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

Theis S Itenov, Rasmus Ehrenfried Berthelsen, Jens-Ulrik Jensen, Thomas A Gerds, Lars M Pedersen, Ditte Strange, Katrin Thormar, Jesper Løken, Mads H Andersen, Hamid Tousi, Nanna Reiter, Jens D Lundgren and Morten H Bestle, for the Procalcitonin and Survival Study Group

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.

Crit Care Resusc 2018; 20 (1): 54-60

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.[1–6] 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.[7–9] 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.[10] The available risk models do not identify patients at high or low chance of recovering kidney function.[11–22] One set of models predicts recovery from AKI demanding renal replacement therapy (RRT), and thus excludes patients with milder AKI.[11,13,16,18–20] These prediction models is inexpedient because all stages of AKI carry an increased risk of adverse long term outcomes.[23,24] The second set of models predicts survival of patients with AKI.[11,12,14,15,21,22] 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.[25,26]

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 elsewhere.[27] 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 ≥ 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.[28] 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; 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^2, 60–90 mL/min/1.73 m^2, > 90 mL/min/1.73 m^2 and "unknown", with the latter category encompassing patients without pre-morbid creatinine measurements. Lastly, age was divided into five categories: ≤ 50 years, 51–60 years, 61–70 years, 71–80 years and ≥ 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).[29] 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.[30]

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.[31]

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

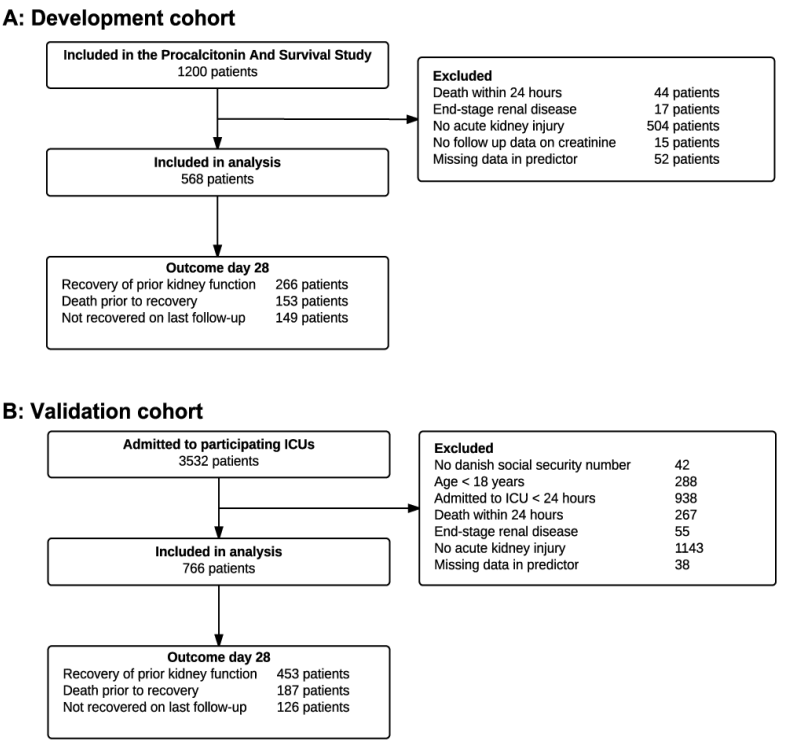
Of the 568 patients in the development cohort, 135 (23.8%) had less than a 25% predicted chance of recovery. In this group of patients, the observed rate of recovery was 19.5%. Conversely, among the 107 patients who had received a predicted chance of recovery > 75% from our model, the observed rate of 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/m²; 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 m²	142 (25.0%)	168 (21.9%)	310 (23.2%)	
60–90 mL/min/1.72 m²	133 (23.4%)	181 (23.6%)	314 (23.5%)	
> 90 mL/min/1.72 m²	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*



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†

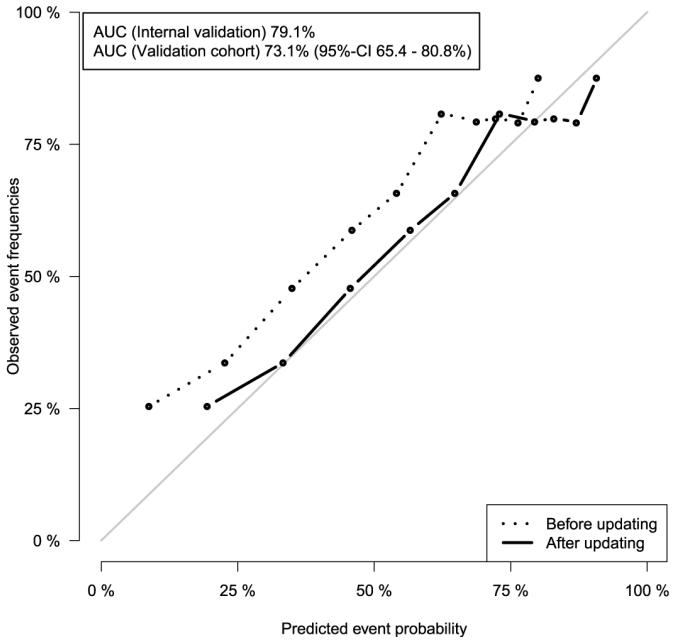
	Univariate			Basic model			Extended model		
Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Creatinine, fold elevation; per 10% increase	0.85	0.83–0.87	< 0.001	0.92	0.87–0.98	< 0.001	0.86	0.83–0.91	< 0.001
Gender									
Female	1.00			1.00			1.00		
Male	0.82	0.64–1.04	0.097	1.88	1.18–2.99	0.01	1.46	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 m²	1.00						1.00		
60–90 mL/min/1.73 m²	0.89	0.64–1.26	0.516				1.15	0.79–1.67	0.458
> 90 mL/min/1.73 m²	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. eGRF = 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.

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

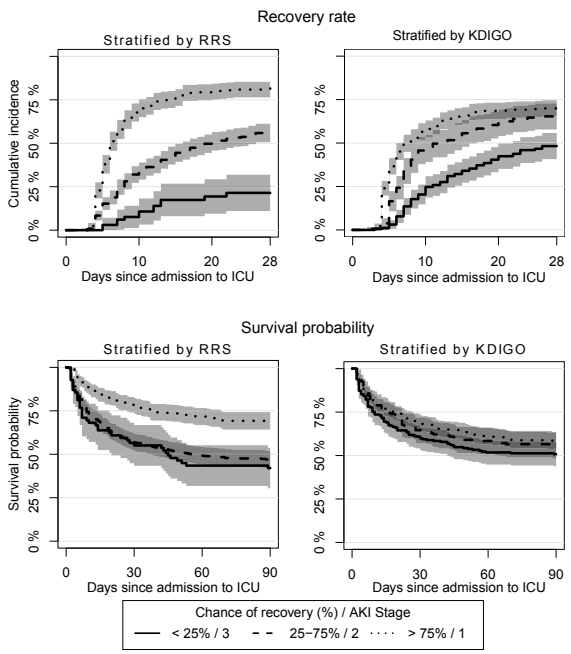
Previous risk prediction models have exclusively focused on identifying patients that recover from severe RRT-demanding AKI or on predicting survival.[12–14,18,21,22,32] However, recovery from any severity of AKI has recently been put forward as an area of focus, and consensus statements have highlighted the potential for increased understanding of epidemiology and pathophysiology of AKI by unravelling the recovery patterns in AKI .[33,34] 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 in external cohorts .[12,15] 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.[7–9,35] 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

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.[23,25,36] 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.

Acknowledgment

This work was supported by the Danish National Research Foundation (grant no. 126), the Centre of Excellence for Health, Immunity and Infections (CHIP), the Centre of Excellence for Personalised Medicine of Infectious Complications in Immune Deficiency (PERSIMUNE), the Lundbeck Foundation, the Research Foundation for the Capital Region of Denmark, the Toyota Foundation, Brahms Diagnostica (unrestricted grant), the Harboe Foundation, the AP Møller Foundation, the Fru Olga Brydes Nielsens Foundation and the Research Board at Nordsjællands Hospital.

Competing interests

None declared.

Author details

Theis S Itenov[1,2]
Rasmus Ehrenfried Berthelsen[1]
Jens-Ulrik Jensen[2,3]
Thomas A Gerds[4]
Lars M Pedersen[5]
Ditte Strange[6]
Katrin Thormar[7]
Jesper Løken[5]
Mads H Andersen[8]
Hamid Tousi[9]
Nanna Reiter[10]
Jens D Lundgren[2]
Morten H Bestle[1]
for the Procalcitonin and Survival Study Group

1 Department of Anaesthesiology, Nordsjællands Hospital, University of Copenhagen, Denmark.
2 CHIP/PERSIMUNE, Department of Infectious Diseases and Rheumatology, Rigshospitalet, the University of Copenhagen, Copenhagen, Denmark.
3 Department of Clinical Microbiology, Hvidovre Hospital, Hvidovre, Denmark.
4 Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark.
5 Department of Anaesthesiology, Hvidovre Hospital, Hvidovre, Denmark.
6 Department of Neuroanaesthesiology, Rigshospitalet, København, Denmark.
7 Department of Anaesthesiology, Landspítali Háskólasjúkrahús, Reykjavik, Iceland.
8 Department of Anaesthesiology, Aarhus University Hospital, Aarhus, Denmark.
9 Department of Anaesthesiology, Herlev Hospital, Herlev, Denmark.
10 Department of Anaesthesiology, Bispebjerg Hospital, København, Denmark.

Correspondence: Theis.skovsgaard.itenov@regionh.dk

References

1 Thakar CV, Christianson A, Freyberg R, et al. Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. *Crit Care Med* 2009; 37: 2552-8.

2 Pannu N, James M, Hemmelgarn B, Klarenbach S; Alberta Kidney Disease Network. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. *Clin J Am Soc Nephrol* 2013; 8: 194-202.

3 Schiffl H, Lang SM, Fischer R. Long-term outcomes of survivors of ICU acute kidney injury requiring renal replacement therapy: a 10-year prospective cohort study. *Clin Kidney J* 2012; 5: 297-302.

4 Triverio PA, Martin PY, Romand J, et al. Long-term prognosis after acute kidney injury requiring renal replacement therapy. *Nephrol Dial Transplant* 2009; 24: 2186-9.

5 Jones J, Holmen J, De Graauw J, et al. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. *Am J Kidney Dis* 2012; 60: 402-8.

6 Schiffl H, Fischer R. Five-year outcomes of severe acute kidney injury requiring renal replacement therapy. *Nephrol Dial Transplant* 2008; 23: 2235-41.

7 Tumlin JA, Finkel KW, Murray PT, et al. Fenoldopam mesylate in early acute tubular necrosis: a randomized, double-blind, placebo-controlled clinical trial. *Am J Kidney Dis* 2005; 46: 26-34.

8 Lewis J, Salem MM, Chertow GM, et al. Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. *Am J Kidney Dis* 2000; 36: 767-74.

9 Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet* 2000; 356: 2139-43.

10 Hingorani AD, Windt DA, Riley RD, et al. Prognosis research strategy (PROGRESS) 4 : stratified medicine research. *BMJ* 2013; 346: e5793.

11 Chertow GM, Christiansen CL, Cleary PD, et al. Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. *Arch Intern Med* 1995; 155: 1505-11.

12 Chertow GM, Soroko SH, Paganini EP, et al. Mortality after acute renal failure: models for prognostic stratification and risk adjustment. *Kidney Int* 2006; 70: 1120-6.

13 Demirjian S, Chertow GM, Zhang JH, et al. Model to predict mortality in critically ill adults with acute kidney injury. *Clin J Am Soc Nephrol* 2011; 6: 2114-20.

14 Lins RL, Elseviers MM, Daelemans R, et al. Re-evaluation and modification of the Stuivenberg Hospital Acute Renal Failure (SHARF) scoring system for the prognosis of acute renal failure: an independent multicentre, prospective study. *Nephrol Dial Transplant* 2004; 19: 2282-8.

15 Mehta RL, Pascual MT, Gruta CG, et al. Refining predictive models in critically ill patients with acute renal failure. *J Am Soc Nephrol* 2002; 13: 1350-7.

16 Paganini EP, Halstenberg WK, Goormastic M. Risk modeling in acute renal failure requiring dialysis: the introduction of a new model. *Clin Nephrol* 1996; 46: 206-11.

17 Uchino S. Outcome prediction for patients with acute kidney injury. *Nephron Clin Pract* 2008; 109: c217-23.

18 d'Avila DO, Cendoroglo M, dos Santos OFP, et al. Acute renal failure needing dialysis in the intensive care unit and prognostic scores. *Ren Fail* 2004; 26: 59-68.

19 Barton IK, Hilton PJ, Taub NA, et al. Acute renal failure treated by haemofiltration: factors affecting outcome. *Q J Med* 1993; 86: 81-90.

20 Schaefer JH, Jochimsen F, Keller F, et al. Outcome prediction of acute renal failure in medical intensive care. *Intensive Care Med* 1991; 17: 19-24.

21 Lins RL, Elseviers M, Daelemans R, et al. Prognostic value of a new scoring system for hospital mortality in acute renal failure. *Clin Nephrol* 2000; 53: 10-7.

22 Liaño F, Gallego A, Pascual J, et al. Prognosis of acute tubular necrosis: an extended prospectively contrasted study. *Nephron* 1993; 63: 21-31.

23 Nisula S, Kaukonen KM, Vaara ST, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. *Intensive Care Med* 2013; 39: 420-8.

24 Gammelager H, Christiansen CF, Johansen MB, et al. Five-year risk of end-stage renal disease among intensive care patients surviving dialysis-requiring acute kidney injury: a nationwide cohort study. *Crit Care* 2013; 17: R145.

25 Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005; 294: 813-8.

26 Cartin-Ceba R, Kashiouris M, Plataki M, et al. Risk factors for development of acute kidney injury in critically ill patients: a systematic review and meta-analysis of observational studies. *Crit Care Res Pract* 2012; 2012: 691013.

27 Jensen JU, Hein L, Lundgren B, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. *Crit Care Med* 2011; 39: 2048-58.

28 Kellum JA, Lameire N, Aspelin P, et al. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; 2: 1-138.

29 Benichou J, Gail MH. Estimates of absolute cause-specific risk in cohort studies. *Biometrics* 1990; 46: 813-26.

30 Aalen O. Nonparametric inference for a family of counting processes. *Ann Stat Institute of Mathematical Statistics* 1978; 6: 701-26.

31 R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2016.

32 Mehta RL, Pascual MT, Soroko S, Chertow GM; PICARD Study Group. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *JAMA* 2002; 288: 2547-53.

33 Forni LG, Darmon M, Ostermann M, et al. Renal recovery after acute kidney injury. *Intensive Care Med* 2017; 43: 655-66.

34 Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol* 2017; 13: 241-57.

35 Smith OM, Wald R, Adhikari NK, et al. Standard versus accelerated initiation of renal replacement therapy in acute kidney injury (STARRT-AKI): study protocol for a randomized controlled trial. *Trials* 2013; 14: 320.

36 Gammelager H, Christiansen CF, Johansen MB, et al. One-year mortality among Danish intensive care patients with acute kidney injury: a cohort study. *Crit Care* 2012; 16: R124. ❑

Appendix

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Supplement 1: Details on methods

Definition of recovery

AKI patients typically recover within the first month of AKI onset [1]. The outcome was time to recovery of prior kidney function within 28 days. We defined recovery of prior kidney function as living for five consecutive days with no renal replacement therapy and creatinine plasma levels consistently below 1.5 x the levels determined before ICU admission over the 28 day follow-up period. The creatinine cut-point was in line with the KDIGO classification[2]. The prior creatinine plasma level was defined as (in order of priority): 1) the median of all creatinine measurements 8-180 days prior to ICU admission, 2) the median of creatinine levels measured < 8 days prior to ICU admission, if the patient's AKI was a 1.5 fold increase in creatinine within the last 7 days or 3) an estimated creatinine using the 4-variable Modified Diet in Renal Disease (MDRD)-formula assuming a glomerular filtration rate (GFR) of 75 ml/min/1,73 m^2.[3,4]

Statistical evaluation

The prediction models were evaluated on calibration and discrimination using an internal cross-validation design [5]. We chose the model with the best performance in internal validation and validated that in the external cohort. Discrimination was assessed by the area under the receiver operations curve (AUC) for competing risk models [6]. Calibration was assessed using a calibration plot. To predict the chance of recovery in the validation cohort the model was updated by adding the average difference in 28-day chances of recovery between the cohorts [7]

Missing data

Missing data were rare in both the development and validation cohorts and only patients with a complete set of prognostic covariates were included in the analysis. Missing creatinine values during follow-up were replaced with the last available observation carried forward, but only for a maximum of four consecutive days after which patients were censored.

Discrimination

Discrimination is a model's ability to separate between patients with and without events at the end of the study. This is presented as the area under the receiver operations curve (AUC) that can be interpreted as the probability that the predicted chance of recovery is higher for a patient who recover compared to a patient who do not. We evaluated this on day 28 after ICU admission. For calculating the sensitivity and specificity we defined a case as a patient with a recovery event on or before day 28 and control is defined as a subject that is not a case on day 28.

Calibration

Calibration is the agreement between predicted and observed event rates. We present calibration as the mean predicted risk vs. the observed proportion in groups of patients separated by the deciles of predicted risk.

Internal bootstrap cross-validation

Prediction performance was evaluated in an internal cross-validation design:

1) Data were randomly split into two parts.

2) All steps of Cox regression modeling (including variable selection) were repeated in one part of the data.

3) The model of step 2 was applied to predict the chance of recovery in the validation set patients.

4) The discrimination and calibration were calculated based on the validation set.

5) Steps 1-4 were repeated 1000 times and reported values were averages and standard deviations.

Supplement 2: Calculating individual patients' risk from the model

The individual patients' chance of recovery can be estimated from the following equation:

$$I_{Recovery}(t) = \int_0^t \lambda_{Recovery}(s) \exp(-\int_0^s (\lambda_{Recovery}(u) + \lambda_{Death\ prior\ to\ recovery}(u))du)ds$$

Where $I_{Recovery}$ is the patients' chance of recovering, $\lambda_{Recovery}$ is the hazard function of recovery, and $\lambda_{Death\ prior\ to\ recovery}$ is the hazard of dying prior to recovery and t is the time point of interest.

The oliguria variable is divided into dummy variables with value (0/1) depending on whether the patient has the level of oliguria in question.

To complete this equation the following information is needed:

1) Regression coefficients:

	Coefficient Recovery	Coefficient Death prior to recovery
Urinary output		
< 0.5 mL / kg / h	1	1
0.5 – 1.00 mL / kg / h (code as dummy variable)	1.1166	-0.320
> 1.00 mL/ kg / h (code as dummy variable)	1.6285	-0.466
Log (elevation in creatinine (in fold from level prior to admission))	-1.07885	-0,819
Age (in years)		
< 51	1	1
51-60	0.4061	0.595
61-70	0.1991	0.297
71-80	-0.0128	1.034
80-92	-0.4279	1.626
Male gender	0.6314	-0.210
Male gender : Log (elevation in creatinine (in fold from level prior to admission))	-1.3385	0.404

2) Baseline hazard functions (covariates have value '0'):

Time	Baseline hazard function Recovery	Baseline hazard function Death prior to recovery
1	0.002	0.001
2	0.003	0.050
3	0.009	0.077
4	0.071	0.104

5	0.165	0.136
6	0.232	0.159
7	0.281	0.178
8	0.337	0.196
9	0.385	0.207
10	0.472	0.242
11	0.522	0.267
12	0.586	0.288
13	0.669	0.342
14	0.742	0.349
15	0.806	0.378
16	0.882	0.404
17	0.924	0.413
18	1.014	0.451
19	1.064	0.451
20	1.124	0.461
21	1.145	0.485
22	1.191	0.485
23	1.215	0.537
24	1.267	0.580
25	1.267	0.595
26	1.326	0.646
27	1.360	0.808
28	1.360	0.865

Supplement 3: Sensitivity analyses

	AUC	95%-CI		
Estimation of premorbid creatinine				
Yes (n = 191)	71.1	(54.7	-	87.6)
No (n = 575)	73.6	(67.4	-	79.7)
Estimation of creatinine for AKI diagnosis				
Yes (n = 103)	72.0	(56.3	-	87.7)
No (n =663)	73.3	(66.0	-	80.6)

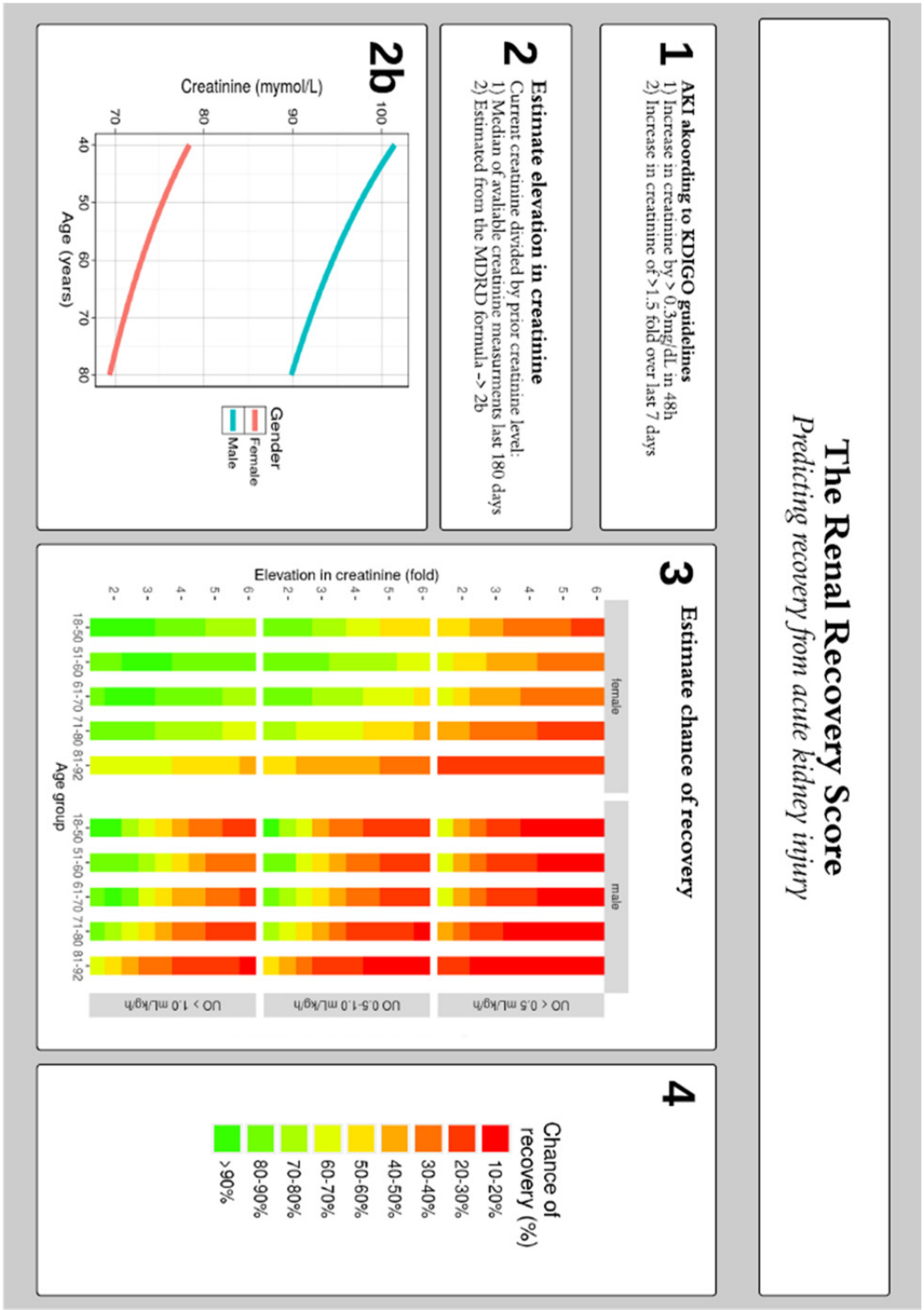
In the validation cohort, 81 (10.5%) of patients had an incomplete follow-up. To evaluate how this might influence the analysis we made two sensitivity analyses. In the first, we estimated these patients outcome based on the predictions made by the model. If the model predicted a chance of recovery > 50% we set the patient's status as 'recovered on the last day of follow-up', and if the chance of recovery was < 50% we set the patient's status as 'not recovered on day 28'. This would be in optimal agreement with the model.

In the second, we did the inverse: If the model predicted at chance of recovery < 50% we set the patient's status as 'recovered on the last day of follow-up', and if the chance of recovery was > 50% we set the patient's status as 'not recovered on day 28'. This would be in maximal disagreement with the model.

These analyses would give us the maximal range that our precision estimate could move if the outcomes of these patients, in reality, were in total agreement or disagreement with the predictions made by the model. The real estimate will be somewhere in between these extremes.

We found that the AUC in these sensitivity analyses were 76.2 (95%-CI 72.3-80.2%) and 68.1% (95%-CI 63.1-73.1), respectively.

Supplement 4: Renal recovery score risk charts



References

1. Pannu N, James M, Hemmelgarn B, Klarenbach S. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. *Clin J Am Soc Nephrol* 2013; **8**: 194–202

2. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl* 2012; **2**: 1–138

3. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130**: 461–70

4. Lafrance J-P, Miller DR. Defining acute kidney injury in database studies: the effects of varying the baseline kidney function assessment period and considering CKD status. *Am J Kidney Dis* Elsevier Inc.; 2010; **56**: 651–60

5. Steyerberg EW, Harrell FE, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001; **54**: 774–81

6. Blanche P, Dartigues J-F, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med* 2013; **32**: 5381–97

7. Gerds TA, Andersen PK, Kattan MW. Calibration plots for risk prediction models in the presence of competing risks. *Stat Med* 2014; **33**: 3191–203