JACC: ADVANCES VOL. 3, NO. 11, 2024

ORIGINAL RESEARCH

Cardiac Surgery-Specific Subtle Perioperative Serum Creatinine Change in Defining Acute Kidney Injury After Coronary Surgery

Juntong Zeng, MD, PhD,[a,b,c,*] Xiaoting Su, PhD,[a,b,c,*] Shen Lin, MD, PhD,[a,b,c,d,e] Zhongchen Li, MD,[a,b,c] Yan Zhao, MD,[a,b,d,e] Zhe Zheng, MD, PhD[a,b,c,d,e]

ABSTRACT

BACKGROUND Cardiac surgery-associated acute kidney injury (CSA-AKI) is prevalent and increasingly reported. Its diagnosis traditionally follows the Kidney Disease: Improving Global Outcomes (KDIGO) AKI criteria. However, little evidence supports its appropriateness for cardiac surgery patients, particularly regarding the subtle serum creatinine change (ΔSCr) that defines mild AKI.

OBJECTIVES The purpose of the study was to investigate the ΔSCr threshold specific to CSA-AKI and compare its impact on CSA-AKI incidence and prognosis with the KDIGO AKI criteria threshold.

METHODS A 10-year coronary surgery cohort with serial perioperative SCr measurements was retrospectively analyzed. The relationship and prognostically significant threshold of 48-hour absolute ΔSCr with 30-day mortality were explored using multivariate restricted cubic spline analysis and receiver-operating characteristic curve analysis. AKI incidence and prognostic value were compared between adopting the KDIGO or new thresholds.

RESULTS Among 37,706 patients, 20,290 (53.8%) developed KDIGO-defined AKI. For stage-1 AKI (18,835, 49.9%), the majority (75.2%) were solely attributed to the KDIGO absolute criterion (48-hour ΔSCr ≥0.3 mg/dL). The 48-hour ΔSCr threshold associated with an adjusted odds ratio ≥1.00 for 30-day mortality was 0.549 mg/dL. A similar threshold (0.553 mg/dL) was also identified based on the Youden index cutoff. Applying the 0.55 mg/dL threshold to define stage 1 CSA-AKI, the overall and stage-1 CSA-AKI incidence decreased to 21.0% and 17.2%, with 27.7% of the stage-1 CSA-AKI solely attributed to the new criterion. The prognostic value for AKI defined by this new threshold was significantly higher than the KDIGO criteria.

CONCLUSIONS A cardiac surgery-specific ΔSCr threshold in defining AKI was notably higher compared with the current general AKI definition. (JACC Adv. 2024;3:101326) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]National Clinical Research Center of Cardiovascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases, Beijing, People's Republic of China; [b]State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Beijing, People's Republic of China; [c]Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China; [d]Department of Cardiovascular Surgery, Fuwai Hospital, National Center for Cardiovascular Diseases, Beijing, People's Republic of China; and the [e]Key Laboratory of Coronary Heart Disease Risk Prediction and Precision Therapy, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China
*Drs Zeng and Su contributed equally to this work.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 21, 2024; revised manuscript received September 2, 2024, accepted September 4, 2024.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101326

ABBREVIATIONS AND ACRONYMS

ΔSCr = serum creatinine change

AKI = acute kidney injury

AUC = area under the receiver-operating characteristic curve

CABG = coronary artery bypass grafting

CSA-AKI = cardiac surgery-associated acute kidney injury

eGFR = estimated glomerular filtration rate

EMR = electronic medical record

KDIGO = Kidney Disease: Improving Global Outcomes

RCS = restricted cubic spline

ROC = receiver operating characteristic

SCr = serum creatinine

Acute kidney injury (AKI) following cardiac surgery is highly prevalent and associated with increasing mortality, prolonged hospital stays, and an elevated risk of progression to chronic kidney disease.[1-3] The incidence rate of cardiac surgery-associated AKI (CSA-AKI) could be estimated to be as high as 40% to 50%, depending on the patient population and diagnostic criteria.[1,2,4] While moderate-to-severe CSA-AKI is well recognized for its devastating impact on patient outcomes, it occurs much less frequently compared to mild AKI characterized by smaller elevation of serum creatinine (SCr).[4-6] Studies indicated that these smaller changes in SCr (ΔSCr) also reflected underlying renal injury and were associated with poorer outcomes.[3,7,8] Therefore, the current Kidney Disease: Improving Global Outcomes (KDIGO) AKI definition considers a minimal SCr elevation, eg, ΔSCr ≥0.3 mg/dL within 48-hour intervals, sufficient to diagnose stage-1 AKI.[9]

However, applying this absolute ΔSCr criterion of the KDIGO AKI definition, which is used primarily in general patient populations, to diagnose CSA-AKI in cardiac surgery patients could be problematic. On one hand, there is limited evidence from cardiac surgery studies supporting the appropriateness of using the current KDIGO threshold of ΔSCr ≥0.3 mg/dL over 48 hours in defining stage-1 CSA-AKI. It is well recognized that CSA-AKI is a heterogeneous disease entity resulting from an intricate interplay of various pathophysiological mechanisms, patient-related risk factors, and procedural impacts, many of which are highly specific to the unique nature of cardiac surgery.[1,2,10-12] Therefore, it raises questions about this one-size-fits-all approach of extending the ΔSCr threshold from the general AKI definition to cardiac surgery patients. On the other hand, since the introduction of consensus definitions and the adoption of electronic medical records (EMRs) with more efficient test result monitoring and disease coding, there has been a dramatic increase in the reported incidence of AKI in both surgery and nonsurgery patient populations.[13-15] Applying such nonspecific and, if overly lenient, diagnostic criteria in the current EMR-based practice could potentially lead to over-diagnosing many less clinically relevant AKI, diverging clinical care and resource allocations.

Therefore, the aim of this study is to explore and identify the cardiac surgery-specific minimal 48-hour ΔSCr threshold level in defining the stage-1 CSA-AKI and compare its impact on the overall CSA-AKI incidence and prognostic value with that based on the KDIGO-defined threshold.

METHODS

STUDY PARTICIPANTS. A consecutive cohort of patients undergoing coronary artery bypass grafting surgery (CABG) from 2013 to 2022 at Fuwai Hospital, National Center for Cardiovascular Disease (Beijing, China) was retrospectively included. Patients were managed following practice guidelines, and all procedures were performed using standard CABG techniques (Supplemental Method 1). The inclusion criteria are adult CABG cases performed between January 1, 2013, and October 1, 2022. Patients without either at least one baseline SCr measurement before surgery or serial SCr measurements (≥2 measurements) during or after surgery were excluded. For the main analysis, patients without the 30-day outcome data were also excluded. Patients lacking outcome data beyond 30 days were excluded for the longer-term secondary analysis. This study complied with the Declaration of Helsinki and was approved by the institutional review board at Fuwai Hospital. Informed consent requirement was waived by the institutional review board as all patient data were collected retrospectively and all case records were de-identified before analysis. Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (Supplemental Table 1).[16]

DATA COLLECTION AND PREPARATION. Data on demographic characteristics, medical history, laboratory tests, surgical procedures, and treatment details were extracted from the EMR system and further supplemented with manual inspection and entry through medical record review by experienced clinical staffs. The accuracy and completeness of these data were verified and ensured through multiple procedures described previously.[17-21] Data variables with missing values were imputed with a random forest-based algorithm.[22] The missingness and imputation consideration were summarized in Supplemental Method 2.

AKI DEFINITION AND OUTCOMES. The diagnosis of AKI was adjudicated following the current KDIGO AKI guidelines based on the comprehensive records of perioperative SCr measurements during the hospital stay (from patient admission to day 7 after surgery). In summary, AKI stages were defined as follows: 1) stage-1: an absolute increase in SCr ≥0.3 mg/dL within 48 hours (the absolute criterion) or a relative increase in SCr ≥150% to 200% of the baseline (the

ratio criterion); 2) stage-2: a relative increase in SCr ≥200% to 300% of the baseline; and 3) stage-3: a relative increase in SCr ≥300% of the baseline, or an increase in SCr to ≥4.0 mg/dL, or initiation of renal replacement therapy, respectively.[9] Among patients adjudicated as stage-1 AKI, they were further categorized based on the specific criteria met: the absolute criterion only, the ratio criterion only, or the dual criteria (meeting both the absolute and ratio criteria) AKI. The detailed method for comprehensively capturing KDIGO-defined AKI in our current study was described in Supplemental Method 3.

The primary outcome of this study was 30-day all-cause mortality. Secondary outcomes included 1-year all-cause mortality and/or dialysis, 6-month, 1-year, 3-year, and 5-year all-cause mortality during the follow-up. Patients were followed up through routine outpatient visits or telephone interviews conducted by trained research nurses as part of standard institutional protocols. In case of adverse events reported during the follow-up, related medical records were required as supportive documents for further adjudication.

STATISTICAL ANALYSIS. Data are presented as mean ± SD or median IQR according to the distribution pattern for continuous variables and percentages for categorical variables. The baseline characteristic differences between groups were compared using either the one-way analysis of variance or Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, where appropriate.

The relationship between the perioperative maximal ΔSCr (ΔSCr_{max}) within 48-hour intervals and 30-day mortality was analyzed using a restricted cubic spline (RCS) in a logistic regression model with multivariate adjustment for patient characteristics and operative variables, including age, sex, body mass index, hyperlipidemia, preoperative left ventricular ejection fraction, preoperative estimated glomerular filtration rate (eGFR),[23] coronary lesion counts, prior cardiac surgery history, combined surgery, nonelective surgery, and on-pump surgery. From the fitted model, we identified the ΔSCr threshold level corresponding to an adjusted odds ratio (OR) estimate of ≥1.00, along with the 95% CI for this specific ΔSCr threshold. A secondary method to identify this specific ΔSCr threshold was also performed through the receiver-operating characteristic (ROC) curve analysis. The ROC curve predicted the 30-day mortality based on the maximal 48-hour ΔSCr level, and the ΔSCr threshold was determined by the Youden index cutoff point.

Using the newly identified 48-hour ΔSCr threshold, patients initially classified as stage-1 KDIGO AKI were reclassified. Multivariate-adjusted logistic regressions were conducted to examine the prognostic effects of different 48-hour ΔSCr threshold levels on 30-day mortality, 1-year all-cause death, and/or dialysis, as well as 5-year all-cause death, as the underlying assumption of proportional hazards in the Cox regression for the 5-year survival outcome was not met. The multivariate performance of meeting stage-1 CSA-AKI criteria based on either the KDIGO criteria or the criteria adopting the new threshold described above in predicting all-cause death at various follow-up time points was also evaluated by the area under the ROC (AUC), with the Delong test for AUC comparison. The sample size was determined using the method recommended by Riley et al.[24] with an outcome rate of 0.8%, resulting in a sample size of 9,940 with 80 events, supporting the sample size adequacy of the current study (Supplemental Methods 4). All comparisons were two-sided, with statistical significance defined as $P < 0.05$, without adjustment for multiple comparisons.

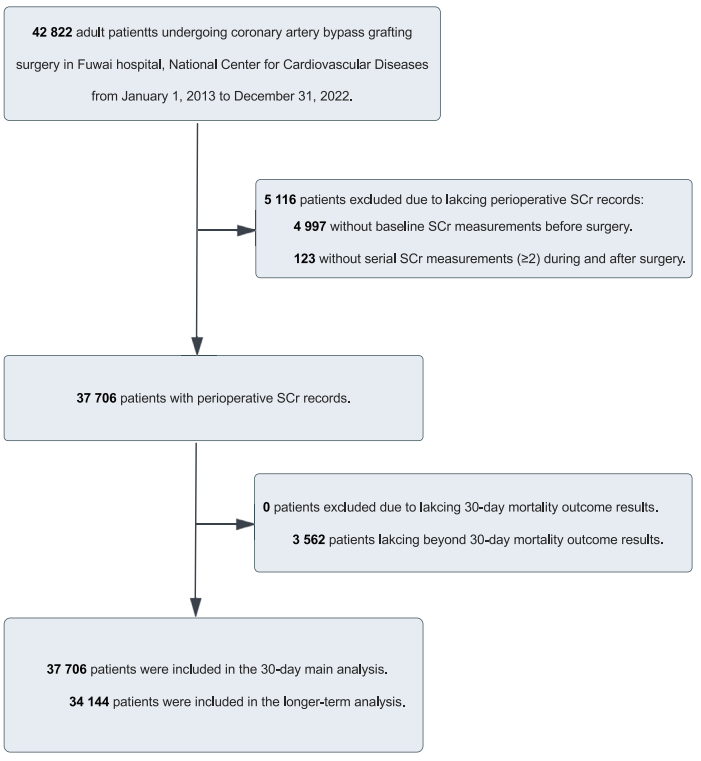
To further support our overall findings, we conducted a series of sensitivity analyses. These included: 1) inclusion of fluid balance, a metric previously reported to reflect the fluid status over a period of time[25] as a covariate in the multivariate adjusted RCS analysis; 2) exploration of the 48-hour ΔSCr_{max} threshold in patients with normal baseline kidney function as defined by preoperative eGFR ≥60 mL/min/1.73 m^2; 3) analysis of the 48-hour ΔSCr_{max} threshold in subgroups of on-pump CABG and off-pump CABG, respectively; and 4) applying RCS processing for other continuous covariables that also demonstrated nonlinear association with 30-day mortality.

Statistical analysis and plotting were conducted with SAS version 9.4 (SAS Institute) and R version 4.0.3 (R Foundation for Statistical Computing).

RESULTS

STUDY POPULATION. Between January 1, 2013, and December 31, 2022, a total of 42,822 adult patients underwent CABG at Fuwai Hospital. After excluding 5,116 patients without perioperative SCr measurements, 37,706 patients were included in the main analysis, all with available 30-day survival outcome data. With beyond 30-day outcome data, 34,144 (90.6%) patients were included in the longer-term analysis, with a mean follow-up duration of 3.0-2.4 years and the longest follow-up duration up to 8.5 years. (**Figure 1**).

FIGURE 1 Flowchart of the Study Cohort



The flowchart depicting the included and excluded patient population in the current study. SCr = serum creatinine.

Among the 37,706 patients, the median age was 62.0 (IQR: 55.0-67.0) years old, and 8,524 (22.6%) were female. **Table 1** summarizes baseline clinical characteristics and operative information for the patients. The median of preoperative eGFR was 90.3 (IQR: 76.9-99.3) ml/min/1.73 m^2. Of cases, 77.0% were isolated CABG and 59.8% were on-pump procedure. Based on the KDIGO AKI criteria, 20,290 (53.8%) patients developed AKI, with the incidence of 49.9% (18,835) for stage-1 AKI and 3.9% for ≥ stage-2 AKI.

FORTY-EIGHT-HOUR ΔSCr_{max} LEVELS AND ITS ASSOCIATION WITH 30-DAY MORTALITY. Among the main analysis cohort, the median value of the 48-hour ΔSCr_{max} following CABG was 0.31 mg/dL (IQR: 0.22-0.44 mg/dL), 19,803 (52.5%) patients' 48-hour $\Delta SCr_{max} \geq$ 0.30 mg/dL (ie, the KDIGO-defined stage-1 AKI absolute criterion threshold). **Table 2** presented the multivariate association of the 48-hour ΔSCr_{max} level with 30-day mortality, adjusted for relevant covariates. **Figure 2** illustrates the distribution of the 48-hour ΔSCr_{max}, which revealed a J-shaped relationship with 30-day mortality after multivariate adjustments. The lowest 30-day mortality risk was observed around 0.20 to 0.30 mg/dL of the 48-hour ΔSCr_{max} levels. Overall, an increased 30-day mortality was associated with higher 48-hour ΔSCr_{max} levels (adjusted OR for each 1-unit increase of the 48-hour ΔSCr_{max} level: 3.15; 95% CI: 2.71-3.67). The distribution and adjusted relationship between the perioperative 48-hour ΔSCr_{max} and the composite outcome of 1-year death and/or dialysis were provided in the Supplemental Figure 1.

Figure 3A presents the multivariate-adjusted OR curves from RCS analysis modeling the relationship between the 48-hour ΔSCr_{max} levels and 30-day mortality, which confirmed the nonlinear relationship ($P < 0.001$). The lowest level of the 48-hour ΔSCr_{max} associated with an adjusted OR of more than 1.0 for 30-day mortality was 0.549 mg/dL (95% CI: 0.426-0.925), a level 1.83 times that of the current KDIGO threshold (0.3 mg/dL). **Figure 3B** depicts the ROC curve predicting the 30-day mortality based on the 48-hour ΔSCr_{max} level (AUC: 0.785; 95% CI: 0.752-0.818). A similar threshold of 0.553 mg/dL was identified based on the Youden index cutoff from the ROC curve. The multivariate-adjusted OR curves modeling the relationship between the perioperative 48-hour ΔSCr_{max} and the composite outcome of 1-year death and/or dialysis are provided in the Supplemental Figure 2.

RECLASSIFICATION OF CSA-AKI BASED ON THE NEW THRESHOLD. Figure 4 illustrates the incidence and staging composition of AKI defined by incorporating either the absolute criterion of the KDIGO threshold (0.3 mg/dL) or the newly identified threshold (0.55 mg/dL) into the overall CSA-AKI diagnostic criteria. Among the 18,835 (49.9%) KDIGO-threshold-based stage-1 AKI cases, 75.2% were diagnosed solely attributed to the absolute criterion of the 48-hour ΔSCr ≥0.3 mg/dL after CABG. However, applying the new threshold of 0.55 mg/dL to define the stage-1 CSA-AKI, 65.5% of these previously KDIGO absolute criterion-defined stage-1 AKI were reclassified as not having CSA-AKI. Among the previously KDIGO dual criteria-defined stage-1 AKI cases, 46.9% (1,980) were reclassified as only meeting the ratio criterion. With the new threshold, the overall incidence of CSA-AKI decreased to 21.0% (7,930), and the stage-1 CSA-AKI incidence rate was reduced to 17.2% (6,475). Among this newly-defined stage-1 CSA-AKI, only 27.7% were diagnosed solely based on this new absolute 48-hour ΔSCr threshold criterion, 37.6% were attributed to the ratio criterion, and 34.7% met the dual criteria.

TABLE 1 Baseline Characteristics

	Overall (N = 37,706)	No KDIGO AKI (n = 17,416)	KDIGO Stage-1 AKI (n = 18,835)	≥ KDIGO Stage-2 AKI (n = 1,455)	*P* Value[a]
Age, y	62.0 (55.0-67.0)	60.0 (54.0-66.0)	63.0 (56.0-68.0)	65.0 (58.0-70.0)	<0.001
Female	8,524 (22 6)	4105 (23.6)	3,906 (20.7)	510 (35.1)	<0.001
BMI, kg/m^2	25.4 (23.5-27.5)	25.5 (23.5-27.6)	25.4 (23.4-27.5)	25.1 (22.9-27.3)	<0.001
Smoking	20,582 (54.6)	9,480 (54.4)	10,412 (55.3)	690 (47.4)	<0.001
Hypertension	24,313 (64.5)	10,740 (61.7)	12,527 (66 5)	1,046 (71.9)	<0.001
Hyperlipidemia	25,608 (67.9)	11,937 (68.5)	12,863 (68.3)	805 (55.5)	<0.001
Diabetes status					<0.001
Nondiabetes	21,563 (57.2)	10,511 (60.4)	10,247 (54.4)	805 (55.3)	
Noninsulin-treated diabetes	12,455 (33.0)	5,548 (31.9)	6,449 (34.2)	458 (31.5)	
Insulin-treated diabetes	3,688 (9.8)	1,357 (7.8)	2,139 (11.4)	192 (13.2)	
CAD types					<0.001
Stable CAD	26,387 (70.0)	12,553 (72.1)	12,815 (68.0)	1,019 (70.0)	
Unstable angina	9,663 (25.6)	4,151 (23.8)	5,161 (27.4)	351 (24.1)	
Acute MI	1,656 (4.4)	712 (4.1)	859 (4.6)	85 (5.8)	
CCS Angina Class					<0.001
No symptoms	6,385 (169)	2,427 (13.9)	3,683 (19.6)	275 (18.9)	
I	3,728 (9.9)	1,730 (9.9)	1784 (9.5)	214 (14.7)	
II	15,085 (40.0)	7,309 (42.0)	7,256 (38.5)	520 (35.7)	
III	10,454 (27.7)	4,929 (28.3)	5,176 (27.5)	349 (24.0)	
IV	2054 (5.4)	1,021 (5.9)	936 (5.0)	97 (6.7)	
CHF	737 (2.0)	265 (1.5)	410 (2.2)	62 (4.3)	<0.001
NYHA functional class					<0.001
I	3,638 (9.6)	1,815 (10.4)	1,680 (8.9)	143 (9.8)	
II	21,652 (57.4)	10,087 (57.9)	10,860 (57.7)	705 (48.5)	
III	11,652 (30.9)	5,233 (30.0)	5,900 (31.3)	519 (35.7)	
IV	764 (2.0)	281 (1.6)	395 (2.1)	83 (6.0)	
Preoperative LVEF	61.0 (57.0-65.0)	62.0 (58.0-65.0)	61.0 (57.0-65.0)	60.0 (54.0-64.0)	<0.001
Preoperative eGFR, mL/min/1.73 m^2	90.3 (76.9-99.3)	94.5 (83.3-101.5)	85.9 (72.5-96.7)	80.8 (64.0-94.8)	<0.001
CKD	710 (1.9)	96 (0.6)	478 (2.5)	136 (9.3)	<0.001
PAD	6,947 (18.4)	2,896 (16.6)	3,705 (19.7)	346 (23.8)	<0.001
AF	1707 (4.5)	500 (2.9)	997 (5.3)	210 (14.4)	<0.001
COPD	1,256 (3.3)	530 (3.0)	653 (3.5)	73 (5.0)	<0.001
Prior MI	9,107 (24.2)	3,983 (22.9)	4,742 (25.2)	382 (26.3)	<0.001
Prior CVE	5,346 (14.2)	2,273 (13.1)	2,820 (15.0)	253 (17.4)	<0.001
Prior PCI	2,885 (7.7)	1,254 (7.2)	1,512 (8.0)	119 (8.2)	0.009
Prior cardiac surgery	1,560 (4.1)	586 (3.4)	823 (4.4)	151 (10.4)	<0.001
Left main disease	8,051 (21.4)	3,798 (21.8)	4,001 (21.2)	252 (17.3)	<0.001
Triple vessel disease	29,365 (77.9)	13,566 (77.9)	14,875 (79.0)	924 (63.5)	<0.001
Isoated CABG	29,037 (77.0)	14,194 (81.5)	14,162 (75.2)	681 (46.8)	<0.001
Nonelective surgery	914 (2.4)	319 (1.8)	442 (2.3)	153 (10.5)	<0.001
On-pump surgery	22,552 (59.8)	9,445 (54.2)	11,944 (63.4)	1,163 (79.9)	<0.001
Bypass duration, min	78.0 (0.0-118.0)	64.0 (0.0-106.0)	86.0 (0.0-124.0)	122.0 (73.0-185.0)	<0.001
Clamp duration, min	52.0 (0.0-84.0)	41.0 (0.0-75.0)	59.0 (0.0-89.0)	83.0 (45.0-122.0)	<0.001
Number of grafts	3.0 (2.0-4.0)	3.0 (1.0-4.0)	3.0 (3.0-4.0)	3.0 (2.0-3.0)	<0.001
LIMA graft use	34,077 (90.4)	15,992 (91.8)	16,901 (89.7)	1,184 (81.4)	<0.001
Lesion count	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (3.0-4.0)	3.0 (2.0-4.0)	<0.001
Baseline serum creatinine, mg/dL	0.9 (0.8-1.0)	0.9 (0.8-1.0)	1.0 (0.8-1.1)	1.0 (0.8-1.2)	<0.001
30-d mortality	297 (0.8)	38 (0.2)	83 (0.4)	176 (12.1)	<0.001
1-y dialysis and/or death	728 (2.1)	185 (1.2)	349 (2.1)	194 (14.9)	<0.001

Values are median (IQR) or n (%). [a]The *P* value represented the comparison between the three groups.

AF = atrial fibrillation; AKI = acute kidney injury; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CHF = congestion heart failure; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; CVE = cerebrovascular events; eGFR = estimated glomerular filtration rate; IQR = interquartile range; KDIGO = Kidney Disease: Improving Global Outcomes; LIMA = left internal mammary artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PAD = peripheral artery disease; PCI = percutaneous coronary intervention.

TABLE 2 Multivariate Association of Perioperative 48-H ΔSCr_{max} Levels and Covariates With Short- and Long-Term Outcomes

	Adjusted Effect Sizes OR (95% CI)	*P* Value
30-d mortality[a]		
Perioperative 48-h SCr_{max} Level		
<0.3 mg/dL	(Reference)	(Reference)
0.3-0.5 mg/dL	1.275 (0.859-1.891)	0.284
≥0.5 mg/dL	6.253 (4.446-8.794)	<0.001
Age (+ΔSD)	1.388 (1.214-1.586)	<0.001
Female	1.098 (0.839-1.438)	0.496
BMI (+ΔSD)	0.841 (0.745-0.949)	0.005
Hyperlipidemia	1.140 (0.890-1.461)	0.300
Preoperative LVEF (+ΔSD)	0.733 (0.661-0.812)	<0.001
Preoperative eGFR (+ΔSD)	0.929 (0.831-1.039)	0.196
Coronary lesion counts (+ΔSD)	0.899 (0.794-1.019)	0.096
Prior cardiac surgery history	2.504 (1.775-3.533)	<0.001
Combined surgery	1.826 (1.379-2.417)	<0.001
Nonelective surgery	3.625 (2.517-5.220)	<0.001
On-pump surgery	1.840 (1.328-2.550)	<0.001
1-y death and/or dialysis[a]		
Perioperative 48-h ΔSCr_{max} level		
<0.3 mg/dL	(Reference)	(Reference)
0.3-0.5 mg/dL	1.205 (0.984-1.475)	0.072
≥0.5 mg/dL	3.374 (2.773-4.106)	<0.001
5-y mortality[b]		
Perioperative 48-h ΔSCr_{max} Level		
<0.3 mg/dL	(Reference)	(Reference)
0.3-0.5 mg/dL	1.078 (0.943-1.232)	0.281
≥0.5 mg/dL	2.377 (2.070-2.729)	<0.001

[a]For both the 30-d mortality and the composite outcome of 1-y death and/or dialysis, the above covariates (n = 11) were included in the multivariate analysis. [b]For the 5-y mortality, in addition to the above covariates (n = 11), five additional covariates of hypertension, smoking, diabetes status, coronary artery disease type, and the number of grafts were also included in the model.

AKI = acute kidney injury; BMI = body mass index; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; OR = odds ratio; SCr = serum creatinine.

PROGNOSTIC VALUE OF DIFFERENT 48-HOUR ΔSCr THRESHOLDS AND THE CORRESPONDING STAGE-1 AKI CRITERIA. From the multivariate-adjusted models, the prognostic effects of different 48-hour ΔSCr_{max} levels were assessed (**Figures 5A to 5C**). Considering the 48-hour ΔSCr_{max} level <0.3 mg/dL as a reference, only the 48-hour ΔSCr_{max} level ≥0.5 mg/dL was significantly associated with increased 30-day mortality (adjusted OR: 6.25; 95% CI: 4.45-8.79), 1-year death and/or dialysis (adjusted OR: 3.37; 95% CI: 2.77-4.11) and 5-year all-cause mortality (adjusted OR: 2.38; 95% CI: 2.07-2.73). **Table 2** and Supplemental Tables 2 and 3 present the above multivariate association of the 48-hour ΔSCr_{max} level stratification, along with pertinent covariates, with long-term outcomes.

The predictive value of meeting stage-1 AKI criteria adopting either the KDIGO or new threshold was also assessed and compared (**Figure 5D**, **Table 3**). In predicting 30-day mortality, the AUC of the new threshold-adopted criteria (AUC: 0.757; 95% CI: 0.732-0.783) was significantly higher than that of the KDIGO criteria (AUC: 0.662; 95% CI: 0.642-0.682; $P < 0.001$). Similar significantly better predictive performances were also observed in predicting 6-month, 1-year, 3-year, and 5-year all-cause death ($P < 0.001$ for all). **Figure 5E** showed the Kaplan-Meier curve comparison for long-term all-cause death (up to 5 years) based on whether or not meeting the stage-1 AKI criteria that adopted these two thresholds, respectively.

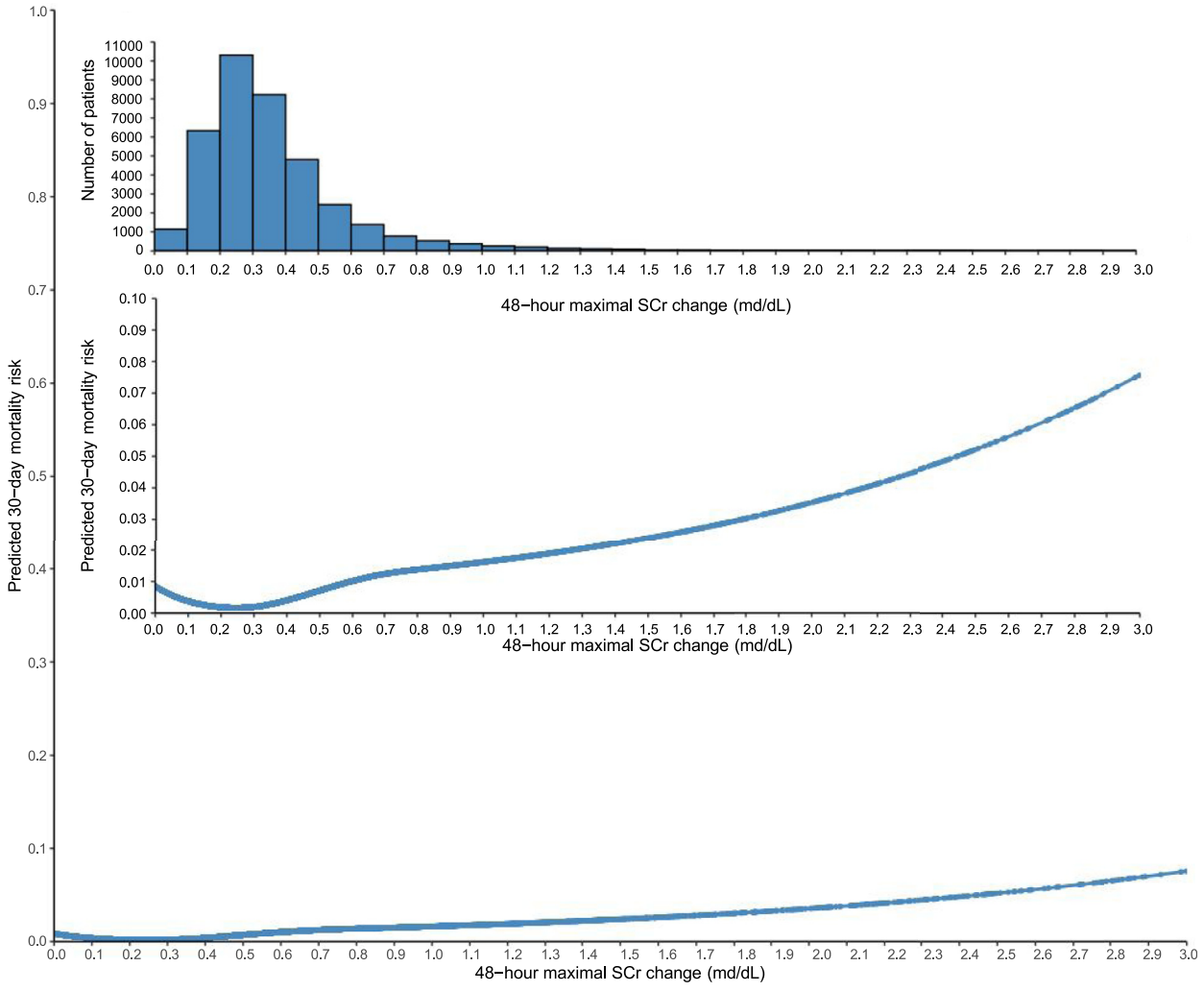
SENSITIVITY ANALYSIS. After including fluid balance as a covariate in the multivariate adjusted RCS analysis, the lowest value of the 48-hour ΔSCr_{max} threshold associated with an adjusted OR of greater than 1.0 for 30-day mortality was 0.533 mg/dL (Supplemental Figure 3), demonstrating overall similar findings to the primary analysis. When the analysis was restricted to patients with normal preoperative renal function, the identified 48-hour ΔSCr_{max} thresholds from the RCS analysis and ROC curve analysis were 0.498 mg/dL and 0.563 mg/dL, respectively. (Supplemental Figure 4). In the on-pump surgery population, the thresholds identified were 0.628 mg/dL from the RCS analysis and 0.677 mg/dL from the ROC curve analysis (Supplemental Figure 5). In the off-pump subgroup, the values were 0.480 mg/dL from RCS analysis and 0.302 mg/dL from ROC curve analysis (Supplemental Figure 6). The model including RCS for both the 48-hour ΔSCr_{max} and other covariables that also showed a nonlinear relationship with 30-day mortality also demonstrated a similar threshold of 0.551 mg/dL.

DISCUSSION

In this large-scale, consecutive cohort study, we investigated the relationship between the perioperative ΔSCr over 48-hour intervals following CABG and short- and long-term prognosis in a contemporary CABG patient population. The identified threshold of 48-hour ΔSCr associated with increased 30-day mortality was approximately 0.55 mg/dL, a level 1.83 times that of the current KDIGO stage-1 AKI threshold (0.3 mg/dL). Applying this new threshold to re-define stage-1 CSA-AKI resulted in a large decrease in both the overall and stage-1 AKI incidence, as well as a more balanced composition of different stage-1 AKI subtypes based on specific criteria components met. The prognostic value of meeting the stage-1 AKI criteria and adopting the new threshold was significantly higher than that of the KDIGO threshold (**Central Illustration**).

The findings of the current study are generally in line with prior evidence and provide additional

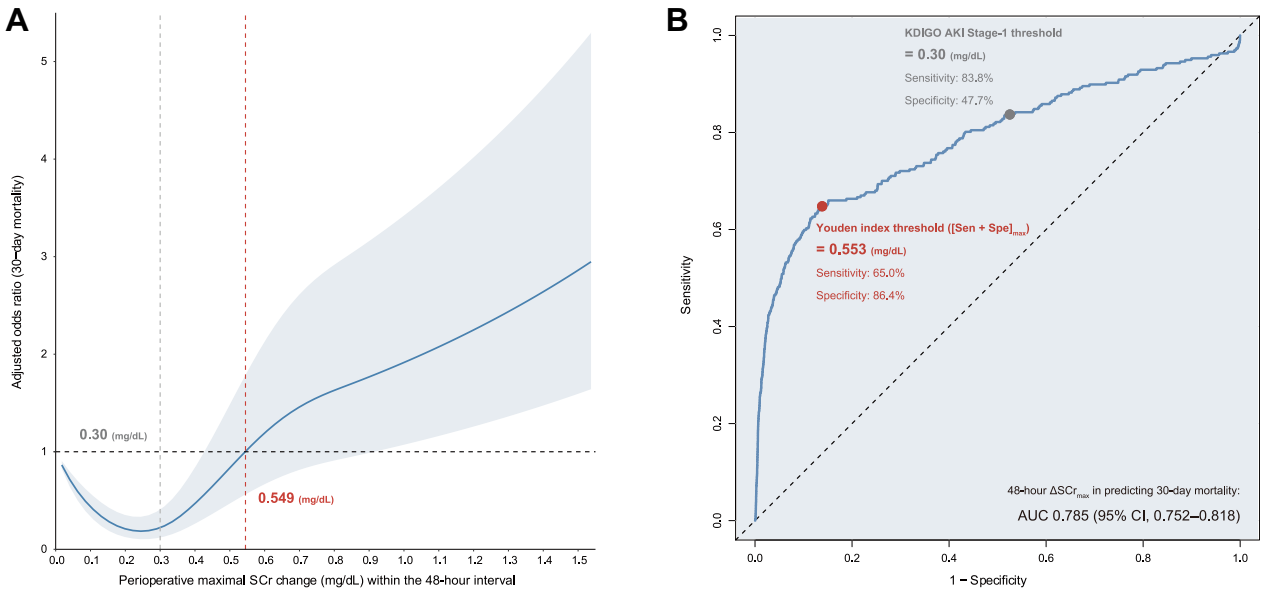
FIGURE 2 Perioperative 48-Hour ΔSCr_{max} and 30-Day Mortality



The distribution of the perioperative 48-hour ΔSCr_{max} and its association with 30-day mortality in the current study cohort. The predicted 30-day mortality was derived from the multivariate adjusted logistic regression between the 30-day mortality and 48-hour ΔSCr_{max}. SCr = serum creatinine.

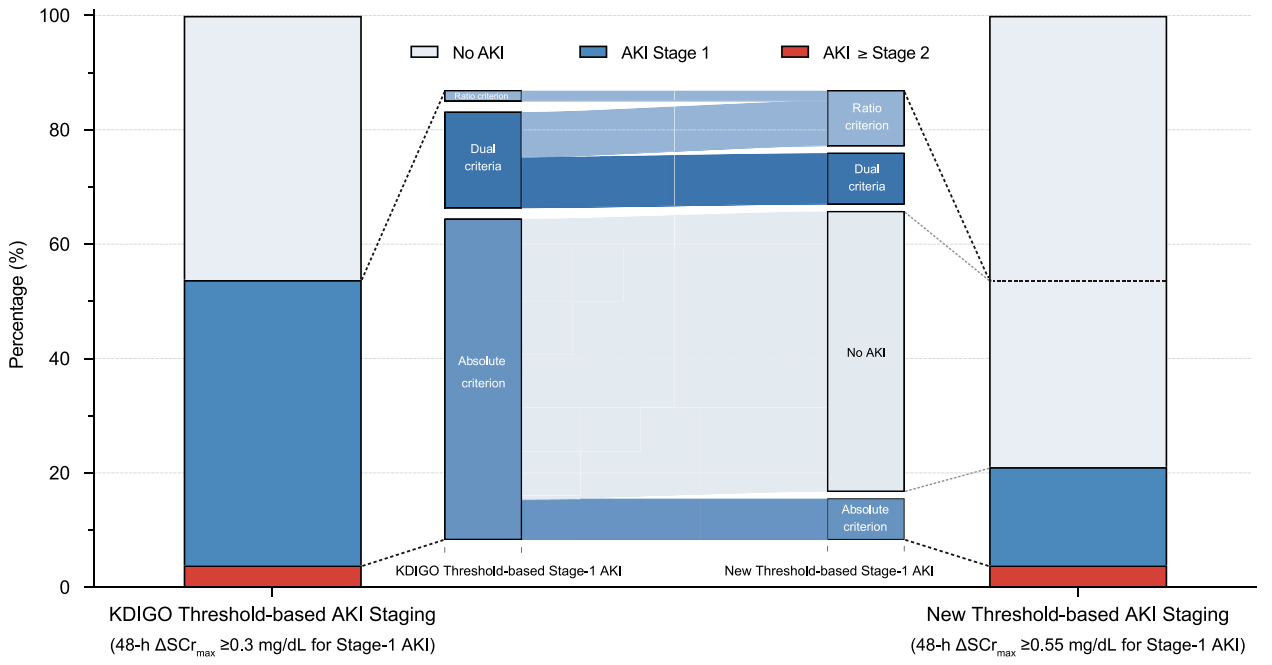
insights.[26,27] In one previous study investigating the prognostic impact of relatively subtle ΔSCr following cardiothoracic surgery, Lassnigg et al[26] explored the relationship between the 48-hour ΔSCr levels and 30-day mortality and identified a similar J-shaped relationship. Notably, they considered an increase of 48-hour ΔSCr ≥0.5 mg/dL as the threshold for a particularly substantial increase in 30-day mortality. Furthermore, when compared with the reference group (48-hour ΔSCr change of −0.3-0.0 mg/dL) that exhibited the lowest 30-day mortality, they found that any increase in 48-hour ΔSCr was associated with increased 30-day mortality. However, regarding this latter finding, we challenge its inadequate granularity and specificity. On one hand, the discretization into a range spanning from 0 to 0.5 was relatively broad, making it unclear which specific ranges or cut-offs were potentially driving this increase in 30-day mortality. On the other hand, the cohort represented a heterogeneous mix of cardiothoracic surgery types (both general cardiac surgery and aorta surgery) with vastly different operative risk and dates back 20 years. Therefore, the identified range of 48-hour ΔSCr might not reflect either the current practice or the widely varying surgery types. Furthermore, in contrast to the findings observed by Lassnigg et al, where the association between 48-hour ΔSCr and the mortality beyond 30 days was not significant, our

FIGURE 3 Exploring the Threshold of Perioperative 48-Hour ΔSCr for 30-Day Mortality



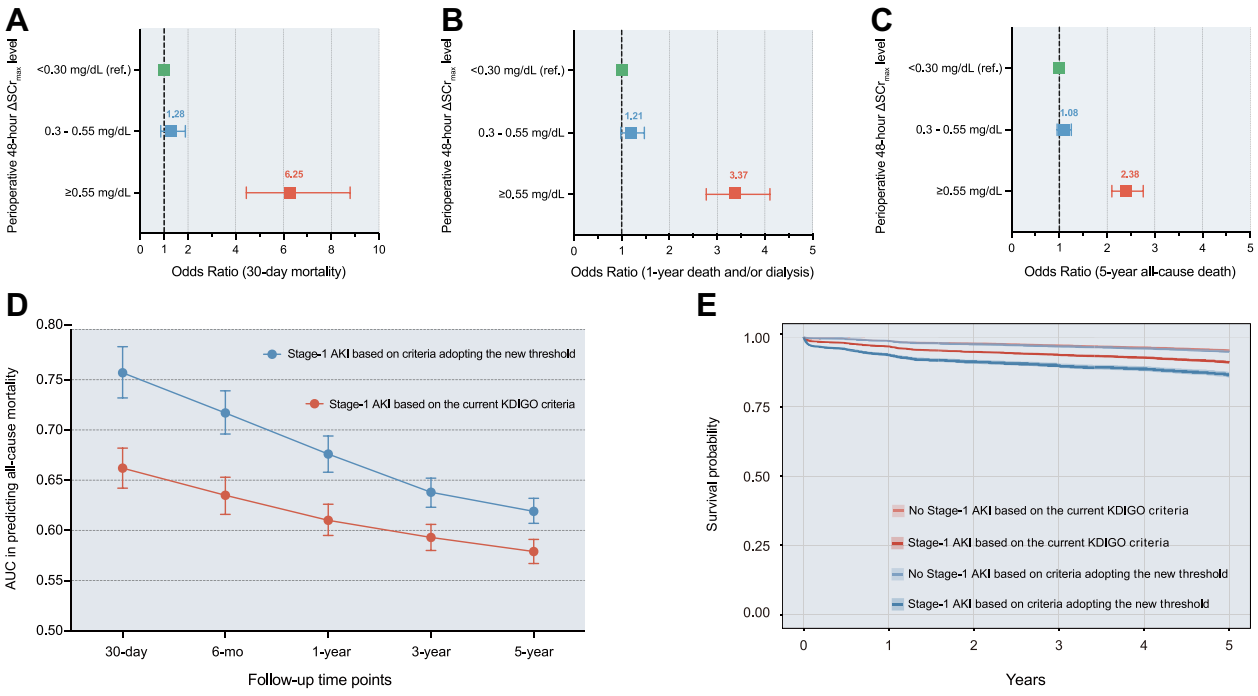
(A) The adjusted odds ratio curve with the restricted cubic spline for 30-day mortality as a function of the 48-hour ΔSCr_{max}; the threshold level was determined with an adjusted odds ratio >1.0 (indicated by the red vertical line [x = 0.549 mg/dL] intersecting with the black horizontal line (y = 1.0); the gray vertical line (x = 0.3 mg/dL) corresponds to the KDIGO threshold for the stage-1 AKI 48-hour ΔSCr absolute criterion). (B) Receiver-operator characteristics curve analysis evaluating the 48-hour ΔSCr_{max} in predicting 30-day mortality; the threshold level was determined by calculating the Youden index where the sum of sensitivity and specificity was maximal (indicated by red), which corresponded to 0.553 mg/dL vs the KDIGO threshold (0.3 mg/dL) for the stage-1 AKI ΔSCr absolute criterion (indicated by gray).
ΔSCr = serum creatinine change; AUC = area under the receiver-operator characteristics curve; AKI = acute kidney injury; KDIGO = Kidney Disease: Improving Global Outcomes; Sen = sensitivity; Spe = specificity.

FIGURE 4 AKI Incidence and Staging Composition Based on Criteria With Different Thresholds



Change of the AKI incidence and staging composition based on the AKI diagnostic criteria adopting either the new or KDIGO 48-hour absolute ΔSCr thresholds.
ΔSCr = serum creatinine change; AKI = acute kidney injury; KDIGO = Kidney Disease: Improving Global Outcomes.

FIGURE 5 Prognostic Value of Different 48-Hour ΔSCr Thresholds in AKI Criteria



(A-C) Effect sizes of the stage-1 AKI criteria when adopting either the new or KDIGO-defined 48-hour absolute ΔSCr thresholds with multivariate adjustment for 30-day mortality, 1-year death and/or dialysis, and 5-year all-cause death, respectively. (D) The predictive value of the stage-1 AKI criteria adopting either the new or KDIGO-defined 48-hour absolute ΔSCr thresholds in predicting all-cause mortality at multiple time points over the 5-year follow-up period. (E) The Kaplan-Meier survival curves for patients with or without stage-1 AKI based on criteria adopting either the new or KDIGO-defined 48-hour absolute ΔSCr thresholds over the 5-year follow-up period, respectively. ΔSCr = serum creatinine change; AKI = acute kidney injury; AUC = area under the receiver-operator characteristics curve; KDIGO = Kidney Disease: Improving Global Outcomes.

study demonstrated a persistent effect of the relatively subtle 48-hour ΔSCr on longer-term survival. This may be due to the much larger sample size and longer follow-up duration in our study, which increased the statistical power to detect outcome significance compared with the previous study.

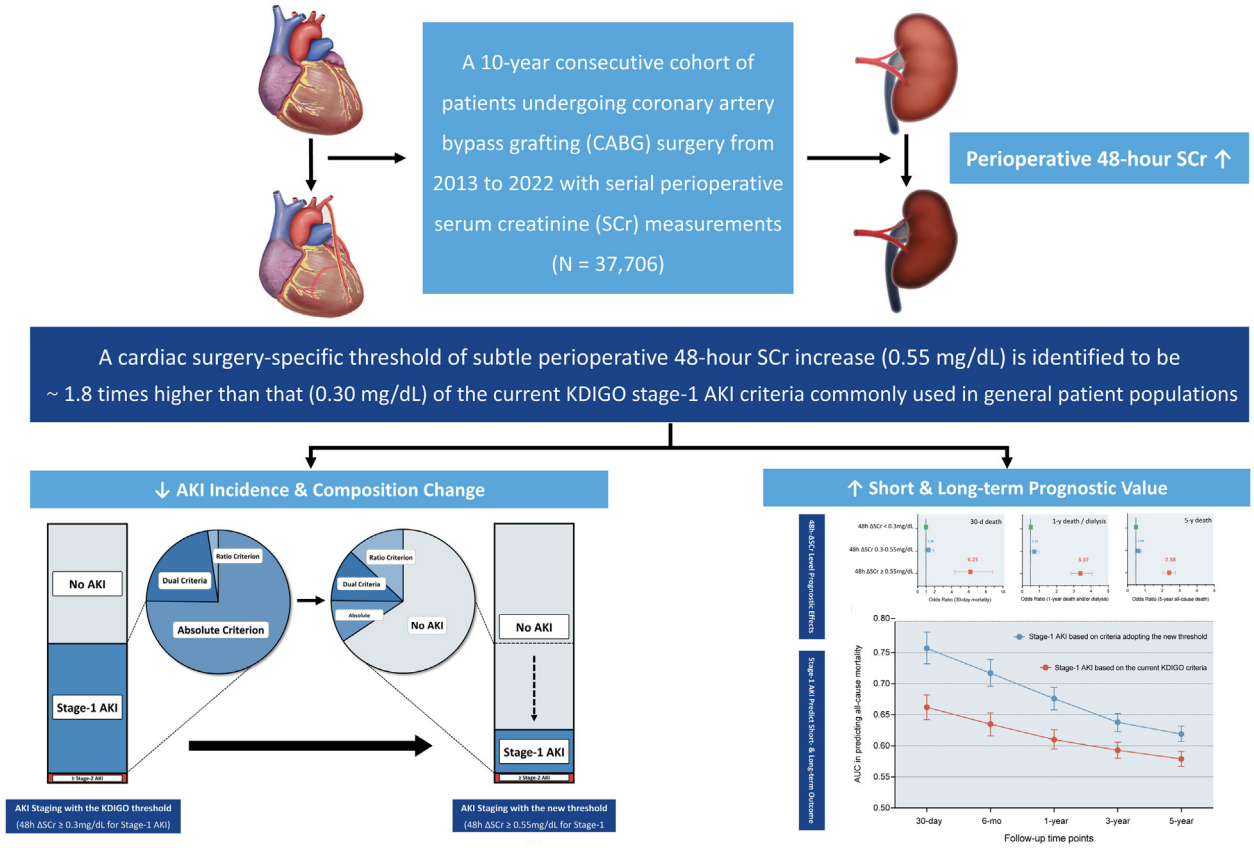
The underlying pathophysiology of CSA-AKI, representing a unique and high-risk AKI patient

TABLE 3 Outcome Prediction of Stage-1 AKI Criteria Adopting the New vs KDIGO 48-H Absolute ΔSCr Thresholds

	Stage-1 AKI Criteria Adopting the KDIGO Threshold (0.3 mg/dL) AUC (95% CI)	Stage-1 AKI Criteria Adopting the New Threshold (0.55 mg/dL) AUC (95% CI)	*P* Value	Continuous NRI
30-d mortality	0.662 (0.642-0.682)	0.757 (0.732-0.783)	<0.0001	Total NRI: 0.071 Event NRI: 0.414 Nonevent NRI: −0.344
6-mo mortality	0.635 (0.616-0.653)	0.717 (0.696-0.739)	<0.0001	Total NRI: 0.364 Event NRI: 0.672 Nonevent NRI: −0.308
1-y mortality	0.610 (0.595-0.626)	0.676 (0.658-0.694)	<0.0001	Total NRI: 0.297 Event NRI: 0.603 Nonevent NRI: −0.306
3-y mortality	0.593 (0.580-0.606)	0.638 (0.623-0.652)	<0.0001	Total NRI: 0.211 Event NRI: 0.516 Nonevent NRI: −0.306
5-y mortality	0.579 (0.567-0.591)	0.619 (0.607-0.632)	<0.0001	Total NRI: 0.195 Event NRI: 0.499 Nonevent NRI: −0.304
1-y death and/or dialysis	0.607 (0.590-0.623)	0.664 (0.646-0.683)	<0.0001	Total NRI: 0.264 Event NRI: 0.571 Nonevent NRI: −0.307

KDIGO = Kidney Disease: Improving Global Outcomes; NRI = Net Reclassification Index.

CENTRAL ILLUSTRATION **Cardiac Surgery-Specific Perioperative Serum Creatinine Change in Defining Acute Kidney Injury After Coronary Surgery**



Zeng J, et al. JACC Adv. 2024;3(11):101326.

Exploring the cardiac surgery-specific perioperative 48-hour ΔSCr threshold level in defining the stage-1 CSA-AKI and comparing with that of the current general KDIGO AKI diagnostic criteria. AKI = acute kidney injury; KDIGO = Kidney Disease: Improving Global Outcomes. Created in BioRender. Joosen, R. (2023) Bio-Render.com/j13u676.

population, necessitates surgery-specific diagnostic criteria that differ from general AKI criteria. Despite sharing a similar pathophysiological framework as general AKI, the primary disease pathways for CSA-AKI have not been fully understood but are thought to be more associated with hypoperfusion, ischemic-reperfusion injury, oxidative stress, inflammation, nephrotoxicity, and external mechanical causes.[1,2,10-12] Underlying these pathophysiological pathways, many cardiac surgery-related factors significantly influence the development, mechanism interactions, manifestations, and interpretation of CSA-AKI. For instance, fluid status plays an important role in the detection and monitoring of CSA-AKI, particularly by influencing the SCr levels.[28-31] On one hand, the use of cardiopulmonary bypass often results in a dramatic change in patient fluid balance, where hemodilution from fluid loading can obscure the elevated SCr levels reflecting renal injury. On the other hand, restricted fluid management during postoperative care and intraoperative blood loss can tilt the SCr scale in the opposite direction, where the observed elevated SCr may be more reflective of a temporal "artifact" of fluid status rather than the "true kidney injury." Therefore, it is crucial to consider the unique and complex perioperative state of cardiac surgery, including patient, procedural, preoperative, intraoperative, and postoperative factors, when defining and diagnosing CSA-AKI.

A trend toward a reduced risk was observed in patients with a small increase in SCr (ie, in the patients with 0-0.3 mg/dL SCr increase when exploring the relationship between 48-hour ΔSCrmax and 30-day mortality, as shown in **Figure 2**). The possible

explanation was twofold. First, in the RCS analysis, we used 48-hour ΔSCr = 0 as the reference group. Compared to this reference group of patients with no perioperative SCr change, the vast majority of cardiac surgery patients will have some degree of SCr elevation after the major stress of cardiac surgery,[32] representing the "normal majority" with "average prognosis." Whereas the relative minority of patients with little increase demonstrated relatively poorer prognosis might be due to: 1) they had a relatively consistently high or low level of SCr throughout the perioperative period due to underlying adverse conditions (eg, baseline renal dysfunction, low muscle mass),[33,34] and/or 2) they had other detrimental factors that offset the postoperative SCr increase,[35] both of which were significantly associated with worse outcomes.

Developing cardiac surgery-specific AKI diagnosing criteria holds important clinical implications. First, in the current era of increased EMR accessibility and high-frequency monitoring, the lack of cardiac surgery-tailored AKI diagnostic criteria may lead to the overdetection and coding of a significant proportion of potentially less clinically relevant AKI with the current general AKI definition. This might, in part, explain the reported rapid rise in AKI among cardiac surgery patients, which may have significantly impacted the downstream management and potentially diverted clinical resource allocation from patients with greater needs.[13,14] Second, no effective pharmacologic prevention strategies have been proven in clinical trials for CSA-AKI.[1,2] Under the current general AKI definition, while stage-1 AKI is highly prevalent among cardiac surgery patients, the more severe stage-2 and/or 3 AKI are rare. Inclusion of these heterogeneous stage-1 AKI cases, with varying prognostic significances under the current definition, as the primary target outcome could potentially dilute the expected treatment effect of any testing strategies aimed to reduce the "true renal injury." Whereas, simply excluding stage-1 AKI would significantly increase the required sample size for testing strategies to detect statistically significant benefits due to the low event rate of stage-2 and/or 3 AKI. Therefore, by developing more cardiac surgery-specific criteria in defining CSA-AKI, we are effectively selecting those more clinically relevant CSA-AKI cases as the target for both clinical practice and research.

STUDY LIMITATIONS. Several limitations of the current study should be acknowledged. First, as a single-center study, the impact of institutional practices might limit the generalizability of the current findings. Therefore, future studies involving broader patient populations are warranted. Second, the current study focuses solely on CABG patient populations, which have a relative more homogeneous surgical profile. This intended focus aims to provide a clearer answer to the question of whether the subtle ΔSCr threshold level in cardiac surgery patients significantly differs from the current general threshold. Third, the study focused only on the absolute ΔSCr criterion component of the current AKI definition framework. Other criterion components, including the relative ratio and the urine output criteria, should theoretically also be investigated for cardiac surgery-specific thresholds given their likely impact during perioperative care. Fourth, although two different threshold-exploring methods were used and confirmed a similar threshold of the 48-hour ΔSCr, other methods and/or considerations from different perspectives (eg, clinical utility, cost-effectiveness) could also be explored to identify thresholds that meet other specific clinical needs. Lastly, given the retrospective nature of this study, it was possible that some cases of AKI might have been missed due to lack of SCr measurements at the time of AKI onset and AKI occurring in the very late postoperative period (ie, beyond 7 days after surgery),[1] which was beyond the scope of our current study. The results of the study were mainly hypothesis-generating given the retrospective design and lack of adjustment for multiplicity and therefore warranted further validation.

CONCLUSIONS

In summary, our study demonstrated the relationship between the perioperative absolute ΔSCr during short periods of time and clinical outcomes in CABG patients. Notably, we identified a cardiac surgery-specific 48-hour ΔSCr threshold that was notably higher than the threshold from the current consensus AKI definition criteria commonly used in general populations. Application of this newly identified threshold could significantly impact the reported incidence and staging composition of CSA-AKI, with important implications for both clinical practice and research. This finding underscores the need for future studies to further investigate more comprehensive cardiac surgery-specific AKI diagnostic criteria.

ACKNOWLEDGMENTS The authors thank staffs at the Information Center, Fuwai Hospital, and the National Center for Cardiovascular Diseases for help with data acquisition and Li He for her coordination of the patient follow-up.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by grants from the high-level hospital clinical research of Fuwai Hospital, the Chinese Academy of Medical Sciences (2022-GSP-GG-28), the National Natural Science Foundation of China (Key Program; 81830072), and the Ministry of Science and Technology of People's Republic of China (2016YFC1302000) to Dr Zheng. The funders had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Zhe Zheng, Department of Cardiovascular Surgery, National Clinical Research Center of Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Key Laboratory of Coronary Heart Disease Risk Prediction and Precision Therapy, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College. No.167 North Lishi Road, Xicheng District, Beijing, 100037, People's Republic of China. E-mail: zhengzhe@fuwai.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The level of absolute serum creatinine change over short periods of time after cardiac surgery was nonlinearly associated with prognosis.

COMPETENCY IN PATIENT CARE: The cardiac surgery-specific threshold for short-period absolute serum creatinine change in defining clinically meaningful acute kidney injury is much higher than the current consensus definition threshold commonly used in general patient populations.

TRANSLATIONAL OUTLOOK: Further studies are warranted to further validate the current hypothesis-generating findings and call for developing a new definition system specific for cardiac surgery-associated acute kidney injury.

REFERENCES

1. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. *Nat Rev Nephrol*. 2017;13(11):697-711. https://doi.org/10.1038/NRNEPH.2017.119

2. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. *Clin J Am Soc Nephrol*. 2006;1(1):19-32. https://doi.org/10.2215/CJN.00240605

3. Ishani A, Nelson D, Clothier B, et al. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. *Arch Intern Med*. 2011;171(3):226-233. https://doi.org/10.1001/ARCHINTERNMED.2010.514

4. Gaffney AM, Sladen RN. Acute kidney injury in cardiac surgery. *Curr Opin Anaesthesiol*. 2015;28(1):50-59. https://doi.org/10.1097/ACO.0000000000000154

5. Demirjian S, Bashour CA, Shaw A, et al. Predictive accuracy of a perioperative laboratory test-based prediction model for moderate to severe acute kidney injury after cardiac surgery. *JAMA*. 2022;327(10):956-964. https://doi.org/10.1001/JAMA.2022.1751

6. Birnie K, Verheyden V, Pagano D, et al. Predictive models for kidney disease: improving global outcomes (KDIGO) defined acute kidney injury in UK cardiac surgery. *Crit Care*. 2014;18(6). https://doi.org/10.1186/S13054-014-0606-X

7. Rydén L, Sartipy U, Evans M, Holzmann MJ. Acute kidney injury after coronary artery bypass grafting and long-term risk of end-stage renal disease. *Circulation*. 2014;130(23):2005-2011. https://doi.org/10.1161/CIRCULATIONAHA.114.010622

8. Hobson CE, Yavas S, Segal MS, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation*. 2009;119(18):2444-2453. https://doi.org/10.1161/CIRCULATIONAHA.108.800011

9. Kellum JA, Lameire N, Aspelin P, et al. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care*. 2013;17(1):204. https://doi.org/10.1186/CC11454

10. Rangaswami J, Bhalla V, Blair JEA, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American heart association. *Circulation*. 2019;139(16):E840-E878. https://doi.org/10.1161/CIR.0000000000000664

11. Massoth C, Zarbock A, Meersch M. Acute kidney injury in cardiac surgery. *Crit Care Clin*. 2021;37(2):267-278. https://doi.org/10.1016/j.ccc.2020.11.009

12. Mariscalco G, Lorusso R, Dominici C, Renzulli A, Sala A. Acute kidney injury: a relevant complication after cardiac surgery. *Ann Thorac Surg*. 2011;92(4):1539-1547. https://doi.org/10.1016/J.ATHORACSUR.2011.04.123

13. Swaminathan M, Shaw AD, Phillips-Bute BG, et al. Trends in acute renal failure associated with coronary artery bypass graft surgery in the United States. *Crit Care Med*. 2007;35(10):2286-2291. https://doi.org/10.1097/01.CCM.0000282079.05994.57

14. Martinelli SM, Patel UD, Phillips-Bute BG, et al. Trends in cardiac surgery-associated acute renal failure in the United States: a disproportionate increase after heart transplantation. *Ren Fail*. 2009;31(8):633-640. https://doi.org/10.3109/08860220903100689

15. Siew ED, Davenport A. The growth of acute kidney injury: a rising tide or just closer attention to detail? *Kidney Int*. 2015;87(1):46-61. https://doi.org/10.1038/KI.2014.293

16. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147(8):573-577. https://doi.org/10.7326/0003-4819-147-8-200710160-00010

17. Li Y, Zheng Z, Hu S. The Chinese coronary artery bypass grafting registry study: analysis of the national multicentre database of 9248 patients. *Heart*. 2009;95(14):1140-1144. https://doi.org/10.1136/HRT.2008.146563

18. Rao C, Zhang H, Gao H, et al. The Chinese cardiac surgery registry: design and data audit. *Ann Thorac Surg*. 2016;101(4):1514-1520. https://doi.org/10.1016/J.ATHORACSUR.2015.09.038

19. Zeng J, Zhang D, Lin S, et al. Comparative analysis of machine learning vs. traditional modeling approaches for predicting in-hospital mortality after cardiac surgery: temporal and spatial external validation based on a nationwide cardiac surgery registry. *Eur Heart J Qual Care Clin Outcomes*. 2024;10(2). https://doi.org/10.1093/EHJQCCO/QCAD028

20. Yuan S, Li F, Zhang H, et al. Impact of high Lipoprotein(a) on long-term survival following coronary artery bypass grafting. *J Am Heart Assoc*. 2024;13(3):e031322. https://doi.org/10.1161/JAHA.123.031322

21. Zeng J, Shao J, Lin S, et al. Optimizing the dynamic treatment regime of in-hospital warfarin anticoagulation in patients after surgical valve

replacement using reinforcement learning. *J Am Med Inf Assoc*. 2022;29(10):1722–1732. https://doi.org/10.1093/JAMIA/OCAC088

22. Stekhoven DJ, Bühlmann P. MissForest-nonparametric missing value imputation for mixed-type data. *Bioinformatics*. 2012;28(1):112–118. https://doi.org/10.1093/BIOINFORMATICS/BTR597

23. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612. https://doi.org/10.7326/0003-4819-150-9-200905050-00006

24. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ*. 2020;368:m441. https://doi.org/10.1136/bmj.m441

25. Wang MP, Jiang L, Zhu B, et al. Association of fluid balance trajectories with clinical outcomes in patients with septic shock: a prospective multicenter cohort study. *Mil Med Res*. 2021;8(1):40. https://doi.org/10.1186/s40779-021-00328-1

26. Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol*. 2004;15(6):1597–1605. https://doi.org/10.1097/01.ASN.0000130340.93930.DD

27. Rydén L, Ahnve S, Bell M, et al. Acute kidney injury after coronary artery bypass grafting and long-term risk of myocardial infarction and death. *Int J Cardiol*. 2014;172(1):190–195. https://doi.org/10.1016/J.IJCARD.2014.01.013

28. Moore E, Tobin A, Reid D, Santamaria J, Paul E, Bellomo R. The impact of fluid balance on the detection, classification and outcome of acute kidney injury after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2015;29(5):1229–1235. https://doi.org/10.1053/J.JVCA.2015.02.004

29. Starr MC, Griffin RL, Harer MW, et al. Acute kidney injury defined by fluid-corrected creatinine in premature neonates: a secondary analysis of the PENUT randomized clinical trial. *JAMA Netw Open*. 2023;6(8):E2328182. https://doi.org/10.1001/JAMANETWORKOPEN.2023.28182

30. Jin J, Chang SC, Xu S, et al. Early postoperative serum creatinine adjusted for fluid balance precisely predicts subsequent acute kidney injury after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2019;33(10):2695–2702. https://doi.org/10.1053/J.JVCA.2019.03.023

31. Young R. Perioperative fluid and electrolyte management in cardiac surgery: a review. *J Extra Corpor Technol*. 2012;44(1):P20.

32. Thielmann M, Corteville D, Szabo G, et al. Teprasiran, a small interfering RNA, for the prevention of acute kidney injury in high-risk patients undergoing cardiac surgery: a randomized clinical study. *Circulation*. 2021;144(14):1133–1144. https://doi.org/10.1161/CIRCULATIONAHA.120.053029

33. Renberg M, Sartipy U, Bell M, Hertzberg D. Association of preoperative renal-resistive index with long-term renal and cardiovascular outcomes after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2024;38(1):101–108. https://doi.org/10.1053/j.jvca.2023.10.035

34. Liu AYL, Wang J, Nikam M, Lai BC, Yeoh LY. Low, rather than high, body mass index is a risk factor for acute kidney injury in multiethnic asian patients: a retrospective observational study. *Internet J Nephrol*. 2018;2018:3284612. https://doi.org/10.1155/2018/3284612

35. Singh R, Watchorn JC, Zarbock A, Forni LG. Prognostic biomarkers and AKI: potential to enhance the identification of post-operative patients at risk of loss of renal function. *Res Rep Urol*. 2024;16:65–78. https://doi.org/10.2147/RRU.S385856

KEY WORDS acute kidney injury, creatinine, cardiac surgery, KDIGO, perioperative

APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.