Serum Creatinine Back-Estimation in Cardiac Surgery Patients: Misclassification of AKI Using Existing Formulae and a Data-Driven Model

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Abstract

Background and objectives A knowledge of baseline serum creatinine (bSCr) is mandatory for diagnosing and staging AKI. With often missing values, bSCr is estimated by back-calculation using several equations designed for the estimation of GFR, assuming a "true" GFR of 75 ml/min per 1.73 m^2. Using a data set from a large cardiac surgery cohort, we tested the appropriateness of such an approach and compared estimated and measured bSCr. Moreover, we designed a novel data-driven model (estimated serum creatinine [eSCr]) for estimating bSCr. Finally, we analyzed the extent of AKI and mortality rate misclassifications.

Design, setting, participants, & measurements Data for 8024 patients (2833 women) in our cardiac surgery center were included from 1997 to 2008. Measured and estimated bSCr were plotted against age for men and women. Patients were classified to AKI stages defined by the Kidney Disease Improving Global Outcomes (KDIGO) group. Results were compared with data from another cardiac surgery center in Zurich, Switzerland.

Results The Modification of Diet in Renal Disease and the Chronic Kidney Disease Epidemiology Collaboration formulae describe higher estimated bSCr values in younger patients, but lower values in older patients compared with the measured bSCr values in both centers. The Pittsburgh Linear Three Variables formula correctly describes the increasing bSCr with age, however, it underestimates the overall bSCr level, being in the range of the 25% quantile of the measured values. Our eSCr model estimated measured bSCr best. AKI stage 1 classification using all formulae, including our eSCr model, was incorrect in 53%–80% of patients in Vienna and in 74%–91% in Zurich; AKI severity (according to KDIGO stages) and also mortality were overestimated. Mortality rate was higher among patients falsely classified into higher KDIGO stages by estimated bSCr.

Conclusions bSCr values back-estimated using currently available eGFR formulae are inaccurate and cannot correctly classify AKI stages. Our model eSCr improves the prediction of AKI but to a still inadequate extent.

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Introduction

AKI is a common complication following cardiac surgery and significantly increases morbidity, mortality, and duration of hospital stay (1–3). An AKI diagnosis relies on changes in serum creatinine (SCr) from a baseline value (baseline serum creatinine [bSCr]), decreases in the GFR, or absolute decreases in urine output (1,4,5). Despite the widespread availability of electronic medical records, the bSCr is frequently missing, which leads to the use of surrogate estimations (1,6).

When the bSCr is missing, it can be back-estimated based on a hypothetical GFR by using GFR formulae. These formulae estimate the GFR from a known SCr value, when the urinary creatinine and urinary volume are unknown. The first and most recommended bSCr estimation method is based on the Modification of Diet in Renal Disease (MDRD) equation for predicting the GFR (4). In 2009, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was developed for estimating the GFR, although it has not yet been used to estimate the bSCr (7). In 2010, Zavadá and colleagues introduced the Pittsburgh Linear Three Variables (PLTV) formula, which uses the same anthropometric variables as the MDRD equation and has shown promising results (8). To estimate the bSCr with all these formulae, we assume that the GFR is equivalent to a standard GFR of 75 ml/min per 1.73 m^2 (1,4,9,10). However, use of a standard GFR is not appropriate because there is high variability in the GFR within a given population due to age or gender. Although these methods for estimation of bSCr based on GFR have been used in several epidemiologic studies, they require further validation and improved methods for estimating bSCr are needed (11–15).

The aim of this study was to assess the accuracy of the MDRD, CKD-EPI, and PLTV formulae, and a new data-driven model (estimated serum creatinine [eSCr])

for the estimation of bSCr in cardiac surgery patients by comparing the estimated with the known measured values. We also tested the appropriateness of the recommended GFR of 75 ml/min per 1.73 m^2 by using population norms for GFR according to age based on a study measuring urinary clearance of inulin (16). In addition, we determined the accuracy of the estimated bSCr for classifying postoperative AKI using Kidney Disease Improving Global Outcomes (KDIGO) criteria (17), and subsequent patient mortalities. Finally, we compared our results with a cohort of similar patients at the University Hospital of Zurich, Switzerland to validate our findings (18).

Materials and Methods

Study Design and Patients

The study protocol was approved by the Ethics Committee of the Medical University of Vienna (EK Nr: 964/2011). Between January 1, 1997, and December 31, 2008, 9596 patients underwent elective open-heart surgery at the Department of Cardiothoracic Surgery, Medical University of Vienna, Vienna, Austria, as recorded in the prospectively collected database of the Department of Cardiothoracic and Vascular Anesthesia and Intensive Care Medicine. For this analysis, we included adult patients (≥18 years) who were scheduled for coronary artery bypass grafting (with or without cardiopulmonary bypass), valve surgery, and combined procedures. To create a homogenous cohort of elective cardiac surgical patients we excluded the following interventions or conditions: transplant surgery, scheduled insertion of a cardiac assist device, operation on the aorta (*e.g.*, thoracic aortic aneurysm repair), thrombendarterectomy of the pulmonary arteries, emergency and urgent procedures, history of CKD (defined by clinicians), and congenital heart disease. Further, we excluded patients without a recorded preoperative SCr (n=106), even though they were elective surgical patients. Patient selection is shown in Figure 1.

Preoperative patient data (age, sex, body mass index, bSCr, and European System for Cardiac Operative Risk Evaluation [EuroSCORE]) were collected prospectively at the time of premedication. At the end of the follow-up period (December 31, 2010), the data from the clinical database were combined with those collected from the central laboratory and hospital central databases, the latter holding information from the Federal Austrian Statistical Office on the death of every patient in Austria. Follow-up was complete for all included patients.

Baseline SCr Data Collection

The bSCr was defined as the SCr value recorded within 10 days prior to surgery. In the case of reoperation within 14 days of the first intervention, the value before the first surgery was used. In 7929 of 8024 patients, the measured SCr values were available within seven postoperative days. SCr concentration was measured using the Jaffe method on a Hitachi 747 analyzer (until 2003) and on an Olympus AU5400 (since 2004); analyzers and specific tests were extensively evaluated and test results were compared with each other before changing platforms. No difference between the analyzers was found.

Baseline SCr Estimations

Because our sample is drawn from a white population, we used the MDRD (Equation 1), CKD-EPI (Equation 2), and PLTV (Equation 3) equations without the race factor for back-estimation of the bSCr.

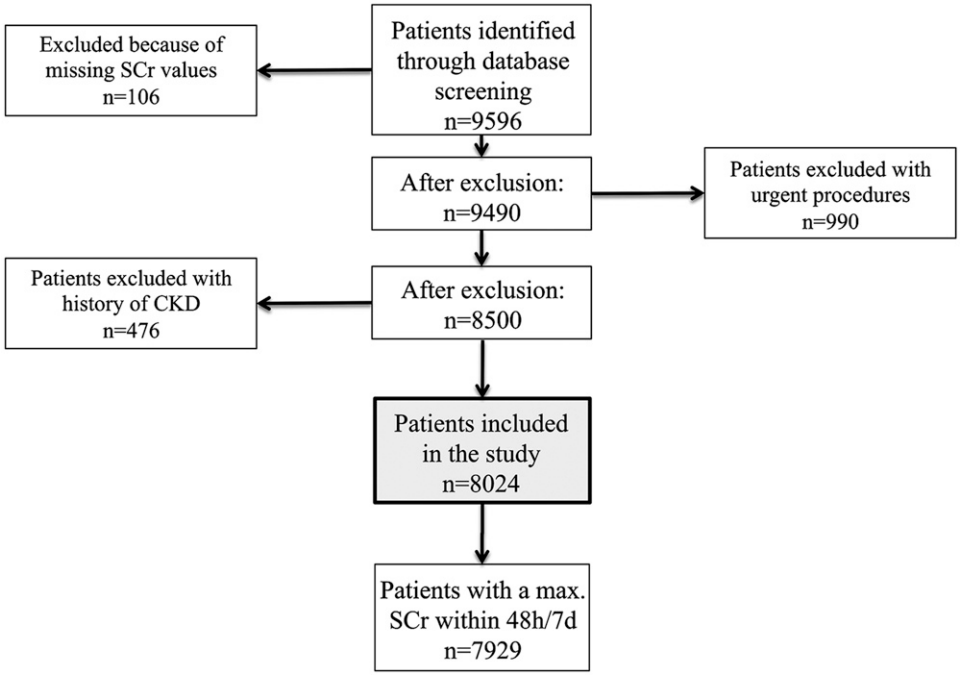

Figure 1. | **The selection process for patients included in the study.** max., maximum; SCr, serum creatinine.

Equation 1: MDRD Model (19).

$$bSCr = \left[\frac{75}{186 \times age^{-0.203} \times (0.742 \ \ if \ \ female)}\right]^{-0.887}$$

Equation 2: CKD-EPI Model (7). The CKD-EPI formula yields GFR as a function of SCr, age, sex, and ethnicity. Because the formula is continuous and strictly monotonically decreasing, it can be inverted. The inverse formulae, which express SCr as a function of GFR, are:

Men, eSCr≤0.9:

$$SCr = 0.7 \times \left(\frac{GFR}{0.993^{Age} \times 144}\right)^{\frac{1}{-0.329}}$$

Men, eSCr>0.9:

$$SCr = 0.7 \times \left(\frac{GFR}{0.993^{Age} \times 144}\right)^{\frac{1}{-1.209}}$$

Women, eSCr≤0.7:

$$SCr = 0.9 \times \left(\frac{GFR}{0.993^{Age} \times 141}\right)^{\frac{1}{-0.411}}$$

Women, eSCr>0.7:

$$SCr = 0.9 \times \left(\frac{GFR}{0.993^{Age} \times 141}\right)^{\frac{1}{-1.209}}$$

A standard GFR value of 75 ml/min per 1.73 m^2 may be substituted into these CKD-EPI equations as is done with the MDRD formula. However, a more sensible approach is to use an age-adjusted GFR for both the MDRD- and CKD-EPI-based prediction of bSCr. We used age- and gender-adjusted mean values of GFR as measured and published by Wesson in 1969, values that were also described in the KDIGO 2012 Guidelines (16,20): by analyzing the association between age and GFR for healthy women and men aged between 20 and 89 years, a piecewise linear function was developed to describe the association of GFR with age based on the urinary clearance of inulin (16). Therefore, in this study, we used Wesson's measured GFR values and applied these values in the MDRD and CKD-EPI for estimation of SCr:

Men: age ≤40, GFR[ml/min]=151–0.65× age; age 41–55, GFR[ml/min]=160–0.87× age; age >55, GFR[ml/min]=193–1.47× age.
Women: age ≤40, GFR[ml/min]=126–0.3× age; age 41–55, GFR[ml/min]=138–0.6× age; age >55, GFR[ml/min]=160–age

Equation 3: PLTV Model (8).

$$bSCr = 0.74 - (0.2 \ \ if \ \ female) + 0.003 \times age(in \ \ years)$$

Equation 4: eSCr Model. We calculated regression models for bSCr on age, separately for men and women, in order to develop better coefficients for SCr determination (Supplemental Table 1). We investigated a linear relationship between bSCr and age, as well as second- and third-degree polynomials. The best models for men and women used a quadratic function as follows:

Men (multiple R^2=0.0278):

$$\text{bSCr} = 1.053 - \text{age} \times (3.619 \times 10^{-3}) + \text{age}^2 \times (8.005 \times 10^{-5})$$

Women (multiple R^2=0.02615):

$$bSCr = 8.259 \times 10^{-1} - \text{age} \times (1.051 \times 10^{-3}) + age^2 \times (2.734 \times 10^{-5})$$

We also included estimated total body water (TBW) as an additional predictor variable (21). Both age and TBW were used as predictor variables separately for men and women, and linear and nonlinear models were fitted. The best linear models for men and women were as follows:

Men (multiple R^2=0.02635):

$$bSCr = 0.689 + 0.0062 \times \text{age} + 0.0018 \times \text{TBW}$$

Women (multiple R^2=0.02624):

$$bSCr = 0.628 \ \ + 0.0045 \times \text{age} + 0.0030 \times \text{TBW}$$

AKI Diagnosis and Validation

We classified our patients according to KDIGO stages (17) on the basis of SCr concentrations alone; urine output criteria were not considered. For comparison, AKI diagnosis was performed on 3123 adult patients who underwent cardiac surgery at the University Hospital of Zurich, Switzerland. This cohort of patients has previously been compared with our patient cohort and used for validation of data (18,22).

Statistical Analyses

To comprehensively describe the data, nonparametric quantile regression of SCr on age was performed using locally weighted linear quantile regression by applying a Gaussian weighting function with a bandwidth of 5 years. All observations were included in the calculations; however, estimated values were only calculated for patients aged 23–89 years in Vienna and 23–85 years in Zurich, because the number of data points outside this range was considered insufficient to generate reliable results. Estimated values were calculated for the following quantiles: 0.05, 0.15, 0.25, 0.5, 0.75, 0.85, and 0.95. The calculations were done separately for men and women. The median and estimated regions that cover 50%, 70%, and 90% of all SCr values for the population at each given age and gender were determined. The estimated bSCr values for each age group and gender are expressed as the median or the mean±SD (SD). For graphical representations, a running mean was calculated with a span of 11 years.

The measured KDIGO stages were compared with estimated KDIGO stages by calculating contingency tables and the Cohen κ statistic. To determine whether AKI classification affected patient outcomes, we performed a mortality

rate (MR) analysis to indicate the percentage of patients who died within a given period after diagnosis. We calculated the number of deceased patients per 100 patient years for KDIGO stages 0–3, as classified by each of the four formulae and compared the results with the MRs in the actual KDIGO stages defined through our measured bSCr values.

The statistical computing environment R3.1.1 and Mathematica 10.1 (Wolfram Research, Champaign, IL) were used to perform calculations.

Results

Demographics

We included a total of 8024 patients with a mean±SD age of 65.5±13 years (range, 18–94). The proportion of women was 35% (n=2833). Detailed results of patient demographics are shown in Table 1.

Age and Gender Dependence of bSCr

The bSCr values were higher among older patients in both sexes, with a difference in median values of approximately 0.2 mg/dl between patients with age 40 years and patients with age 80 years (Figure 2, Table 2). The bSCr values were generally higher in men than in women; the estimated median bSCr was 0.32 mg/dl higher for men.

Accuracy of the Four Models for Estimating bSCr Values

The estimated bSCr values from all formulae are shown in Figure 2. The overall difference in bSCr values between men and women appears to be estimated correctly in all four models. However, in both centers, the MDRD and CKD-EPI formulae did not accurately describe the increasing bSCr in older patients. Instead, they showed a monotonically decreasing function of bSCr with increasing age when a GFR of 75 ml/min per 1.73 m^2 is assumed, therefore older patients showed lower bSCr values. When age-adjusted GFRs were used in the MDRD or the CKD-EPI formula, the predicted bSCr values were higher with increasing age, matching the observed direction of the association. However, the bSCr values were still underestimated, *i.e.*, they were below the 25th percentile of the measured bSCr values in both sexes, with a more severe underestimation in men. This observation raised doubts about the usefulness of the age adjustment.

Table 1. Patient and surgical characteristics

Variable	Main Cohort		Missing bSCr Cohort		P Value
	n	Mean±SD	n	Mean±SD	
Patient characteristics					
No. patients	8024		106		
Women	2833 (35.3)		34 (32.1)		0.56
Age, yr	8024	65.5±12.5	106	60.6±14.2	<0.001
BMI, kg/m^2	7876	26.8±4.2	103	26.60±3.88	0.53
bSCr, mg/dl	8024	1.11±0.41			
$eGFR_{MDRD}$, ml/min per 1.73m^2	8024	69.4±19.4			
$eGFR_{CKD\text{-}EPI}$, ml/min per 1.73m^2	8024	67.6±19.1			
Logistic EuroSCORE	8024	6.9±8.1	106	7.6±9.8	0.51
Surgical characteristics					
CABG	3070 (38.3)		45 (42.5)		
Combined procedure	1590 (19.8)		29 (27.4)		
Off-pump CABG	568 (7.1)		6 (5.6)		
Valve procedure	2796 (34.8)		26 (24.5)		0.07
Surgery time, min	8024	227.0±75.0	106	224.8±63.9	0.73
ECC time, min	8024	101.2±55.2	106	102.6±48.6	0.77
AoCC time, min	8024	63.1±35.3	106	60.7±35.5	0.49
Reoperation	656 (8.2)		12 (11.3)		0.32
Postoperative complications					
Revision ≤48 h	288 (3.6)		7 (6.6)		0.17
Revision >48 h	596 (7.4)		5 (4.7)		0.38
SCr ICU Admission, mg/dl	7473	1.01±0.37	102	1.23±1.03	0.04
Follow-up time, yr	8024	6.4±3.8	106	6.21±3.86	0.67
KDIGO Stage 0	6747 (85.1)		73 (71.6)		
KDIGO Stage 1	702 (8.9)		19 (18.6)		
KDIGO Stage 2	119 (1.5)		1 (0.9)		
KDIGO Stage 3	361 (4.6)		9 (8.5)		
RRT	321 (4.0)		6 (5.6)		0.54
Deceased	2618 (32.6)		38 (35.9)		0.55
MR per 100 patient years	8024	5.13	106	5.93	0.81

Values are given as numbers (n), percentages (%), or means±SD. bSCr, baseline serum creatinine; BMI, body mass index; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EuroSCORE, European System for Cardiac Operative Risk Evaluation; CABG, coronary artery bypass graft; ECC, extracorporeal circulation; AoCC, aortic crossclamp; SCr, serum creatinine; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; MR, mortality rate.

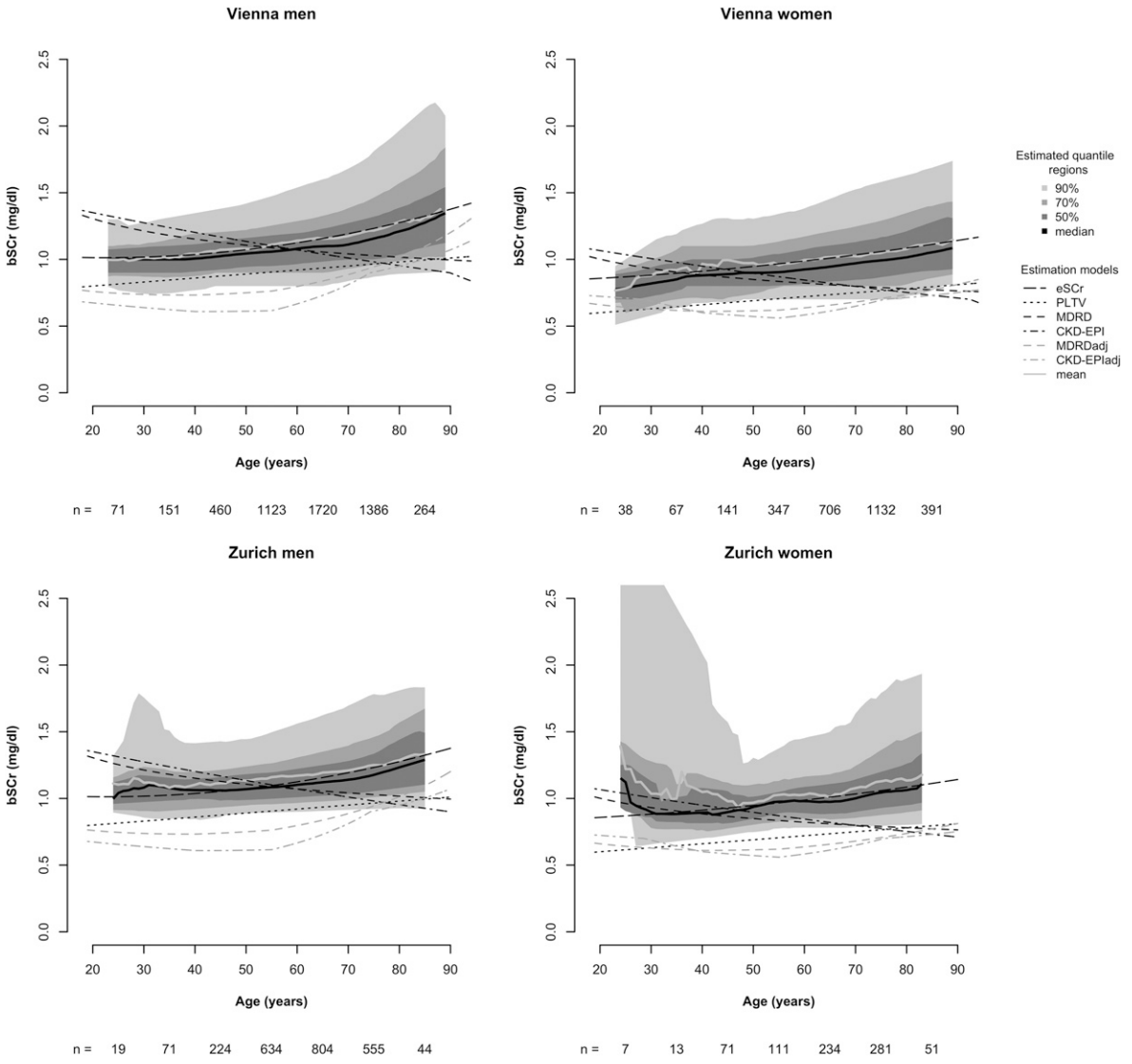

Figure 2. | Quantile regression models of baseline serum creatinine (bSCr) according to age in men and women in the Vienna and Zurich cardiac centers. Measured bSCr median (black) and mean (gray) are shown as solid lines; estimated serum creatinine (eSCr) values are shown as long black dashes for the eSCr model, short black dashes for the Modification of Diet in Renal Disease (MDRD) model, a dotted black line for the Pittsburgh Linear Three Variables (PLTV) model, and a dashed-dotted black line for the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) model. The age-adjusted models are shown as a dashed gray line (MDRDadj) and a dashed-dotted gray line (CKD-EPIadj). Estimates are only shown for ages 23–89 for the Vienna data set and ages 23–85 for the Zurich data set. The mean and median estimates and regions containing 50%, 70%, and 90% of bSCr values at a given age and sex in the studied population are shown as different shades of gray. The number of men and women in the data set for each 10-year age interval is shown underneath the graphic. The estimation of the extreme quantiles (border of the 90% region) is the least robust and can become unreliable for age groups with small sample sizes.

The PLTV and data-driven eSCr models correctly described a positive correlation between age and bSCr. The PLTV formula also underestimated the bSCr values, with all estimated values below the 25th percentile in both sexes. The values estimated from the data-driven eSCr model were between the 25th and 75th percentiles of our patients and are around the observed mean.

Evaluation and Comparison of AKI Diagnosis

All models incorrectly categorized patients at all measured KDIGO stages. The MDRD, CKD-EPI, and PLTV formulae all overestimated the AKI incidence and severity. The MDRD, CKD-EPI, and PLTV formulae categorized KDIGO stage 1 correctly in only 28%, 26%, and 20% (n=391, n=386, and n=394) of cases, respectively. Most patients were incorrectly categorized as KDIGO stage 1 when the measured KDIGO stage was 0 using the MDRD (71%, n=992), CKD-EPI (73%, n=1081), and PLTV (79%, n=1532) formulae. Although the models showed a better prediction of KDIGO stage 3, this is mostly due to the risk indicator of RRT, which occurred in 318 patients. The κ coefficients for the accuracy of the MDRD, CKD-EPI, and PLTV models in predicting the KDIGO stages in our study cohort were 0.49, 0.46, and 0.39, respectively; whereas in

Table 2. bSCr values grouped by age and sex

Age group, yr	Men		Women	
	Median, mg/dl	Mean±SD, mg/dl	Median, mg/dl	Mean±SD, mg/dl
20–24	1.00	1.00±0.16	0.79	0.78±0.12
25–29	1.00	1.00±0.14	0.80	0.76±0.15
30–34	1.00	1.01±0.18	0.82	0.95±0.58
35–39	1.00	1.03±0.20	0.90	0.91±0.16
40–44	1.00	1.05±0.29	0.81	0.90±0.27
45–49	1.06	1.07±0.21	0.90	1.04±0.84
50–54	1.05	1.08±0.27	0.91	0.94±0.18
55–59	1.05	1.12±0.52	0.90	0.97±0.26
60–64	1.10	1.15±0.51	0.92	0.99±0.34
65–69	1.10	1.17±0.46	0.98	1.03±0.35
70–74	1.10	1.17±0.30	0.97	1.02±0.28
75–79	1.20	1.26±0.55	1.00	1.06±0.32
80–84	1.22	1.31±0.45	1.02	1.11±0.32
85–89	1.30	1.33±0.33	1.10	1.17±0.32
90–94	1.25	1.41±0.43	0.98	1.00±0.19

the validation patient cohort from Zurich, the resulting κ coefficients for the three formulae were 0.40, 0.38, and 0.27, respectively.

The eSCr model showed a slight improvement, however, it still overestimated the severity and incidence of AKI, with only 47% (n=391) of patients correctly categorized as KDIGO stage 1. Most of these patients (48%, n=402) were incorrectly categorized as KDIGO stage 1 when the measured KDIGO stage was 0. In our study cohort, the κ coefficient for the accuracy of eSCr model in predicting the KDIGO stages was 0.64, whereas the κ coefficient for the eSCr model was 0.55 in the Zurich validation cohort. The mean measured bSCr values for each age group (Table 2) were nearly identical to the predicted values estimated from the data-driven eSCr model. The mean bSCr values of Table 2 could be used to perform KDIGO classification, for the validation dataset the resulting κ coefficient is 0.54.

Although the eSCr model captures the trend of an increasing population average of bSCr with increasing age, it is still insufficient to explain the large variation between individual bSCr values. Also, the model containing age and TBW cannot sufficiently explain the population variability in measured bSCr.

Evaluation and Comparison of Mortality Rates

We calculated an MR of 4.1 deaths per 100 patients per year when no AKI was present. The MR of patients that are misclassified into higher KDIGO stages is in general higher than in correctly classified patients (Table 3). The misclassification of KDIGO stages showed similar outcomes on MRs in the Zurich validation cohort (Table 4).

Analysis of Missing bSCr Values

It could be argued that the 106 patients with missing bSCr values are likely a very different population of patients from those included in the analysis, and therefore, our results are not applicable to patients requiring bSCr estimates. To assess this issue, we compared the demographics and the SCr values measured upon admission to the intensive care unit, which was available for 102 of the 106 patients with missing bSCr values (Table 1). These patients were slightly younger and had a slightly higher mean SCr at admission (mean±SD: 1.0±0.4 versus 1.23±1.0, P=0.04). However, median SCr values at admission were not different (0.96 versus 0.98 mg/dl) and both cohorts had a similar long-term outcome and MR (*i.e.,* 5.1 deaths per 100 patients for the main cohort versus 5.9 deaths per 100 patients for the missing cohort).

Discussion

This study investigated the accuracy of bSCr estimation methods on AKI classification in cardiac surgery patients. First, we showed that inverting formulae to back-estimate bSCr is of very limited value and it does not seem surprising that back-estimating bSCr for a fixed GFR would lead to a lower estimated bSCr among older individuals using the MDRD and CKD-EPI formulae. Rather, this is entirely predictable according to the equations. Second, because a distinct bSCr is a cornerstone of an AKI diagnosis, the prediction capacity of back-estimated bSCr is of almost no value. Third, our data-driven eSCr model led to a somewhat better result, but does not change the need for real SCr measurements; in any case, a solid AKI diagnosis is needed. Last, we showed that between 80% and 90% of patients were misclassified into KDIGO stages based on estimated bSCr values.

Currently, a standard definition for estimating bSCr does not exist, leading to heterogeneity across research studies (23) and to misinterpretation of perturbed kidney function in hospitalized patients (24,25). Improved methods are clearly required to measure and/or estimate a baseline of kidney function (23,25). As Gaião stated in 2010: "We do not want to find ourselves in 2015 with everyone using RIFLE/AKIN, but having 30 more different definitions of baseline creatinine" (23). Unfortunately, all current AKI classification schemes (*i.e.,* RIFLE, Acute Kidney Injury Network, KDIGO) (4,5,26) rely on a bSCr value, and therefore, inaccurate bSCr estimations will affect AKI classification

Table 3. Contingency tables and mortality-rates for our Vienna patient cohort

Estimated AKI stages	MDRD Model (Cohen κ: 0.49)						CKD-EPI Model (Cohen κ: 0.46)				
Measured AKI stages	0	1	2	3	Sum		0	1	2	3	Sum
0	5650 (97.8) †3.5	992 (70.6) †8.0	98 (30.1) †14.0	7 (1.6) †21.0	6747 †4.1	0	5521 (97.9) †3.5	1081 (72.6) †7.8	136 (36.7) †15.9	9 (2.1) †29.5	6747 †4.1
1	123 (2.1) †5.2	391 (27.8) †8.7	169 (51.8) †16.9	25 (6.0) †26.8	708 †9.8	1	113 (2.0) †4.4	386 (25.9) †8.3	182 (49.1) †17.7	27 (6.3) †28.3	708 †9.8
2	6 (0.1) †6.4	22 (1.6) †5.7	57 (17.5) †12.6	31 (7.4) †37.3	116 †13.6	2	6 (0.1) †6.4	22 (1.5) †4.9	51 (13.8) †12.3	37 (8.6) †33.0	116 †13.6
3	0	0	2 (0.6)	356 (85.0) †23.3	358 †23.1	3	0	0	2 (0.5)	356 (83.0) †23.3	358 †23.1
Sum	5779 †3.6	1405 †8.1	326 †15.1	419 †24.2	7929 †5.1	Sum	5640 †3.5	1489 †7.8	371 †16.1	429 †24.4	7929 †5.1

Estimated AKI stages	PLTV Model (Cohen κ: 0.39)						eSCr Model (Cohen κ: 0.64)				
Measured AKI stages	0	1	2	3	Sum		0	1	2	3	Sum
0	5044 (98.8) †3.6	1532 (79.0) †5.7	156 (36.4) †11.2	15 (3.3) †27.3	6747 †4.1	0	6318 (96.2) †3.9	402 (48.4) †8.7	26 (15.9) †23.3	1 (0.3)	6747 †4.1
1	56 (1.1) †5.6	394 (20.3) †7.9	220 (51.3) †14.0	38 (8.3) †22.0	708 †9.8	1	235 (3.6) †7.9	391 (47.1) †9.7	74 (45.1) †18.7	8 (2.2) †24.0	708 †9.8
2	4 (0.1) †4.3	14 (0.7) †7.8	52 (12.1) †11.5	46 (10.1) †22.0	116 †13.6	2	11 (0.2) †8.7	36 (4.3) †7.8	61 (37.2) †19.9	8 (2.2) †19.2	116 †13.6
3	0	0	1 (0.2)	357 (78.3) †23.1	358 †23.1	3	0	1 (0.1)	3 (1.8) †4.8	354 (95.4) †23.5	358 †23.1
Sum	5104 †3.6	1940 †6.1	429 †12.6	456 †23.0	7929 †5.1	Sum	6564 †4.0	830 †9.1	164 †19.2	371 †23.3	7929 †5.1

Values are given as numbers (n), column percentages (%), mortality rates per 100 patient years (†), or Kidney Disease Improving Global Outcomes stages. MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; PLTV, Pittsburgh Linear Three Variables; eSCr, estimated serum creatinine.

Table 4. Contingency tables and mortality rates for the Zurich patient cohort

Estimated AKI stages	MDRD Model (Cohen κ: 0.40)						CKD-EPI Model (Cohen κ: 0.38)				
Measured AKI stages	0	1	2	3	Sum		0	1	2	3	Sum
0	2539 (99.7) †2.7	344 (84.3) †5.5	49 (63.6) †16.3	2 (2.2)	2934 †3.2	0	2507 (99.7) †2.6	372 (85.3) †5.8	53 (66.3) †17.7	2 (2.2)	2934 †3.2
1	7 (0.3)	64 (15.7) †7.0	24 (31.2) †18.3	3 (3.3) †53.2	98 †9.4	1	7 (0.3)	64 (14.7) †7.0	23 (28.8) †18.5	4 (4.3) †22.0	98 †9.4
2	0	0	4 (5.2)	0	4	2	0	0	4 (5.0)	0	4
3	0	0	0	87 (94.6) †39.4	87 †39.4	3	0	0	0	87 (93.5) †39.4	87 †39.4
Sum	2546 †2.7	408 †5.8	77 †16.5	92 †38.0	3123 †4.0	Sum	2514 †2.6	436 †6.0	80 †17.5	93 †37.1	3123 †4.0

Estimated AKI stages	PLTV Model (Cohen κ: 0.27)						eSCr Model (Cohen κ: 0.55)				
Measured AKI stages	0	1	2	3	Sum		0	1	2	3	Sum
0	2272 (100.0) †2.8	591 (90.8) †4.3	65 (64.4) †11.7	6 (6.1)	2934 †3.2	0	2729 (99.3) †3.0	185 (73.7) †6.5	20 (55.6) †9.2	0	2934 †3.2
1	0	60 (9.2) †5.4	33 (32.7) †15.6	5 (5.1) †26.8	98 †9.4	1	18 (0.7) †3.0	66 (26.3) †9.5	13 (36.1) †20.9	1 (1.1)	98 †9.4
2	0	0	3 (3.0)	1 (1.0)	4	2	0	0	3 (8.3)	1 (1.1)	4
3	0	0	0	87 (87.9) †39.4	87 †39.4	3	0	0	0	87 (97.8) †39.4	87 †39.4
Sum	2272 †2.8	651 †4.4	101 †12.9	99 †34.1	3123 †4.0	Sum	2747 †3.0	251 †7.4	36 †13.1	89 †38.2	3123 †4.0

Values are given as numbers (n), column percentages (%), mortality rates per 100 patient years (†), or Kidney Disease Improving Global Outcomes stages. MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; PLTV, Pittsburgh Linear Three Variables; eSCr, estimated serum creatinine.

and clinical care (23,27). Misclassified patients may be subjected to unnecessary treatment to prevent AKI progression, leading to side effects and increased therapy cost. Alternatively, a false-negative AKI diagnosis may lead to complacent treatment, disease progression, and eventually death. Therefore, the correct classification and diagnosis of AKI are extremely important.

Missing patient bSCr data and the necessity to diagnose AKI have provided motive to apply formulae to estimate bSCr. However, the incorrect estimation of bSCr using back-estimation methods is a known problem (6,11,28). The main cause of inaccuracies in estimates of bSCr is the assumption of a fixed GFR of 75 ml/min per 1.73 m^2, which obviously is an unjustified simplification considering the age dependence of GFR. Nevertheless, even after age-adjustment of the back-estimation formulae, the results did not improve. Unfortunately, many investigations have used an estimation of bSCr in up to 50% of their patients (11–15,29,30). As we and others have found (6,11,24), the estimated bSCr is inadequate when precise case adjudication is required, for example, in defining mild AKI stages (25). Indeed, the MDRD method has previously been shown to generate misleading results. For example, it can overestimate bSCr in young patients, which mostly leads to a false-negative AKI diagnosis (11), or can underestimate bSCr in older patients leading to a false-positive AKI diagnosis (17). Similarly, nearly 70% of our patients were >60 years (an age group that had not been tested previously) (7,19), and we could not accurately diagnose AKI stage using either the MDRD or CKD-EPI model, probably due to the fact that transformation estimations for those formulae were not made to define AKI stages.

The fact that patients misclassified into higher AKI stages with estimated bSCr also have a higher MR than correctly classified patients may be explained by the circumstance that these patients have a higher measured bSCr than predicted for their age and gender. Small increases in measured bSCr have been shown to be associated with a profound increase in mortality (22).

Additionally, the bSCr values we measured in this study showed a high degree of variation at all ages. Because the current models used to estimate bSCr values explain only a very limited amount of variation for any given age group, they have little validity for estimating bSCr as a replacement for the measured values. Therefore, the use of these formulae to classify a state of disease in clinical investigations (11–15,29,30) induces an important bias, and results should be interpreted very carefully.

There were some limitations to this study. First, the patients included in this study were all admitted for cardiac surgery, and thus, they differ from the general population, especially regarding their risk for preoperative kidney dysfunction. We may have further selected for patients with preoperative kidney dysfunction by excluding those who had undergone transplant surgery, who were scheduled for insertion of a cardiac assist device, who had an operation on the aorta, or were thrombendarterectomy of the pulmonary artery and congenital heart disease patients. Despite this, preoperative morbidity concomitant with renal function impairment is a general health care problem, and thus, the cohorts in the present study are somewhat representative of the wider patient population. Second, the exclusion criteria have probably been too generous even if the number of excluded patients in the different subgroups is low. Third, while we questioned whether it is appropriate to use formulae to estimate bSCr without additional information on muscle mass, we do not think that our cohort has a muscle mass above normal, as suggested by the overall higher measured creatinine than estimated by the PLTV formula at all ages. Fourth, we could not study the effect of race because nonwhites were not present in these cohorts.

The degree to which patients with and without missing bSCr resemble each other is fundamental to the question of whether the study results are valid. In our cohort, patients with missing bSCr had a similar long-term outcome but were more often in KDIGO stages 1 and 3 when SCr level at ICU admission was used to determine AKI stages.

In conclusion, estimation of SCr values using available formulae that have been designed to calculate eGFR is inaccurate and cannot be used to accurately predict AKI according to KDIGO stages. Generally, this inaccuracy results from the assumption of a fixed baseline GFR of 75 ml/min per 1.73 m^2. Because kidney function changes with age, using a constant GFR does not result in a proper description of the association of all three variables, SCr, age, and GFR, and the resulting inverse formulae wrongly predict decreasing SCr values with increasing age. Although in our data-driven eSCr model the relationship between bSCr and age is included in a more accurate way, and the agreement between AKI stage of measured and estimated bSCr is increased, it still overestimated AKI severity according to KDIGO stage and mortality. The high variability in SCr values even between patients of the same age and sex, as seen in Figure 2, makes it impossible to accurately determine the bSCr of an individual patient using these predictors. Therefore, only measured bSCr should be used to predict AKI.

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Disclosures

None.

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