Appendix

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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)

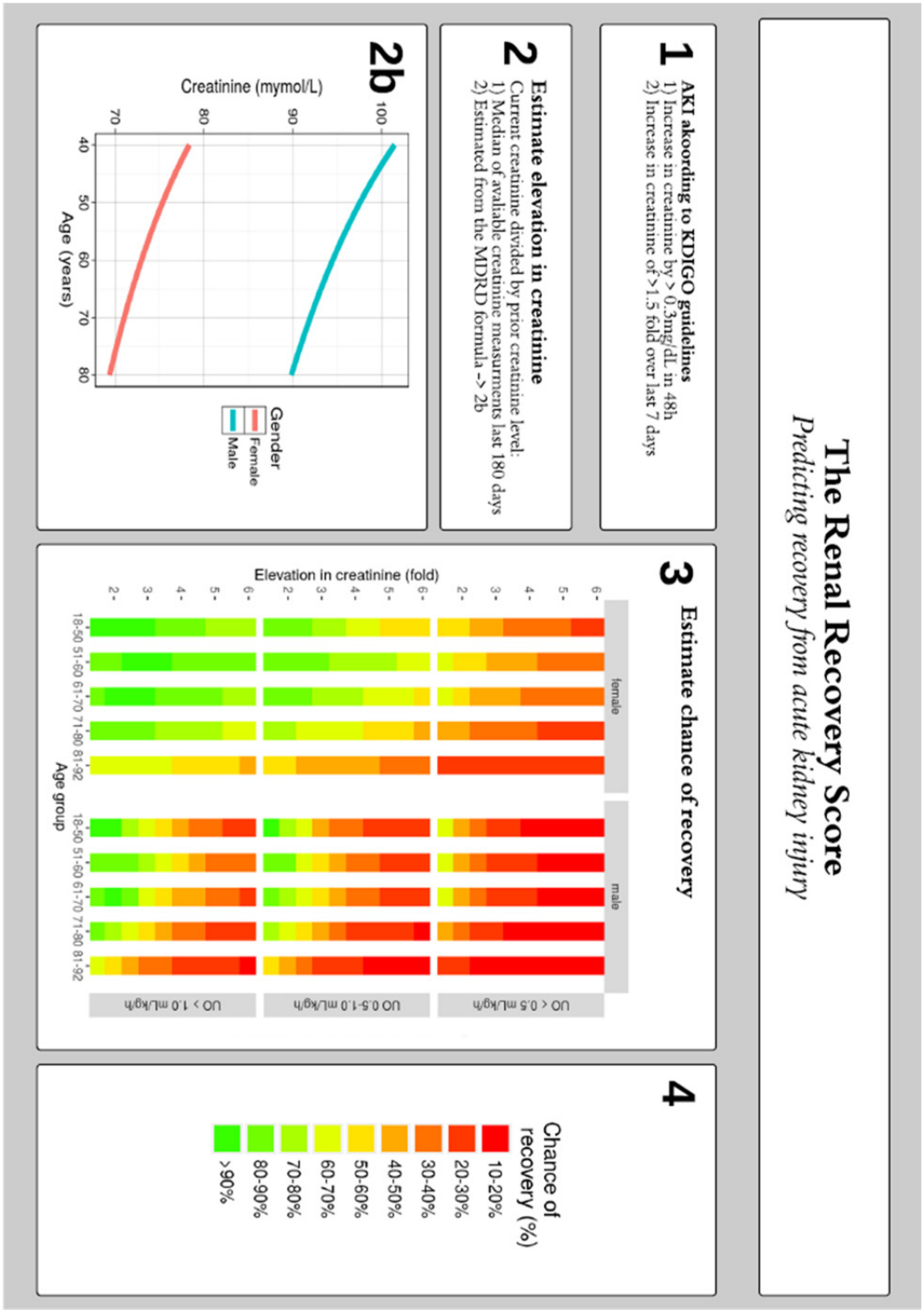
In the validation cohort, 81 (10.5%) of patients had an incomplete follow-up. To evaluate how this might influence the analysis we made two sensitivity analyses. In the first, we estimated these patients outcome based on the predictions made by the model. If the model predicted a chance of recovery > 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



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