metabolic modifications are observed in the early phases of SAKI[18]. Therefore, it is supposed that an early strategy which can reduce kidney injury may benefit to improve survival. Unfortunately, there are currently no pharmacological treatments available to SAKI therapy. CRRT is considered to be the most effective therapy to SAKI when the renal function becomes insufficient to maintain internal environmental stability. However, when to start CRRT remains a particularly challenging question during SAKI in critical ill patients. In 2018, IDEAL-ICU study shown that there is no difference between the two strategies. However, 41 patients (17 %) in the delayed group needed emergency RRT and have higher mortality[27]. On the one hand, Barbar et al.[33] thought it is unacceptable to expose 30% of patients to the potential risks of an extracorporeal support technique if they do not actually need it. On the other hand, others argued that although there may be a risk of "unnecessary" RRT, there could be an even greater risk associated with not providing it. To the best of our knowledge, only one such large randomized controlled study focusing on timing of RRT in patients with SAKI has been published. Therefore, more studies are needed to clarify this issue.

Look at the previous studies on RRT timing of AKI, not only the conclusions were different, the definitions of "early" or "late" were different. In ELAIN study[11], "early RRT" was initiated at stage 2 of KDIGO classification. In AKIKI study[12], all patients were required to have KDIGO stage 3 AKI. "Early" meant initiating RRT within 6 hours after randomization. In IDEAL-ICU study, "early" meant initiating RRT within 12 hours following the diagnosis of RIFLE-F AKI (equivalent to KDIGO stage 3). Considering that the patients with SAKI are generally sicker than the patients with non-SAKI, the "early strategy" in AKIKI study and IDEAL-ICU study may still be too late. It might be preferred to initiate RRT at an earlier stage which was similar to that in ELAIN study. Therefore, we chose all patients with KDIGO stage 2 AKI.

CRRT was initiated within 8 hours after randomization in the early group, and 8 hours after AKI developing to stage 3 of KDIGO classification or presence of one of the emergent CRRT conditions after randomization.

We hypothesize that initiating CRRT early enough may attenuate renal injury from systemic inflammation, acidemia, uremia and fluid overload in sepsis patients. If this study confirms our hypothesis, it may help to improve mortality for patients with SAKI. Negative result will also encourage us to pay a deeper attention to details underlines insightful information: is there a way to better predict which patients are likely to require RRT and which patients have a high likelihood of spontaneous recovery?

**Supplementary file**

Online supplementary file 1: consent form.

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**Contributors** Xu-ming Xiong, Zhen-hui Zhang, Wei-yan Chen and Li-hua Cai designed the trial. Xu-ming Xiong obtained funding for the trial. Wei-yan Chen and Li-hua Cai drafted the manuscript. Xu-ming Xiong and Zhen-hui Zhang provided a critical revision of the manuscript. Li-li Tao, Yi-chao Wen, Zhi-bo Li, Li Li, Yun Ling, Jian-wei Li, Rui Xing, Xue-yan Liu, Zhuan-di Lin, Zhe-tong Deng, Shou-hong Wang, Qin-han Lin, Dun-rong Zhou and Zhi-jie He discussed and help to improve the protocol. All authors read and approved the final manuscript.

**Funding** This study was funded by a Grant from Guangzhou Medical University (B195001009).

**Competing interests** None declared.

**Patient consent for publication** Not required.

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## Figure legend:

**Figure 1. Flow chart of the trial.** SAKI, sepsis-associated acute kidney injury; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcome; CRRT, continuous renal replacement therapy; D90, day 90.

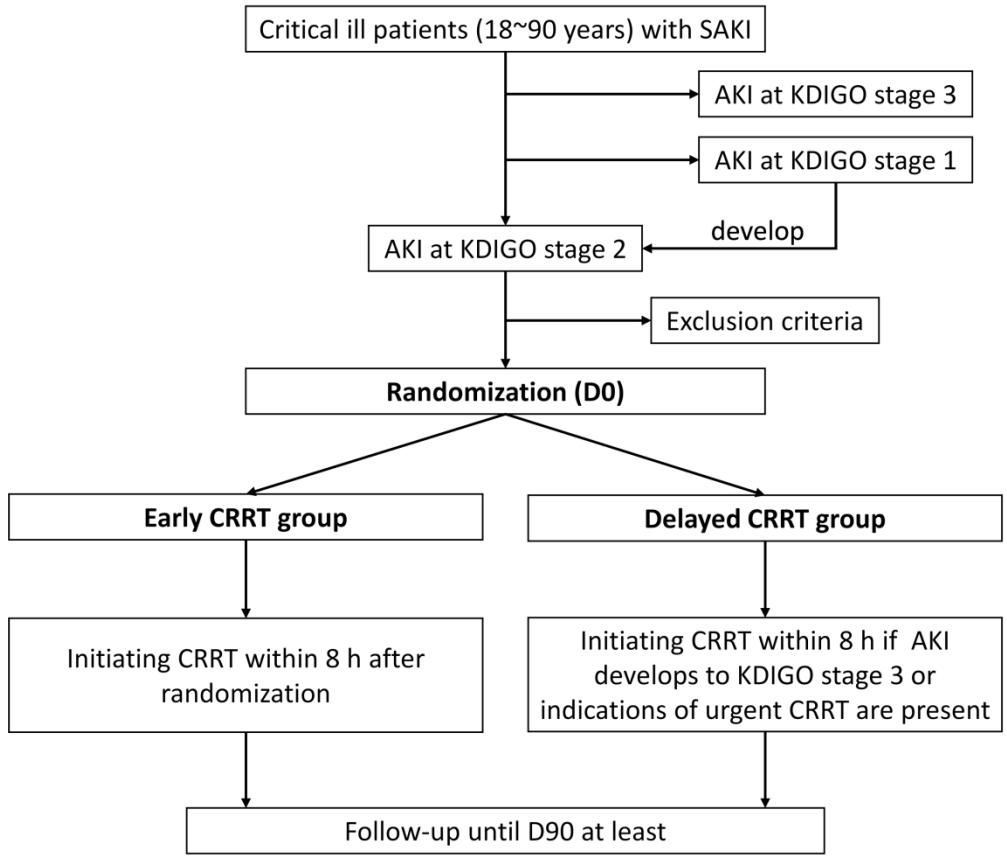


Figure 1. Flow chart of the trial. SAKI, sepsis-associated acute kidney injury; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcome; CRRT, continuous renal replacement therapy; D90, day 90.

265x228mm (300 x 300 DPI)

# Consent form

**Research name：** The Timing of Continuous Renal Replacement Therapy Initiation in Sepsis-associated Acute Kidney Injury in the Intensive Care Unit: the CRTSAKI study (Continuous RRT Timing in Sepsis-associated AKI in ICU)

**Research number：** B195001009, Version 2.0, Date: 2018/06/21

**Research institute：** the Second Affiliated Hospital of Guangzhou Medical University

**The physician in charge of the study：** Xu-ming Xiong.

You will be invited to participate in a clinical study. This informed consent gives you some information to help you decide whether to participate in this clinical study or not. Please read it carefully. If you have any questions, please ask the researchers responsible for the study.

Your participation in this study is voluntary. This study has been reviewed by the ethics review committee of the research institute. If you have questions related to the subjects' rights and interests, please contact the ethics committee of The Second Affiliated Hospital of Guangzhou Medical University at 020-34152225.

1. **Research purpose：** Sepsis is a life-threatening syndrome with organ dysfunction caused by infection. Acute kidney injury (AKI) is one of the most common organs dysfunction in sepsis, and increases the risk of unfavorable outcomes. Continuous renal replacement therapies (CRRT) is the predominant

treatment for sepsis-associated AKI (SAKI). The study is used for the purpose of compare early with delayed strategy on the outcomes of patients with SAKI in intensive care unit (ICU).

2. **Research process:** If you agree to participate in this study, we will number each subject and create a medical record file. You will be randomized into the early group or the delayed group. Due to the need of clinical diagnosis or treatment, Blood sample will be collected at baseline, D1, D3, D7 and D14. The expression levels of some inflammatory factors are measured to understand the inflammatory response of the body. This part of the test is free of charge.
3. **Risk and discomfort:** For you, all information will be confidential. The possible risks of this study are mainly attributable to complications of CRRT, Including bleeding, catheter-related bloodstream infections, hypothermia and hypotension. In case of complications, we will take appropriate measures for treatment in a timely manner, and you also have the right to suspend treatment at any time.
4. **Benefits:** The results of this study may provide useful information for clinical treatment, and lead to clinical optimization.
5. **As a study subject, you have the following responsibilities:** Provide true information about your medical history and current physical condition; Inform the study physician of any discomfort during the study period; Not to take

restricted drugs, food, etc.; Tell your research doctor if you have been involved in other studies recently or are currently involved in other studies.

6. **Privacy issue:** if you decide to participate in this study, your personal data in and during the study are confidential. Your blood samples will be identified by a study number rather than your name. Information that identifies you will not be disclosed to anyone other than members of the research group unless your permission is obtained. All research members and research bidders are required to keep your identity confidential. Your file will be kept in a locked filing cabinet for researchers only. To ensure that the study is conducted in accordance with the regulations, if necessary, members of the government management department or the ethics review committee may refer to your personal data in the research unit as required. When the results of this study are published, no information about you will be disclosed.
7. **If you are injured by participating in this study:** You can receive free treatment and/or compensation if there is any harm associated with the clinical study.

You may choose not to participate in this study, or at any time inform the researcher to request withdrawal from the study. Your data will not be included in the study results, and any medical treatment and benefits will not be affected.

If you need additional treatment, or if you don't follow the study plan, or if you have any injuries related to the study or for any other reason, the investigator

may terminate your continued participation in the study.

You can keep track of the information and information related to this study and the progress of the study. If you have any questions related to this study, or if you have any discomfort or injury during the study, or if you have any questions about the rights and interests of participants in this study, you can contact us by 020-34152225/020-34153241.

**Signature for Consent**

I have read an informed consent form.

I have the opportunity to ask questions and all questions have been answered.

I understand that participation in this study is voluntary.

I can choose not to participate in this study, or quit at any time after informing the researcher without any discrimination or reprisals, and my medical treatment and rights will not be affected.

If I need other treatment, or if I don't follow the study plan, or if there is any injury related to the study or if there is any other reason, the research physician may terminate my involvement in this study.

I will receive a signed copy of the informed consent.

Patient's name: _____

Signature of patient: _____

Signature of the agent of patient: _____

Continuous RRT Timing in Sepsis-associated AKI in ICU, version 2.0, 2018/06/21

Date: _____

I have accurately informed the subject of this document that he/she has read this informed consent and has demonstrated that the subject has the opportunity to ask questions. I certify that he/she consented voluntarily.

Researcher's name: _____

Signature of researcher: _____

Date: _____

(note: if the subject is illiterate, the fashion requires the signature of the witness; if the subject is incompetent, the signature of the agent is required.)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |

| | | | |
|---|---|---|---|
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 1, 3 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | N/A |
| Protocol version | #3 | Date and version identifier | 20 |
| Funding | #4 | Sources and types of financial, material, and other support | 23 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 1, 22,23 |
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | N/A |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | N/A |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and | 8,16-18 |

| | | | |
|---|---|---|---|
| | | other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | |
| **Introduction** | | | |
| Background and rationale | #6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4-7 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 7 |
| Objectives | #7 | Specific objectives or hypotheses | 7, 13-14 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 7 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7-8 |

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|---|---|---|---|
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 7-10 |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 11-12 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | 13 |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | N/A |
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 13 |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 13-15 |

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|---|---|---|---|
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 16-18 |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 15-16 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 16 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 16 |
| Allocation concealment mechanism | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 16 |

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|---|---|---|---|
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 16 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 16 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 16-17 |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be | 16-17 |

| | | | |
|---|---|---|---|
| | | collected for participants who discontinue or deviate from intervention protocols | |
| Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 16 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 18-20 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 19 |
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 18-19 |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the | 18 |

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| | | protocol. Alternatively, an explanation of why a DMC is not needed | |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 14-15, 19 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 18 |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 20 |
| Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) | N/A |

| | | | |
|---|---|---|---|
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 7, 20 |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 20 |
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 23 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 18 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | N/A |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 20 |

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|---|---|---|---|
| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | N/A |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 20 |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | 7, supl |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | 17, supl |