

# Predicting recovery from acute kidney injury in critically ill patients: development and validation of a prediction model

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Critically ill patients who develop acute kidney injury (AKI) are at increased risk of long term adverse outcomes, including severe chronic kidney impairment and death, but recovering prior kidney function early may mitigate this risk.<sup>1–6</sup> This risk reduction warrants a tool to identify these patients at the beginning of the clinical course to guide new interventions for the patients who could potentially benefit.

Previous attempts to identify interventions that increase the rate of recovery in critically ill patients with AKI have been negative.<sup>7–9</sup> These trials have included an unidentified group of patients with a high chance of recovery, which may partly explain the negative results. Inclusion of such a group reduces the power to show an effect, since a large group of patients has no potential to benefit and may even sustain side effects from the intervention. In other settings, risk stratification approaches have identified positive effects of interventions that in previous non-stratified trials were ineffective.<sup>10</sup> The available risk models do not identify patients at high or low chance of recovering kidney function.<sup>11–22</sup> One set of models predicts recovery from AKI demanding renal replacement therapy (RRT), and thus excludes patients with milder AKI.<sup>11,13,16,18–20</sup> These prediction models is inexpedient because all stages of AKI carry an increased risk of adverse long term outcomes.<sup>23,24</sup> The second set of models predicts survival of patients with AKI.<sup>11,12,14,15,21,22</sup> However, because AKI usually develops secondary to other conditions with a high mortality rate (eg, severe sepsis, major surgery and cardiogenic shock), such models are prone to identify patients with the most severe precipitating disease, rather than patients where kidney-specific interventions could be beneficial.<sup>25,26</sup>

The aim of this study was to develop a model that identifies patients with AKI who recover prior kidney function and, subsequently, to validate the performance in an unselected cohort of critically ill patients with AKI.

## Methods

### Development cohort

The Procalcitonin and Survival Study (PASS) was a multicentre, randomised trial that included 1200 adult critically ill patients, who were followed for 28 days from 2006 to 2010. The inclusion criteria, intervention and primary results from the PASS study have been described

## ABSTRACT

**Objective:** Intensive care unit (ICU) patients with acute kidney injury (AKI) who recover kidney function within 28 days experience less severe chronic kidney impairment and have increased long term survival. The aims of this study were to develop and validate a risk prediction model to identify these patients.

**Design:** Observational study with development and validation of a risk prediction model.

**Setting:** Nine academic ICUs in Denmark.

**Participants:** Development cohort of critically ill patients with AKI at ICU admission from the Procalcitonin and Survival Study cohort ( $n = 568$ ), validation cohort of adult patients with AKI admitted to two university hospitals in Denmark in 2012–13 ( $n = 766$ ).

**Interventions:** None.

**Main outcome measures:** Recovery of kidney function was defined as living for 5 consecutive days with no renal replacement therapy and with creatinine plasma levels below 1.5-fold the levels determined before ICU admission.

**Results:** A total of 266 patients (46.8%) recovered prior kidney function in the development cohort, and 453 patients (59.1%) in the validation cohort. The prediction model included elevation in creatinine, urinary output, sex and age. In the validation cohort, 69 patients (9.0%) had a predicted chance of recovery < 25%, and their observed rate of recovery was 21.5%. This observed rate of recovery was 81.7% among the 325 patients who had a predicted chance > 75%. The area under the receiver operations curves for predicting recovery in the validation cohort was 73.1%.

**Conclusion:** We constructed and validated a simple model that can predict the chance of recovery from AKI in critically ill patients.

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elsewhere.<sup>27</sup> We checked all patients for end-stage renal disease in a nationwide registry. The local ethical committee approved the PASS trial (ref. no. H-KF-272-753) and the Danish Data Protection Agency (ref. no. 2005-54-1779). All patients, or their legal substitute, gave written informed consent before inclusion.

### Validation cohort

The validation cohort comprised all consecutive adult patients (aged  $\geq 18$  years) admitted to the intensive care unit (ICU) at two university hospitals in Denmark (Nordsjællands Hospital and Rigshospitalet) between 1 January 2012 and 31 December 2013. The Danish National Board of Health (ref. no. 3-3013-532) and the Danish Data Protection Agency (ref. no. 2007-58-0015) approved the study and waived the need for individual patient consent.

### Inclusion criteria

From both the development and validation cohort, we included adult critically ill patients admitted to the ICU for at least 24 hours and with AKI as defined by the creatinine criterion of Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on ICU admission.<sup>28</sup> We excluded patients without a Danish civil registration number, known end-stage renal disease or no follow-up on creatinine.

### Outcome

The outcome was time to recovery of prior kidney function within 28 days. We defined recovery of prior kidney function as living for 5 consecutive days with no RRT and with creatinine plasma levels consistently below 1.5-fold the levels determined before ICU admission over the 28 day follow-up period (Appendix available online at [cicm.org.au/Resources/Publications/Journal](http://cicm.org.au/Resources/Publications/Journal); Supplement 1).

### Prognostic factors

We identified potential predictors of recovery in the literature. For prognostic factors assessed more than once during the first 24 hours of admission, we used the most extreme value. We separated urinary output in three categories:  $< 0.5$  mL/kg/h,  $0.5$ – $1.0$  mL/kg/h and  $> 1.0$  mL/kg/h, based on urinary production in the preceding 24 hours. Prior estimated glomerular filtration rate (eGFR) was divided into four categories:  $eGFR < 60$  mL/min/1.73 m<sup>2</sup>,  $60$ – $90$  mL/min/1.73 m<sup>2</sup>,  $> 90$  mL/min/1.73 m<sup>2</sup> and “unknown”, with the latter category encompassing patients without pre-morbid creatinine measurements. Lastly, age was divided into five categories:  $\leq 50$  years,  $51$ – $60$  years,  $61$ – $70$  years,  $71$ – $80$  years and  $\geq 81$  years.

### Statistical analysis

The prediction models were developed by combining cause-specific Cox regression models: one for the hazard of recovery and one for death without recovery (online Appendix; Supplement 2).<sup>29</sup> The associations between outcome and predictors are presented as cause-specific hazard ratios (HR) with 95% confidence intervals (CIs). We developed two different models. The first “basic” model included the most likely predictors: age, gender, level

of urinary output and creatinine level. The second “full” model included all the potential predictors. We tested for interactions if it was clinically relevant. The observed probability of recovering prior kidney function within 28 days is presented as the cumulative incidence adjusted for the risk of death.<sup>30</sup>

We have described the methods used to evaluate missing data, model performance, validation and updating in detail in the online Appendix; Supplement 1.

Counts (%) and median (interquartile range [IQR]) were presented for categorical and continuous variables, respectively. Statistical significance was set at  $P < 0.05$ . All analyses were performed using R, version 3.0.2.<sup>31</sup>

## Results

### Patients and outcomes in development cohort

A total 1200 patients were enrolled in the PASS study cohort in 2006–2010, of whom 568 (47.8%) had AKI at admission. During the 28-day follow-up, 266 patients (46.8%) recovered prior kidney function, 153 (26.9%) died without recovering and 149 (26.2%) failed to recover. The chance of recovery within 28 days after adjusting for competing risks was 53.2% (95% CI, 48.7–57.6%), and the risk of death without recovery was 31.7% (95% CI, 27.5–36.0%), leaving a 15.1% risk of not recovering.

### Patients and outcomes in validation cohort

The validation cohort included a total 3532 patients. Of these participants, 766 (21.6%) had AKI and were included in the study. During follow-up, 453 patients (59.1%) recovered prior kidney function, 187 (24.4%) died before recovering and 126 (16.4%) failed to recover. The chance of recovery (adjusted for the risk of death) was 63.8% (95% CI, 60.2–67.4%) and the risk of death before recovery was 26.2% (95% CI, 22.9–29.4%), leaving a 10.0% risk of not recovering. Table 1 and Figure 1 present baseline characteristics and reasons for exclusions in both cohorts.

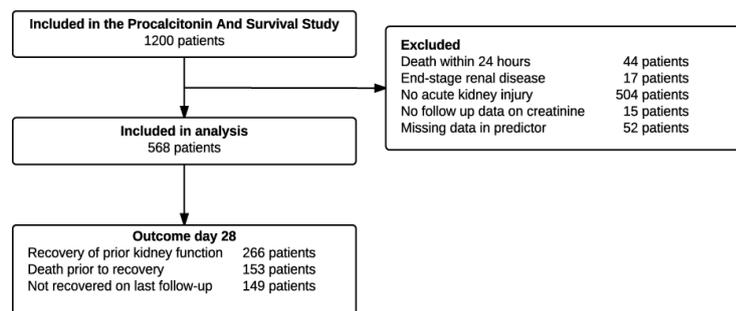
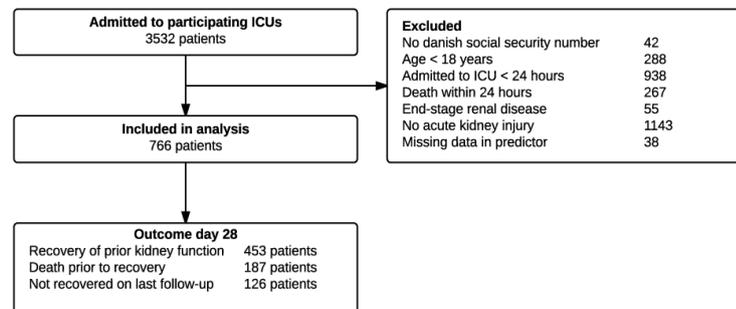
### Prediction of recovery in the development cohort

Of the 568 patients in the development cohort, 135 (23.8%) had less than a 25% predicted chance of recovery. In this group of patients, the observed rate of recovery was 19.5%. Conversely, among the 107 patients who had received a predicted chance of recovery  $> 75\%$  from our model, the observed rate of recovery was 84.1%. Patients predicted to have an intermediate chance of recovery (25–75%) had an observed rate of recovery of 58.7%. Table 2 shows the two candidate prediction models. The basic model discriminated between patients who recovered and those who failed to recover better than the full model (area under the receiver operations curve [AUC] basic, 79.1%,

**Table 1. Baseline characteristics of patients in the development and validation cohorts**

Variable*	Development (n = 568)	Validation (n = 766)	Total (n = 1338)	P
Age, years; median (IQR)	68 (60–76)	68.0 (59–76)	68 (59–76)	0.98
Gender, female	240 (42.3%)	303 (39.6%)	543 (40.6%)	0.33
BMI, kg/m <sup>2</sup> ; median (IQR)	25.7 (22.9–29.3)	24.8 (22.5–28.4)	25.2 (22.6–29.1)	0.09
Surgery	188 (33.1%)	350 (45.7%)	538 (40.3%)	< 0.001
Apache II score; median (IQR)	22 (15–27)	26 (21–32)	24 (18–30)	< 0.001
Severe sepsis or septic shock	338 (59.5%)	319 (41.6%)	657 (49.3%)	< 0.001
Mechanical ventilation	454 (79.9%)	656 (85.6%)	1110 (83.2%)	0.01
Vasopressor treatment†	376 (66.2%)	547 (71.4%)	923 (69.2%)	0.04
Inotropic treatment‡	196 (34.5%)	120 (15.7%)	316 (23.7%)	< 0.001
Dialysis	198 (34.9%)	164 (21.4%)	362 (27.1%)	< 0.001
Creatinine, µmol/L ; median (IQR)	199 (137–285)	168 (120–243)	177 (126–265)	< 0.001
Urinary output, mL/kg/h; median (IQR)	0.9 (0.3–1.5)	0.9 (0.3–1.6)	0.9 (0.3–1.5)	0.45
Prior eGRF				0.01
< 60 mL/min/1.72 m <sup>2</sup>	142 (25.0%)	168 (21.9%)	310 (23.2%)	
60–90 mL/min/1.72 m <sup>2</sup>	133 (23.4%)	181 (23.6%)	314 (23.5%)	
> 90 mL/min/1.72 m <sup>2</sup>	122 (21.5%)	226 (29.5%)	348 (26.1%)	
Unknown	171 (30.1%)	191 (24.9%)	362 (27.1%)	

APACHE = Acute Physiologic and Chronic Health Evaluation. BMI = body mass index. eGRF = estimated glomerular filtration rate. IQR = interquartile range. \* The most extreme value is used if a variable is assessed more than once during the first 24 hours of admission. † Vasopressor treatment includes norepinephrine and epinephrine. ‡ Inotropic treatment includes dopamine and dobutamine.

**Figure 1. Patient flow in the study\*****A: Development cohort****B: Validation cohort**

ICU = intensive care unit. \* Patient flow in the development (A) and validation (B) cohorts

v AUC full, 78.7%;  $P = 0.64$ ). Thus, the simpler model had better performance and we chose to validate the basic models performance in an external cohort.

**Prediction of recovery in the validation cohort**

To adjust for the difference in recovery incidence between the development and validation cohort, we added 10.6% points to each patient's predicted chance of recovery. The resulting predictions were nicely calibrated (Figure 2). After recalibrating the model, 69 patients (9.0%) had a predicted chance of recovery < 25%, and their observed rate of recovery was 21.5%, with a sensitivity of 92.7%, a specificity of 30.1%, a positive predictive value (PPV) of 69.7% and a negative predictive value (NPV) of 70.3%. Whereas the observed rate of the 325 patients (51.4%) with a predicted chance of recovery > 75% was 81.7%, with a sensitivity of 24.1%, a specificity of 81.2%, a PPV of 83.6% and an NPV of 41.1%. In the intermediate group (25–75% chance of recovery), the incidence was 55.9% (Figure 3).

**Table 2. Predictors of recovery of prior kidney function\* within 28 days: Cox regression†**

Variable	Univariate			Basic model			Extended model		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Creatinine, fold elevation; per 10% increase	0.85	0.83–0.87	< 0.001	0.92	0.87–0.98	< 0.001	0.86	0.83–0.91	< 0.001
Gender									
Female	1.00			1.00			1.00		
Male	0.82	0.64–1.04	0.097	1.88	1.18–2.99	0.01	1.46	0.90–2.37	0.126
Creatinine, fold elevation; per 10% increase; gender (female)				0.89	0.86–0.93	< 0.001	0.86	0.83–0.91	< 0.001
Creatinine, fold elevation; per 10% increase; gender (male)				0.77	0.75–0.82	< 0.001	0.78	0.74–0.81	< 0.001
Urinary output									
< 0.5 mL/kg/h	1.00			1.00			1.00		
0.5–1.0 mL/kg/h	2.59	1.77–3.80	< 0.001	3.05	2.04–4.56	< 0.001	3.02	1.98–4.61	< 0.001
> 1.0 mL/kg/h	4.79	3.47–6.61	< 0.001	5.10	3.65–7.12	< 0.001	4.87	3.37–7.04	< 0.001
Age (years)									
18–50	1.00			1.00			1.00		
51–60	1.01	0.65–1.59	0.954	1.50	0.95–2.36	0.080	1.23	0.77–1.98	0.386
61–70	1.00	0.67–1.50	0.995	1.22	0.81–1.84	0.342	0.97	0.63–1.48	0.882
71–80	0.83	0.55–1.25	0.373	0.99	0.65–1.50	0.952	0.62	0.38–0.99	0.044
81–92	0.68	0.40–1.15	0.152	0.65	0.38–1.12	0.119	0.47	0.26–0.84	0.011
Severe sepsis or septic shock	0.71	0.56–0.91	0.007				1.07	0.79–1.46	0.657
Bilirubin, mg/dL; per 10% increase	0.97	0.95–0.98	< 0.001				0.98	0.97–0.99	0.002
Carbamid, mmol/L; per 10% increase	0.94	0.92–0.97	< 0.001				1.01	0.98–1.04	0.371
Mechanical ventilation	0.64	0.48–0.84	0.002				0.50	0.36–0.70	< 0.001
Vasopressor treatment‡	0.80	0.62–1.04	0.091				1.04	0.75–1.45	0.817
Inotropic treatment§	0.73	0.56–0.95	0.019				0.75	0.57–0.99	0.045
Haemoglobin	0.93	0.85–1.02	0.132				1.04	0.99–1.08	0.124
Platelets	1.00	1.00–1.00	< 0.001				1.00	1.00–1.00	0.222
Hypertension	1.02	0.76–1.36	0.890				1.28	0.93–1.76	0.125
Diabetes	0.99	0.72–1.37	0.959				1.07	0.75–1.52	0.712
Prior eGFR									
< 60 mL/min/1.73 m <sup>2</sup>	1.00						1.00		
60–90 mL/min/1.73 m <sup>2</sup>	0.89	0.64–1.26	0.516				1.15	0.79–1.67	0.458
> 90 mL/min/1.73 m <sup>2</sup>	1.08	0.78–1.51	0.643				1.02	0.68–1.53	0.915
Unknown	0.67	0.48–0.95	0.024				0.74	0.51–1.09	0.131

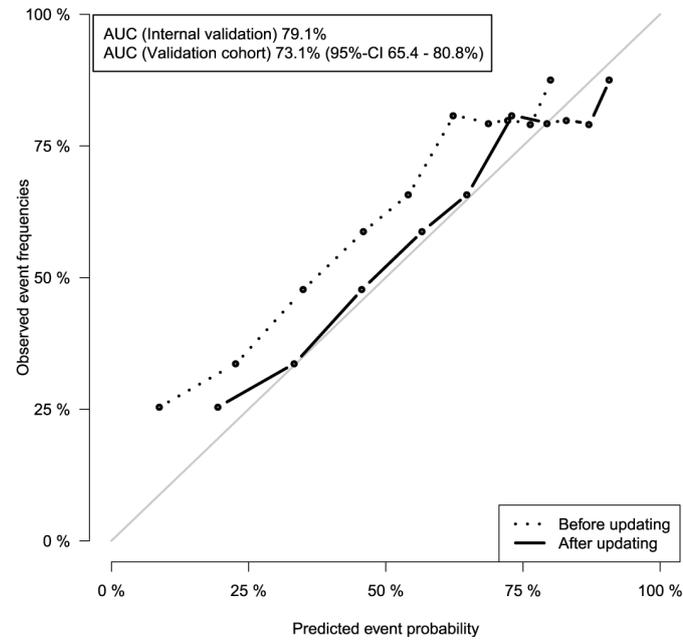
CI = confidence interval. eGFR = estimated glomerular filtration rate. HR = hazard ratio. \* Recovery of prior kidney function: living for 5 consecutive days with no renal replacement therapy and creatinine plasma levels consistently below 1.5 × the level of those determined before ICU admission over the 28-day follow-up period. The HRs express the relative chance of recovery, that is, a high HR is associated with a high rate of recovery. † Unadjusted and adjusted Cox regression estimates (cause-specific HRs) for known and suspected predictors of recovery of prior kidney function. All patients presented with AKI during the first 24 hours of admission and all variables are collected during the first 24 hours of admission. If there are more values available, the most extreme value is used. ‡ Vasopressor treatment includes norepinephrine and epinephrine. § Inotropic treatment includes dopamine and dobutamine.

In comparison, the rate of recovery among the 408 patients in the best and 197 patients in the worst KDIGO classes were 69.9% and 48.2%, respectively (Figure 3). The model's AUC for predicting recovery was 73.1% (95% CI, 65.4–80.8%).

We explored the effect of estimating pre-admission levels of creatinine and patients lost to follow-up, without

evidence of impact on the model performance (online Appendix; Supplement 3). To facilitate clinical translation, we constructed risk charts and an electronic calculator (online Appendix; Supplements 4 and 5).

**Figure 2. Calibration and discrimination of the risk prediction model before and after recalibration\***



AUC = area under the receiver operations curve. CI = confidence interval. ICU = intensive care unit. \* Calibration of risk prediction model in the validation cohorts before and after updating. Calibration is the agreement between predicted and observed incidence of recovery in groups of patients grouped by deciles of risk.

in external cohorts.<sup>12,15</sup> A probable reason for this low performance is that the statistical methods used tend to be quite complex models. Such models are more prone to be unstable in external validation. Therefore, we applied a conservative methodology without feature selection. We ensured that we did not miss important variables by comparing the performance with a more complex model. Further, we validated our model in an independent and unselected ICU population to ensure its stability.

**Study implications**

Patients at high risk of not recovering should receive particular attention to avoid progression or consolidation of established kidney injury. However, no interventions are known to reduce the negative impact of AKI. Randomised trials of interventions aimed at improving kidney function in critically ill patients have frequently included unselected patients with AKI.<sup>7-9,35</sup> The disappointing negative results from most of these interventional trials have frustrated researchers and physicians, since it is tempting to think that renal failure may increase the risk of death. Nevertheless, spontaneous recovery is frequent in an unselected AKI population, and thus the signal-to-noise ratio in the patients recruited

**Discussion**

**Main findings**

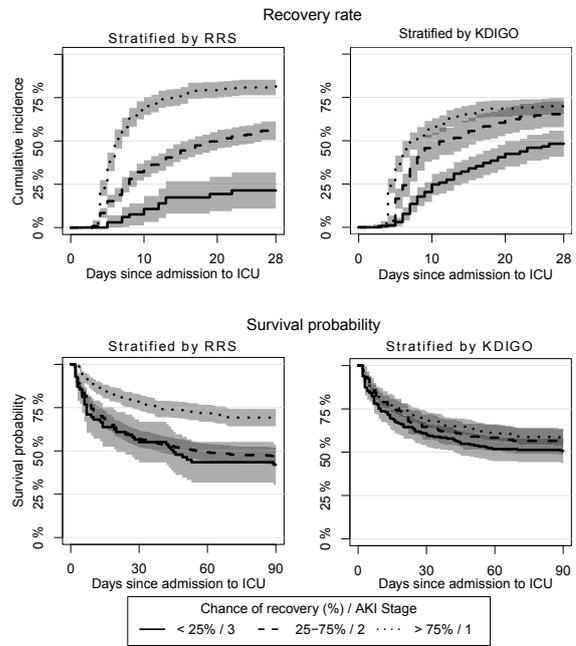
We have developed and validated a model that accurately predicts if critically ill patients with AKI recover prior kidney function. We found that the model consisting of age, gender, creatinine elevation and urinary output could predict recovery of kidney function with a higher precision than previous models and KDIGO. A model that included additional variables did not improve prediction.

**Comparison with previous studies**

Previous risk prediction models have exclusively focused on identifying patients that recover from severe RRT-demanding AKI or on predicting survival.<sup>12-14,18,21,22,32</sup> However, recovery from any severity of AKI has recently been put forward as an area of focus, and consensus statements have highlighted the potential for increased understanding of epidemiology and pathophysiology of AKI by unravelling the recovery patterns in AKI.<sup>33,34</sup> By predicting recovery, we get a measure of the intensity of kidney disease that is less biased by other organ failures, and is meaningful in terms of quantifying the potential for improvement from interventions.

Despite impressive performance in the original studies, previous models have all had low performance when tested

**Figure 3. Performance of risk prediction model in validation cohort**



AKI = acute kidney injury. ICU = intensive care unit. KDIGO = Kidney Disease: Improving Global Outcomes. RRS = renal recovery score. Cumulative incidence (chance) of recovery on day 28 and survival probability within 90 days when stratified according to the Renal Recovery Score and the KDIGO classification.

into these trials may have been unfavourable, even if the intervention was effective.<sup>23,25,36</sup> With the current model, investigators can ensure balance on the chance of recovery in future trials, and select a patient cohort where the effect of kidney injury is most pronounced.

With our model, after 24 hours of ICU admission, it is possible to identify a patient population where the recovery probability is very low, a feature no other published model can match. Therefore, using the model we developed, we can exclude a large group of patients where the recovery chance is nearly nine in ten, thus not diluting a possible positive signal. A major strength of the model is that in contrast to other ICU risk stratification tools, this model can readily be calibrated according to the local conditions in any ICU.

### Strengths and limitations

This study was an observational study with the limitations this implies. We identified three potential sources of bias in our study:

- estimating prior creatinine levels for diagnosing AKI;
- estimating prior creatinine levels for diagnosing recovery; and
- including patients lost to follow-up.

We explored these limitations potential to affect our results in sensitivity analyses without evidence of impact on the analysis.

### Future research

This new model can be implemented into clinical practice. It could serve as an outcome-directed risk assessment tool to select or stratify patients for interventional trials that test protective kidney regimens or kidney-specific interventions. However, further studies are necessary to validate the findings and the clinical utility of the proposed model. Inclusion of novel biomarkers may potentially improve the model.

### Conclusion

We constructed a model that can predict the recovery chance after ICU-related AKI. The model is stable in external validation, but we recommend calibration of the tool in new populations before clinical introduction. The model is easy to implement, since the parameters it requires are readily available for ICU patients. We suggest that the tool should be used in the clinical assessment of critically ill patients with AKI to estimate the chance of recovering prior kidney function. In addition, the tool can select the patients who are most likely to benefit from a kidney protective intervention applied in a randomised interventional trial.

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### Competing interests

None declared.

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