Predictors of renal recovery in patients with severe acute kidney injury on renal replacement therapy

Protocol version 10

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BACKGROUND

The incidence of acute kidney injury (AKI) is increasing (1-3), about 1 in 5 adults worldwide experience AKI during a hospital episode of care (4). Patients with severe AKI often require renal replacement therapy (RRT), which is associated with high mortality rate of up to 60%(5) and economic burden. Survivors of AKI also carry significant prolongation of hospitalisation, requiring institutional care (3, 6) and increased risk of progression to chronic and ESKD(7).

Recovery of kidney function is a fundamental long-term outcome for survivors of critical illness. Non-recovery is likely associated with long term morbidity and mortality, increased risk of dialysis dependence, and poor quality of life, along with increased healthcare costs. There is sparse evidence on predictors for renal recovery in severe AKI on RRT. The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study (8) is an international, multicentre, prospective study to determine the prevalence of AKI requiring RRT in the ICU.

Its post hoc analysis showed that about 50% of patients who survived from severe AKI on RRT were able to successfully come off RRT during the index admission (8). It also demonstrated that serum creatinine and urine output on the date of CRRT discontinuation, pre-existing chronic kidney disease, and duration of CRRT predicted successful cessation of RRT.

AIMS

The primary aim of this study is to identify the predictors for renal recovery at day 28 in critically ill patients with severe acute kidney injury (AKI) requiring RRT by using individual patient data analysis.

The secondary aim of this study is to investigate the predictors for successful cessation of RRT (no need for dialysis for at least 2 weeks) in critically ill patients with severe acute kidney injury (AKI) requiring RRT by using individual patient data analysis.

The additional secondary aim is to identify the predictors of successful cessation of RRT for those patients who had RRT stopped for ≥3 days.
METHODS

Data sources/Collection

The IMPROVE-AKI study is an individual patient data meta-analysis of previous studies of RRT dose intensity in severe AKI to assess the effects of RRT dose intensity with focus on mortality and RRT independence.

The data were entirely from the existing datasets associated with the completed participating studies. The principal investigators (or their delegates) provided de-identified data for individual participants from each study including demographic characteristics (age, sex, co-morbidities, co-morbidity scores assessed by acute physiology and chronic health evaluation III (APACHEIII) score (9), sequential organ failure assessment (SOFA) score (10), as well as biochemical measures), RRT characteristics (modality, frequency, timing, allocated and received dose intensity), date of death, dates of RRT dependence and cessation, and the details of other treatments received.

Some of these factors might carry predictive ability for renal recovery to RRT independence.

Statistical analyses

Definitions

Successful renal recovery to dialysis independence at 28 days will be defined by a patient receiving no RRT by 28 days. This time point has been chosen because it is the furthest time point from randomization where data can be obtained from the greatest number of patients.

Sustained renal recovery to dialysis independence will be defined by a patient receiving no RRT for ≥7 days.

Successful cessation of RRT will be defined by no need to have dialysis for ≥14 days or until either death or end of observation period.

Statistical analysis

Pooled variables at baseline and on the date of discontinuation of RRT will be summarized.
Continuous variables will be described as means (\( \bar{x} \)) with standard deviation (SD) for approximately normal distributed variables and as medians with interquartile interval (IQI) for non-normally distributed variables. Discrete variables will be summarized as frequencies (f) and percentages (%).

Predictors for renal recovery will be analysed using logistic regression analysis.

Primary outcomes
- Successful renal recovery to dialysis independence at day 28 (8).

Secondary outcomes
- Sustained renal recovery to dialysis independence at 28 days.
- Successful cessation of RRT.

As we are limited to complete datasets only to 28 days, we will assess the above outcomes at day 28.

The following sensitivity analysis will be used to assess the robustness of any findings.

Models will be tested with each of these assumptions:

- Assume that any patient who stops RRT before day 28 and who cannot be evaluated for recovery to day 7 or day 14 has actually recovered.
- Assume that any patient who stops RRT before day 28 and who cannot be evaluated for recovery to day 7 or day 14 has actually NOT recovered.
- Assume that any patient who stops RRT before day 28 and who cannot be evaluated for recovery to day 7 or day 14 has a chance of recovery similar to the whole population and therefore a proportion of such patients will be considered recovered and a proportion will be considered non recovered in a manner equal to the rest of the cohort.
- Exclude patients where recovery as defined cannot be evaluated.

Considering that the use of IHD in the ATN study was not random but was dictated by protocol and clinical factors, further sensitivity analysis will be performed to minimise confounding factors. Patients expose to IHD or PIRRT will be studied according to these definitions.

- Had IHD as first treatment
- Had IHD and PIRRT only
- Had at least one IHD or PIRRT exposure during the first 3 days
- Had at least one IHD and/or PIRRT exposure during the first week
- Had only IHD and/or PIRRT during the study period
Subgroup analysis
- Non CRRT vs CRRT
- IHD vs CRRT
- PIRRT vs CRRT

After adjustment for being enrolled in an individual study, the following pre-specified baseline demographic variables will be included in the logistic regression model as candidate predictors based on pre-existing literatures and likely clinical relevance:

1. age (11, 12)
2. sex (13)
3. body weight as recorded by each trial as baseline value (14)
4. presence of diabetes mellitus (15)
5. diagnosis of chronic kidney disease at randomization (8)
6. sepsis/septic shock (13)
7. illness severity defined by APACHE III score (16)*
8. presence of mechanical ventilation at randomization
9. allocated treatment arms
10. first prescribed modality of RRT (non CRRT vs. CRRT then IHD vs. CRRT) (17)
11. region of treatment (Europe, North America or ANZ)
12. urine output at randomization (8)
13. serum creatinine at baseline (8)
14. plasma urea at baseline
15. serum bicarbonate
16. serum albumin at baseline
17. pH if missing data is <20%

We will also perform a univariate analysis to identify other explanatory variables that are potentially statistically relevant (P<0.1) and then put them into a multivariate model. Moreover, we will exclude any of the clinically relevant variables listed above if on univariate analysis, they have a P value >0.2

*APACHE II score are converted in APACHE III score (and vice versa) using the following equation:
\[ \text{APACHE III} = 3.13 \times \text{APACHE II} + 7.99 (18) \]

Collinearity between variables will be assessed and only one selected when this is high. Additional factors beyond the above list will be used at cessation of RRT to help predict successful cessation

1. duration of RRT (days) prior to cessation (8),
2. diagnosis of chronic kidney disease at randomization, stratified by severity of CKD (8)
3. urinary output on RRT discontinuation date
**Special consideration in constructing a prediction model**

1. **Missing values:** missing covariate data over 10% will be imputed with use of a multiple imputation technique (the multiple imputation with chained equations (MKE) method) (19). If missing covariate data over 40% within individual study, we won’t use the covariate in the prediction model analysis due to lack of data.

2. **Continuous predictors:** all continuous variables will be model as linear functions after testing for the assumption of linearity to increase the predictive accuracy of the prediction model(20). However, continuous variables might be transformed to approximate normality if it has a skewed distribution.

3. **Developing the full model (predictors selection):** A full model approach will be used: all a priori selected candidate predictors are included in the multivariable analyses and no further predictor selection will be used: all candidate predictors will be included in the final prediction model.

4. **Model performance measures** will be using the receiver operating characteristic (ROC) curve method including the C-statistics, and a goodness-of-fit test and a calibration plot plus the Hosmer-Lemeshow test will be added.

5. **Internal validation** will be performed using bootstrapping techniques.

6. We will also use cross validation, leaving one study out at a time, and pooling the seven C statistics.

Statistical significance for all analyses was established when a two-tailed P value was less than 0.05. All analyses were performed using SAS version 9.3.

**REFERENCES**


