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Development and Validation of a Clinical Prediction Model for Stages of Acute Kidney Injury in Critically Ill Patients

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Keywords
Acute kidney injury · Critically ill · Intensive care · Kidney Disease: Improving Global Outcomes · Prediction model

Abstract
Introduction: Among critically ill patients, acute kidney injury (AKI) has a high incidence and leads to poor prognosis. As AKI is often only detected well after onset, early risk stratification is crucial. This study aimed to develop and internally validate the first clinical prediction model for different stages of AKI in critically ill adults. ***Methods:*** We utilized data from the Simple Intensive Care Studies II (SICS-II), a prospective cohort study at the University Medical Center Groningen, the Netherlands. The prognostic outcome was the highest KDIGO-based stage of AKI within the first 7 days of ICU stay. Candidate predictors included fifty-nine readily available variables in critical care. Least absolute shrinkage and selection operator and proportional odds logistic regression were used for variable selection and model estimation, respectively. Receiver operating characteristic (ROC) curve, calibration plot, and decision curve analysis were applied to evaluate model performance and clinical usefulness. ***Results:*** Of the SICS-II cohort, 976 patients were eligible for our analyses (median [interquartile range] age 64 [52–72] years, 38% female). Within 7 days after ICU admission, 29%, 23%, and 14% of patients progressed to their highest severity of AKI at stages 1, 2, and 3, respectively. We derived a 15-variable model for predicting this maximum ordinal outcome with an area under the ROC curve of 0.76 (95% CI, 0.74–0.78) in bootstrap validation. The model showed good calibration and improved net benefit in decision curve analysis over a range of clinically plausible thresholds. ***Conclusion:*** Using readily available predictors in the ICU setting, we could develop a prediction model for different stages of AKI with good performance and promising clinical usefulness. Our findings serve as an initial step towards applying a valid and timely prediction model for AKI severity, possibly helping to limit morbidity and improve patient outcomes.

Introduction

Acute kidney injury (AKI) is a sudden loss of kidney function [1, 2]. It frequently complicates critical illness: up to 75% of all critically ill patients may develop some stage of AKI during their illness [3]. AKI increases the

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risks of subsequent chronic kidney disease (CKD), heart failure, myocardial infarction, stroke, and kidney cancer by 91%, 58%, 40%, 15%, and 101%, respectively, and substantially reduces health-related quality of life [4–7]. AKI is clinically detected either by a rise in serum creatinine (SCr) or a decrease in urine output (UO), which is typically delayed after the onset of the condition, so underlying kidney injury may progress before it is diagnosed [2]. By the time appropriate interventions are taken to prevent further kidney dysfunction, most patients probably already have more severe AKI, possibly with concomitant irreversible damage.

Not only the occurrence of AKI but also its severity is associated with poor outcomes, even when AKI resolves [1, 2, 8]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) definition providing the most recent criteria, AKI is classified into three stages (1<2<3), with a higher stage reflecting a more severe condition [1]. Higher stages were associated with increased mortality and higher incidences of long-term CKD [1, 2, 8]. The mortality rate associated with AKI was estimated at 23% but may increase to around 50% in those requiring renal replacement therapy [8]. Also, guidelines for AKI management recommend specific bundles for different stages of AKI [1, 2].

Early recognition and prevention of AKI and limiting its severity seem essential to reduce morbidity and mortality. Despite the relevance of AKI severity to patient outcomes, all existing prediction models for AKI only attempted to predict a binary outcome which is the occurrence of an event, such as AKI at any stage or severe AKI (e.g., stage 2 or 3), rather than a more informative ordinal outcome involving the specific stages of AKI [9–19]. This study aimed to develop and internally validate the first clinical prediction model for estimating the absolute risks of various AKI stages occurring within the first 7 days following an acute ICU admission.

Methods

This paper was reported following the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000545150) [20].

Study Design, Setting, and Participants

We used data from a prospective cohort study, the Simple Intensive Care Studies II (SICS-II), conducted at the University Medical Center Groningen (UMCG), the Netherlands, between May 2018 and July 2019 [21]. SICS-II included all critically ill patients aged 18 years or older who were acutely admitted to the ICU. Exclusion criteria were as follows: discharge within 24 h, readmissions after previous inclusion, elective admissions after surgery or other reasons, strict isolation due to contagious disease, non-trauma neurological admission reason, or defiance of informed consent. Inhospital data of all patients were collected until day seven after ICU admission, death, or discharge from the ICU, whichever happened first. The research was done in accordance with the Declaration of Helsinki and was approved by UMCG Institutional Review Boards.

The Prognostic Outcome and Candidate Predictors

The outcome variable was assessed by trained researchers blinded to patient characteristics. The primary outcome was the maximum AKI stage (0<1<2<3) within the first 7 days after ICU admission according to KDIGO definition based on SCr, UO, and renal replacement therapy [1]. The lowest recorded SCr value within a year before ICU admission was designated baseline SCr. If unavailable, baseline SCr was estimated using the Modification of Diet in Renal Disease (MDRD) formula, assuming an estimated glomerular filtration rate of 75 mL/min/1.73 m^2. For UO criteria, hourly registered data were used and grouped in 6-hour time windows to assess AKI.

We selected an initial list of fifty-nine candidate predictors representing all important domains on the pathways to kidney injury based on clinical reasoning and literature review (online suppl. Table S2). Candidate predictors were categorized into four types: demographics (4 variables), indicators of acute physiology (23 variables), concomitant medical conditions (13 variables), and preadmission medication use (19 variables). All candidate predictors were recorded within 24 h of ICU admission, except for the preadmission medication use, which was obtained from the notes and letters written by several health providers in the electronic medical charts and checked at hospital admission by pharmacy personnel.

Statistical Analysis Methods and Modeling Approach

All data analyses were performed using R v4.2.2. First, we assessed the need for (natural) log transformation of continuous predictors by visually inspecting their distributions in histograms. Second, we investigated the predictive contribution of each data layer (demographics, indicators of acute physiology, concomitant medical conditions, and preadmission medication use), defined as the increase in prediction performance after sequentially adding all layers' corresponding variables to the model. Third, least absolute shrinkage and selection operator

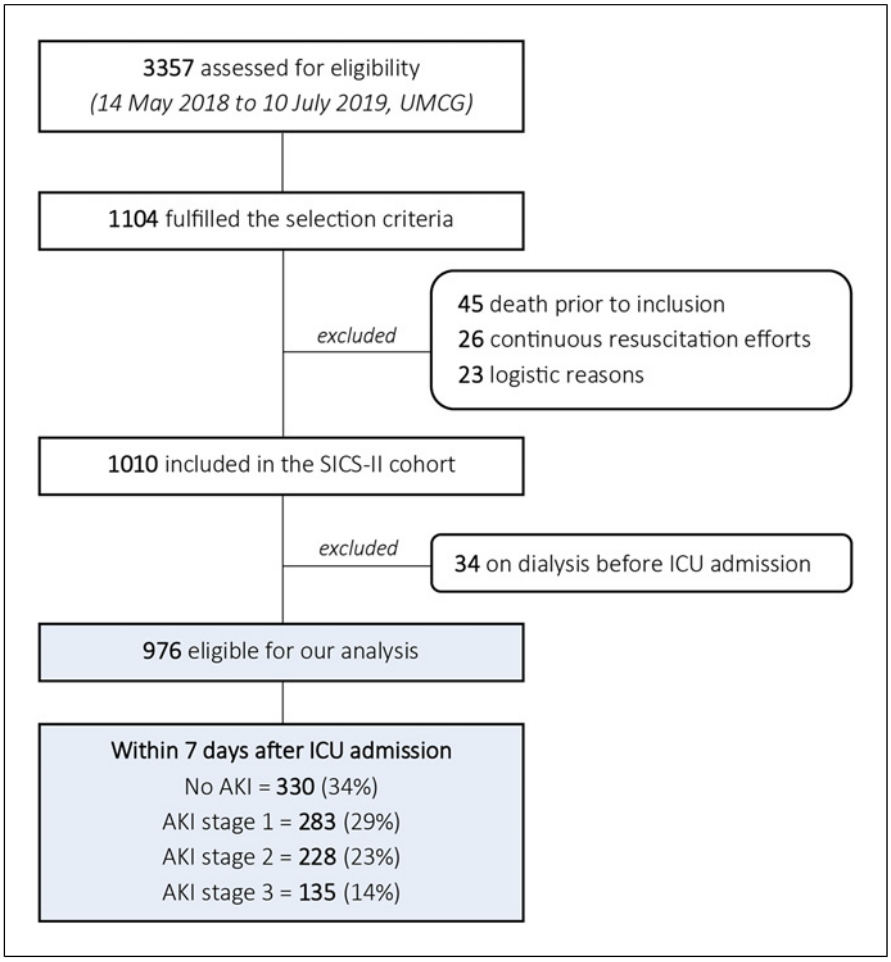


Fig. 1. Participant flow diagram. UMCG, University Medical Center Groningen; SICS-II, Simple Intensive Care Studies II; ICU, intensive care unit; AKI, acute kidney injury.

(LASSO) [22] was applied for variable selection. Although R packages such as *ordinalNet* are available for fitting ordinal outcome models using LASSO, they have not been well established in clinical prediction settings. Therefore, we dichotomized our 4-level ordered outcome (0<1<2<3) into three binary outcomes (i.e., AKI stage ≥1, ≥2, and 3) and performed three LASSO models. The union of selected predictors in those three models, chosen at a one-standard-error larger value of the lowest 10-time repeated 10-fold cross-validated λ value, was included in the final prediction model. Before running LASSO models, we also included quadratic terms of age, mean arterial pressure, arterial pH, and white blood cell count, as prior clinical knowledge suggests likely non-linear relationships with the outcome. All model parameters for the ordinal outcome were estimated by proportional odds logistic regression. Internal validation was then performed using bootstrapping [20, 23]. Specifically, we repeated the model estimation in 500 bootstrap samples and computed the optimism-corrected performance, including discrimination (i.e., C-statistic, or area under the curve [AUC]) and calibration measures (i.e., calibration slope and calibration intercepts) [20, 24].

As secondary analyses, we evaluated the model regarding its prediction of different dichotomized outcomes mentioned above. Accordingly, in addition to AUCs, calibration was graphically assessed by plotting observed proportions versus predicted probabilities [20, 24]. We also used decision curve analysis to compare the clinical usefulness of the model to the renal component of the Sequential Organ Failure Assessment [renal SOFA] score [25–27] and two default policies ("treat all" and "treat none"). The decision curves plot the "net benefit" across a range of predicted probability thresholds and quantify the effect of using a model at a chosen threshold [20, 28, 29]. The net benefit of a model is the weighted difference between the proportion of true positives and false positives, where the weight depends on the selected threshold. A model is superior to another if it has a higher net benefit across a range of clinically relevant threshold probabilities.

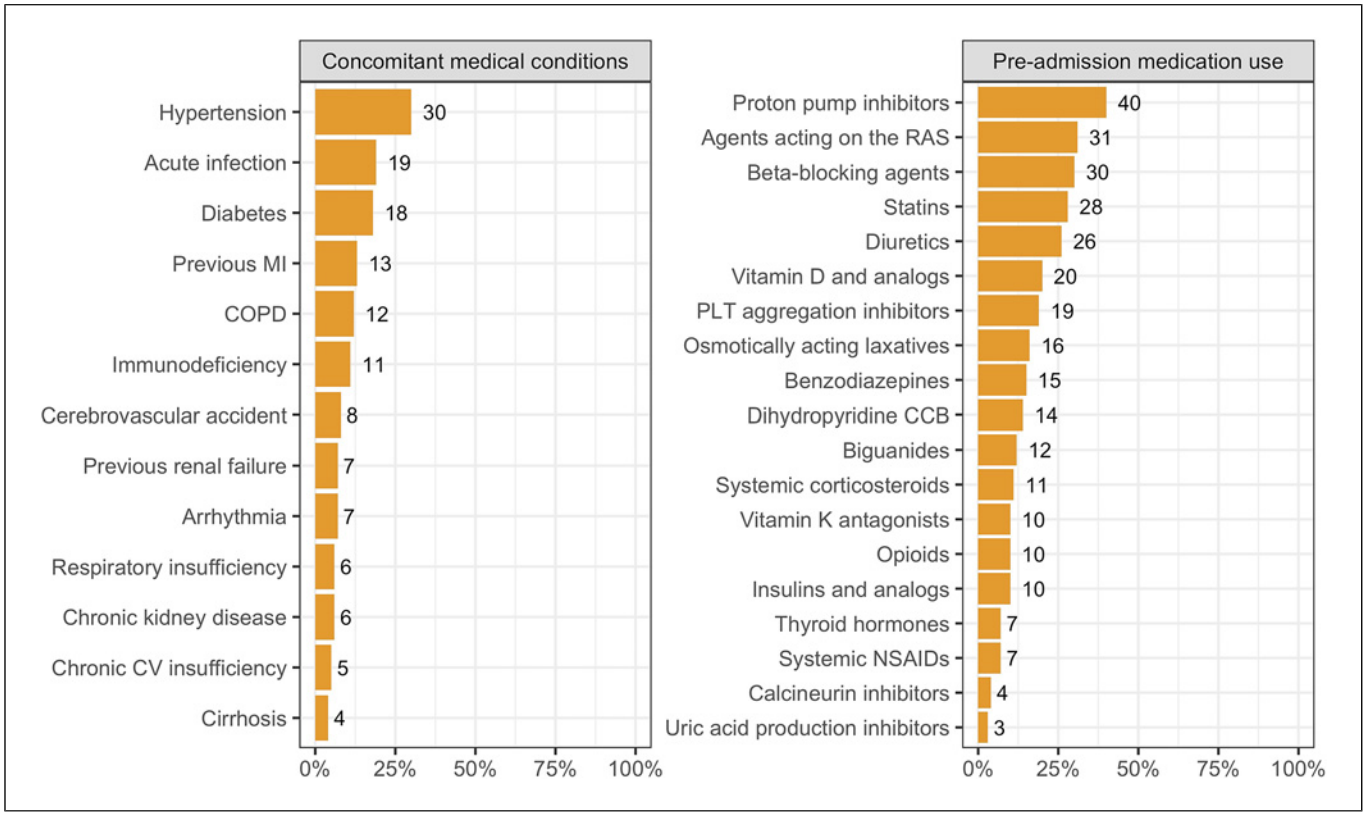


Fig. 2. Proportion of patients with specific concomitant medical conditions and preadmission medications (%). MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; RAS, renal-angiotensin system; PLT, platelet; CCBs, calcium channel blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.

Dealing with Missing Data

Among included patients, 22% had missing values for one or more candidate predictors; however, only 0.7% of the total data items were missing (shown in online suppl. Fig. S1). We performed multiple imputation using chained equations in which 20 imputed datasets were generated. The modeling strategies were applied to each imputed dataset, and resulting estimates were pooled to produce overall estimates using Rubin's rule. The procedure was implemented using the R package *mice* in combination with our analyses of interest [30].

Results

Characteristics of the Study Cohort

In total, 1,010 patients were enrolled in the SICS-II cohort, representing 91% of all eligible patients. We further excluded 34 participants who were on dialysis before ICU admission as they had already reached the highest severity of AKI. Finally, 976 patients were available for our analysis (shown in Fig. 1). The median age for included patients was 64 years (interquartile range, 52–72 years), and they were predominantly male (62%). Almost two-thirds of the patients were acutely admitted to the ICU for medical reasons, and others were admitted after surgery. Fifty-four patients (6%) already had CKD before admission. The most commonly prescribed home medications were proton pump inhibitors (40%), followed by agents acting on the renal-angiotensin system (i.e., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, 31%) and β-blockers (30%) (shown in Fig. 2 and online suppl. Table S3).

Among 976 patients, 425 (44%) had information on baseline SCr. Within 7 days after ICU admission, 283 (29%), 228 (23%), and 135 (14%) progressed to their highest severity of AKI at stage 1, stage 2, and stage 3, respectively. Higher AKI stages were associated with worse clinical outcomes (Table 1). The 90-day mortality in the population with AKI stage 3 was double that of

Table 1. Characteristics of the included critically ill patients (*N* = 976)

Characteristics	Missing	All patients (*N* = 976)	Stratified by the highest AKI stage			
			no AKI (*N* = 330)	AKI stage 1 (*N* = 283)	AKI stage 2 (*N* = 228)	AKI stage 3 (*N* = 135)
Demographics (D)						
Age, years	0 (0%)	64.0 (52.0–72.0)	62.0 (48.2–70.8)	64.0 (51.5–72.0)	66.0 (57.0–73.0)	64.0 (53.0–73.0)
Sex (female)	0 (0%)	368 (38%)	136 (41%)	104 (37%)	76 (33%)	52 (39%)
BMI, kg/m^2	2 (0%)	25.4 (22.9–28.7)	24.7 (22.1–27.5)	25.3 (23.1–28.3)	26.6 (23.5–30.6)	26.1 (23.5–29.3)
Sources of ICU admission	11 (1%)					
Planned surgery		35 (3.6%)	14 (4.3%)	12 (4.3%)	8 (3.6%)	1 (0.8%)
Medical admission		618 (64%)	196 (60%)	176 (63%)	145 (64%)	101 (76%)
Acute surgery		312 (32%)	117 (36%)	92 (33%)	72 (32%)	31 (23%)
Indicators of acute physiology (A)						
MAP, mm Hg	1 (0%)	82.3 (18.4)	87.1 (18.7)	81.2 (18.6)	80.5 (16.2)	75.8 (17.8)
MV upon ICU admission	6 (1%)	108 (11%)	5 (1.5%)	16 (5.7%)	24 (11%)	63 (47%)
MV 24 h post-ICU admission	0 (0%)	521 (53%)	174 (53%)	156 (55%)	125 (55%)	66 (49%)
FiO2, %	1 (0%)	40.0 (30.0–50.0)	40.0 (25.0–48.8)	40.0 (30.0–50.0)	40.0 (33.0–60.0)	40.0 (31.5–52.5)
PaO2, kPa	1 (0%)	12.6 (10.3–16.8)	12.9 (10.6–17.6)	12.6 (10.4–17.2)	12.4 (10.0–15.5)	12.5 (10.4–16.3)
PaCO2, kPa	0 (0%)	4.6 (1.0)	4.8 (1.0)	4.7 (0.9)	4.7 (1.0)	4.1 (1.0)
Arterial pH	0 (0%)	7.34 (7.26–7.39)	7.36 (7.32–7.40)	7.34 (7.28–7.39)	7.33 (7.25–7.39)	7.24 (7.16–7.33)
Sodium, mEq/L	0 (0%)	138.0 (136.0–141.0)	138.0 (136.0–141.0)	138.0 (136.0–140.5)	139.0 (136.0–141.0)	138.0 (134.0–141.0)
Urine output, mL/24 h	0 (0%)	1,125.0 (792.0–1,612.8)	1,125.0 (1,125.0–1,907.2)	1,125.0 (880.0–1,680.0)	1,125.0 (623.8–1,400.0)	740.0 (295.0–1,125.0)
Serum creatinine, μmol/L	0 (0%)	88.0 (65.8–123.2)	72.0 (57.0–90.0)	85.0 (64.0–111.5)	98.0 (72.0–139.2)	206.0 (129.5–301.0)
Serum urea, mmol/L	0 (0%)	7.7 (5.4–11.4)	6.0 (4.7–7.7)	7.4 (5.2–10.0)	8.1 (6.2–11.8)	15.2 (10.2–24.9)
Serum albumin, g/L	0 (0%)	32.8 (7.5)	34.0 (6.9)	33.3 (7.1)	32.6 (7.4)	29.0 (8.3)
Direct bilirubin, μmol/L	0 (0%)	8.0 (6.0–14.0)	8.0 (5.0–12.0)	8.0 (6.0–14.0)	8.0 (6.0–14.0)	11.0 (6.5–24.0)
Hematocrit, %	0 (0%)	40 (10)	40 (10)	40 (10)	40 (10)	30 (10)
Glasgow Coma Scale	1 (0%)	15 (11–15)	15 (10–15)	15 (11–15)	15 (12–15)	15 (14–15)
WBC, ×10^9/L	0 (0%)	13.1 (9.6–17.5)	13.1 (10.1–17.0)	12.8 (9.4–17.2)	13.2 (9.4–18.4)	13.4 (8.2–18.1)
CRP, mg/dL	26 (3%)	19.0 (3.4–110.0)	11.0 (2.2–66.0)	12.0 (2.5–114.5)	20.0 (4.7–106.5)	93.0 (20.8–269.0)
Potassium, mEq/L	24 (2%)	4.4 (4.1–4.9)	4.3 (4.0–4.6)	4.4 (4.1–4.9)	4.5 (4.1–5.1)	4.9 (4.4–5.7)
Creatine kinase, U/L	51 (5%)	139.0 (70.0–332.0)	119.5 (67.0–251.8)	148.0 (75.5–344.8)	138.0 (69.0–337.0)	177.0 (76.5–463.5)
Glucose, mmol/L	82 (8%)	10.1 (8.4–12.5)	10.2 (8.4–12.5)	10.3 (8.8–13.0)	10.2 (8.2–12.4)	9.5 (8.1–11.4)
Phosphate, mmol/L	95 (10%)	1.1 (0.9–1.4)	1.0 (0.8–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.6)	1.6 (1.1–2.0)

Table 1 (continued)

Characteristics	Missing	All patients (*N* = 976)	Stratified by the highest AKI stage			
			no AKI (*N* = 330)	AKI stage 1 (*N* = 283)	AKI stage 2 (*N* = 228)	AKI stage 3 (*N* = 135)
Hs-troponin, ng/L	65 (7%)	35.0 (14.0–105.0)	23.0 (11.0–58.0)	33.0 (14.0–78.0)	45.0 (18.0–157.0)	76.0 (34.0–241.2)
Hemoglobin, mmol/L	10 (1%)	7.3 (1.7)	7.5 (1.5)	7.4 (1.7)	7.4 (1.7)	6.6 (1.6)
Clinical outcomes						
Length of ICU stay	0 (0%)	1.9 (1.0–4.7)	1.4 (0.8–2.9)	2.0 (1.1–4.8)	2.6 (1.5–4.7)	4.0 (1.8–10.0)
ICU mortality	0 (0%)	160 (16%)	39 (12%)	44 (16%)	32 (14%)	45 (33%)
7-day mortality	1 (0%)	132 (14%)	34 (10%)	37 (13%)	29 (13%)	32 (24%)
30-day mortality	10 (1%)	215 (22%)	55 (17%)	59 (21%)	48 (21%)	53 (39%)
90-day mortality	11 (1%)	253 (26%)	62 (19%)	69 (25%)	59 (26%)	63 (47%)

Data were presented as mean (standard deviation) or median (interquartile range) for continuous variables and *n* (%) for categorical variables. Missing values were removed before the computation process (see online suppl. Table S2 for detailed definition of variables). AKI, acute kidney injury; BMI, body mass index; ICU, intensive care unit; MAP, mean arterial pressure; MV, mechanical ventilation; FiO2, fraction of inspired oxygen; PaO2, partial arterial pressure of oxygen; PaCO2, partial arterial pressure of carbon dioxide; WBC, white blood cell count; CRP, C-reactive protein; Hs, high-sensitivity.

those who only developed AKI stage 1 (47% vs. 25%) and 2.5 times higher than patients without any AKI (47% vs. 19%). In addition, patients with more severe AKI were more likely to stay longer in the ICU. Most patients (84%) were discharged from the ICU before or on the seventh day following ICU admission.

Predictive Contribution of Layers of Clinical Information

Indicators of acute physiology emerged as the most important source of information for predicting AKI severity, increasing the AUC of the basic model (including only demographic characteristics) from 0.591 to 0.759 in the internal validation. In contrast, preadmission medication data provided little relevant information to predict the stages of AKI (AUC changed from 0.591 to 0.606). While the predictive contribution of concomitant medical conditions was considerable, boosting the bootstrap AUC of the basic model to 0.637, their information seemed to be effectively embedded in indicators of acute physiology as their added value became negligible once the model had already accounted for the latter (shown in Fig. 3).

Model Development and Specification

We selected the final predictors for the ordinal outcome by combining candidate predictors with nonzero coefficients in three separate LASSO models for the three dichotomized outcomes of AKI stages (Table 2). These included fifteen readily available variables in daily practice dominated by indicators of acute physiology. From a set of these fifteen strongest predictors, we derived a proportional odds logistic regression model for predicting AKI severity within 7 days after ICU admission in critically ill adults (Tables 2, 3). To evaluate potential collinearity among predictors, we calculated variance inflation factors (VIFs), which indicated low collinearity (online suppl. Table S4). Our final model showed that patients with higher BMI, mechanical ventilation upon ICU admission, lower PaCO2, higher SCr, higher serum urea, lower 24-h UO, lower arterial pH, higher creatine kinase, and confirmed infection at admission were more likely to develop more severe AKI. An increase in hs-troponin and preadmission use of diuretics were also associated with a higher likelihood of progressing to AKI, although they did not reach statistical significance.

Model Performance and Clinical Usefulness

We validated the ability of our established model to predict the different stages of AKI severity. Overall, the bootstrap AUC was 0.763 (95% CI, 0.740–0.784) in the internal validation. In addition, the model was well calibrated: bootstrap calibration slope of 0.949 and calibration intercepts approaching 0 (Table 4). When it came to predicting the three dichotomized outcomes, the

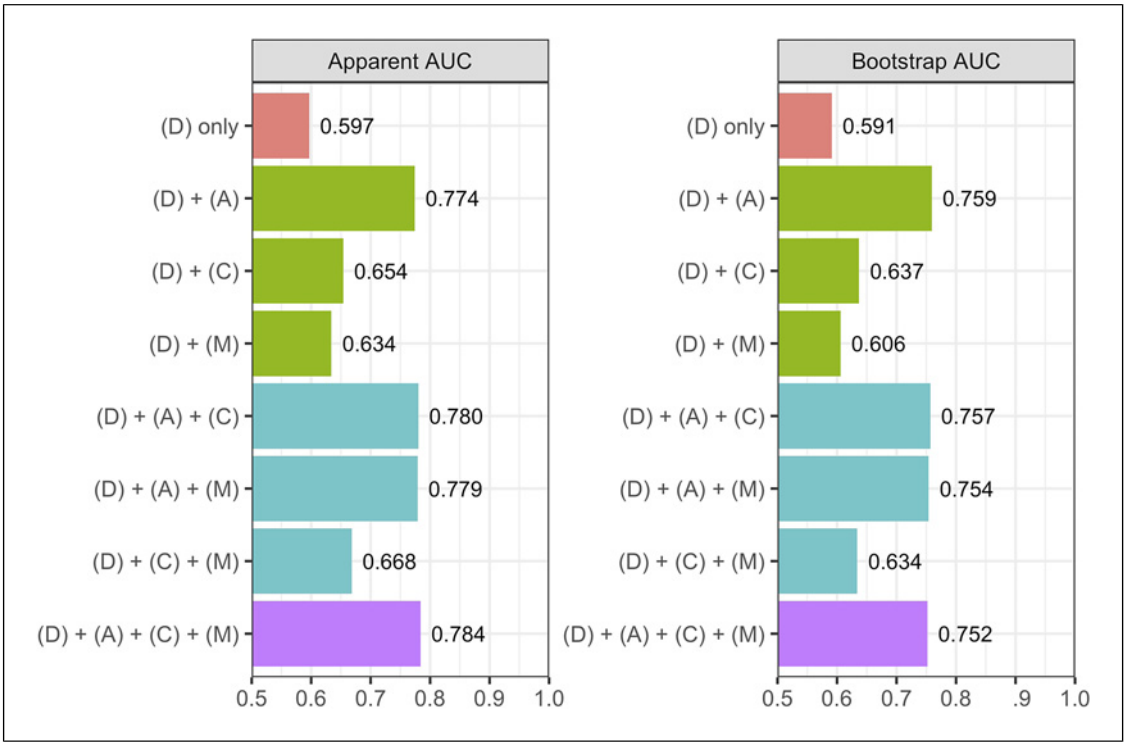


Fig. 3. Predictive contribution of different types of clinical data (N = 976). AUC, area under the ROC curve; (D), 4 predictors of demographics; (A), 23 indicators of acute physiology; (C), 13 predictors of concomitant medical conditions; (M), 19 predictors of preadmission medications. The added predictive value of each data layer was defined as the uplift in the AUC after adding all of its corresponding variables to the model (with log transformation as appropriate). Negative contributions could happen if the added variables had low predictive values, which would result in an increase in model overfitting. The apparent AUC was estimated directly from the dataset used to develop the model. The bootstrap AUC was computed with 500 bootstrap repetitions. The x-axis was set to start at 0.5 as AUCs should never drop below this value, which represents chance.

model continued to demonstrate good discrimination, especially when predicting AKI at more severe stages: with AUCs of 0.781, 0.793, and 0.920 for AKI stage ≥1, AKI stage ≥2, and AKI stage 3, respectively. Our model also showed improved net benefit in decision curve analysis over a range of clinically plausible thresholds compared to the renal SOFA score and default policies of "treat all" and "treat none" (shown in Fig. 4).

Discussion

A key innovation of our study was the prediction of the specific AKI severity, reflected by KDIGO-based stages, within 7 days post-admission in critically ill patients. We carefully defined our outcome using the most recent definition and staging system of AKI with both SCr and UO criteria [1]. Our data confirmed that more adverse outcomes were expected in critically ill patients who progressed to more severe levels of AKI based on the KDIGO definition during their ICU stay [1, 2, 31, 32], emphasizing the prognostic importance of differentiating between different degrees of AKI severity. Using information readily available in daily practice, our model discriminated well between patients at varying risks of AKI. The model was also well calibrated and showed promising clinical usefulness over a wide range of clinically plausible thresholds through visual predictive checks and bootstrapping. Of note, the 7-day window of prediction is optimal for both clinical reasons and the model's predictability. Patients with critical illness require intensive support to preserve their vital organ functions, and intensivists try to foresee what will likely happen to their patients in the coming days so they can modify the interventions, avoid further organ failure at an early stage, and prevent unfavorable outcomes [33, 34]. This relatively short time window also provides opportunities to optimize the model performance.

On top of the basic model augmented by indicators of acute physiology, little improvements in the model

Table 2. Model specification including 15 predictor variables ($N = 976$)

Final predictor	Binary outcome, LASSO nonzero β[a]			Ordinal outcome, POLR odds ratio (95% CI)[b]	
	Y ≥1	Y ≥2	Y ≥3	univariable[c]	multivariable
Demographics					
ln(BMI)	✓	✓		5.08 (2.80–9.25)	4.10 (2.11–7.95)[d]
Indicators of acute physiology					
MV on ICU admission	✓	✓	✓	13.19 (8.71–20.27)	2.70 (1.66–4.37)[d]
MAP	✓			0.98 (0.97–0.99)	0.99 (0.99–1.00)
PaCO2			✓	0.74 (0.66–0.84)	0.83 (0.73–0.95)[d]
ln1p(SCr)	✓	✓	✓	7.03 (5.47–9.09)	2.34 (1.66–3.28)[d]
ln(Serum urea)	✓	✓	✓	4.83 (3.89–6.02)	1.72 (1.25–2.37)[d]
ln1p(Direct bilirubin)			✓	1.47 (1.26–1.71)	1.08 (0.91–1.27)
ln1p(UO)	✓	✓	✓	0.54 (0.47–0.62)	0.69 (0.60–0.79)[d]
(Arterial pH)^2	✓	✓	✓	0.69 (0.64–0.75)	0.84 (0.77–0.92)[d]
ln(Hs-troponin)	✓	✓		1.36 (1.26–1.47)	1.05 (0.96–1.15)
ln(Potassium)			✓	30.00 (13.54–67.26)	1.37 (0.54–3.45)
ln(Creatine kinase)	✓			1.14 (1.03–1.26)	1.13 (1.00–1.26)[d]
Serum phosphate		✓		3.01 (2.37–3.82)	1.09 (0.80–1.47)
Concomitant medical conditions					
Acute infection	✓			2.11 (1.58–2.83)	1.50 (1.09–2.07)[d]
Preadmission medication use					
Diuretics	✓			2.08 (1.61–2.69)	1.23 (0.92–1.64)

LASSO, least absolute shrinkage and selection operator; POLR, proportional odds logistics regression; CI, confidence interval; ln, natural logarithm; ln1p, natural logarithm of the variable plus one; BMI, body mass index; MV, mechanical ventilation; ICU, intensive care unit; MAP, mean arterial pressure; PaCO2, partial arterial pressure of carbon dioxide; SCr, serum creatinine; UO, urine output. [a]The optimal lambdas were chosen by 10-time repeated 10-fold cross-validation at 0.030, 0.041, and 0.032 for AKI ≥1, AKI ≥2, and AKI ≥3, respectively. [b]Odds ratios are expressed per 1-unit increase for the corresponding (transformed) scale of continuous variables and for the condition present in dichotomous variables (see Table 1 for the measurement scale of continuous predictors). [c]Results from available-case analysis if total numbers of missing values <3% and multiple imputations otherwise. [d]The effect was statistically significant at the significance level of 0.05.

performance were observed with the addition of variables obtained from the history taking of home medications and concomitant medical conditions. Our findings are consistent with the literature in which acute variables were the predominant predictors of many previously published models [35–37]. Although the variables of concomitant medical conditions and preadmission medications are important for intensivists' subjective prognostication of diminished kidney function, the lack of improvement in model performance suggests that indicators of acute physiology efficiently capture those variables. Chronic conditions and home medications may represent underlying factors influencing kidney (dys) function; however, patients often suffer multiple acute conditions when admitted to the ICU, and as such, the predictive values of chronic information could be superseded by contemporary physiological and laboratory tests. It should be noted that the presence of certain illnesses is not as important as their corresponding severity, particularly regarding their impact on organ failure. In addition, the predictive capacity of home medications appeared negligible as these medications might not actually be taken by the patients and/or their effects may be largely reversible when patients stop taking them upon ICU admission.

As our model is the first model of its type, we could not compare the findings to any reference models. However, given that most previously published models for dichotomized outcomes of AKI had internally validated AUCs between 0.78 and 0.88 [16], we believe our model achieved relatively good, though not perfect, performance considering its simple predictors and the more informative

Table 3. A fifteen-predictor model for progression to the highest AKI stages within 7 days after ICU admission

Formula for estimating absolute risks of different levels of AKI severity

$$\textit{Risk of AKI stage} \geq 1\ (\%) = \frac{1}{1+exp\left[-(2.774+\beta^{*}X)\right]}{}^{*}100\%$$

$$\textit{Risk of AKI stage} \geq 2\ (\%) = \frac{1}{1+exp\left[-(1.193+\beta^{*}X)\right]}{}^{*}100\%$$

$$\textit{Risk of AKI stage } 3\ (\%) = \frac{1}{1+exp\left[-(-0.720+\beta^{*}X)\right]}{}^{*}100\%$$

where: β*X = 1.410*ln(*BMI*) + 0.992**Mechanical ventilation upon ICU admission* − 0.007**MAP* − 0.184**PaCO2* + 0.849*ln1p(*Serum creatinine*) + 0.542*ln(*Serum urea*) + 0.075*ln(*Serum direct bilirubin*) − 0.373*ln1p(*urine output*) − 0.170*(*Arterial pH*)^2 + 0.050*ln(*Hs-troponin*) + 0.313*ln(*Potassium*) + 0.119*ln(*Creatine kinase*) + 0.083**Serum phosphate* + 0.406**Acute infection* + 0.204**Diuretics*

ln, natural logarithm; ln1p, natural logarithm of the variable plus one; BMI, body mass index; MAP, mean arterial pressure; UO, urine output; PaCO2, partial arterial pressure of carbon dioxide. *Measurement scale of continuous predictors: BMI* kg/m^2, *MAP* mm Hg, *PaCO2* kPa, *serum creatinine* μmol/L, serum *urea* mmol/L, *serum direct bilirubin* μmol/L, *UO* mL/24 h, *arterial pH* no unit, *hs-troponin* ng/L, *potassium* mEq/L, *creatine kinase* U/L, *serum phosphate* mmol/L. All were recorded within 24 h of ICU admission. *Mechanical ventilation upon ICU admission* has a value of 1 if the patient required a ventilator at the moment of ICU admission or immediately (within 15 min) thereafter. *Acute infection* has a value of 1 if the patient developed acute infection within 24 h following ICU admission and 0 otherwise. *Diuretics* is 1 if the patient's home medication list includes any type of diuretics and 0 otherwise.

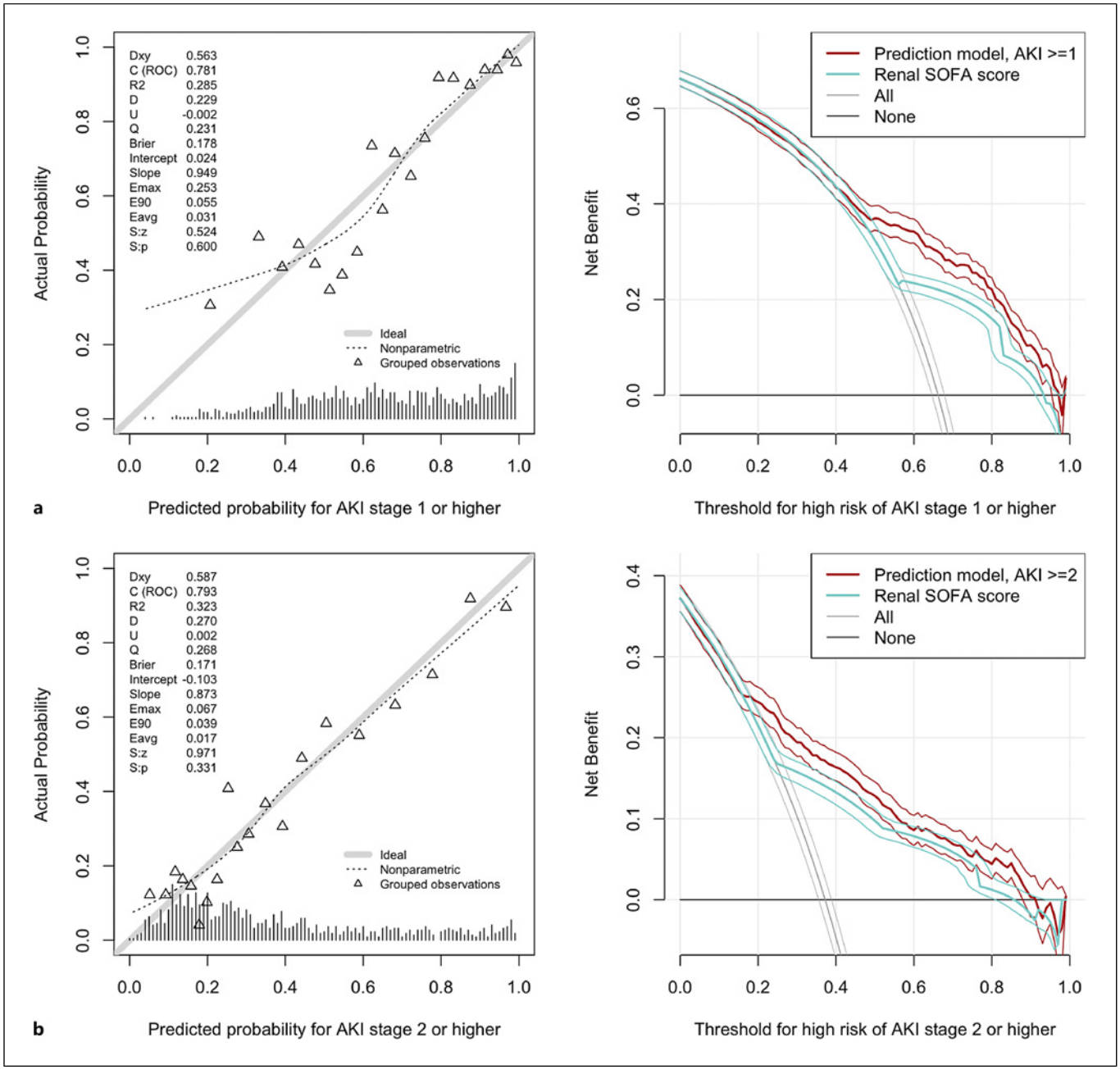
Table 4. Model performance for the prediction of AKI stages occurring within 7 days after ICU admission

Measure of performance	Apparent performance	Bootstrap performance
Nagelkerke's R^2	0.399	0.377
AUC	0.770	0.763
Calibration slope	1.000	0.949
Calibration intercept, Y ≥1	0.000	0.024
Calibration intercept, Y ≥2	0.000	−0.024
Calibration intercept, Y ≥3	0.000	−0.066

The performance indices were pooled across 20 multiply imputed datasets using Rubin's rule. The apparent performance was estimated directly from the dataset used to develop the model. The bootstrap (internal) performance was computed using 500 bootstrap repetitions. CI, confidence interval; AUC, area under the ROC curve.

prognostic outcome. Furthermore, our findings suggest that predicting the more advanced stages of AKI is easier. This could be because the higher stages of AKI result from more severe renal dysfunction, which leads to greater imbalances in the levels of electrolytes and extracellular volume, as well as a higher degree of retention of SCr, serum urea, and other nitrogenous waste products [1]. The model also demonstrated fairly good calibration through bootstrapping and visual checks and could be useful in practice (especially when predicting AKI stage ≥1 or ≥2, as it improved net benefit across a range of clinically plausible thresholds over other strategies). Although the model necessitates using 15 elements of clinical and laboratory information, they are easily obtainable in each intensive care.

In the present study, achieving adequate predictions was more important than insight into whether a single variable is prognostic or the predictor effects per se. However, it is worth noting that we found comparable sets of selected predictors for the three dichotomized outcomes, emphasizing their importance in predicting AKI severity. The effect of every predictor in the final model is clinically plausible according to contemporary subject matter knowledge. They were either already reported as prognostic factors or were included in previously published models for AKI: BMI [38], $PaCO_2$ [39], hs-troponin [40], creatinine kinase [41], serum phosphate [42, 43], mechanical ventilation [44–46], mean arterial pressure [47], arterial pH [9, 36], UO [36], SCr [35, 37, 48], serum urea [36, 37], bilirubin [35], serum



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(Figure continued on next page.)

potassium [36, 37], acute infection [2], and use of diuretics [49]. We acknowledge that while some of those variables may represent underlying etiology (such as acute infection [2]), not every predictor causally explains the development of AKI upon ICU admission.

Our study offers a valuable starting point for the application of a reliable and clinically relevant model that allows for a flexible prognostication of AKI severity in critically ill adults and possibly improves patient outcomes [50]. The first potential application is to identify patients at greater risk of AKI in clinical practice, enabling healthcare providers to intervene and prevent adverse events from occurring in a timely manner. Another potential use is in the clinical investigation of interventions targeting AKI prevention and treatment. Specifically, the prediction model can be used for the efficient

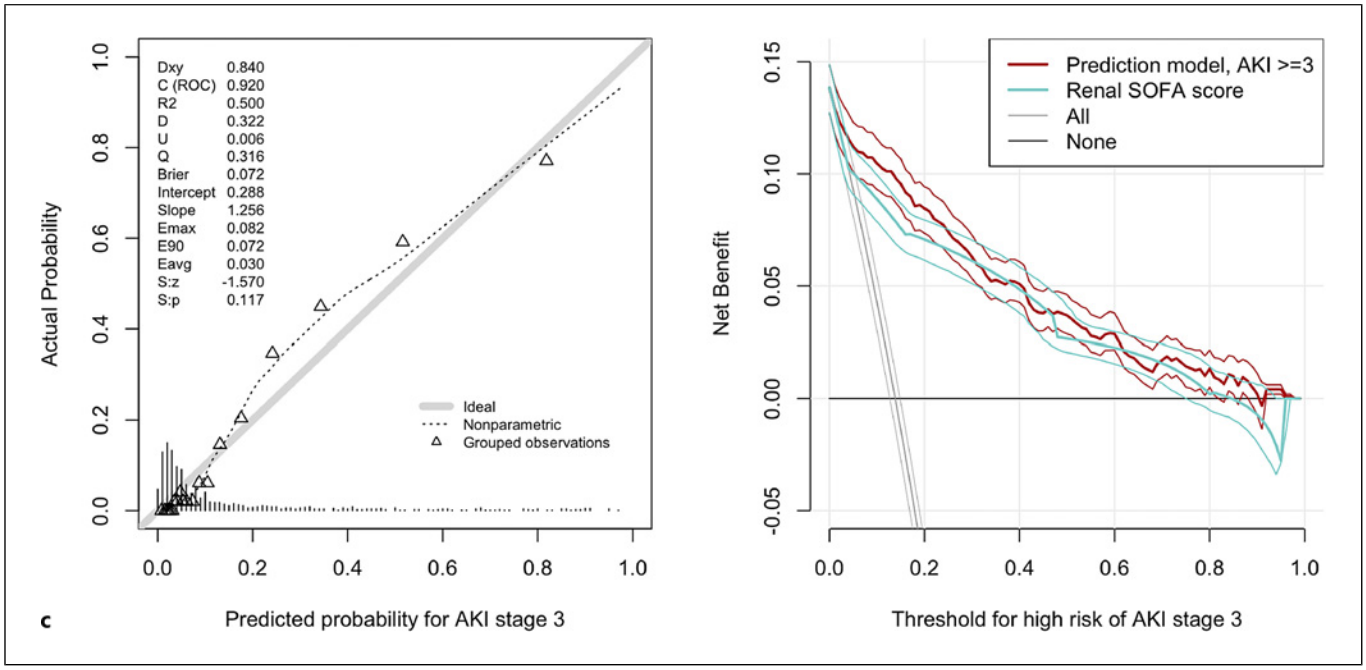

Fig. 4. Calibration plots and decision curve analyses for the prediction of the three dichotomized outcomes. **a** Prediction of AKI stage ≥1. **b** Prediction of AKI stage ≥2. **c** Prediction of AKI stage 3. Results on the full dataset are shown. Calibration plots were presented on the left-hand side in which 20 quantile groups were specified. Decision curves on the right-hand side showed net benefit obtained by using our prediction model, renal SOFA score (reference model), and default policies of "treat all" and "treat none". One-standard-error intervals of net benefit were also plotted. As an example of interpreting net benefit gain, at the threshold of 50% used to designate an individual at high risk of developing AKI stage 1 or higher (**a**, right), our model increased the net benefit of the renal SOFA score by 0.05, indicating that the excess of true-positive over false-positive calls increases by 5 per 100 patients when using our model. This could be because the model identified 5 more true-positive cases or made 3 fewer false-positive calls and 2 more true-positive calls, etc., compared to the renal SOFA score. At threshold probabilities other than 50%, the weights assigned to true-positive and false-positive cases will differ accordingly.

and timely selection of patients (for example, excluding those with an extreme prognosis, either very low or very high risk of AKI), thereby increasing the power to detect the effects of potential interventions in a more homogeneous population. However, as our model was developed using data from a tertiary ICU in a developed country, its applicability to other settings, including non-tertiary ICUs and resource-limited contexts, remains uncertain. External validation in diverse populations is necessary to confirm its broader generalizability.

We suggest several topics for future research. As single time-point measurements may not provide enough information to identify and forecast AKI in ICU patients who often experience multiple and temporary kidney injuries, tracking changes over time could enhance the ability to predict AKI in these patients. A clinical prediction model may gain added value by allowing continuous updates as new patient information becomes available [36, 51], improving its accuracy and providing clinicians with more actionable insights. In addition, the model's predictability could be boosted by the addition of novel kidney biomarkers (e.g., neutrophil gelatinase-associated lipocalin, kidney injury molecule 1) and/or genomic components (potentially in the form of polygenic risk scores). Importantly, future research is required to evaluate the additional benefit of using the model, in combination with early care bundles guided by the model, to patient outcomes.

This study has several limitations. First, over half of the study population lacked the baseline SCr level, and we back-calculated the baseline SCr using the MDRD formula in such patients. We recognize its limitations; however, it is a widely used approach in research into AKI in ICU patients [10, 11, 35, 52]. Second, we did not include clinical examinations and critical care ultrasonography as candidate predictors, although they have been suggested to be prognostic factors [19, 53]. This is because these variables had such high missing rates in our dataset that imputation of their missing values likely led to major bias. Furthermore, incorporating such variables would limit the practical application and/or generalizability of the model when those pieces

of information were frequently missing. Nevertheless, we believe our 59 candidate predictors likely capture this information, as clinical information from different sources is hardly ever completely independent. Finally, although we performed internal validation with bootstrapping as a proxy for the model's expected performance in similar future patients [23], no external validation was performed. Thus, the established model must be externally validated before its application in any (new) practical settings.

In conclusion, we discovered that simple predictors (especially indicators of acute physiology) predicted AKI severity well in critically ill patients within 7 days after ICU admission. We also derived the first prediction model for stages of AKI using routinely available variables in daily practice. Our model was well-validated through visual checks and bootstrapping. Although its performance was not perfect, the study serves as an initial step to applying a valid and timely prediction model of multiple AKI stages. After external validation and additional updates, such a model could help doctors and patients in future clinical management, possibly helping to limit morbidity and improve patient outcomes.

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Statement of Ethics

This study protocol was reviewed and approved by the University Medical Center Groningen Institutional Review Boards (Approval No. METc 2018/203). Written informed consent was obtained from the legal representatives of patients incapable of providing consent due to their acute illnesses. Patient consent for using their data was asked at a later time whenever possible.

Conflict of Interest Statement

G.L. has a contractual relationship with Boehringer Ingelheim for a collaborative project unrelated to this paper. Other authors have no conflict of interest to declare.

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Author Contributions

N.N.-H., E.K., G.L., and H.S. created ideas for the study. N.N.-H. conducted the analyses and drafted the manuscript. E.K., G.L., and H.S. reviewed the analyses. W.Z., J.K., E.K., G.L., and H.S. contributed to interpreting the findings and critically reviewed the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The SICS-II dataset that supports the findings of this study is not publicly available because it contains information that could compromise the privacy of research participants, but it is available from the corresponding author (N.N.-H.) upon reasonable request.

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