Published in final edited form as:

Am J Kidney Dis. 2016 June ; 67(6): 872–880. doi:10.1053/j.ajkd.2015.07.022.

Acute Kidney Injury After Major Surgery: A Retrospective Analysis of Veterans Health Administration Data

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Abstract

Background—Few trials of acute kidney injury (AKI) prevention after surgery have been conducted and most observational studies focus on AKI following cardiac surgery. The frequency of, risk factors for, and outcomes after AKI following other types of major surgery have not been well characterized, and may present additional opportunities for trials in AKI.

Study Design—Observational cohort study.

Setting & Participants—3.6 million US veterans followed up from 2004–2011 for the receipt of major surgery (cardiac; general; ear, nose, and throat [ENT], thoracic, vascular, urologic, orthopedic) and post-operative outcomes.

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Contributions: Research idea and study design: MEG, YS, JC; data acquisition: MZM, ZS, KK-Z, CPK; data analysis/interpretation: CPK, YS, MEG, KM, SB; statistical analysis: YS; supervision or mentorship: JC, CPK, KK-Z. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. MEG takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Financial Disclosure: None of the authors have relevant conflicts of interest. JC has consulted for Amgen and Merck and has an investigator-initiated grant from Amgen. JC also has a provisional patent submitted for glomerular filtration rate estimation using a panel of biomarkers. CPK and KKZ are employees of the US Department of Veterans Affairs.

Factors—Demographics, health characteristics, and type of surgery.

Outcomes—Post-operative AKI defined by the KDIGO creatinine criteria, post-operative length of stay, end-stage renal disease (ESRD), and mortality.

Results—Post-operative AKI occurred in 11.8% of the 161,185 major surgery hospitalizations (stage 1, 76%; stage 2, 15%, stage 3 [without dialysis], 7%; AKI requiring dialysis, 2%). Cardiac surgery had the highest post-operative AKI risk (relative risk [RR], 1.22; 95% CI, 1.17-1.27), followed by general (reference), thoracic (RR, 0.92; 95% CI, 0.87-0.98), orthopedic (RR, 0.70; 95% CI, 0.67-0.73), vascular (RR, 0.68; 95% CI, 0.64-0.71), urologic (RR, 0.65; 95% CI, 0.61-0.69), and ENT (RR, 0.32; 95% CI, 0.28-0.37) surgery. Risk factors for post-operative AKI included older age, African-American race, hypertension, diabetes mellitus, and, when eGFR < 90 ml/min/1.73 m², lower eGFR. Participants with post-operative AKI had longer length of stay (15.8 vs. 8.6 days) and higher rates of 30-day hospital readmission (21% vs. 13%), 1-year ESRD (0.94% vs. 0.05%) and mortality (19% vs. 8%), with similar associations by type of surgery and more severe stage of AKI relating to poorer outcomes.

Limitations—Urine output was not available to classify AKI; cohort included mostly men.

Conclusions—AKI was common after major surgery, with similar risk factor and outcome associations across surgery type. These results can inform the design of clinical trials in post-operative AKI to the non-cardiac surgery setting.

Keywords

acute kidney injury (AKI); postoperative AKI; surgery; surgical complication; end-stage renal disease (ESRD); mortality; hospital length of stay; KDIGO creatinine criteria; kidney function

Acute kidney injury (AKI) is increasingly recognized as a serious post-operative complication.¹⁻⁴ Approximately one-third of all hospital-acquired cases of AKI occur in the post-operative setting,^{4, 5} and observational evidence links AKI incidence to a host of adverse outcomes, including progression to chronic kidney disease (CKD), end-stage renal disease (ESRD), and death.^{1, 2, 6, 7} Unfortunately, few effective preventative or therapeutic interventions for AKI have been identified. Novel strategies and therapeutics are under development, but randomized clinical trials are needed to test their efficacy.

Clinical prevention trials are most efficient when they capture a relatively frequent event of homogeneous etiology which occurs with predictable timing. Major surgery is thus a convenient setting for studying AKI prevention. Past clinical trials have focused largely on the efficacy of interventions in the setting of cardiac surgery.⁸⁻¹⁸ Few trials have assessed interventions in non-cardiac surgery, in part because the incidence, risk factors, and outcomes of post-operative AKI in this setting are not well established. Indeed, existing studies of post-operative AKI risk in the non-cardiac setting are limited by outdated definitions of AKI, variable assessment of baseline creatinine, and characterization of AKI by diagnostic codes – a method which has low sensitivity for identifying the milder cases of AKI.¹⁹⁻²²

The objective of this study was to determine the frequency of, risk factors for, and outcomes after AKI following multiple types of major surgery for the dual purpose of informing

clinical trial design and identifying patients at high risk for AKI in the context of major surgery. Using a cohort of 3.5 million US veterans, we evaluated the incidence of AKI defined according to the KDIGO (Kidney Disease: Improving Global Outcomes) creatinine criteria after major cardiac, general, ENT (ear, nose, and throat), thoracic, vascular, urological, and orthopedic surgeries, assigning baseline creatinine as the mean outpatient creatinine in the year prior to surgery. We also investigated risk factors for post-operative AKI and its associated outcomes, both overall and by type of surgery.

METHODS

Study Population

The study population was derived from a large cohort consisting of all patients with eGFR ≥ 60 ml/min/1.73 m² (calculated by the CKD-EPI [CKD Epidemiology Collaboration] creatinine equation²³) measured between October 1, 2004 and September 30, 2006 in the national Veterans Affairs (VA) Corporate Data Warehouse LabChem data files, with follow up until September 15, 2011 (N=3,582,478).²⁴ For the present study, patients were included at the first instance of major surgery; for these patients, hospital admission date was considered baseline. Patients undergoing major surgery more than 30 days after admission, as well as kidney surgeries, transplant surgeries, or gynecological surgeries, were not included, the latter two due to very small numbers (<1% of major surgeries in the VA). Persons who developed eGFR <60 ml/min/1.73 m² between original cohort inclusion date and major surgery date were included (12% of the cohort), but those developing ESRD were excluded, for a final study population of 161,185 participants (**Figure S1**, available as online supplementary material).

AKI Definition

Staging of AKI was according to KDIGO creatinine-based criteria from the date of surgery. Stage 1 encompassed a creatinine increase of 0.3 mg/dL over 48 hours or 50%-99% increase within 7 days; stage 2, a 100%-200% increase within 7 days; stage 3, 200% increase or the receipt of renal replacement therapy (RRT).²⁵ Stage 3 AKI was further subdivided according to the presence or absence of a procedural code for dialysis (39.95). Baseline creatinine was defined as mean outpatient serum creatinine 7-365 days prior to hospitalization. This time window was designed to exclude acute fluctuations related to the need for surgery. In sensitivity analysis, baseline creatinine was defined as the first inpatient creatinine prior to surgery.

Definitions of Covariates and Outcomes

Surgery type was determined from *ICD-9-CM* procedure codes in the VA Inpatient Medical Dataset and categorized according to the Clinical Classifications Software procedural classification system: cardiac; ENT; general (gastrointestinal/abdominal); orthopedic; thoracic; urological; and vascular (**Table S1**). Laparoscopic surgery, hypertension, diabetes, coronary artery disease, congestive heart failure, peripheral artery disease, cerebrovascular disease, liver disease, and lung disease were defined by a qualifying inpatient or outpatient ICD-9-CM code (**Table S2**).^{26, 27} Systolic and diastolic blood pressure and body mass index (BMI) were defined as the average outpatient value in the 7-365 days prior to admission

using the VA Corporate Data Warehouse files. Medication use (angiotensin-converting enzyme [ACE] inhibitor, angiotensin receptor blocker [ARB], diuretic, and statin) was determined by VA Pharmacy dispensation records in the 3 months prior to surgery. Outcomes included total hospital length of stay (days), post-procedure length of stay (days), and in-hospital mortality, as well as hospital readmission (from time of hospital discharge), ESRD, and mortality within 30 days, 90 days, 6 months and 1 year after surgery. Mortality and ESRD were determined through linkage to the VA Vital Status Files and the US Renal Data System, respectively.

Statistical Analysis

Baseline characteristics were compared by AKI status and stage using ANOVA. Modified Poisson regression was used to determine the association of baseline characteristics with AKI (any stage) in three models: univariate, demographic-adjusted (age, sex, and race), and fully adjusted (age, sex, race, BMI, hypertension, baseline eGFR, diabetes, congestive heart failure, peripheral artery disease, cerebrovascular disease, lung disease, liver disease, BMI, ACE inhibitor/ARB use, diuretic use, statin use, surgery type, laparoscopic procedure, and hospital day of surgical procedure [hospital day 0-4, 5-14, 15-30]).²⁸ Because BMI had a nonlinear relationship with AKI, it was modeled as a linear spline, with a knot at 25 kg/m². Similarly, eGFR was modeled as a linear spline with knots at 60 and 90 ml/min/1.73 m². Proteinuria was considered as a covariate but was missing in 90% of the study population and thus not included in the primary analysis. The relationship between AKI (any stage) and subsequent adverse outcomes was assessed using Poisson regression using the same models. Absolute risks of adverse outcomes were estimated using a Kaplan-Meier approach (censoring for death in the case of ESRD and hospital readmission). All analyses were performed in the overall population and by subgroup of surgery type using Stata MP 12 (StataCorp LP, College Station, TX).

RESULTS

Baseline Characteristics

Among the 161,185 participants who underwent an eligible major surgery during the study period, mean age was 64 years, 96.3% were male, and 16.9% were African-American (**Table 1**). Average blood pressure in the year prior to surgery was 133/76 mmHg; average BMI was 29 kg/m². Mean eGFR was 80 ml/min/1.73 m², and 12.0% of the population had eGFR <60 ml/min/1.73 m². The most common type of surgery was general (27.7%), followed by orthopedic (20.8%), vascular (16.5%), and cardiac (13.8%). Persons undergoing ENT, general, and orthopedic surgery tended to be slightly younger (61, 63, and 63 years, respectively), whereas those undergoing cardiac and vascular surgery were slightly older (65 and 66 years, respectively). Baseline eGFR <60 ml/min/1.73 m² was most common among patients undergoing cardiac (13.1%), orthopedic (12.4%), and vascular (15.2%) surgery.

Risk of Postoperative AKI

Overall, 11.8% (19,025) of the cases of major surgery were complicated by post-operative AKI. Stage 1 AKI made up 76.1% of the cases, followed by stage 2 (14.6%), stage 3 without RRT (7.1%), and stage 3 with RRT (2.2%). The occurrence of post-operative AKI (all

stages) varied by type of surgery, with the highest rates after cardiac (18.7%), general (13.2%), and thoracic (12.0%) surgeries (**Figure 1**). On the other hand, the absolute number of cases was greatest after general surgery (n=5,877). In fully adjusted models with general surgery as the reference, the relative risk (RR) of AKI was higher in cardiac surgery (RR, 1.22; 95% confidence interval [CI], 1.17-1.27), and lower in other types of surgery, including thoracic (RR, 0.92; 95% CI, 0.87-0.98) and orthopedic (RR, 0.70; 95% CI, 0.67-0.73) (**Table 2**). Laparoscopic surgery was associated with lower risk of AKI (RR, 0.72; 95% CI, 0.68-0.77). Surgeries performed later in the hospital course had higher risk of AKI than those performed within the first 5 days of admission (5-14 days after admission: RR, 1.33 [95% CI, 1.28-1.38]; 15-30 days after admission: RR, 1.58 [95% CI, 1.46-1.71]).

Risk Factors for Postoperative AKI

In the overall population, older age, male sex, African American race, and higher BMI (if over 25 kg/m²) were among the most consistent risk factors, with each associated with higher risk of post-operative AKI in univariate, demographic-adjusted, and fully-adjusted models. There was a non-linear association of eGFR and AKI, with both lower (when levels were <90 ml/min/1.73 m²) and higher (when levels were ≥ 90 ml/min/1.73 m²) levels of eGFR conferring higher AKI risk (**Figure S2**). Liver disease had a particularly strong relationship with post-operative AKI (RR, 1.71; 95% CI, 1.56-1.87). Use of ACE inhibitor/ARB or diuretics was associated with slightly higher risk of post-operative AKI (ACE inhibitor/ARB: RR, 1.20 [95% CI, 1.16-1.23]; diuretics: RR, 1.18 [95% CI, 1.14-1.21]); statin use was associated with slightly lower risk (RR, 0.96; 95% CI, 0.93-0.99). Additional risk factors for post-operative AKI are shown in **Table 2**.

By subgroup of surgery type, associations were fairly similar (**Table S3**). Risk factors that most consistently demonstrated significant associations with AKI across types of surgery were African American race and higher BMI. Notable differences in risk relationships included the relationship between diabetes mellitus and post-operative AKI, which was strongest in orthopedic surgery, and malignancy and AKI, which was strongest in urological surgery. In addition, later timing of surgery during the hospital stay was associated with higher risk of post-operative AKI for nearly all types of surgery compared with general surgery.

Outcomes After Postoperative AKI

Patients with post-operative AKI had longer hospital length of stay (15.8 vs. 8.6 days), higher rates of 30-day post-discharge readmission (21.1% vs. 13.3%), higher inpatient mortality (8.2% vs. 1.1%), higher 1-year mortality (18.9% vs. 8.0%), and higher 1-year ESRD (0.94% vs. 0.05%) (**Table 3**). There was also an increase in postoperative length of stay, inpatient mortality, 1-year mortality, and 1-year ESRD with increasing severity of AKI. For example, the unadjusted risk of in-hospital mortality was 7.8-times higher in stage 3 AKI-RRT compared with stage 1 AKI; the comparable RRs of 1-year mortality and ESRD were 3.7 and 20.0, respectively. By type of surgery, unadjusted associations with any-stage AKI as well as increasing stage of AKI were similar. For example, the unadjusted RR associated with any-stage AKI for 1-year mortality ranged from 1.61 after ENT surgery to 3.02 after vascular surgery.

In fully adjusted analyses, the incidence rate ratio of 30-day readmission after any stage AKI compared with no AKI was 1.52 (95% CI, 1.46-1.57); the risk of in-hospital mortality associated with post-operative AKI was 6.69 (95% CI, 6.20-7.21), 1-year mortality was 2.43 (95% CI, 2.33-2.54), and 1-year ESRD was 10.46 (95% CI, 7.61-14.38). These associations were statistically significant and similar in magnitude in nearly all surgical subtypes (**Table 4**). Compared to AKI after general surgery, AKI after thoracic and orthopedic surgery had slightly better outcomes, and AKI after vascular surgery had slightly higher mortality.

Sensitivity Analysis

There were 128,867 participants with an inpatient pre-operative serum creatinine to use as baseline; 120,017 also had an outpatient baseline creatinine. There was an 89% concordance in AKI status using the different strategies for assigning baseline creatinine. The inpatient baseline was higher than the outpatient baseline creatinine in 55% of participants (AKI concordance, 91%) and lower than the outpatient baseline in 37% of participants (AKI concordance, 83%). The overall rate of AKI was 12.3% using the inpatient baseline, and most risk factors for AKI were similar. Associations with adverse outcomes were similar if slightly attenuated: the risk of 30-day readmission associated with any stage AKI was 1.45 (95% CI, 1.39-1.51), whereas the risk of in-hospital mortality was 4.78 (95% CI, 4.44-5.14), 1-year mortality was 2.02 (95% CI, 1.92-2.12), and 1-year ESRD was 7.14 (95% CI, 5.25-9.70).

DISCUSSION

In this national study of US veterans undergoing major surgery, the overall rate of post-operative AKI was 11.8%, ranging from 4.1% after ENT surgery, to 13.2% after general surgery, to 18.7% after cardiac surgery. Risk factors for post-operative AKI were fairly uniform by type of surgery and consistently included African American race, higher BMI, liver disease, and lower eGFR if $eGFR < 90 \text{ ml/min/1.73 m}^2$. Higher AKI stage was associated with worse outcomes. Results were robust to different strategies for assigning baseline creatinine and different types of major surgery. They suggest that postoperative AKI is common – not only in cardiac surgery, but also in general, thoracic, orthopedic, and vascular surgery – and relatively homogeneous in terms of risk factors and outcomes. These findings should be useful in the design of clinical trials of post-operative AKI prevention among persons undergoing major surgery, and potentially enable extension from the traditional trial setting of cardiac surgery to other more common types of major surgery. Results also provide detailed prognostic information by type of surgery which could be used by health care providers in patient counseling.

This study greatly expands upon present knowledge of the risks of post-operative AKI after non-cardiac surgery. Prior studies in this area have focused on specific types of surgery, such as bariatric surgery²⁹ or liver transplantation^{30, 31} or used different definitions of AKI. For example, Kheterpal et al evaluated the incidence of AKI in a single university hospital after any non-cardiac, non-transplant, non-urolological surgery that required a hospital stay of at least 2 days.¹⁹ Among 15,102 persons with a creatinine clearance $\geq 80 \text{ ml/min}$, 0.8% of participants developed a creatinine clearance $< 50 \text{ ml/min}$, and 0.1% required RRT. In a

subsequent study using the American College of Surgeons–National Surgical Quality Improvement Program (ACS-NSQIP) data, 1.0% of participants had an increase in serum creatinine >2 mg/dL above the pre-operative value and 0.6% required in-hospital dialysis.²⁰ Neither definition is directly comparable to current guideline recommendations; however, most cases identified in the ACS-NSQIP study²⁰ would reflect stage 3, and thus rates are quite similar to those observed in the present study. In contrast, AKI incidence in the single center study was low, possibly reflecting the selection of a low-risk population, with higher eGFR, lower age, and lower rates of diabetes and hypertension. Part of this variation in incidence may also reflect the era of the study. Siddiqui et al. observed that the rate of dialysis-requiring AKI after major surgery increased over time, from an incidence of 0.2% in 1995 to 0.6% incidence in 2009.³² Our study adds to this body of literature by examining AKI incidence across the full range of severity using the international consensus definition of AKI, and evaluating differences by type of surgery.

The observed associations between baseline characteristics and post-operative AKI were remarkably similar across categories of major surgery. Consistent with large meta-analyses of hospitalized AKI, older age, male sex, African American race, diabetes, and hypertension were associated with AKI overall and in most surgery types.^{33, 34} In contrast, the relationship between eGFR and AKI was slightly different than previous work.³³⁻³⁵ In our study, eGFR had a U-shaped association with post-operative AKI, with lower levels below 90 ml/min/1.73 m² and higher levels at or above 90 ml/min/1.73 m² associated with higher AKI risk. Previous studies have shown higher risk with lower eGFR below 60 ml/min/1.73 m² but a flat association between eGFR and AKI in the upper ranges of eGFR.³³⁻³⁵ The difference in pattern of association may be due to the method of identifying AKI, since previous studies used billing codes, which tend to identify more severe cases.²¹ Because creatinine-based criteria define stage 1 AKI by a 50% increase in serum creatinine, those with lower baseline creatinine may be more likely to meet AKI criteria through laboratory errors or fluctuations in volume status. Alternatively, persons with higher eGFR may be at particular risk in the peri-operative setting, perhaps due to smaller body size or the presence of frailty.

Our findings provide support for the notion that AKI leads to adverse outcomes, although causality cannot be definitively determined in an observational study.^{36, 37} Associations with outcomes (particularly in-hospital mortality and 1-year ESRD) were strong, with most fully adjusted risk ratios exceeding 5. Moreover, associations were consistent across subgroups of surgery type and using different strategies for assigning baseline creatinine. There was a clear risk gradient in that persons with more advanced stages of AKI had worse outcomes. Future clinical trials are needed to quantify differences in outcomes – length of stay, hospital readmission, mortality, and CKD progression – when AKI is avoided.

Because of the retrospective nature of our study, certain data elements were not available. There is likely interplay between the baseline risk factors and intraoperative elements. Tenuous hemodynamic status during surgery may result in inadequate kidney perfusion. Persons with a history of AKI may be predisposed to post-operative AKI. Persons with liver disease have altered splanchnic and systemic circulation and may be especially susceptible to hemodynamic fluctuations.³⁸ Older age, hypertension, and CKD may associate with a

stiffer vasculature, leading to higher intraoperative blood pressure requirement.³⁹ On the other hand, our study was designed to inform clinical trials, and intraoperative elements would generally not be available nor considered at patient enrollment. Other limitations include a reliance on laboratory data obtained as part of routine clinical care to establish “baseline” kidney function and AKI, and a lack of information about urine output. However, we tested other definitions of baseline creatinine with reassuringly similar results. The use of additional biomarkers of kidney function, such as cystatin C, might have more robust results, although data are mixed.⁴⁰⁻⁴² Finally, the VA population represents a select cohort within the US population: majority male with excellent access to health care. Hospital readmissions reflect only those within the VA system.

The strengths of this study include its large study population, identification of AKI through laboratory values, and careful evaluation of incidence, risk factors, and outcomes across categories of major surgery and stage of AKI. Long-term outcomes were obtained through linkage to reliable US sources. The results provide important information for clinical trial design in non-cardiac surgery settings, which may greatly expand the pool of potential AKI prevention trial participants. Furthermore, our results suggest that AKI risk prediction and prognosis may be similar across surgical setting. Thus, this study can be used to both predict frequency of events and enrich trial populations for high-risk participants in the setting of major surgery.

In summary, AKI is common after both cardiac and non-cardiac major surgery, with similar risk factor and adverse outcome associations across surgery type. These findings provide important information that can inform future research in the development of AKI prevention strategies, particularly within clinical trials in the peri-operative setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Some aspects of this study were presented as a poster at the American Society of Nephrology Annual Kidney Week on November 13, 2014, in Philadelphia, Pennsylvania. Some of the data reported here have been supplied by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

Support: MG receives support from the National Institute of Diabetes and Digestive and Kidney Diseases (K08DK092287). The current project was also supported by a grant from the National Kidney Foundation (which received funding from Thrasos and Abbvie) as well as grant R01DK096920 to CPK and KKZ and is the result of work supported with resources and the use of facilities at the Memphis VA Medical Center and the Long Beach VA Medical Center. Support for VA/Centers for Medicare & Medicaid Services data is provided by the US Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, VA Information Resource Center (project numbers SDR 02-237 and 98-004). Opinions expressed in this paper are those of the authors and do not necessarily represent the opinion of the Department of Veterans Affairs. The sponsors had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; in the preparation, review, or approval of the manuscript; and in the decision to submit the manuscript for publication.

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Figure 1.
Unadjusted rates of acute kidney injury, by surgery type and stage

Table 1

Baseline characteristics of persons undergoing major surgery, overall and by surgery type

	Overall (N=161185)	Cardiac (n=22179)	ENT (n=4741)	General (n=44597)	Orthopedic (n=33564)	Thoracic (n=11779)	Urologic (n=17704)	Vascular (n=26621)
Demographics								
Age, y	64 (10)	65 (9)	61 (11)	63 (12)	63 (11)	64 (10)	65 (9)	66 (9)
Female sex	5992 (3.7%)	273 (1.2%)	438 (9.2%)	2599 (5.8%)	1381 (4.1%)	844 (7.2%)	6 (0.03%)	451 (1.7%)
African American race	27265 (17%)	2260 (10%)	984 (21%)	7834 (18%)	6704 (20%)	2058 (17%)	4085 (23%)	3340 (13%)
Comorbidities								
Systolic BP, mmHg	133 (14)	133 (14)	133 (13)	131 (13)	133 (13)	131 (13)	134 (13)	135 (14)
Diastolic BP, mmHg	76 (9)	75 (9)	77 (9)	76 (9)	76 (9)	75 (8)	77 (8)	74 (9)
BMI, kg/m ²	29 (6)	30 (5)	30 (7)	29 (7)	29 (6)	27 (6)	29 (5)	28 (5)
Baseline eGFR, ml/min/1.73m ²	80 (17)	77 (16)	83 (17)	81 (18)	81 (18)	82 (17)	79 (16)	77 (17)
eGFR<60 ml/min/1.73m ²	19340 (12%)	2900 (13%)	408 (8.6%)	4852 (11%)	4151 (12%)	1107 (9.4%)	1870 (11%)	4052 (15%)
eGFR<45 ml/min/1.73m ²	3289 (2.0%)	400 (1.8%)	65 (1.4%)	765 (1.7%)	889 (2.6%)	146 (1.2%)	365 (2.1%)	659 (2.5%)
Diabetes mellitus	56706 (35%)	10170 (46%)	1442 (30%)	13948 (31%)	13400 (40%)	3153 (27%)	4868 (27%)	9725 (37%)
Hypertension	121539 (75%)	19107 (86%)	3337 (70%)	31264 (70%)	25063 (75%)	8170 (69%)	12361 (70%)	22237 (84%)
Coronary artery disease	57043 (35%)	17788 (80%)	1030 (22%)	10813 (24%)	8657 (26%)	3165 (27%)	3429 (19%)	12161 (46%)
Congestive heart failure	16805 (10%)	4340 (20%)	322 (6.8%)	3870 (8.7%)	3422 (10%)	936 (7.9%)	866 (4.9%)	3049 (11%)
Cerebral vascular disease	29381 (18%)	4751 (21%)	512 (11%)	4843 (11%)	4245 (13%)	1458 (12%)	1400 (7.9%)	12172 (46%)
Peripheral arterial disease	32093 (20%)	3878 (17%)	394 (8.3%)	4440 (10%)	6399 (19%)	1478 (13%)	1236 (7.0%)	14268 (54%)
Lung disease	52572 (33%)	6856 (31%)	1500 (32%)	14159 (32%)	9529 (28%)	6468 (55%)	4098 (23%)	9962 (37%)
Malignancy	48511 (30%)	2739 (12%)	2329 (49%)	15233 (34%)	4515 (13%)	7671 (65%)	11645 (66%)	4379 (16%)
Liver disease	1860 (1.2%)	105 (0.47%)	50 (1.1%)	885 (2.0%)	403 (1.2%)	101 (0.86%)	69 (0.39%)	247 (0.93%)
Statin use	45401 (28%)	9316 (42%)	1048 (22%)	10011 (22%)	8397 (25%)	2984 (25%)	4150 (23%)	9495 (36%)
Diuretic use	42514 (26%)	7360 (33%)	1049 (22%)	10759 (24%)	9334 (28%)	2661 (23%)	3531 (20%)	7820 (29%)
ACE inhibitor/ARB use	64973 (40%)	12932 (58%)	1590 (34%)	15267 (34%)	13076 (39%)	3796 (32%)	5726 (32%)	12586 (47%)
Surgical Factors								
Laparoscopic	10611 (6.6%)	0 (0%)	0 (0%)	10611 (24%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Note: Values for categorical variables are given as number (percentage); for continuous variables, as mean ± standard deviation.

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ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blockers, BMI, body mass index; BP, blood pressure; eGFR: estimated glomerular filtration rate, ENT: ear, nose, and throat

Table 2

Risk factor associations with post-operative acute kidney injury in persons undergoing major surgery

	Unadjusted RR (95% CI)	Demographic-adjusted RR (95% CI)	Fully adjusted RR (95% CI)
Baseline variables			
Age, per 10 years older	1.13 (1.11, 1.14)	1.13 (1.11, 1.14)	1.10 (1.09, 1.12)
Female sex	0.52 (0.47, 0.57)	0.57 (0.52, 0.63)	0.59 (0.54, 0.66)
African American Race	1.28 (1.24, 1.33)	1.33 (1.29, 1.38)	1.29 (1.25, 1.34)
BMI, per 5 kg/m ² higher			
For BMI ≤ 25 kg/m ²	1.03 (0.98, 1.08)	1.05 (1.00, 1.10)	1.03 (0.98, 1.08)
For BMI >25 kg/m ²	1.20 (1.19, 1.21)	1.25 (1.23, 1.26)	1.16 (1.15, 1.17)
Hypertension	1.74 (1.68, 1.81)	1.63 (1.57, 1.69)	1.24 (1.19, 1.29)
eGFR, per 10 ml/min/1.73 m ² higher			
For eGFR <60 ml/min/1.73 m ²	0.75 (0.74, 0.77)	0.76 (0.74, 0.78)	0.80 (0.78, 0.82)
For eGFR 60-89 ml/min/1.73 m ²	0.88 (0.87, 0.90)	0.90 (0.89, 0.92)	0.94 (0.93, 0.96)
For eGFR ≥ 90 ml/min/1.73 m ²	1.12 (1.09, 1.14)	1.12 (1.09, 1.15)	1.15 (1.12, 1.18)
Diabetes mellitus	1.56 (1.52, 1.60)	1.51 (1.47, 1.56)	1.16 (1.12, 1.19)
Congestive heart failure	1.80 (1.74, 1.86)	1.72 (1.66, 1.78)	1.21 (1.17, 1.26)
Coronary artery disease	1.33 (1.29, 1.36)	1.30 (1.26, 1.33)	0.96 (0.93, 0.99)
Cardiovascular disease	0.95 (0.91, 0.98)	0.90 (0.87, 0.93)	0.87 (0.83, 0.90)
Peripheral artery disease	1.06 (1.02, 1.09)	1.01 (0.98, 1.05)	1.01 (0.97, 1.04)
Lung disease	1.12 (1.09, 1.15)	1.11 (1.08, 1.15)	1.05 (1.02, 1.08)
Malignancy	0.99 (0.96, 1.02)	0.94 (0.91, 0.97)	1.07 (1.03, 1.10)
Liver disease	1.78 (1.63, 1.95)	1.84 (1.68, 2.01)	1.71 (1.56, 1.87)
ACE inhibitor/ARB use	1.58 (1.54, 1.62)	1.54 (1.50, 1.58)	1.20 (1.16, 1.23)
Diuretic use *	1.62 (1.58, 1.67)	1.56 (1.52, 1.61)	1.18 (1.14, 1.21)
Statin use	1.13 (1.10, 1.17)	1.11 (1.08, 1.15)	0.96 (0.93, 0.99)
Surgical variables			
Laparoscopic surgery, vs. open	0.81 (0.77, 0.86)	0.88 (0.83, 0.93)	0.72 (0.68, 0.77)
Hospital stay pre-surgery, vs. <5 days			
5-14 days	1.62 (1.57, 1.68)	1.57 (1.51, 1.63)	1.33 (1.28, 1.38)
15 days	1.93 (1.79, 2.08)	1.83 (1.70, 1.97)	1.58 (1.46, 1.71)
Type of surgery, vs. General			
Cardiac	1.42 (1.37, 1.47)	1.41 (1.36, 1.46)	1.22 (1.17, 1.27)
ENT	0.31 (0.27, 0.36)	0.32 (0.28, 0.37)	0.32 (0.28, 0.37)
Orthopedic	0.78 (0.75, 0.81)	0.77 (0.74, 0.80)	0.70 (0.67, 0.73)
Thoracic	0.91 (0.86, 0.96)	0.91 (0.86, 0.96)	0.92 (0.87, 0.98)
Urologic	0.66 (0.62, 0.69)	0.62 (0.58, 0.65)	0.65 (0.61, 0.69)
Vascular	0.70 (0.67, 0.73)	0.67 (0.64, 0.70)	0.68 (0.64, 0.71)

Note: Associations with any-stage AKI estimated by a modified Poisson model that was unadjusted (1st column), adjusted for age, sex, and race (2nd column), and adjusted for all covariates shown (3rd column). Bold indicates statistical significance. All covariates were treated as binary variables unless otherwise noted.

ACE: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blockers, BMI: body mass index, CI, confidence interval eGFR: estimated glomerular filtration rate, ENT: ear, nose, and throat; RR, relative risk

*
Thiazide/loop.

Table 3

Outcomes by stage of AKI following major surgery

	By AKI severity				All Post-surgical Patients	
	KDIGO Stage 1	KDIGO Stage 2	KDIGO Stage 3 no RRT	RRT requirement *	With AKI	Without AKI
No. of participants	14477	2780	1348	420	19025	142160
Hospital Length of stay, d						
Total hospital stay	9 (5, 16)	12 (7, 22)	14 (7, 26)	35.5 (20.5, 61)	10 (6, 18)	5 (3, 10)
Post-surgery stay	7 (4, 13)	9 (6, 18)	11 (6, 21)	48 (58)	8 (5, 14)	5 (2, 8)
Hospital Re-admission, %						
Within 30 d	20 (19-20)	26 (24-27)	28 (26-31)	28 (23-34)	21 (21-22)	13 (13-13)
Within 90 d	30 (29-31)	37 (35-39)	40 (37-43)	43 (37-49)	32 (31-32)	22 (22-22)
Within 6 mo	38 (37-39)	45 (43-47)	49 (45-52)	55 (49-62)	40 (39-40)	29 (29-30)
Within 1 y	48 (47-49)	55 (53-58)	57 (54-60)	69 (63-75)	50 (49-51)	39 (39-39)
Mortality, %						
In-hospital	4.6 (4.1-5.0)	15 (14-17)	24 (22-27)	35 (31-40)	8.2 (8.0-8.4)	1.1 (1.0-1.2)
Within 30 d	6.7 (6.3-7.2)	19 (18-21)	30 (28-33)	40 (36-45)	11 (11-11)	2.2 (2.1-2.3)
Within 90 d	9.0 (8.5-9.4)	22 (21-24)	33 (31-36)	45 (40-50)	13 (13-14)	3.6 (3.5-3.7)
Within 6 mo	11 (11-12)	25 (23-26)	36 (33-39)	49 (44-53)	16 (15-16)	5.4 (5.2-5.5)
Within 1 y	14 (14-15)	28 (26-30)	39 (36-42)	54 (49-59)	19 (18-20)	8.0 (7.9-8.2)
ESRD, %						
Within 30 d	0.072 (0.039-0.134)	0.36 (0.19-0.69)	0.95 (0.52-1.71)	8.0 (5.7-11.3)	0.33 (0.26-0.43)	0.0036 (0.0015-0.0086)
Within 90 d	0.19 (0.13-0.29)	0.64 (0.38-1.06)	1.1 (0.6-1.9)	10 (8-14)	0.50 (0.41-0.62)	0.012 (0.008-0.020)
Within 6 mo	0.35 (0.26-0.47)	0.74 (0.46-1.19)	1.7 (1.0-2.7)	12 (8-16)	0.68 (0.57-0.82)	0.026 (0.018-0.036)
Within 1 y	0.58 (0.46-0.73)	1.1 (0.7-1.7)	2.1 (1.3-3.2)	12 (8-16)	0.94 (0.80-1.10)	0.053 (0.042-0.068)

Note: Unless otherwise indicated, values are given as median [interquartile range] or percentage (95% confidence interval).

AKI: acute kidney injury, ESRD: end-stage renal disease; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, renal replacement therapy

* Proportions determined using a Kaplan-Meier approach (censored for death for non-mortality outcomes).

Fully-adjusted incidence rate ratio associations of post-operative AKI with adverse outcomes, overall and by surgery type

Table 4

	Overall	Cardiac	ENT	General	Ortho	Thoracic	Urologic	Vascular
Hospital readmission within 30 d	1.52 (1.46, 1.57)	1.38 (1.27, 1.49)	1.39 (0.94, 2.07)	1.53 (1.43, 1.63)	1.52 (1.39, 1.66)	1.21 (1.04, 1.41)	1.70 (1.44, 2.01)	1.49 (1.35, 1.64)
In-hospital mortality	6.69 (6.20, 7.21)	4.73 (3.86, 5.79)	8.28 (3.44, 19.90)	6.40 (5.75, 7.12)	4.91 (3.90, 6.18)	4.31 (3.38, 5.48)	20.26 (8.81, 46.56)	9.43 (7.74, 11.50)
90-d mortality	3.69 (3.49, 3.90)	3.45 (2.96, 4.02)	4.53 (2.42, 8.47)	3.74 (3.43, 4.09)	2.85 (2.47, 3.30)	2.71 (2.25, 3.26)	3.54 (2.48, 5.06)	4.81 (4.17, 5.56)
1-y mortality	2.43 (2.33, 2.54)	2.42 (2.13, 2.74)	2.08 (1.35, 3.22)	2.50 (2.32, 2.69)	2.09 (1.87, 2.35)	1.77 (1.55, 2.03)	2.28 (1.80, 2.89)	3.10 (2.77, 3.48)
1-y ESRD	10.46 (7.61, 14.38)	14.48 (6.50, 32.26)		17.53 (8.39, 36.60)	6.91 (3.73, 12.78)		15.16 (3.47, 66.21)	10.30 (5.35, 19.83)

Note: Values are given as incidence rate ratios (95% confidence intervals), which were determined using a fully adjusted Poisson model of any-stage post-operative AKI (i.e., adjusted for all covariates shown in Table 1).

* Denotes significant interaction ($p < 0.05$) of surgery type and AKI with outcome compared with general surgery as a reference.

AKI: acute kidney injury, ENT: ear, nose, and throat, ESRD: end-stage renal disease