Stage 1 acute kidney injury is independently associated with infection following cardiac surgery

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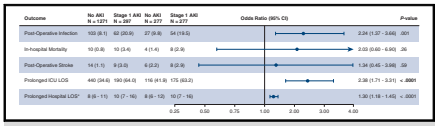
ABSTRACT

Objectives: Severe acute kidney injury (AKI) is a known risk factor for infection and mortality. However, whether stage 1 AKI is a risk factor for infection has not been evaluated in adults. We hypothesized that stage 1 AKI following cardiac surgery would independently associate with infection and mortality.

Methods: In this retrospective propensity score–matched study, we evaluated 1620 adult patients who underwent nonemergent cardiac surgery at the University of Colorado Hospital from 2011 to 2017. Patients who developed stage 1 AKI by Kidney Disease Improving Global Outcomes creatinine criteria within 72 hours of surgery were matched to patients who did not develop AKI. The primary outcome was an infection, defined as a new surgical-site infection, positive blood or urine culture, or development of pneumonia. Secondary outcomes included in-hospital mortality, stroke, and intensive care unit (ICU) and hospital length of stay (LOS).

Results: Stage 1 AKI occurred in 293 patients (18.3%). Infection occurred in 20.9% of patients with stage 1 AKI compared with 8.1% in the no-AKI group ($P < .001$). In propensity-score matched analysis, stage 1 AKI independently associated with increased infection (odds ratio [OR]; 2.24, 95% confidence interval [CI], 1.37-3.17), ICU LOS (OR, 2.38; 95% CI, 1.71–3.31), and hospital LOS (OR, 1.30; 95% CI, 1.17-1.45).

Conclusions: Stage 1 AKI is independently associated with postoperative infection, ICU LOS, and hospital LOS. Treatment strategies focused on prevention, early recognition, and optimal medical management of AKI may decrease significant postoperative morbidity. (J Thorac Cardiovasc Surg 2021;161:1346-55)



Stage 1 acute kidney injury is associated with increased odds of postoperative morbidity.

CENTRAL MESSAGE

Postoperative infection is a serious complication of cardiac surgery. In this study, we demonstrate that stage 1 acute kidney injury is an independent risk factor for postoperative infection.

PERSPECTIVE

Stage 1 AKI, defined as a rise in creatinine of 0.3 mg/dL, is independently associated with an increased risk of postoperative infection. AKI impacts multiple organ systems, including the brain, lungs, liver, and, in this study, the immune system. Given the widespread deleterious effects of AKI, prevention of kidney injury after cardiac surgery should be a future research priority.

See Commentary on page 1356.

Acute kidney injury (AKI) is a common postoperative complication that has been shown to significantly increase rates of morbidity and mortality.[1-3] AKI has been defined since 2012 by the Kidney Disease Improving Global Outcomes (KDIGO) criteria and is divided into 3 stages based on increases in serum creatinine or decreases in urine output.[4] Stage 1 AKI is defined by an absolute increase in serum creatinine of 0.3 mg/dL from baseline. Stage 2 is defined as a doubling of creatinine from baseline,

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Abbreviations and Acronyms

AKI = acute kidney injury
CABG = coronary artery bypass grafting
CI = confidence interval
KDIGO = Kidney Disease Improving Global Outcomes
ICU = intensive care unit
LOS = length of stay
OR = odds ratio
STS = Society of Thoracic Surgeons

and stage 3 is defined as a tripling in creatinine, new initiation of dialysis, or an absolute creatinine value ≥4.0 mg/dL.

Postoperative AKI is a strong predictor of mortality, and severe AKI independently increases mortality by 3- to 8-fold.[5] Even small increases in creatinine of 0.5 mg/dL following cardiac surgery have been shown to have strong deleterious effects.[6,7] However, there are few studies specifically evaluating mortality outcomes using the KDIGO stage 1 definition, and results have been mixed.[8,9]

Sepsis is the leading cause of death in patients with AKI.[10] Although sepsis as a cause of AKI has been well documented,[11] AKI is also increasingly recognized as a risk factor for subsequent sepsis.[12,13] Postoperative infections, including mediastinitis, sepsis, and pneumonia, are serious complications of cardiothoracic surgery. These complications have been shown to increase mortality rates by more than 5-fold.[14] Numerous risk factors for postoperative infection have been identified, including age, female sex, smoking status, diabetes, hypertension, chronic lung disease, peripheral vascular disease, immunosuppressive treatment, New York Heart Association class, ejection fraction, intraoperative blood products, and, importantly, severe AKI.[15-17]

Severe postoperative AKI following cardiac surgery has been shown in several studies to independently increase the risk of subsequent infection.[18-20] Zanardo and colleagues[20] evaluated 737 patients with baseline creatinine values <1.5 mg/dL and found that the development of AKI, defined as a postoperative peak creatinine of ≥2.5 mg/dL, increased the rates of postoperative infection from 0.8% to 25.9%. Thakar and colleagues[19] later found that in postsurgical patients, the development of AKI, defined as a 50% decline in creatinine clearance, increased rates of infection to 23.7%, and 58.5% in cases where dialysis was required. Previous studies have only assessed the impact of KDIGO stage 2 and stage 3 AKI on subsequent infectious complications. The impact of stage 1 AKI on subsequent rates of infection following cardiac surgery is, therefore unknown.

In this retrospective study, we evaluate the impact of postoperative stage 1 AKI on rates of infection following cardiac surgery. We hypothesized that stage 1 AKI would be independently associated with increased rates of postoperative infection and mortality.

METHODS

Study Population

We conducted a retrospective chart review from January 2011 to July 2017 using the University of Colorado Society of Thoracic Surgeons (STS) database. Institutional review board approval was obtained from the University of Colorado (COMIRB #17-0198, approval date February 6, 2017.). Subjects were included if they were ≥18 years of age, underwent elective or urgent cardiac surgery at the University of Colorado Hospital, and had at least 1 preoperative creatinine value available. Subjects were excluded for the following reasons: (1) intraoperative death, (2) serum creatinine measures not available for the first 3 postoperative days, (3) received antibiotics within 2 weeks before surgery, (4) developed an infection within 48 hours of surgery, (5) AKI at the time of surgery, (6) end-stage renal disease, (7) cardiogenic shock at the time of surgery, (8) transcatheter aortic valve replacement or thoracic endovascular aneurysm repair procedures, (9) procedures performed for infectious endocarditis or aortic dissection, and (10) solid-organ transplant recipients.

Definitions of Predictor Variable

Postoperative AKI was defined using KDIGO guidelines[4] as an increase in creatinine of at least 0.3 mg/dL. Stage 1 AKI was defined as an increase in creatinine of at least 0.3 mg/dL without more than a doubling from baseline. AKI had to occur within 72 hours of surgery to determine that the AKI was temporally related to surgery, and preceded infection.

Outcomes

The primary outcome was infection, which was defined as having one of the following: (1) documented surgical-site infection that included deep sternal wound infection, superficial wound infection, and cellulitis of incision or vein harvest sites; (2) positive blood culture or urine culture with >100,000 colony-forming units; or (3) imaging suggestive of new-onset pneumonia based on radiology reports. Secondary outcomes were in-hospital mortality, prolonged intensive care unit (ICU) and hospital length of stay (LOS), and postoperative stroke.

Matching Variables

We adjusted our analyses for variables that have been shown to be associated with infection, including age, sex, BMI, hematocrit, smoking status, use of immunosuppressive medication preoperatively, comorbidities including hypertension, diabetes mellitus, chronic lung disease, previous cardiovascular interventions, as well as perfusion time, and intraoperative blood product transfusions. We also matched patients based on surgical type, such as aneurysm repair, valvular surgery, coronary artery bypass grafting (CABG), ventricular assist device placement, and combination, which included combined operations (CABG with valve replacement, for instance). Due to the lower number of patients, when matching patients with stage 2 or 3 AKI, sex, age, perfusion time, surgical time, and intraoperative blood product were used.

Statistical Analysis

For each of the outcomes, we adjusted for covariates using propensity-score matching.[21] A propensity score for each patient was calculated using a multivariable logistic regression model in which the dependent variable was the presence of stage 1 AKI or stage 2 and 3 AKI and the independent variables were the preoperative and operative adjustment variables. For the

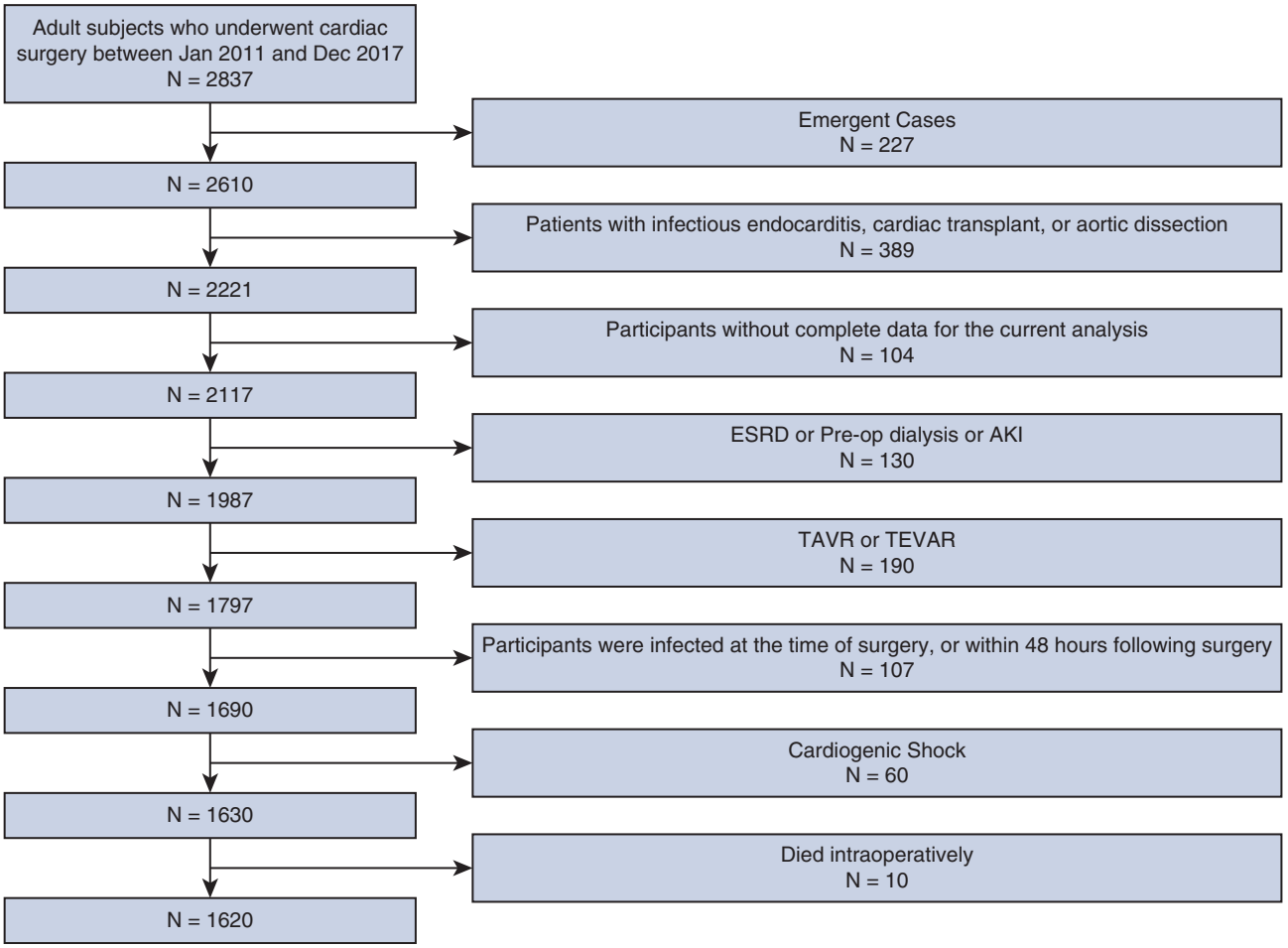

FIGURE 1. Study cohort selection. The flow diagram depicts the details of patients screened and reasons for patient exclusion. *ESRD*, End-stage renal disease; *AKI*, acute kidney injury; *TAVR*, transcatheter aortic valve replacement; *TEVAR*, thoracic endovascular aneurysm repair.

propensity model, the β coefficients were combined with the patient's values for each covariate to generate individual propensity scores. In the stage 1 AKI match, patients were first stratified by surgical type, and then these patient-level propensity scores were then used to match patients with AKI stage 1 to similar patients without AKI using the 1-to-1 greedy matching method. When matching patients with AKI stage 2 or 3, stratification based on the surgical type was not possible, and so surgical type was included as part of the propensity score generation. A 2-to-1 greedy matching method was used for stage 2 or 3 AKI.[22] Generalized estimating equation models were used to test the propensity-matched cohort to account for correlation within each matched pair. For all outcomes and risk-adjusted results, statistical significance and confidence intervals (CIs) were adjusted for multiple comparisons (ie, 4 outcomes and 2 risk-adjustment methods) using the Bonferroni method by multiplying the *P* values or dividing the alpha levels by the number of comparisons. All statistical tests were considered to be significant at a 2-sided $P < .05$. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Patient Characteristics and Unadjusted Comparison of the Study Population

A total of 2837 patients underwent cardiac surgery at the University of Colorado during the study period, of whom 1620 met inclusion criteria (Figure 1). Before matching, significant differences existed in the baseline characteristics of patients with no AKI, stage 1 AKI, and stage 2 or 3 AKI (Table 1). A total of 297 patients (18.3%) developed stage 1 AKI, and 52 patients (3.2%) developed stage 2 or 3 AKI. Unadjusted comparisons demonstrated that patients who developed AKI were less often female, had greater body mass index, lower preoperative hematocrit, and greater numbers of comorbidities than those who did not develop AKI. Particularly, patients in both stage 1 and stage 2 or 3 AKI had a greater incidence of hypertension, diabetes, peripheral vascular disease, and left ventricular dysfunction (ejection fraction <50%). Also, their surgeries were prolonged with longer cardiopulmonary bypass times, and they had greater rates of intraoperative blood product administration. Patients with AKI were also more likely to undergo combined surgical procedures. Finally, baseline estimated glomerular filtration rate was slightly lower in the Stage 1 AKI group than the no AKI group, although this difference was not observed in patients who developed stage 2 or 3 AKI (Table 1). Patient characteristics after propensity-score matching are given in Figure E1.

TABLE 1. Comparison of baseline characteristics of 1620 patients undergoing cardiac surgery by the occurrence of AKI

Characteristics	No AKI (n = 1271) N (%)*	Stage 1 AKI (n = 297) N (%)*	*P* value†	Stage 2 and 3 AKI (n = 52) N (%)*	*P* value†
Female	394 (31.0)	65 (21.9)	**.002**	19 (36.5)	.40
Age, y, mean (SD)	60.6 (13.8)	62.6 (13.5)	**.02**	61.9 (14.8)	.53
Race/ethnicity					
White	950 (74.7)	212 (71.4)	.39	39 (75.0)	.99
Hispanic	186 (14.6)	43 (14.5)		8 (15.4)	
Black	79 (6.2)	25 (8.4)		3 (5.8)	
Other/unknown	56 (4.4)	17 (5.7)		2 (3.9)	
Body mass index, mean (SD)	28.2 (6.1)	29.3 (6.5)	**.01**	29.3 (6.8)	.28
Comorbidities					
Sleep apnea	250 (19.7)	64 (21.6)	.47	9 (17.3)	.67
Hypertension	862 (67.8)	237 (79.8)	**<.001**	41 (78.9)	.09
Diabetes mellitus	359 (28.3)	126 (42.4)	**<.001**	18 (34.6)	.32
Chronic lung disease	244 (19.2)	72 (24.2)	.05	12 (23.1)	.49
Liver disease	33 (2.6)	13 (4.4)	.10	1 (1.9)	.99
Congestive heart failure	474 (37.3)	138 (46.5)	**.004**	24 (46.2)	.20
Cancer within 5 years	117 (9.2)	17 (5.7)	.05	8 (15.4)	.14
Peripheral vascular disease	62 (4.9)	30 (10.1)	**<.001**	4 (7.7)	.36
Cerebrovascular disease	137 (10.8)	43 (14.5)	.07	6 (11.5)	.86
Dyslipidemia	726 (57.1)	188 (63.3)	.05	31 (59.6)	.72
Baseline platelets, mean (SD)	220.1 (63.4)	213.2 (68.1)	.14	212.5 (59.9)	.58
Baseline eGFR, mean (SD)	79.1 (18.1)	72.0 (12.6)	**<.001**	77.4 (13.9)	.60
Smoker at time of surgery	284 (22.3)	80 (26.9)	.09	11 (21.2)	.84
History of IV drug abuse	56 (4.4)	12 (4.0)	.78	1 (1.9)	.72
Last hematocrit, mean (SD)	41.5 (5.5)	39.8 (6.2)	**<.001**	39.8 (5.5)	**.03**
Last white blood cell count, mean (SD)	7.3 (2.4)	7.7 (2.4)	**.04**	6.7 (2.1)	.08
Ejection fraction, mean (SD)	54.0 (14.6)	51.6 (15.8)	**.02**	51.9 (13.6)	.29
Perfusion time, mean (SD)	130.9 (68.2)	149.9 (79.8)	**<.001**	163.0 (87.9)	**.01**
Surgical time, h, mean (SD)	6.3 (1.8)	6.9 (2.1)	**<.001**	7.6 (2.7)	**<.001**
Intraoperative blood products	457 (6.0)	143 (48.2)	**<.001**	31 (59.6)	**<.001**
Red blood cell units, mean (SD)	0.6 (2.4)	1.1 (2.7)	**.002**	2.2 (4.1)	**.01**
Platelet units, mean (SD)	0.6 (1.0)	0.8 (1.1)	**.003**	1.1 (1.4)	**<.001**
Fresh-frozen plasma, mean (SD)	1.2 (3.3)	1.8 (3.2)	**.01**	3.5 (6.1)	**.01**
Cryoprecipitate units, mean (SD)	0.05 (0.3)	0.08 (0.4)	.30	0.08 (0.3)	.51
Immunosuppressive medication before surgery			.56		.39
No	1006 (79.2)	239 (80.5)		40 (76.9)	
Yes	33 (2.6)	10 (3.4)		3 (5.8)	
Unknown	232 (18.3)	48 (16.2)		9 (17.3)	
Steroid use			.94		.11
No	1127 (88.7)	263 (88.6)		42 (80.8)	
Yes	38 (3.0)	8 (2.7)		4 (7.7)	
Unknown	106 (8.3)	26 (8.8)		6 (11.5)	
Previous cardiovascular intervention	398 (31.3)	102 (34.3)	.31	17 (32.7)	.83
Surgical type			**<.001**		.52
Aortic aneurysm repair	149 (11.8)	23 (7.7)		8 (15.4)	
Valve surgery	390 (30.7)	59 (19.9)		11 (21.2)	
Coronary artery bypass	350 (27.5)	112 (37.7)		14 (26.9)	
Left ventricular assist device	21 (1.7)	6 (2.0)		0 (0)	

(Continued)

TABLE 1. Continued

Characteristics	No AKI (n = 1271) N (%)*	Stage 1 AKI (n = 297) N (%)*	*P* value†	Stage 2 and 3 AKI (n = 52) N (%)*	*P* value†
Combined	175 (13.8)	60 (20.2)		10 (19.2)	
Other	186 (14.6)	37 (12.5)		9 (17.3)	
Family history cardiovascular disease	276 (21.7)	60 (20.2)	.57	13 (25.0)	.57
New York Heart Association class			**.004**		.36
None	802 (63.1)	162 (54.6)		28 (53.9)	
Class I	28 (2.2)	1 (0.3)		0 (0)	
Class II	141 (11.1)	37 (12.5)		7 (13.5)	
Class III	216 (17.0)	70 (23.6)		11 (21.2)	
Class IV	84 (6.6)	27 (9.1)		6 (11.5)	

"Other" surgical cases refer to any case that does not fit into another category (eg, surgical repair of ventricular septal defect). *AKI*, Acute kidney injury; *SD*, standard deviation; *eGFR*, estimated glomerular filtration rate; *IV*, intravenous. *Values are frequency and column percent unless otherwise stated. †*P* values are from χ^2 or Fisher exact and *t* tests and are shown in bold when less than .05.

Early Postsurgical Outcomes in Unmatched Cohort

Bivariate comparison of the subgroups demonstrated that overall postoperative infections were significantly greater in patients with stage 1 AKI (20.9%) and patients with stage 2 or 3 AKI (34.6%) than patients without AKI (8.1%, $P < .001$ each). Overall, there were 24 deaths (1.5%) within 30 days of surgery. The mortality rates in stage 1 AKI and stage 2 or 3 AKI were 3.4% ($P = .002$) and 7.7% ($P = .002$), respectively, compared with 0.8% in the no-AKI group. Postoperative stroke was significantly greater in the stage 1 AKI group than the no-AKI group (1.1 vs 3.0%, $P = .03$). The rate of stroke in stage 2 or 3 AKI was slightly greater than the stage 1 AKI group (3.9%), although this did not achieve statistical significance compared with the no-AKI group. ICU LOS and Hospital LOS were both significantly longer in the AKI groups than in the no-AKI group (Table 2).

Early Postsurgical Outcomes in Propensity Score–Matched Cohort

The propensity score matching models paired 277 patients with stage 1 AKI to 277 no-AKI controls and 49 patients with stage 2 or 3 AKI with 92 no-AKI controls. Only 20 patients with stage 1 AKI (6.7%) and 3 patients with stage 2 or 3 AKI (5.8%) were unable to match successfully. Following the propensity-score matching, there was a significant reduction in variables with standard deviations >0.1 (Table E1).

Outcomes by AKI group after propensity-score matching are given in Table 3. The rate of infection was 9.8% compared with 19.5% in the stage 1 AKI match ($P = .002$) and 12.0% versus 32.7% ($P = .01$) in the stage 2 or 3 match. These differences were due primarily to increased rates of positive blood or urine cultures in those with AKI. The mortality rate in stage 1 AKI was more than double the rate in no AKI (1.4% vs 2.9%) but did not reach statistical significance. The mortality rate in stage 2 or 3 AKI was 8.2%, with a strong trend toward significance ($P = .05$). ICU LOS and hospital LOS were both significantly longer in the AKI groups than in the no-AKI groups, and differences in rates of stroke were nonsignificant in both groups.

TABLE 2. Bivariate comparison of unadjusted outcomes of 1620 patients by the occurrence of AKI

Outcomes	No AKI (n = 1271) N (%)*	Stage 1 AKI (n = 297) N (%)*	*P* value†	Stage 2 and 3 AKI (n = 52) N (%)*	*P* value†
In-hospital mortality	10 (0.8)	10 (3.4)	**.002**	4 (7.7)	**.002**
Infection	103 (8.1)	62 (20.9)	**<.001**	18 (34.6)	**<.001**
Postoperative SSI (superficial)	25 (2.0)	12 (4.0)	**.04**	5 (9.6)	**<.001**
Postoperative SSI (deep)	13 (1.0)	4 (1.3)	.6	2 (3.8)	.06
Postoperative blood or urine culture (+)	43 (3.4)	31 (10.1)	**<.001**	10 (19.2)	**<.001**
Pneumonia	35 (2.8)	24 (8.1)	**<.001**	7 (13.5)	**<.001**
Stroke	14 (1.1)	9 (3.0)	**.03**	2 (3.9)	.13
ICU length of stay greater than 72 h	440 (34.6)	190 (64.0)	**<.001**	41 (78.9)	**<.001**
Hospital length of stay, d, median (IQR)	8 (6-11)	10 (7-16)	**<.001**	12 (8-19)	**<.001**

AKI, Acute kidney injury; *SSI*, surgical-site infection; *ICU*, intensive care unit; *IQR*, interquartile range. *Values are frequency and column percent unless otherwise stated. †*P* values are from the Fisher exact and Wilcoxon rank-sum tests and are shown in bold when less than .05.

TABLE 3. Outcomes of patients by the occurrence of AKI for propensity-matched cohort

Outcomes	No AKI (n = 277) N (%)*	Stage 1 AKI (n = 277) N (%)*	*P* value†	No AKI (n = 92) N (%)*	Stage 2 and 3 AKI (n = 49) N (%)*	*P* value†
In-hospital mortality	4 (1.4)	8 (2.9)	.38	1 (1.1)	4 (8.2)	.05
Infection	27 (9.8)	54 (19.5)	**.002**	11 (12.0)	16 (32.7)	**.01**
Postoperative surgical-site infection	9 (3.3)	14 (5.1)	.39	4 (4.4)	7 (12.3)	.05
Postoperative blood or urine culture (+)	11 (4.0)	26 (9.4)	**.02**	2 (2.2)	9 (18.4)	**.001**
Pneumonia	13 (4.7)	22 (7.9)	.16	5 (5.4)	6 (12.2)	.19
Stroke	6 (2.2)	8 (2.9)	.79	1 (1.1)	2 (4.1)	.28
ICU length of stay greater than 72 h	116 (41.9)	175 (63.2)	**<.001**	32 (34.8)	39 (79.6)	**<.001**
Hospital length of stay, days, median (IQR)	8 (6-12)	10 (7-16)	**<.001**	8 (6-11)	12 (8-18)	**<.001**

AKI, Acute kidney injury; *ICU*, intensive care unit; *IQR*, interquartile range. *Values are frequency and column percent unless otherwise stated. †*P* values are from the Fisher exact and Wilcoxon rank-sum tests and are shown in bold when less than .05.

Early Postsurgical Outcomes Based on the Surgical Type

Bivariate comparison of primary and secondary endpoints among the patients undergoing various types of surgeries are shown in Table 4. Although caution should be exercised in the interpretation, given the lower event rates in subgroup analysis, there was a significantly greater in-hospital mortality in aortic aneurysm repair patients who developed postoperative AKI compared with no AKI. Moreover, among CABG, valve surgery or other procedures groups, patients who sustained stage 1 AKI had significantly greater rates of postoperative infection.

Stage 1 AKI Is Associated With Infection and Prolonged Hospital and ICU LOS

After we adjusted for the differences in baseline comorbidities and surgical complexity using propensity-score matching, the patients with stage 1 AKI had significantly increased odds of infection when compared with matched controls. In the 277 matched pairs determined by the propensity-matched model, the odds ratio (OR) for infection was 2.24 (95% CI, 1.37-3.66). Stage 1 AKI was associated with in-hospital mortality in the unadjusted analysis although not the propensity-score matched model. Prolonged ICU and hospitals LOS were more likely in the stage 1 AKI group both unadjusted and propensity-score matched models. Finally, although postoperative stroke was associated with stage 1 AKI in the unadjusted models, there were no differences between the groups after multivariable analysis and propensity matching (Table 5, Figure 2). The main findings of the study are summarized in Figure 3.

Stage 2 and 3 AKI Is Associated With Infection and Prolonged Hospital and ICU LOS

In the patients with stage 2 or 3 AKI, there was a statistically significant increase in odds of infection in the propensity-score matched analyses (OR, 3.57; 95% CI, 1.45-8.80). The adjusted OR for mortality was 8.09 but did not meet statistical significance. ICU and hospital LOS were significantly increased across all models, and postoperative stroke was not associated with stage 2 or 3 AKI (Table 5).

DISCUSSION

To our knowledge, this is the first study in adults to demonstrate an association between postsurgical KDIGO stage 1 AKI and subsequent infection in cardiac surgery patients. Stage 1 AKI was also associated with increased ICU and hospital LOS, although not with postoperative stroke or in-hospital mortality after statistical adjustments.

The STS database defines postoperative AKI as either a 3-fold increase from baseline creatinine, a creatinine ≥4.0 mg/dL, or the initiation of dialysis. This definition corresponds to KDIGO stage III disease and captures only severe cases of AKI. Mortality rates are especially high in patients who meet these criteria for AKI.[23] Although several early studies have reported increased mortality with a creatinine rise of 0.5 mg/dL of greater,[6,7] there are few studies specifically evaluating the mortality impact of KDIGO stage 1 AKI (rise of 0.3 mg/dL or greater). Machado and colleagues[8] evaluated 2804 cardiac surgery patients and found stage 1 AKI rates of 35% (42% for all stages of AKI), with mortality rates of 8.2% within the stage 1 AKI group. The hazard ratio for mortality was 3.35 (2.19-5.12). A second study, by Howitt and colleagues,[9] sought to validate the KDIGO criteria in a population of 2267 cardiac surgery patients and reported AKI rates of 44%. The outcome of 2-year mortality was not significantly different between patients with stage 1 AKI and those without.[9] In our study, although there was a large difference in unadjusted odds of mortality with stage 1 AKI (OR, 4.4), statistical significance was lost following propensity-score matching. However, a similar pattern was seen in the stage 2 and 3 AKI group, which did not achieve significance after matching despite an OR of 8.1. Given the

TABLE 4. Bivariate comparison of outcomes in 1620 cardiac surgery patients based on the type of surgery and occurrence of AKI

Surgical type	No AKI (n = 1271) N (%)*	Stage 1 AKI (n = 297) N (%)*	*P* value†	Stage 2 and 3 AKI (n = 52) N (%)*	*P* value†
Aortic aneurysm repair	149 (11.7)	23 (7.7)		8 (15.4)	
In-hospital mortality	1 (0.7)	2 (8.7)	**.05**	1 (12.5)	NS
Infection	11 (7.4)	1 (4.4)	NS	3 (37.5)	**.02**
Stroke	1 (0.7)	0 (0)	NS	1 (12.5)	NS
ICU length of stay greater than 72 h	34 (22.8)	9 (33.1)	NS	5 (62.5)	**.02**
Hospital length of stay, d, median (IQR)	7 (5-9)	8 (6-9)	NS	9 (6-15)	NS
Valve surgery	390 (30.7)	59 (19.9)		11 (21.2)	
In-hospital mortality	5 (1.3)	2 (3.4)	NS	1 (9.1)	NS
Infection	24 (6.2)	11 (18.6)	**.003**	3 (27.3)	**.03**
Stroke	7 (1.8)	2 (3.4)	NS	0 (0)	NS
ICU length of stay greater than 72 h	130 (33.3)	34 (57.6)	**<.001**	9 (81.8)	**.002**
Hospital length of stay, d, median (IQR)	7 (5-10)	9 (7-14)	**<.001**	12 (8-24)	**.003**
Coronary artery bypass	350 (27.5)	112 (37.7)		14 (26.9)	
In-hospital mortality	1 (0.3)	3 (2.7)	NS	0 (0)	NS
Infection	31 (8.9)	25 (22.3)	**<.001**	5 (35.7)	**.01**
Stroke	4 (1.1)	4 (3.6)	NS	1 (7.1)	NS
ICU length of stay greater than 72 h	117 (33.4)	69 (61.6)	**<.001**	11 (78.6)	**<.001**
Hospital length of stay, d, median (IQR)	8 (6-11)	11 (8-15)	**<.001**	14 (8-17)	**<.001**
Left ventricular assist device	21 (1.7)	6 (2.0)		0 (0)	
In-hospital mortality	1 (4.8)	0 (0)	NS	0 (0-0)	NS
Infection	3 (14.3)	1 (16.7)	NS	0 (0-0)	NS
Stroke	0 (0)	0 (0)	NS	0 (0-0)	NS
ICU length of stay greater than 72 h	11 (52.4)	6 (100)	NS	0 (0-0)	NS
Hospital length of stay, d, median (IQR)	24 (17-29)	32 (22-42)	NS	0 (0-0)	NS
Combination‡	175 (13.8)	30 (20.2)		10 (19.2)	
In-hospital mortality	2 (1.1)	3 (5.0)	NS	0 (0)	NS
Infection	20 (11.4)	13 (21.7)	NS	2 (20.0)	NS
Stroke	2 (1.1)	3 (5.0)	NS	0 (0)	NS
ICU length of stay greater than 72 h	78 (44.6)	46 (76.7)	**<.001**	9 (90.0)	**.01**
Hospital length of stay, d, median (IQR)	9 (6-12)	12 (8-19)	**<.001**	12 (7-20)	NS
Other‡	186 (14.6)	37 (12.5)		9 (17.3)	
In-hospital mortality	0 (0)	0 (0)	NS	2 (22.2)	**.002**
Infection	14 (7.5)	11 (29.7)	**<.001**	5 (55.6)	**<.001**
Stroke	0 (0)	0 (0)	NS	0 (0)	NS
ICU length of stay greater than 72 h	70 (37.6)	26 (70.3)	**<.001**	7 (77.8)	**.03**
Hospital length of stay, d, median (IQR)	8 (6-11)	12 (7-20)	**<.001**	15 (7-25)	NS

AKI, Acute kidney injury; *NS*, not significant; *ICU*, intensive care unit; *IQR*, interquartile range. *Values are frequency and column percent unless otherwise stated. †*P* values are from the Fisher exact and Wilcoxon rank-sum tests and are shown in bold when less than .05. ‡Other are all surgeries that did not fall under the listed procedure, and the combination refers to surgeries that featured components of more than 1 category.

low event rate in our database, it is likely that our study was underpowered to show a difference in mortality.

Previous reports have demonstrated an association between severe post-surgical AKI and subsequent infection but did not evaluate stage 1 AKI. As early as 1989, Corwin and colleagues[24] were able to demonstrate in a propensity-matched study a significant increase in postoperative infections in patients with severe AKI. Subsequently, Zanardo and colleagues[20] reported outcomes in 775 postsurgical patients that moderate and severe AKI increased rates of infection to 6.1% and 25.9% respectively, compared to 0.8% in those who did not develop AKI. Similarly, Thakar and colleagues[19] analyzed 24,660 patients and found that the development of AKI increased infection rates to 58.5% if dialysis was required and to 23.7% in those not requiring dialysis. These studies clearly demonstrate that severe AKI is associated with increased postoperative infection in adults but don't indicate whether stage 1 AKI similarly worsens outcomes. SooHoo and colleagues[18] evaluated the incidence of infectious complications following AKI development in neonates undergoing the Norwood procedure. In this study, AKI occurred in 40% of subjects, of whom 68% were classified as stage 1 disease. Infectious complications occurred in

TABLE 5. Unadjusted and adjusted primary and secondary outcomes of the entire cohort by AKI

Outcomes	Stage 1 AKI		Stage 2 and 3 AKI	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
In-hospital mortality				
Unadjusted*	4.394 (1.812-10.656)	**.001**	10.508 (3.181-34.709)	**<.001**
Propensity matched†	2.030 (0.597-6.902)	.26	8.089 (0.865-75.664)	.07
Infection				
Unadjusted*	2.992 (2.120-4.224)	**<.0001**	6.003 (3.276-11.003)	**<.001**
Propensity matched†	2.242 (1.373-3.662)	**.001**	3.570 (1.449-8.799)	**.01**
Stroke				
Unadjusted*	2.806 (1.203-6.546)	**.02**	3.592 (0.795-16.231)	.10
Propensity matched†	1.343 (0.454-3.977)	.59	3.872 (0.336-44.602)	.28
ICU length of stay greater than 72 h				
Unadjusted*	3.353 (2.576-4.365)	**<.0001**	7.036 (3.581-13.825)	**<.001**
Propensity matched†	2.381 (1.714-3.309)	**<.0001**	7.674 (3.521-16.728)	**<.001**
Hospital length of stay‡				
Unadjusted*	1.449 (1.353-1.551)	**<.0001**	1.822 (1.578-2.103)	**<.001**
Propensity matched†	1.301 (1.167-1.451)	**<.0001**	1.858 (1.394-2.475)	**<.001**

Values less than .05 are in bold. *AKI*, Acute kidney injury; *CI*, confidence interval; *ICU*, intensive care unit. *Sample size was 1271 for no AKI and 297 for stage 1 AKI and 1271 for no AKI and 52 for stage 2 and 3 AKI. †Sample size was 277 for no AKI and 277 for stage 1 AKI and 92 for no AKI and 49 for stage 2 and 3 AKI. ‡Length of stay was fitted to a negative binomial model.

44% of subjects, and the odds of infectious complications were more than 3-fold greater in patients with AKI compared with those without, after adjusting for confounders ($P = .01$). This particular population lacked the comorbid conditions commonly encountered in adults undergoing cardiac surgery, which limits generalizability. In this study, we are able to demonstrate that stage 1 AKI is independently associated with increased risk of infection, this time in a large adult population.

The mechanism by which AKI increases the risk of infectious complications is currently unknown. However, recent advances in immunobiology suggest that immunoparalysis may play a role. Immunoparalysis is an acquired immunodeficiency[25] that has been observed following sepsis,[26] burns,[27] trauma,[28] and, notably, cardiac bypass surgery.[29] When present, it has been found to increase the risk of subsequent infection and death.[30] While immunoparalysis may be present for as many as 7 days in patients with sepsis, the time course following surgery is often much shorter, with resolution seen within 24 hours.[29] Widespread derangements in the plasma metabolome have been noted in critically ill adult patients with pneumonia and AKI compared with pneumonia without AKI, demonstrating that the metabolome in AKI is distinct and identifiably different from similarly ill patients without AKI.[31] These changes in metabolites could impact immune function, leading to either increased severity or prolonged time to resolution of immunoparalysis. Further studies evaluating the impact of AKI on underlying immune function are necessary and could suggest novel methods to decrease postoperative infection in this population.

On the basis of our results, we would advocate that providers evaluate patients using the KDIGO stage of AKI following surgery, rather than the STS definition of "renal failure," which captures only stage 3 disease. This will allow for better stratification of patients with clinically significant stage 1 AKI and earlier implementation of

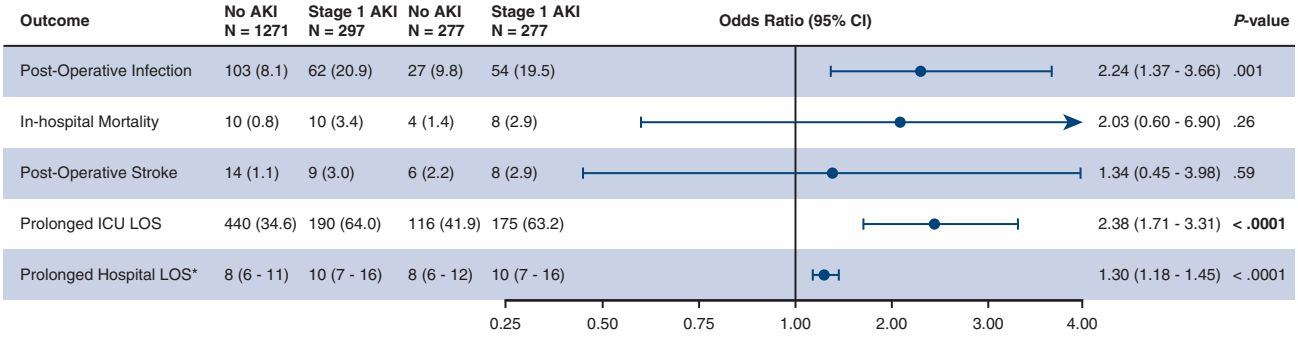

FIGURE 2. Forest plot stage showing odds ratio and 95% CIs for postoperative infection, in-hospital mortality, postoperative stroke, prolonged ICU LOS, and prolonged hospital LOS in patients with stage 1 AKI compared with patients who did not develop AKI. Also shown are rates of primary and secondary outcomes in unmatched and propensity-score matched patients. Data are displayed as numbers and percentages, except where indicated. *Mean and interquartile range. *AKI*, Acute kidney injury; *CI*, confidence interval; *ICU*, intensive care unit; *LOS*, length of stay.

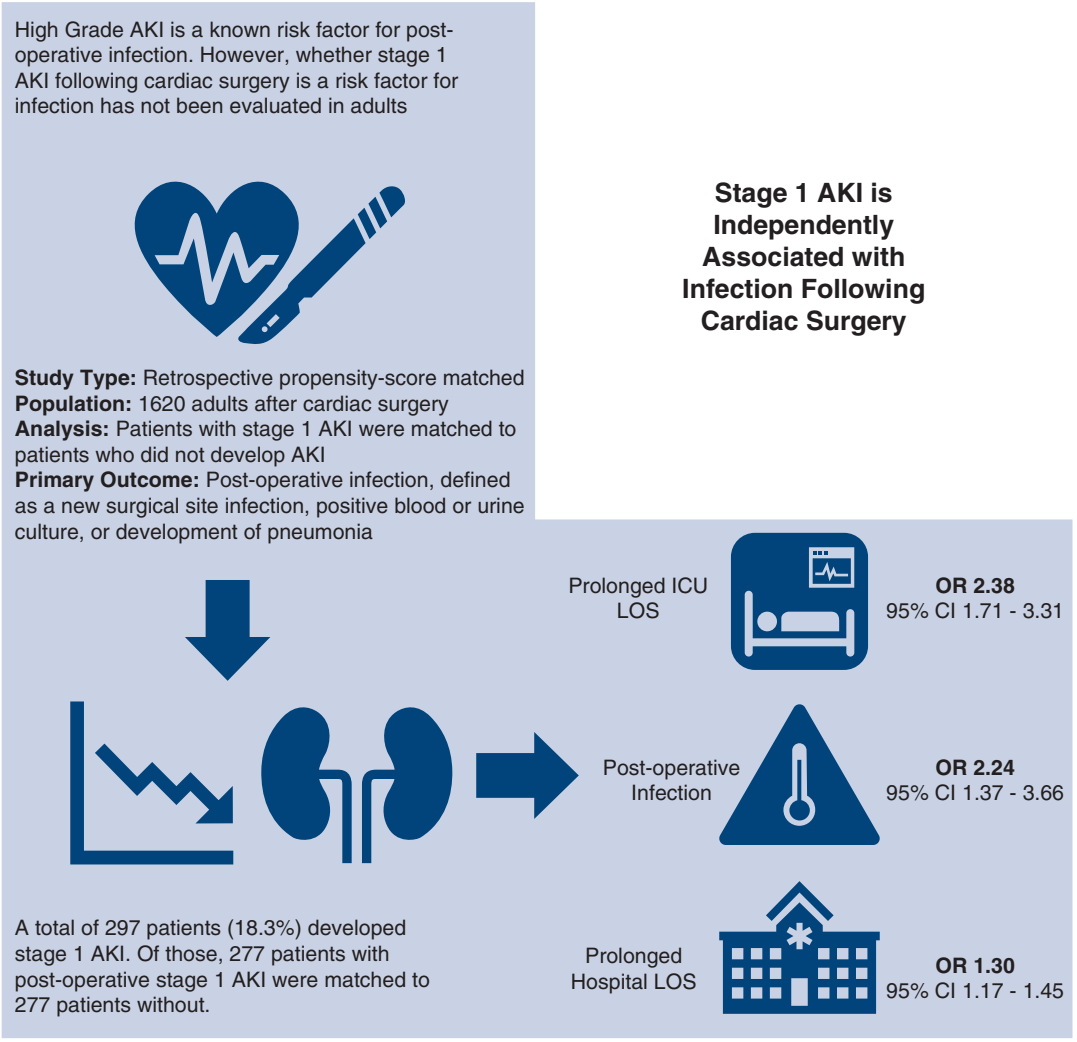

FIGURE 3. Summary of methods and results. *AKI*, Acute kidney injury; *ICU*, intensive care unit; *LOS*, length of stay; *OR*, odds ratio; *CI*, confidence interval.

interventions, such as renal bundles that have been shown to improve patient outcomes.[32] The recently published PrevAKI trial[33] showed that implementation of a "KDIGO-based care bundle," which consisted of avoidance of nephrotoxic agents, discontinuation of angiotensin-converting enzyme inhibitors for the first 48 hours after surgery, avoidance of hyperglycemia (glucose >150 mg/dL), avoidance when possible of contrast, and volume optimization using a pulse contour cardiac output catheter, significantly reduced the rates of AKI compared with standard care alone. The PrevAKI trial also used AKI biomarkers, which have the potential to further identify high-risk patients. Although there was insufficient biomarker data available in this retrospective study, future research should focus on incorporating these tests into a protocol to identify and intervene as early as possible in patients at risk for kidney injury.[34]

Our report does, however, have several important limitations. Given the retrospective nature of this study, it is possible that other confounding factors, such as returns to the operating room, may be present that were not accounted for in the analysis. We are also unable to evaluate the mechanism of increased infection in this population and cannot definitively say whether AKI plays a causal role in subsequent infection. We used a large database combined with the meticulous chart review allowing adjustment for a large number of covariates, and the use of a robust propensity-matching model using variables known to be associated with postoperative infection. We also used median baseline creatinine to define AKI, and associations with subsequent infectious complications persisted.

In conclusion, our study demonstrates that stage 1 postsurgical AKI is associated with increased risk of

postoperative infection and prolonged ICU and hospital LOS in adult patients undergoing nonemergent cardiac surgery. Future studies assessing the pathophysiologic link between AKI and immune dysfunction leading to subsequent infectious complications are needed. Early identification of stage 1 AKI will allow for earlier implementation of renal bundles, which have been shown to improve patient outcomes. Treatment strategies focused on prevention, early recognition, and optimal medical management of AKI may decrease significant postoperative morbidity.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: acute kidney injury, postoperative infection, cardiopulmonary bypass, postoperative complications, propensity-score matching, cardiac surgery

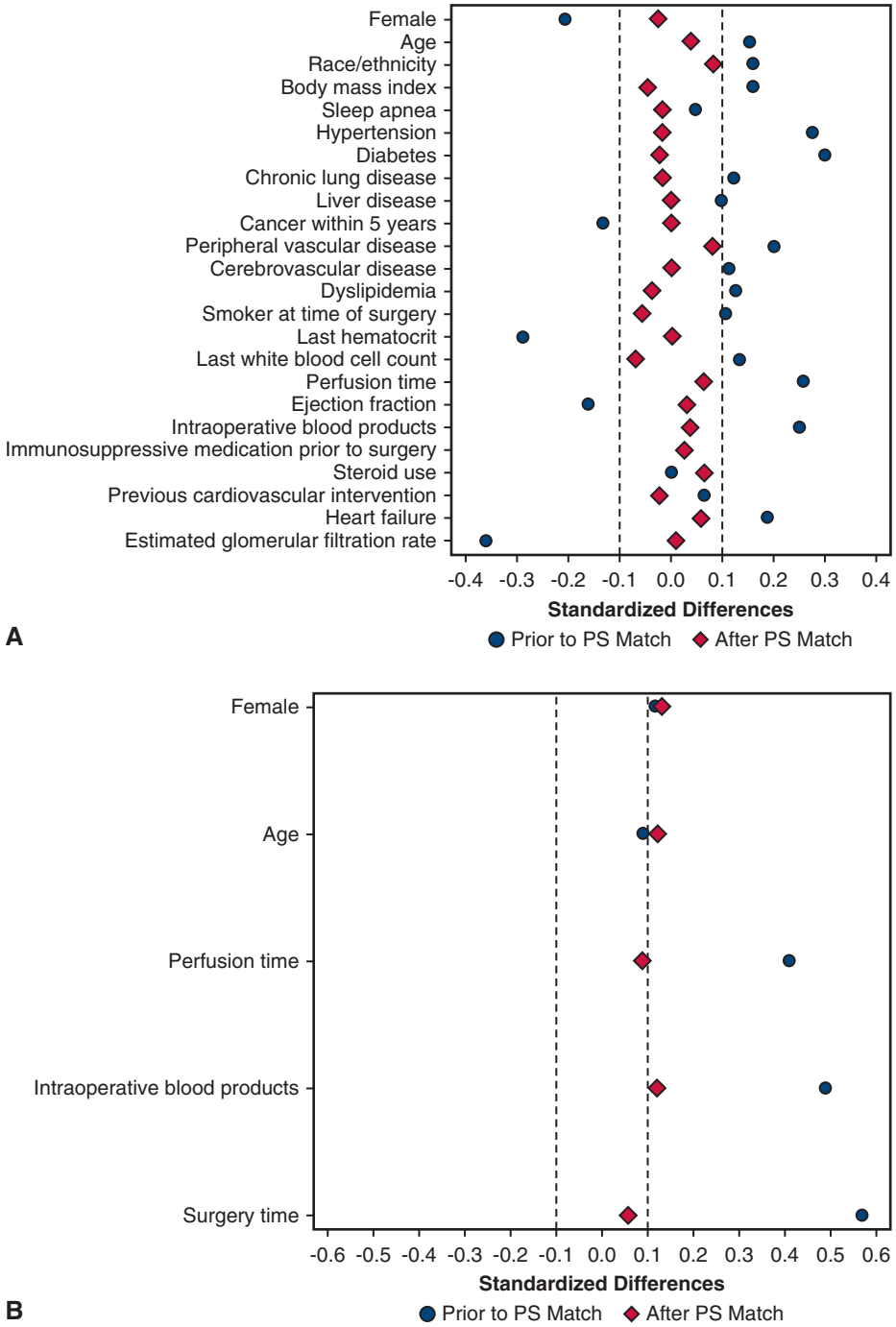

FIGURE E1. A, Standardized differences before and after propensity match for patients with stage 1 acute kidney injury. B, Standardized differences before and after propensity match for patients with stage 2 and 3 acute kidney injury. *PS*, Propensity score.

TABLE E1. Comparison of baseline characteristics of patients by occurrence of AKI after propensity-score matching

Characteristics	No AKI (n = 277) N (%)*	Stage 1 AKI (n = 277) N (%)*	*P* value†	No AKI (n = 92) N (%)*	Stage 2 and 3 AKI (n = 52) N (%)*	*P* value†
Female	65 (23.5)	62 (22.4)	.76	30 (32.6)	19 (38.8)	.46
Age, y, mean (SD)	62.5 (13.3)	63.0 (13.4)	.65	60.3 (12.6)	62.0 (15.0)	.51
Race/ethnicity						
White	193 (69.7)	203 (73.3)	.69	69 (75.0)	38 (77.6)	.92
Hispanic	44 (15.9)	41 (14.8)		12 (13.0)	7 (14.3)	
Black	26 (9.4)	19 (6.9)		6 (6.5)	2 (4.1)	
Other/unknown	14 (5.1)	14 (5.1)		5 (5.4)	2 (4.1)	
Body mass index, mean (SD)	29.3 (6.5)	29.0 (6.3)	.59	28.6 (5.9)	29.3 (7.0)	.54
Comorbidities						
Sleep apnea	62 (22.4)	60 (21.7)	.84	25 (27.2)	8 (16.3)	.15
Hypertension	220 (79.4)	218 (78.7)	.83	71 (77.2)	39 (79.6)	.74
Diabetes mellitus	114 (41.2)	111 (40.1)	.80	29 (31.5)	18 (36.7)	.53
Chronic lung disease	64 (23.1)	62 (22.4)	.84	21 (22.8)	11 (22.5)	.96
Liver disease	9 (3.3)	9 (3.3)	1.0	0 (0)	1 (2.0)	.35
Congestive heart failure	117 (42.2)	125 (45.1)	.49	38 (41.3)	22 (44.9)	.68
Cancer within 5 years	17 (6.1)	17 (6.1)	1.0	11 (12.0)	8 (16.3)	.47
Peripheral vascular disease	19 (6.9)	25 (9.0)	.35	4 (4.4)	3 (6.1)	.69
Cerebrovascular disease	36 (13.0)	36 (13.0)	1.0	14 (15.2)	5 (10.2)	.46
Dyslipidemia	178 (64.3)	173 (62.5)	.66	59 (64.1)	20 (61.2)	.73
Baseline platelets, mean (SD)	221.9 (58.8)	214.1 (69.1)	.20	219.9 (58.0)	216.4 (90.2)	.82
Baseline eGFR, mean (SD)	73.7 (18.4)	13.8 (20.3)	.93	77.2 (21.2)	76.6 (24.3)	.90
Smoker at time of surgery	78 (28.2)	71 (25.6)	.50	25 (27.2)	9 (18.4)	.24
History of IV drug abuse	14 (5.1)	11 (4.0)	.54	6 (6.5)	1 (2.0)	.42
Last hematocrit, mean (SD)	40.1 (6.3)	40.2 (6.0)	.97	40.9 (6.1)	39.7 (5.7)	.25
Last white blood cell count, mean (SD)	7.8 (2.6)	7.6 (2.2)	.42	7.4 (2.6)	6.6 (2.1)	.09
Ejection fraction, mean (SD)	51.4 (14.9)	51.9 (15.4)	.73	52.0 (15.5)	51.4 (13.8)	.80
Perfusion time, mean (SD)	142.9 (75.1)	147.7 (78.5)	.47	147.9 (71.8)	153.9 (60.9)	.62
Surgical time, hours, mean (SD)	6.8 (2.0)	6.8 (2.1)	.79	7.1 (2.1)	7.2 (2.1)	.75
Intraoperative blood products	123 (44.4)	128 (46.2)	.67	47 (51.1)	28 (57.1)	.49
Red blood cell units, mean (SD)	0.7 (1.8)	1.0 (2.7)	.14	1.0 (2.9)	1.9 (3.9)	.18
Platelet units, mean (SD)	0.6 (1.0)	0.8 (1.1)	.27	0.7 (1.1)	0.9 (1.2)	.24
Fresh frozen plasma, mean (SD)	1.4 (2.7)	1.8 (3.1)	.16	1.8 (4.0)	2.4 (4.0)	.38
Cryoprecipitate units, mean (SD)	0.06 (0.3)	0.08 (0.4)	.59	0.11 (0.5)	0.07 (0.3)	.59
Immunosuppressive medication before surgery						
No	218 (78.7)	222 (80.1)	.84	74 (80.4)	38 (77.6)	.72
Yes	7 (2.5)	8 (2.9)		3 (3.3)	3 (6.1)	
Unknown	52 (18.8)	47 (17.0)		15 (16.3)	8 (16.3)	
Steroid use						
No	246 (88.8)	245 (88.5)	.96	80 (87.0)	40 (81.6)	.60
Yes	6 (2.2)	7 (2.5)		4 (4.4)	4 (8.2)	
Unknown	25 (9.0)	25 (9.0)		8 (8.7)	5 (10.2)	

(Continued)

TABLE E1. Continued

Characteristics	No AKI (n = 277) N (%)*	Stage 1 AKI (n = 277) N (%)*	*P* value†	No AKI (n = 92) N (%)*	Stage 2 and 3 AKI (n = 52) N (%)*	*P* value†
Previous cardiovascular intervention	95 (34.3)	92 (33.2)	.79	36 (39.1)	15 (30.6)	.32
Surgical type						
Aneurysm repair	20 (7.2)	20 (7.2)	1.0	11 (12.0)	7 (14.3)	.99
Valve surgery	56 (20.2)	56 (20.2)		22 (23.9)	11 (22.5)	
Coronary artery bypass	104 (37.6)	104 (37.6)		28 (30.4)	14 (28.6)	
Left ventricular assist device	5 (1.8)	5 (1.8)		0 (0)	0 (0)	
Other	36 (13.0)	36 (13.0)		13 (14.1)	8 (16.3)	
Combined	556 (20.2)	56 (20.2)		18 (19.6)	9 (18.4)	
Family history cardiovascular disease	74 (26.7)	56 (20.2)	.07	20 (21.7)	13 (26.5)	.52
New York Heart Association class						
None	163 (58.8)	154 (55.6)	.58	55 (59.8)	27 (55.1)	.21
Class I	4 (1.4)	1 (0.4)		5 (5.4)	0 (0)	
Class II	29 (10.5)	35 (12.6)		7 (7.6)	5 (10.2)	
Class III	58 (50.9)	63 (22.7)		21 (22.8)	11 (22.5)	
Class IV	23 (8.3)	24 (8.7)		4 (4.4)	6 (12.2)	

AKI, Acute kidney injury; *SD*, standard deviation; *eGFR*, estimated glomerular filtration rate; *IV*, intravenous. *Values are frequency and column percent unless otherwise stated.
†*P* values are from the χ^2 or Fisher exact and *t* test.