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Cardiac surgery-associated acute kidney injury: risk factors analysis and comparison of prediction models

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Abstract

OBJECTIVES: Cardiac surgery-associated acute kidney injury (AKI) is a well-known factor influencing patients' long-term morbidity and mortality. Several prediction models of AKI requiring dialysis (AKI-D) have been developed. Only a few direct comparisons of these models have been done. Recently, a new, more uniform and objective definition of AKI has been proposed [Kidney Disease: Improve Global Outcomes (KDIGO)-AKI]. The performance of these prediction models has not yet been tested.

METHODS: Preoperative demographic and clinical characteristics of 1056 consecutive adult patients undergoing cardiac surgery were collected retrospectively for the period 2012–2014. Multivariable logistic regression analysis was used to determine the independent predictors of AKI-D and the KDIGO-AKI stages. Risk scores of five prediction models were calculated using corresponding subgroups of patients. The discrimination of these models was calculated by the c-statistics (area under curve, AUC) and the calibration was evaluated for the model with the highest AUC by calibration plots.

RESULTS: The incidence of AKI-D was 3.5% and for KDIGO-AKI 23% (17.3% for Stage 1, 2.1% for Stage 2 and 3.6% for Stage 3). Older age, atrial fibrillation, NYHA class III or IV heart failure, previous cardiac surgery, higher preoperative serum creatinine and endocarditis were independently associated with the development of AKI-D. For KDIGO-AKI, higher body mass index, older age, female gender, chronic obstructive pulmonary disease, previous cardiac surgery, atrial fibrillation, NYHA class III or IV heart failure, higher preoperative serum creatinine and the use of cardiopulmonary bypass were independent predictors. The model by Thakar *et al.* showed the best performance in the prediction of AKI-D (AUC 0.837; 95% CI = 0.810–0.862) and also in the prediction of KDIGO-AKI stage 1 and higher (AUC = 0.731; 95% CI = 0.639–0.761), KDIGO-AKI stage 2 and higher (AUC = 0.811; 95% CI = 0.783–0.838) and for KDIGO-AKI stage 3 (AUC = 0.842; 95% CI = 0.816–0.867).

CONCLUSIONS: The performance of known prediction models for AKI-D was found reasonably well in the prediction of KDIGO-AKI, with the model by Thakar having the highest predictive value in the discrimination of patients with risk for all KDIGO-AKI stages.

Keywords: Acute kidney injury • Cardiac surgery • Renal replacement therapy • Dialysis • Risk factors • Kidney Disease: Improve Global Outcomes

INTRODUCTION

Acute kidney injury (AKI), developing after cardiac surgery, is an important factor determining patients' outcome. It is associated with an increased morbidity and mortality, as well as with prolonged duration and costs of hospitalization [1–3]. Therefore, it is important to identify risk factors for postoperative AKI, and to prevent those adverse outcomes. Several predictive models of cardiac surgery-associated acute kidney injury (CS-AKI) have been developed [4–14]. The models of Chertow *et al.* [4], Fortescue *et al.* [5], Thakar *et al.* [6], Mehta *et al.* [7] and Wijeysundera *et al.* [8] have been externally validated several times, showing reasonable discrimination of patients with the risk for AKI [15–20]. The reported incidence of CS-AKI is variable, and depends on definition of AKI as well as on inclusion and exclusion criteria.

Reported incidence of CS-AKI defined with the need for renal replacement therapy (RRT; dialysis and AKI-D) ranges from 0.4 to 10.9%, with an average between 1 and 2% [4–8, 14, 15, 18, 20]. Some authors found that AKI with even small increases in serum creatinine was also associated with an increased risk of morbidity and mortality [1, 3, 21]. When defined with smaller reduction in renal function, reported incidence of CS-AKI ranges from 2.7 to

39% [9–12, 14, 22]. Recently, the 'Kidney Disease: Improve Global Outcomes' (KDIGO) AKI study group has suggested a modified definition of AKI, levelling the differences between earlier AKI definitions and enabling better reproducibility and comparison between different prediction models [23].

The aim of our study was to identify potential preoperative risk factors for CS-AKI defined as AKI-D and AKI according to KDIGO criteria (KDIGO-AKI) in our University Hospital. Furthermore, we evaluated the performance of several known models [5–9] in the prediction of KDIGO-AKI in our patient cohort.

MATERIALS AND METHODS

We conducted a retrospective cohort study, which included all consecutive patients aged >18 years undergoing cardiac surgery at the Department of Cardiac and Transplant Surgery of University Hospital Dubrava in Zagreb, Croatia, between 1 January 2012 and 31 December 2014. Exclusion criteria were preoperative RRT, including dialysis and renal transplant recipients, death within 24 h after surgery, infrequent surgical procedures (heart transplantation, ventricular assist device(s) implantation, pericardiectomy and isolated heart tumour resection) and preoperative use of extracorporeal membrane oxygenation.

Demographic characteristics and potential preoperative predictors of AKI were extracted from the cardiac surgery database, hospital database and medical records. The variables extracted were those included in the original studied models [5–9]: age, gender, weight, height, smoking habits, history and treatment of diabetes, chronic obstructive pulmonary disease (COPD) or asthma, hypertension, peripheral arterial vascular disease, previous cardiac surgery, recent myocardial infarction (within 3 weeks before surgery), atrial fibrillation (AF), systolic blood pressure, preoperative renal function parameters, white blood cell count (the last preoperative value), left ventricular ejection fraction (LVEF; measured preoperatively with transthoracic echocardiography), use of intra-aortic balloon pump before surgery, congestive heart failure (CHF, defined with NYHA class III or IV), cardiogenic shock, endocarditis, operative status (elective or non-elective, i.e. emergent or urgent), use of cardiopulmonary bypass (CPB) and types of surgery: coronary artery bypass grafting (CABG), aortic valve (AV) surgery, mitral valve (MV) surgery, other valves surgery and combinations of former surgery.

Preoperative renal function was defined by serum creatinine (using the last preoperative value measured within 3 days before surgery) and by estimated glomerular filtration rate (EGFR), calculated with Cockroft–Gault, MDRD and CKDEPI equations [24].

If there were more than one cardiac surgery procedures performed during the same hospitalization, only the data before the first surgery were considered.

To avoid any interpretation bias, especially those regarding predictors inclining subjective interpretation, like CHF, the evaluation of all patients was done by one physician.

The primary outcome was the development of AKI, defined with the initiation of dialysis in the postoperative course, until the discharge of the patient (AKI-D). The dialysis was started at the discretion of the attending physician based on the standard criteria such as uraemia, acidosis, hyperkalaemia or severe fluid overload. The secondary outcome was AKI defined and staged with KDIGO criteria (KDIGO-AKI) into stages 1–3 (no AKI development was marked as KDIGO-AKI stage 0), using the highest postoperative serum creatinine within the time frames as in the KDIGO definitions [23]. KDIGO-AKI stage 1 was defined with an increase of serum creatinine by 1.5–1.9 times baseline or by ≥26.5 μmol/l from baseline. KDIGO-AKI stage 2 was defined with an increase of serum creatinine by 2.0–2.9 times baseline. KDIGO-AKI stage 3 was defined with an increase of serum creatinine by ≥3.0 times baseline or with serum creatinine of ≥353.6 μmol/l or with the initiation of RRT. Owe to incomplete data on urine output, only data on serum creatinine were used to determine the stage of KDIGO-AKI.

In the performance evaluation of different models, the prediction scores were calculated as in the original studies [5–9]. Patients who did not meet the original inclusion criteria for a certain model were excluded from the analysis of that specific model (Fig. 1 and Supplementary Table 1).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median with an interquartile range as appropriate after checking for normality. The categorical variables are reported as frequency number and percentage. Univariable analysis of predictors for dichotomous outcomes was done by Student's *t*-test or Mann–Whitney *U*-test for continuous variables and by the χ^2 test or Fischer's exact test for categorical variables. In the univariable analysis of predictors for KDIGO-AKI stages 1–3, ANOVA (with the *post hoc* Bonferroni method) or Kruskal–Wallis test (*post hoc* Mann–Whitney *U*-test) was used as appropriate to compare continuous variables and χ^2 test or Fisher's exact test for comparison of categorical variables. Multivariable analysis of predictors was

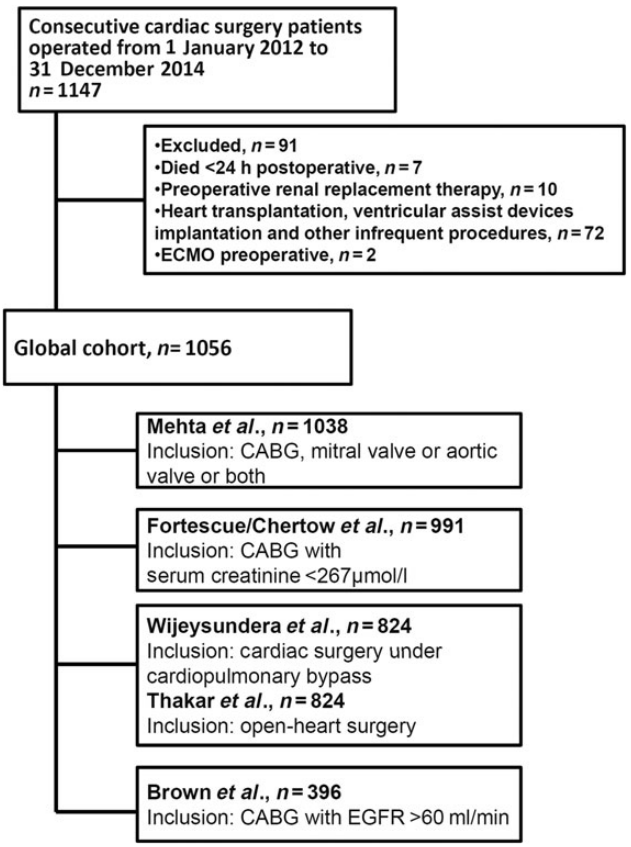

Figure 1: Patient cohort and subgroup selection for the analysis of the different models.

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done by logistic regression with a stepwise method using significant predictors found in the univariable analysis.

Evaluation of the performance of different prediction models of CS-AKI was done by discrimination and calibration analysis. Discrimination analysis of each predictive model score was made by calculating the c-statistics, i.e. area under curve (AUC) for each model. Comparison of dependent or independent AUC for different outcomes within the same model or for the same outcome between different models was done by the DeLong method [25]. The model with the greatest AUC was then used for calibration analysis in our patient cohort by creating calibration plots and graphic comparison of observed and expected (as in the original study) outcome rates for the same risk category.

A two-sided *P*-value of <0.05 was considered as statistically significant. The data were analysed using SPSS version 17.0 and MedCalc version 11.4.2.0.

RESULTS

The study population consisted of 1147 patients, of which 91 were excluded, so our global cohort included 1056 Caucasian patients (Fig. 1). Baseline demographic and clinical characteristics of the global patient cohort and their association with AKI-D are given in Table 1. AKI-D was found in 37 patients (3.5%). In univariable analysis, older age, diabetes, previous cardiac surgery, AF, CHF (NYHA class III or IV), higher serum creatinine (lower EGFR), endocarditis and type of surgery were associated with AKI-D (Table 1).

KDIGO-AKI developed in 244 patients (23.1%), of which 183 (17.3%) were KDIGO-AKI stage 1, 23 (2.2%) were stage 2 and 38 (3.6%) were KDIGO-AKI stage 3. Distribution of baseline demographic and clinical characteristics of patients and their association with KDIGO-AKI stages are given in Table 2. Older age, female gender, higher body mass index (BMI), diabetes, COPD, previous

Table 1: Baseline patient characteristics and the association with AKI-D

	Global cohort (*n* = 1056)	No AKI-D (*n* = 1019)	AKI-D (*n* = 37)	*P*-value
Age (years)	64 (57–71)	64 (57–71)	70 (64–74)	0.001[a]
Male sex (%)	766 (72.5)	741 (72.7)	25 (67.6)	n.s.
Weight (kg)	82.24 (13.98)	82.10 (13.73)	85.95 (19.55)	n.s.
Height (cm)	171.14 (9.08)	171.17 (9.12)	170.35 (7.80)	n.s.
BMI (kg/m^2)	28.05 (4.07)	28.00 (3.98)	29.51 (5.79)	n.s.
BSA (m^2)	1.94 (0.19)	1.94 (0.19)	1.97 (0.23)	n.s.
Smoking (%)	163 (15.4)	160 (15.7)	3 (8.1)	n.s.
Diabetes				0.027[b]
On OHG (%)	197 (18.7)	191 (18.7)	6 (16.2)	
On insulin (%)	107 (10.1)	98 (9.6)	9 (24.3)	0.009[b]
COPD (%)	95 (9.0)	89 (8.7)	6 (16.2)	n.s.
PVD (%)	63 (6.0)	61 (6.0)	2 (5.4)	n.s.
Previous cardiac surgery (%)	38 (3.6)	32 (3.1)	6 (16.2)	0.001[b]
Hypertension (%)	818 (77.5)	788 (77.3)	30 (81.1)	n.s.
SBP (mmHg)	129.01 (15.84)	129.16 (15.66)	125.0 (20.0)	n.s.
Atrial fibrillation (%)	136 (12.9)	119 (11.7)	17 (45.9)	<0.0001[b]
Recent MI (<3 weeks) (%)	83 (7.9)	82 (8.0)	1 (2.7)	n.s.
CHF or NYHA III–IV (%)	153 (14.5)	134 (13.2)	19 (51.4)	<0.0001[b]
Cardiogenic shock (%)	2 (0.2)	2 (0.2)	0 (0.0)	n.s.
LVEF (%)	54.66 (11.12)	54.83 (11.01)	49.76 (13.04)	0.025[c]
White blood cell count (×10^{12}/l)	7.4 (6.1–9.0)	7.4 (6.1–8.9)	8.0 (6.3–9.2)	n.s.
Serum creatinine (μmol/l)	97 (86–112)	97 (86–111)	122 (92–185)	<0.0001[a]
EGFR–CG (ml/min)	77.00 (25.07)	77.74 (24.72)	56.56 (26.39)	<0.0001[c]
EGFR–CKDEPI (ml/min)	76.35 (19.29)	77.20 (18.58)	53.0 (23.54)	<0.0001[c]
Preoperative IABP (%)	8 (0.8)	7 (0.7)	1 (2.7)	n.s.
Emergency surgery (%)	215 (20.4)	203 (19.9)	12 (32.4)	n.s.
Endocarditis (%)	51 (4.8)	43 (4.2)	8 (21.6)	<0.0001[b]
Cardiopulmonary bypass (%)	824 (78.03)	791 (77.6)	33 (88.2)	n.s.
Surgery type (%)				0.002[b]
CABG only	531 (50.3)	521 (51.1)	10 (27.0)	0.003[b]
AV surgery only	268 (25.4)	260 (25.5)	8 (21.7)	
MV surgery only	101 (9.6)	91 (8.9)	10 (27.0)	
CABG + AV surgery	74 (7.0)	70 (6.9)	4 (10.8)	
CABG + MV surgery	32 (3.0)	31 (3.0)	1 (2.7)	
CABG + AV + MV surgery	4 (0.4)	4 (0.4)	0 (0.0)	
AV + MV surgery	28 (2.6)	24 (2.4)	4 (10.8)	
Other	18 (1.7)	18 (1.8)	0 (0.0)	

Continuous variables are presented as mean (SD) or median (IQ range) where appropriate, and categorical variables are presented as number (%).
AKI: acute kidney injury; AKI-D: acute kidney injury requiring dialysis; AV: aortic valve; BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass grafting; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CPB: cardiopulmonary bypass; EGFR: estimated glomerular filtration rate (CG—according to Cockroft–Gault equation; CKDEPI: according to the CKDEPI equation); IABP: intra-aortic balloon pump; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MV: mitral valve; n.s.: not significant; NYHA: class according to New York Heart Association; OHG: oral hypoglycaemic drugs; PVD: peripheral vascular disease; SBP: systolic blood pressure.
[a]Mann–Whitney *U*-test.
[b]χ^2 or Fisher's exact test.
[c]Student's *t*-test.

Table 2: Baseline patient characteristics and the association with KDIGO-AKI stages

	Global cohort (*n* = 1056)	KDIGO-AKI 0 (*n* = 812)	KDIGO-AKI 1 (*n* = 183)	KDIGO-AKI 2 (*n* = 23)	KDIGO-AKI 3 (*n* = 38)	*P*-value
Age (years)	64 (57–71)	63 (56–70)	69 (60–73)	70 (66–76)	69 (64–74)	<0.001[a] *Post hoc* AKI-0 versus AKI-1 <0.001 *Post hoc* AKI-0 versus AKI-2 <0.001 *Post hoc* AKI-0 versus AKI-3 <0.001
Male sex (%)	766 (72.5)	605 (74.5)	123 (67.2)	12 (52.2)	26 (68.4)	0.026[b]
Weight (kg)	82.24 (13.98)	81.68 (13.73)	83.69 (13.79)	84.57 (12.96)	85.71 (19.34)	n.s.
Height (cm)	171.14 (9.08)	171.49 (8.88)	169.99 (9.99)	169.0 (9.62)	170.55 (7.79)	n.s.
BMI (kg/m^2)	28.05 (4.07)	27.73 (3.87)	28.98 (4.27)	29.66 (4.01)	29.37 (5.77)	<0.001 *Post hoc* AKI-0 versus AKI-1 <0.001
BSA (m^2)	1.94 (0.19)	1.94 (0.19)	1.95 (0.19)	1.95 (0.18)	1.97 (0.22)	n.s.
Smoking (%)	163 (15.4)	137 (16.9)	21 (11.5)	2 (8.7)	3 (7.9)	n.s.
Diabetes						0.008[b]
On OHG (%)	197 (18.7)	150 (18.5)	33 (18.0)	8 (34.8)	6 (15.8)	
On insulin (%)	107 (10.1)	69 (8.5)	27 (14.8)	2 (8.7)	9 (23.7)	
COPD (%)	95 (9.0)	62 (7.6)	25 (13.7)	2 (8.7)	6 (15.8)	0.025[b]
PVD (%)	63 (6.0)	43 (5.3)	16 (8.7)	2 (8.7)	2 (5.3)	n.s.
Previous cardiac surgery (%)	38 (3.6)	22 (2.7)	8 (4.4)	2 (8.7)	6 (15.8)	0.001[b]
Hypertension (%)	818 (77.5)	624 (76.8)	145 (79.2)	18 (78.3)	31 (81.6)	n.s.
SBP (mmHg)	129.01 (15.84)	129.14 (15.25)	129.61 (16.59)	125.43 (21.53)	125.66 (20.14)	n.s.
Atrial fibrillation (%)	136 (12.9)	79 (9.7)	31 (16.9)	9 (39.1)	17 (44.7)	<0.001[b]
Recent MI (<3 weeks) (%)	83 (7.9)	59 (7.3)	20 (10.9)	3 (13.0)	1 (2.6)	n.s.
CHF or NYHA III–IV (%)	153 (14.5)	79 (9.7)	48 (26.2)	7 (30.4)	19 (50.0)	<0.001[b]
Cardiogenic shock (%)	2 (0.2)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	n.s.
LVEF (%)	54.66 (11.12)	55.44 (10.57)	52.57 (12.10)	50.65 (14.02)	50.29 (13.27)	<0.001[c] *Post hoc* AKI-0 versus AKI-1 0.009 *Post hoc* AKI-0 versus AKI-3 0.03
White blood cell count (×10^{12}/l)	7.4 (6.1–9.0)	7.4 (6.1–8.85)	7.6 (6.2–9.4)	6.9 (5.3–9.7)	8.0 (6.3–9.2)	n.s.
Serum creatinine (μmol/l)	97 (86–112)	95 (85–107)	104 (91–125)	103 (83–116)	126.5 (92–189)	<0.001[a] *Post hoc* AKI-0 versus AKI-1 <0.001 *Post hoc* AKI-0 versus AKI-3 <0.001 *Post hoc* AKI-1 versus AKI-3 0.003 *Post hoc* AKI-2 versus AKI-3 0.002
EGFR—CG (ml/min)	77.00 (25.07)	79.92 (24.3)	69.52 (25.27)	68.58 (16.46)	55.71 (26.55)	<0.001[c] *Post hoc* AKI-0 versus AKI-1 <0.001 *Post hoc* AKI-0 versus AKI-3 <0.001 *Post hoc* AKI-1 versus AKI-3 0.009
EGFR—CKDEPI (ml/min)	76.35 (19.29)	79.68 (17.37)	67.64 (20.31)	67.93 (14.93)	52.15 (23.81)	<0.001[c] *Post hoc* AKI-0 versus AKI-1 <0.001 *Post hoc* AKI-0 versus AKI-2 0.013 *Post hoc* AKI-0 versus AKI-3 <0.001 *Post hoc* AKI-1 versus AKI-3 <0.001 *Post hoc* AKI-2 versus AKI-3 0.006
Preoperative IABP (%)	8 (0.8)	4 (0.5)	3 (1.6)	0 (0.0)	1 (2.6)	n.s.
Emergency surgery (%)	215 (20.4)	151 (18.6)	45 (24.6)	7 (30.4)	12 (31.6)	0.041[b]
Endocarditis (%)	51 (4.8)	33 (4.1)	8 (4.4)	2 (8.7)	8 (21.1)	0.001[b]
Cardiopulmonary bypass (%)	824 (78.03)	609 (75.0)	163 (89.1)	18 (78.3)	34 (89.5)	<0.001[b]
Surgery type (%)						<0.0001[b]
CABG only	531 (50.3)	457 (56.3)	59 (32.2)	5 (21.8)	10 (26.3)	
AV surgery only	268 (25.4)	196 (24.1)	57 (31.1)	7 (30.4)	8 (21.1)	
MV surgery only	101 (9.6)	67 (8.3)	21 (11.5)	3 (13.0)	10 (26.3)	
CABG + AV surgery	74 (7.0)	43 (5.3)	21 (11.5)	5 (21.8)	5 (13.2)	
CABG + MV surgery	32 (3.0)	15 (1.8)	13 (7.2)	3 (13.0)	1 (2.6)	
CABG + AV + MV surgery	4 (0.4)	3 (0.4)	1 (0.5)	0 (0.0)	0 (0.0)	
AV + MV surgery	28 (2.6)	17 (2.1)	7 (3.8)	0 (0.0)	4 (10.5)	
Other	18 (1.7)	14 (1.7)	4 (2.2)	0 (0.0)	0 (0.0)	

Continuous variables are presented as mean (SD) or median (IQ range) where appropriate, and categorical variables are presented as number (%).
AKI: acute kidney injury; AV: aortic valve; BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass grafting; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; EGFR: estimated glomerular filtration rate (CG—according to the Cockroft–Gault equation; CKDEPI: according to the CKDEPI equation); LVEF: left ventricular ejection fraction; MI: myocardial infarction; MV: mitral valve; n.s.: non-significant ($P \geq 0.05$); NYHA: class according to New York Heart Association; OHG: oral hypoglycaemic drugs; PVD: peripheral vascular disease; SBP: systolic blood pressure; KDIGO-AKI stages 1–3 (stage 0 = no AKI): according to Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group [23].
[a]Kruskal–Wallis test and *post hoc* Mann–Whitney *U*-test.
[b]χ^2 or Fisher's exact test.
[c]ANOVA and *post hoc* Bonferroni.

cardiac surgery, AF, CHF (NYHA class III or IV), lower LVEF, higher preoperative serum creatinine (lower EGFR), emergency surgery, endocarditis, type of surgery (other versus isolated CABG) and use of CPB were associated with the development of KDIGO-AKI (Table 2). Bivariable associations of patient characteristics with the KDIGO-AKI stages 1 and higher are given in Supplementary Table 2, with KDIGO-AKI stages 2 and higher in Supplementary Table 3 and with KDIGO-AKI stage 3 in Supplementary Table 4.

Multivariable logistic regression showed older age, AF, CHF (NYHA class III or IV), previous cardiac surgery, higher serum creatinine and endocarditis independently associated with the development of AKI-D (Table 3). Also in Table 3, the results of multivariable logistic regression analysis for the development of different stages of KDIGO-AKI are given. For KDIGO-AKI stage 1 and higher (versus no AKI), greater BMI, older age, female gender, COPD, previous cardiac surgery, AF, CHF (NYHA class III or IV), higher serum creatinine and the use of CPB were independent predictors.

Performance evaluation of different prediction models (scores)

The tested models were not applicable to all global cohort patients due to inclusion and exclusion criteria of the tested models (Fig. 1 and Supplementary Table 1). The discrimination of each model (risk score), measured with AUC, for occurrence of AKI-D and for the each stage of KDIGO-AKI is given in Table 4. Reliable calculation of AUC was not possible for the AKI-D and KDIGO-AKI stages 2 and 3 using the Brown *et al.* model [9], due to a small number of events. For the original outcome of the Brown *et al.* model (EGFR <30 ml/min) [9], the AUC was also not calculated due to the same reason.

The comparison of different models shows that the highest AUC for all outcomes and stages of CS-AKI has the model of Thakar *et al.* [6]. Compared with the model of Wijeysundera *et al.* [8] (the same patient subgroup), this was statistically significant for all outcomes: for AKI-D versus no AKI-D ($P = 0.0021$), for KDIGO-AKI stages 1 and higher versus KDIGO-AKI 0 ($P = 0.0001$), for KDIGO-AKI stages 2 and higher versus KDIGO-AKI 0–1 ($P = 0.0015$) and for KDIGO-AKI stage 3 versus KDIGO-AKI 0–2 ($P = 0.0008$). The results also show that smaller AUC was found in all the models for the lower stages of KDIGO-AKI (Table 4).

Analysis of calibration of the best performing model in the discrimination for CS-AKI (the model of Thakar *et al.* [6]) is shown in Fig. 2. Patient characteristics between the Thakar *et al.* [6] original cohort and our subgroup for the model analysis are given in Supplementary Table 5, and frequencies of AKI-D at different score levels and risk categories are given in Supplementary Table 6.

Table 3: Predictors of AKI in multivariable logistic regression in the global cohort ($n = 1056$)

	OR (95% CI)	*P*-value	AUC (95% CI)
For acute kidney injury—dialysis versus no dialysis			
Age (years)	1.072 (1.023–1.124)	0.0035	0.896 (0.876–0.914)
Atrial fibrillation (yes versus no)	4.642 (2.015–10.698)	0.0003	
CHF/NYHA class III or IV (yes versus no)	2.689 (1.189–6.078)	0.0175	
Previous cardiac surgery (yes versus no)	5.323 (1.635–17.325)	0.0055	
Serum creatinine (μmol/l)	1.022 (1.014–1.023)	<0.0001	
Endocarditis (yes versus no)	9.408 (2.702–32.764)	0.0004	
For KDIGO-AKI stages 1–3 versus stage 0 (no AKI)			
BMI (kg/m^2)	1.105 (1.061–1.151)	<0.0001	0.780 (0.753–0.804)
Age (years)	1.034 (1.016–1.053)	0.0002	
Gender (female versus male)	1.572 (1.085–2.278)	0.0169	
COPD (yes versus no)	1.757 (1.065–2.897)	0.0273	
Previous cardiac surgery (yes versus no)	2.888 (1.313–6.355)	0.0084	
Atrial fibrillation (yes versus no)	1.599 (1.033–2.475)	0.0352	
CHF/NYHA class III or IV (yes versus no)	3.314 (2.195–5.004)	<0.0001	
Serum creatinine (μmol/l)	1.021 (1.015–1.027)	<0.0001	
CPB (yes versus no)	2.243 (1.407–3.577)	0.0007	
For KDIGO-AKI stages 2–3 versus stages 0–1			
BMI (kg/m^2)	1.111 (1.037–1.189)	0.0026	0.872 (0.850–0.891)
Age (years)	1.086 (1.045–1.129)	<0.0001	
Previous cardiac surgery (yes versus no)	4.917 (1.725–14.016)	0.0029	
Atrial fibrillation (yes versus no)	4.164 (2.182–7.946)	<0.0001	
CHF/NYHA class III or IV (yes versus no)	2.437 (1.252–4.741)	0.0087	
Serum creatinine (μmol/l)	1.017 (1.010–1.023)	<0.0001	
Endocarditis (yes versus no)	9.693 (3.204–29.324)	0.0001	
For KDIGO-AKI stage 3 versus stages 0–2			
Age (years)	1.071 (1.022–1.122)	0.0043	0.897 (0.878–0.915)
Previous cardiac surgery (yes versus no)	5.533 (1.698–18.034)	0.0045	
Atrial fibrillation (yes versus no)	4.411 (1.917–10.149)	0.0005	
CHF/NYHA class III or IV (yes versus no)	2.521 (1.112–5.718)	0.0269	
Serum creatinine (μmol/l)	1.024 (1.017–1.032)	<0.0001	
Endocarditis (yes versus no)	8.768 (2.491–30.855)	0.0007	

Continuous variables are presented as mean (SD) or median (IQ range) where appropriate, and categorical variables are presented as number (%).
AKI: acute kidney injury; AUC: area under curve; BMI: body mass index; CI: confidence interval; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CPB: cardiopulmonary bypass; NYHA: class according to New York Heart Association; KDIGO-AKI stages 1–3 (stage 0 = no AKI): according to Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group [23].

Table 4: Evaluation by discrimination (measured with AUC) of five risk scores for outcomes: AKI requiring dialysis and KDIGO-AKI stages 1–3 in our patient cohort

	AKI-dialysis AUC (95% CI)	KDIGO-AKI 1–3 AUC (95% CI)	KDIGO-AKI 2–3 AUC (95% CI)	KDIGO-AKI 3 AUC (95% CI)
Brown *et al.* (*n* = 396)	N/A (*n* = 2)	0.634 (0.584–0.681) (*n* = 34)	N/A (*n* = 4)	N/A (*n* = 2)
Fortescue *et al.* (*n* = 991)	0.755 (0.727–0.781) (*n* = 26)	0.715 (0.686–0.743) (*n* = 219)	0.751 (0.723–0.778) (*n* = 47)	0.755 (0.727–0.781) (*n* = 26)
Mehta *et al.* (*n* = 1038)	0.776 (0.750–0.801) (*n* = 37)	0.716 (0.688–0.744) (*n* = 240)	0.746 (0.718–0.772) (*n* = 61)	0.783 (0.756–0.807) (*n* = 38)
Thakar *et al.* (*n* = 824)	0.837 (0.810–0.862) (*n* = 33)	0.731 (0.699–0.761) (*n* = 215)	0.811 (0.783–0.838) (*n* = 52)	0.842 (0.816–0.867) (*n* = 34)
Wijeysundera *et al.* (*n* = 824)	0.706 (0.674–0.737)[a] (*n* = 33)	0.657 (0.623–0.689)[a] (*n* = 215)	0.702 (0.669–0.733)[a] (*n* = 52)	0.698 (0.665–0.729)[a] (*n* = 34)

Continuous variables are presented as mean (SD) or median (IQ range) where appropriate, and categorical variables are presented as number (%).
AKI: acute kidney injury; KDIGO-AKI stages 1–3: according to Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group [23]; AUC: area under curve; CI: confidence interval.
[a]$P < 0.05$ compared with Thakar *et al.* in the DeLong test.

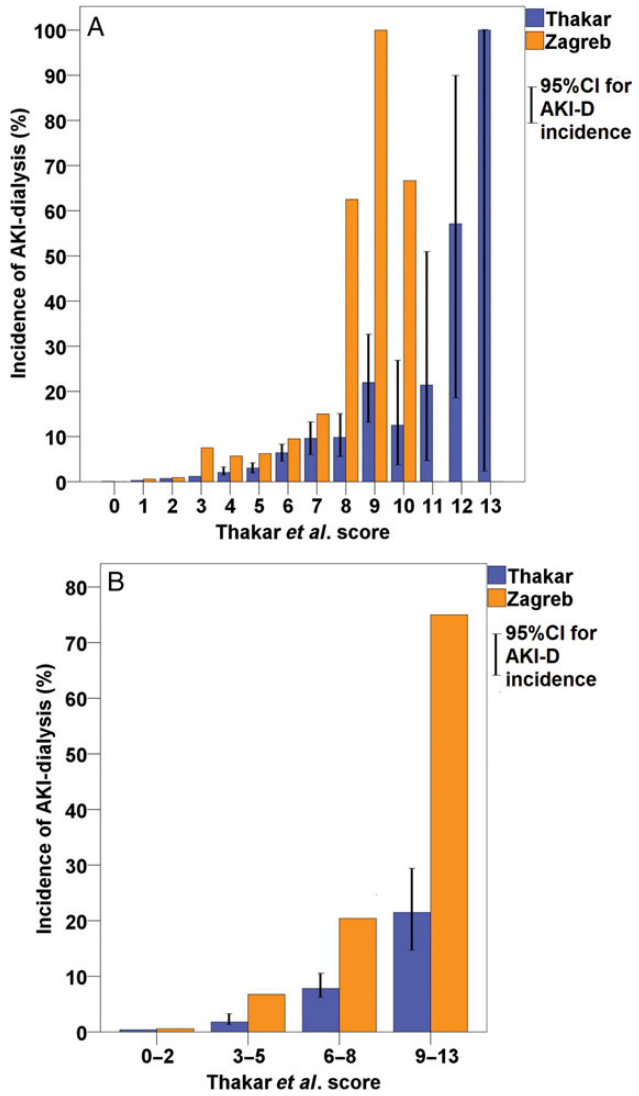

Figure 2: Acute kidney injury-dialysis (AKI-D) incidence of the individual (**A**) and grouped (**B**) score values in Thakar *et al.* and our patient cohort (calibration plots).

The calibration of the model was poor, as shown by calibration-in-large analysis (Fig. 2). When applied to our patients, the model of Thakar *et al.* [6] underestimated the risk of AKI-D except in the lower risk categories (Fig. 2). The optimal cut-off value for the Thakar model score in the prediction of AKI-D was 2 in our patient cohort, with sensitivity of 90.91%, specificity of 65.23%, positive-likelihood ratio 2.61 and negative-likelihood ratio of 0.14.

DISCUSSION

In this study, we aimed to explore risk factors for the development of AKI after cardiac surgery, as well as to evaluate the performance of well-known prediction models [5–9] in our population cohort.

Preoperative evaluation and identification of patients, who are at greater risk for the development of AKI, could lead to more optimal perioperative care and improve patients outcome. The most often used prediction models of CS-AKI have been developed in the USA and Canada [5–9], and later validated in other regions of the world, including European population cohorts as well [15–20]. The definition of the primary outcome (AKI) in this setting is the first big issue that needs to be addressed, because different definitions of AKI make the comparison and validation of studies difficult. Most authors defined AKI with the initiation of RRT (dialysis) [5–9], but other definitions were also used [10–14]. To overcome the differences in the definition of AKI in general, KDIGO-AKI criteria have been proposed recently [23]. We chose AKI-D as the primary outcome, because the original, most often utilized and tested prediction models, had the same outcome [5–8, 15–20]. Also, we studied KDIGO-AKI as the secondary outcome and the association of predictors with different stages of KDIGO-AKI, as well as performance of known prediction models regarding this outcome. There has been only one study evaluating CS-AKI according to KDIGO-AKI criteria, by Machado *et al.*, but the primary goal of this study was to evaluate the prognostic significance of KDIGO-AKI stages and not to explore the risk factors for AKI [3]. In our study, we included all cardiac surgery patients operated with and without CPB, with usual exclusion criteria as mentioned before and in concordance with the majority of studies.

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The incidence of AKI-D in our study was 3.5%, which is higher than in the original prediction models that we validated, where the incidence of AKI-D ranged from 1.1 to 2.7% [5–9]. In other studies that validated these original prediction models, incidence of AKI-D ranged from 1.9 to 10.9% [15–20]. The incidence of AKI according to KDIGO criteria in our study was 17.3% for stage 1, 2.1% for stage 2 and 3.6% for stage 3. Machado *et al.* [3] found similar incidences for stages 2 and 3 (4 and 3%, respectively), whereas the incidence of KDIGO-AKI stage 1 in their study was higher (35%). There could be several reasons for the inequality in AKI-D incidences between studies. The most important seems to be variable criteria for the initiation of dialysis, prone to subjective decisions of attending physician. Also, not strictly defined time period for the development of AKI, could lead to higher incidence if longer time period is used. This again emphasizes the need for more objective and uniform criteria for the AKI and also for the postoperative period tested, both embedded in KDIGO-AKI criteria.

We choose to investigate only models with preoperative predictors of AKI, because we find that possible preventive measures should start preoperatively, as early as possible. Predictive scores that use intra- or postoperative variables could delay applying those measures to the time where AKI has already started. Thereby, we do not want to diminish the significance of the intra- and postoperative factors. As potential predictors, we evaluated only the factors that were found to be significant in original studies (Supplementary Table 1) [5–9]. In our study, we found higher age, presence of AF, NYHA III or IV class CHF, prior cardiac surgery, higher serum creatinine and endocarditis was independently associated with AKI-D in multivariable analysis (Table 3). There are differences found in predictors of AKI-D compared with the studies that we evaluated [5–9]. Other validation studies also found such differences compared with original studies [15–20]. The main reason for this is the difference in patient characteristics, which was found in validation studies and in our study too, compared with the original studies. Also, as mentioned, some predictors, such as CHF, cardiogenic shock, COPD and emergent status of the surgery, could be interpreted subjectively by the investigators.

We also explored potential predictors for the KDIGO-AKI. To our knowledge, this was the first study that used this definition of AKI to evaluate only preoperative predictors. For the KDIGO-AKI stage 3, the predictors were similar as for AKI-D, which is to be expected considering that the definition of KDIGO-AKI stage 3 also includes the initiation of dialysis. In addition to those predictors, higher BMI, female gender, COPD and the use of CPB were associated with the development of less severe stages of KDIGO-AKI (Table 3).

Evaluation of five most widely used prediction models of CS-AKI then followed, where we applied both definitions of AKI. Models were applicable to selected subgroups of patients (Fig. 1) according to inclusion and exclusion criteria of the original studies (Supplementary Table 1) [5–9]. The models of Fortescue *et al.* [5], Mehta *et al.* [7], Thakar *et al.* [6] and Wijeysundera *et al.* [8] discriminated well in the prediction of AKI-D, with AUC ranging from 0.706 (0.674–0.737) to 0.837 (0.810–0.862) (Table 4), whereas for the model of Brown *et al.* [9], reliable calculation of AUC was not possible due to a small number of AKI-D events. Other validation studies found variable discrimination parameters of the original studies.

In most of the validation studies, the model of Thakar *et al.* [6] showed the best discrimination as in our study too, with AUC ranging from 0.662 (0.646–0.678) to 0.93 (0.91–0.94) [8, 16, 18–20]. Comparison of the tested models in our population cohort showed that this difference was statistically significant compared with the model of Wijeysundera *et al.* [8]. Direct comparison of different models in the same population cohort was also done by Kiers *et al.* [20], and the difference was statistically significant between the models of Thakar *et al.* [6] and Mehta *et al.* [7].

Then, we tested the calibration of the model with the highest AUC (Thakar *et al.* [6]) by calibration-in-large plots (Fig. 2 and Supplementary Table 6). Calibration in our subgroup of patients was poor and the model underestimated the risk for AKI-D, except for the lower risk categories. Similar findings of poor calibration of the original models were reported also by Candela-Toha *et al.* [16] and Heise *et al.* [18]. The main reason for this poor calibration is the difference in the demographic and clinical characteristics of our patients compared with the original study cohort (Supplementary Table 5). Among other differences, our patients in the subgroup for this analysis were all Caucasians, of younger age, had lower serum creatinine and also differed in the type of surgery performed compared with the Thakar *et al.* cohort [6]. There are also possible differences in the thresholds for the initiation of dialysis.

Five available prediction models were then evaluated in the prediction of KDIGO-AKI. Four models discriminated reasonably, well with the model of Thakar *et al.* [6], showing again the highest predictive value in all stages of KDIGO-AKI (Table 4). The difference was statistically significant compared with the model of Wijeysundera *et al.* [8] at all stages of KDIGO-AKI. The model of Brown *et al.* [9] was only validated in the prediction of KDIGO-AKI stage 1 and higher with the lowest discrimination found. To our knowledge, this is the first study to evaluate this prediction models regarding KDIGO-AKI stages. Kiers *et al.* [20] evaluated these models in the prediction of CS-AKI according to earlier RIFLE criteria. We found that our multivariable analysis predictors of CS-AKI showed higher AUC for all outcomes tested in comparison with tested models. This finding supports the need for local re-evaluation of widely used prediction models and also for implementing possible corrections of those models with respect to local population cohorts.

The strength of this study is the inclusion and evaluation of all available models of CS-AKI that include only preoperative factors in the prediction of not only AKI-D, but also newly more uniformly defined AKI by KDIGO criteria.

There are also some limitations to our study. First, our study was retrospective and therefore dependent on medical records and history, so ascertainment error, recall, informative censoring and lead-time biases cannot be avoided. The number of patients analysed was relatively small compared with that of original studies, with the consecutive lower statistical power of our study. The differences in patient populations compared with original studies could have influenced the outcomes. In the analysis of KDIGO-AKI stages, the urine output was not always documented, although measured, and therefore could not be used as a criterion for KDIGO-AKI. When evaluating differently defined outcomes against those in original studies (KDIGO-AKI versus AKI-D), predictive models may perform differently compared with the original setting.

CONCLUSIONS

Our study identified several independent risk factors for the development of cardiac surgery-associated AKI, defined as AKI-D and KDIGO-AKI stages. Evaluation of well-known prediction models showed that the model of Thakar *et al.* [6] had the highest predictive

value in the discrimination of patients with risk for AKI-D as well as for all KDIGO-AKI stages. Although it showed miscalibration, it could still be used to detect patients who are at high risk of AKI-D and also for less severe stages of CS-AKI. More studies are, however, needed to develop and/or validate scores to predict non-dialysis CS-AKI.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

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