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# Postoperative Acute Kidney Injury by Age and Sex: A Retrospective Cohort Association Study

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## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Acute kidney injury after noncardiac surgery is not uncommon and has a substantial health impact. Previous studies, which generally have not considered possible age-related differences, have found conflicting results with respect to the impact of sex on acute kidney injury.

### What This Article Tells Us That Is New

- In this large retrospective cohort analysis, younger females were at lower odds of postoperative acute kidney injury than females of older age and males of all ages.

## ABSTRACT

**Background:** Acute kidney injury (AKI) after noncardiac surgery is common and has substantial health impact. Preclinical and clinical studies examining the influence of sex on AKI have yielded conflicting results, although they typically do not account for age-related changes. The objective of the study was to determine the association of age and sex groups on postoperative AKI. The authors hypothesized that younger females would display lower risk of postoperative AKI than males of similar age, and the protection would be lost in older females.

**Methods:** This was a multicenter retrospective cohort study across 46 institutions between 2013 and 2019. Participants included adult inpatients without pre-existing end-stage kidney disease undergoing index major noncardiac, nonkidney/urologic surgeries. The authors' primary exposure was age and sex groups defined as females 50 yr or younger, females older than 50 yr, males 50 yr or younger, and males older than 50 yr. The authors' primary outcome was development of AKI by Kidney Disease-Improving Global Outcomes serum creatinine criteria. Exploratory analyses included associations of ascending age groups and hormone replacement therapy home medications with postoperative AKI.

**Results:** Among 390,382 patients, 25,809 (6.6%) developed postoperative AKI (females 50 yr or younger: 2,190 of 58,585 [3.7%]; females older than 50 yr: 9,320 of 14,4047 [6.5%]; males 50 yr or younger: 3,289 of 55,503 [5.9%]; males older than 50 yr: 11,010 of 132,447 [8.3%]). When adjusted for AKI risk factors, compared to females younger than 50 yr (odds ratio, 1), the odds of AKI were higher in females older than 50 yr (odds ratio, 1.51; 95% CI, 1.43 to 1.59), males younger than 50 yr (odds ratio, 1.90; 95% CI, 1.79 to 2.01), and males older than 50 yr (odds ratio, 2.06; 95% CI, 1.96 to 2.17).

**Conclusions:** Younger females display a lower odds of postoperative AKI that gradually increases with age. These results suggest that age-related changes in women should be further studied as modifiers of postoperative AKI risk after noncardiac surgery.

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Acute kidney injury (AKI) is one of the most common forms of postoperative organ injury, occurring in 6 to 39% of noncardiac surgical patients.[1–3] AKI increases morbidity and mortality and results in longer intensive care unit and hospital stays, leading to increased hospital costs.[4] Even mild AKI is associated with increased perioperative and long-term mortality.[1,5,6] The heightened morbidity and mortality after an episode of AKI are due, at least in part, to the increased risk for future development of chronic kidney disease and end-stage kidney disease.[7,8] Moreover, AKI is a frequent component of multiorgan dysfunction, and AKI can be caused by, and induce, failure of other major organ systems.[9] Thus, AKI is a common postoperative complication that significantly worsens patient outcomes.

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Despite its significant morbidity and impact on mortality, postoperative AKI remains inadequately studied, and there are currently no therapeutic modalities to prevent or treat AKI once it occurs. A number of previous studies have helped to provide an incidence and associated risk factors for postoperative AKI after noncardiac surgery.[1,2,10–14] Although this provides a solid framework, a number of important questions remain that have implications for postoperative AKI diagnosis, prognosis, and future therapeutic treatment options.

One existing knowledge gap is the influence of age and sex on AKI development. Preclinical studies indicate protection for female animals from AKI[15–20]; however, the Kidney Disease Improving Global Outcomes clinical practice guideline actually suggests that female sex is an important risk susceptibility for development of AKI.[21] In contrast to the Kidney Disease Improving Global Outcomes guideline, a clinical study reported female sex to be a protective factor for hospital-associated AKI.[22] These discrepant preclinical and clinical results may be due to preclinical studies typically being carried out in young, ovulating female animals, whereas most clinical studies examining postoperative AKI in female patients are in older, postmenopausal female patient populations. Thus, it is possible that young age in females and/or female sex hormones confer protection; however, this has not been well-studied in human AKI populations. If female-associated hormones such as estrogen and/or progesterone are protective, this has possible therapeutic implications for both males and females. As such, further investigation is needed to determine rates of postoperative AKI in females based on age and sex hormone status and whether these outweigh other associated risk factors.

The primary objective of our study was to determine the association of age and sex groups with postoperative AKI development after noncardiac surgery. We hypothesized that females of younger age would display lower incidence of postoperative AKI than males of similar age, and the protection would be lost in older females compared to males of similar age.

## Materials and Methods

### Study Design and Database

We conducted a retrospective cohort study of the Multicenter Perioperative Outcomes Group database. The Multicenter Perioperative Outcomes Group is a collaboration of academic and community hospitals across the United States and uses health data to analyze the relationships between patient characteristics, healthcare systems, surgical procedures, perioperative care, and postoperative outcomes. Multicenter Perioperative Outcomes Group data acquisition, validation, secure transfer to a coordinating center, and processing into publicly available phenotypes for research have been previously described[23] and used in multiple studies.[24,25] The analysis of the data set for this study was deemed exempt from human subjects review and requirement of consent, was approved by the Duke University Health System (Durham, North Carolina) Institutional Review Board, and follows the Strengthening the Reporting of Observational Studies in Epidemiology guideline. Before data analysis, the statistical analysis plan was written, registered, and posted on the Open Science Framework (https://doi.org/10.17605/OSF.IO/D5X6F).

### Study Population

The study population included patients 18 yr and older undergoing procedures at all participating Multicenter Perioperative Outcomes Group institutions between January 1, 2013, and December 31, 2019. Exclusion criteria employed by the Multicenter Perioperative Outcomes Group before data release were the following: outpatient procedures, cardiac surgery procedures, transplant surgical procedures, urological procedures, obstetrical procedures, American Society of Anesthesiology (ASA; Schaumburg, Illinois) Physical Status VI (organ procurement), electroconvulsive therapy, pain procedures, cases less than 60 min in length, existing diagnosis of Elixhauser Comorbidity Index renal failure, centers with missing or invalid home medication data, and previous

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organ transplant recipients. After Multicenter Perioperative Outcomes Group exclusions, we then further applied the following exclusions (fig. 1): missing surgical Current Procedural Terminology codes, nonsurgical procedures (*i.e.*, chest radiograph), procedures that should have been excluded (*i.e.*, cardiac surgery, cases less than 60 min), procedures with missing creatinine values to call AKI, nonindex procedures on the same patient (to avoid clustering within-person and potential change in risk due to repeated procedures), missing sex, and missing covariates. For surgical exclusions, we used surgical Current Procedural Terminology codes for exclusions when anesthesia Current Procedural Terminology codes were ambiguous. For ambiguous anesthesia Current Procedural Terminology codes (*i.e.*, anesthesia for surgery on perineum), we additionally performed procedure text review to ensure proper exclusions.

## Exposures

For our primary exposure, we *a priori* determined to use listed patient sex and age-based cutoffs defined by the following four groups: females 50 yr and younger, males 50 yr and younger, females older than 50 yr, and males older than 50 yr. We chose a threshold of 50 yr because 50 yr is often used as a reference cutoff for menopause and therefore an age that may impact AKI risk. Secondary exposures included home medication hormone replacement therapy (estrogen, estrogen plus progesterone, estrogen plus progesterone plus testosterone, estrogen plus testosterone, progesterone alone) in females older than 55 yr, and ascending 5-yr increment age groups greater than 20 yr in males and females.

## Primary Outcome

The *a priori* outcome for both primary and secondary exposures was the development of postoperative AKI. The Multicenter Perioperative Outcomes Group AKI-01 phenotype is a binary variable based on Kidney Disease Improving Global Outcomes serum creatinine criteria[22]: creatinine rise 0.3 mg/dl or greater within 48 h or greater than 1.5 times baseline within first 7 days. We also categorized

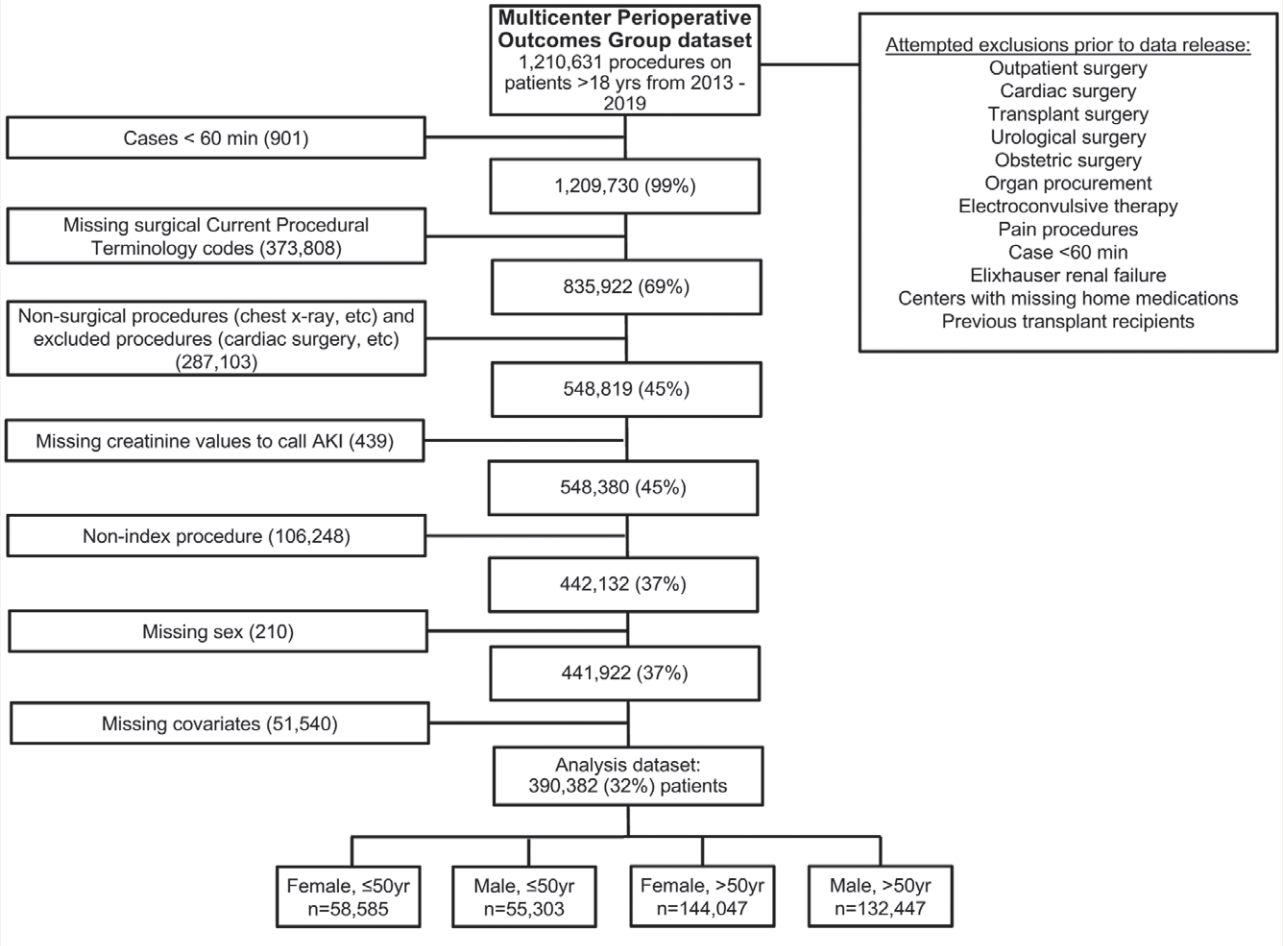


**Fig. 1.** Study design. CONsolidated Standards of Reporting Trials diagram of study population. AKI, acute kidney injury.

AKI by Kidney Disease Improving Global Outcomes stage as follows: stage 1 AKI, creatinine rise 0.3 mg/dl or greater within 48 h or 1.5 to 1.9 times baseline within first 7 days after surgery; stage 2 AKI, creatinine rise 2.0 to 2.9 times baseline within 7 days after surgery; and stage 3 AKI, creatinine rise to 4.0 mg/dl or greater or 3.0 times baseline. Regarding reliability of measurements to determine the primary outcome, it should be noted that in the Multicenter Perioperative Outcomes Group database, patient laboratory values are validated utilizing precomputed, publicly available, Multicenter Perioperative Outcomes Group–specific perioperative electronic health record phenotype algorithms; each Multicenter Perioperative Outcomes Group center uses a standardized set of data diagnostics to evaluate and address data quality on a monthly basis; and random cases are manually audited by a clinician at each center to assess and attest to the accuracy of data extraction and source data.[14,23]

## Covariates

Patient covariates were prespecified and selected based on literature review, previous published studies,[14] and subject matter expertise of the author team. Patient covariates ascertained included body mass index, race/ethnicity, ASA Physical Status classification, admission type, preoperative hemoglobin level within 30 days of surgery, preoperative serum creatinine level within 30 days of surgery, and medical comorbidities including blood loss anemia, iron deficiency anemia, hypertension, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, previous myocardial infarction based on medical history, peripheral vascular disease, metastatic cancer, neurologic disorders, obesity, and tumor without metastasis. We also calculated estimated glomerular filtration rate category by the Chronic Kidney Disease Epidemiology Collaboration equation without race multiplier and used glomerular filtration rate category for adjustment in our regression model and to exclude patients with glomerular filtration rate category 5 (less than 15 ml · $min^{-1}$ · $1.73m^{-2}$) who had not previously been excluded by Elixhauser renal failure diagnosis. Procedure characteristics ascertained included emergent status, surgical type by surgical Current Procedural Terminology code, anesthesia base units (assigned value by the ASA for each Current Procedural Terminology code and considers the complexity, risk, and skill required to perform the service), surgery duration, estimated blood loss, crystalloid volume administered, and perioperative drugs administered including propofol, celecoxib, etomidate, ketamine, ketorolac, and ibuprofen.

## Statistical Analyses

Before data collection, a formal power calculation was conducted. For the purposes of our study, we initially considered a 25% relative reduction in postoperative AKI rates for females younger than 50 yr (reference group), compared to males younger than 50 yr, to be a clinically meaningful effect. Based on recent Multicenter Perioperative Outcomes Group data,[14] at a power level of 80%, we determined that 1,705 patients would be necessary to detect such a reduction, at a significance level $\alpha = 0.01$. The Multicenter Perioperative Outcomes Group requires single center preliminary data analysis from the respective institution (in our case, Duke University) as part of their review process before data release. Analyzed data from our single institution revealed a 20% difference in AKI rates between males and females younger than 50 yr. Thus, we targeted a relative minimum clinically relevant effect size to be an unadjusted 20% reduction in AKI rate between females younger than 50 yr and males younger than 50 yr since even small changes in postoperative creatinine are associated with worse outcomes.[1,5]

Descriptive statistics were used to examine demographic, clinical, surgical, and treatment characteristics of the cohort, stratified by age and sex groups, as described above. Chi-square tests were used to compare categorical variables, and ANOVA or Kruskal–Wallis tests were used to compare continuous variables, depending on distribution characteristics of the variable. For the primary outcome, a mixed effects multivariable logistic model was used to examine the association of age and sex groups with postoperative AKI. Fixed effects were included to adjust for differences in baseline demographic and medical characteristics including body mass index, preoperative hemoglobin, race, admission type, duration of anesthesia, anesthesia base units, ASA Physical Status, emergent status, crystalloid equivalent volume, colloid equivalent volume, estimated blood loss, medical comorbidities, and perioperative medication use (including propofol, celecoxib, etomidate, ketamine, ketorolac, and ibuprofen). Random effects for institution were included to account for clustering of patients within centers. A *P* value less than 0.01 was considered statistically significant.

Several sensitivity analyses were conducted *post hoc* to further examine the relationship between age, sex, and risk of AKI and avoid the potential loss of information associated with the dichotomization of age in our primary exposure. In the first sensitivity analysis, we used a cutoff of 55 yr instead of 50 yr. In a second sensitivity analysis, we used age groups of 5 yr in males and females between the ages of 20 yr and 90 yr. Finally, we performed a sensitivity analysis modeling age as a restricted cubic spline with 5-percentile-based knots. This analysis included an interaction between age and sex to allow for different age-based risk profiles in men and women. To account for missing data, we performed an additional model excluding the most common missing covariates: body mass index, ASA Physical Status, and Elixhauser comorbidities.

In the *a priori* proposed secondary subgroup analyses, we used propensity matching to examine rates of postoperative AKI in females older than 55 yr in the following

five groups based on hormone replacement therapy listed in home medications: estrogen alone, estrogen plus progesterone/progestin, estrogen plus progesterone/progestin plus testosterone, estrogen plus testosterone, and progesterone/progestin alone. We chose to examine our secondary outcome in females older than 55 yr to reduce confounding from endogenous sex hormones in those premenopausal. The propensity models for matching included the same covariates as the model used in the primary analysis. For each of these subgroups, a multivariable logistic regression model was used to obtain the propensity scores of the patients with the exposure. We used greedy propensity score techniques (in a 1:3 fashion) without replacement and a caliper within 0.10 SDs of the propensity score distribution. After matching, we tested the balance of the covariates by looking for the matching approach that resulted in the lowest absolute standardized mean difference, with low defined as $|0.1|$. Finally, in the propensity-matched exploratory analyses, we used univariable logistic regression models to assess the association between exposure and outcome. Since these were all exploratory and hypothesis-generating subgroup analyses, we did not pursue a formal strategy for adjustment for multiple comparison testing. Statistical analysis was performed using SAS (SAS Institute, USA).

## Results

After exclusions, our dataset consisted of 390,382 adult patients undergoing surgery at 46 institutions (fig. 1). To study the association of age and sex groups with postoperative AKI development, we separated males and females into age groupings of less than or greater than 50 yr old (table 1). Patients older than 50 yr (whether male or female) were more likely to present with ASA Physical Status III or greater, indicative of more medical comorbidities such as congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, glomerular filtration rate categories 2 to 4, peripheral vascular disease, and previous myocardial infarction. Females of all age categories had lower preoperative hemoglobin levels and higher rates of iron deficiency anemia and obesity. Males younger than 50 yr were more likely to present as ASA Physical Status V and undergo emergent surgery. Surgical characteristics and administered perioperative medications were similar between the groups.

The primary outcome of AKI was seen in 6.6% of patients (table 1). Compared to females older than 50 yr (AKI rate of 6.5%), men younger than 50 yr (5.9%), and men older than 50 yr (8.3%), females younger than 50 yr had the lowest rate of AKI at 3.7%. In the multivariable model adjusting for covariates, the lowest odds of AKI were in females younger than 50 yr (reference category), with higher odds in women older than 50 yr (odds ratio, 1.51, 95% CI, 1.43 to 1.59; $P < 0.001$), males younger than 50 yr (odds ratio, 1.90; 95% CI, 1.79 to 2.01; $P < 0.001$), and males older than 50 yr (odds ratio, 2.06; 95% CI, 1.96 to 2.17; $P < 0.001$; fig. 2; see table, Supplemental Digital Content 1, http://links.lww.com/ALN/C963, covariates in multivariable model). A sensitivity analysis of our primary outcome included increasing the age cutoff to 55 yr old, which resulted in similar findings as our primary analysis (see table, Supplemental Digital Content 2, http://links.lww.com/ALN/C964, association of age and sex on AKI based on age cutoff of 55 yr). Thus, females had an age-associated increase in odds of postoperative AKI, whereas an age discrepancy in AKI odds was not observed in males.

To further explore the impact of age on AKI risk, in secondary analysis we examined the association of ascending age groups greater than 20 yr in both sexes. Males in age groups between 20 and 40 yr had higher odds of AKI than females of similar age groups, although the odds of AKI did not increase between age groups within each sex (*i.e.*, females 21 to 25 yr had similar odds, as did females 31 to 35 yr; fig. 3). However, after age 40 yr, females had a gradual and persistent increase in AKI odds, compared to males of similar age, that resulted in AKI odds similar to males in age groups after 85 yr (fig. 3; see table, Supplemental Digital Content 3, http://links.lww.com/ALN/C965, association of age and sex on odds of postoperative AKI between increasing age groups of males and females). Further sensitivity analysis utilizing a restricted cubic spline model revealed that males and females showed parallel increases in predicted probability of AKI risk before age 50 yr, although after age 50 yr, females showed progressive acceleration of AKI risk, an effect not mirrored in males (see figure, Supplemental Digital Content 4, http://links.lww.com/ALN/C966, risk of AKI by age and sex; see table, Supplemental Digital Content 5, http://links.lww.com/ALN/C967, interaction analysis of continuous age and sex on postoperative AKI risk).

To assess the extent to which differences in AKI risk in females could be due to decreasing levels of sex hormones with aging (*i.e.*, menopause), we grouped female patients older than 55 yr into five separate groups based on hormone replacement drugs listed on home medications. There were 1,384 females older than 55 yr who were listed as taking home hormone replacement therapy among the five hormone replacement groups (0.3% of the total 390,382 patient cohort). We pursued a propensity-matching strategy with females older than 55 yr who did not have hormone therapy on their home medication list to compare AKI risk. Preoperative hormone replacement treatments did not appear to modify risk for postoperative AKI, although it should be noted that our analysis was underpowered to detect a difference due to small numbers of patients taking preoperative hormone treatments and the overall low event rate in propensity-matched groups (table 2).

## Discussion

In this study, we observed that younger-age females were at lower odds of postoperative AKI than were females of older age and males of all ages. Moreover, we show here that groups of females of ascending age groups experience

**Table 1.** Baseline, Demographic, and Surgical Characteristics

| | Women ≤50 yr (n = 58,585) | Women >50 yr (n = 144,047) | Men ≤50 yr (n = 55,303) | Men >50 yr (n = 132,447) |
|---|---|---|---|---|
| Patient characteristics | | | | |
| Age, mean ± SD | 38.0 ± 9.0 | 66.7 ± 9.6 | 36.9 ± 9.5 | 65.9 ± 9.1 |
| Body mass index, mean ± SD | 31.1 ± 9.9 | 29.1 ± 7.6 | 28.9 ± 7.7 | 28.7 ± 6.0 |
| Race, n (%) | | | | |
| American Indian or Alaska Native | 363 (0.6) | 519 (0.4) | 404 (0.7) | 507 (0.4) |
| Asian or Pacific Islander | 2,320 (4.0) | 4,178 (2.9) | 2,006 (3.6) | 3,618 (2.7) |
| Biracial or multiracial | 402 (0.7) | 521 (0.4) | 473 (0.9) | 489 (0.4) |
| Black, not of Hispanic origin | 8,200 (14.0) | 13,405 (9.3) | 6,740 (12.2) | 9,630 (7.3) |
| Hispanic, Black | 140 (0.2) | 127 (0.1) | 128 (0.2) | 92 (0.1) |
| Hispanic, White | 1,123 (1.9) | 1,400 (1.0) | 966 (1.7) | 1,166 (0.9) |
| Middle Eastern | 30 (0.1) | 29 (0.0) | 27 (0.0) | 26 (0.0) |
| Unknown race | 6,217 (10.6) | 10,993 (7.6) | 6,125 (11.1) | 10,163 (7.7) |
| White, not of Hispanic origin | 39,790 (67.9) | 112,875 (78.4) | 38,434 (69.5) | 106,756 (80.6) |
| ASA Physical Status, n (%) | | | | |
| I | 2,757 (4.7) | 1,111 (0.8) | 4,320 (7.8) | 1,079 (0.8) |
| II | 25,096 (42.8) | 41,403 (28.7) | 23,450 (42.4) | 31,611 (23.9) |
| III | 27,738 (47.3) | 89,953 (62.4) | 23,101 (41.8) | 84,983 (64.2) |
| IV | 2,767 (4.7) | 11,076 (7.7) | 3,942 (7.1) | 14,120 (10.7) |
| V | 227 (0.4) | 504 (0.3) | 490 (0.9) | 654 (0.5) |
| Emergent, n (%) | 5,874 (10.0) | 10,044 (7.0) | 8,636 (15.6) | 11,217 (8.5) |
| Admission type, n (%) | | | | |
| Admit | 14,389 (24.6) | 37,656 (26.1) | 10,691 (19.3) | 32,836 (24.8) |
| Emergency | 718 (1.2) | 817 (0.6) | 806 (1.5) | 823 (0.6) |
| Inpatient | 43,257 (73.8) | 105,082 (72.9) | 43,576 (78.8) | 98,334 (74.2) |
| Other admission type | 103 (0.2) | 253 (0.2) | 80 (0.1) | 193 (0.1) |
| Unknown admission type | 103 (0.2) | 185 (0.1) | 128 (0.2) | 227 (0.2) |
| Baseline hemoglobin, g/dl, mean ± SD | 12.2 ± 1.9 | 12.4 ± 1.8 | 13.3 ± 2.3 | 13.2 ± 2.2 |
| Baseline creatinine, mg/dl, median [interquartile range] | 0.7 [0.6–0.8] | 0.8 [0.7–0.9] | 0.9 [0.8–1.0] | 0.9 [0.8–1.1] |
| Comorbidities, n (%) | | | | |
| Blood loss anemia | 810 (1.4) | 2,089 (1.5) | 673 (1.2) | 1,723 (1.3) |
| Iron deficiency anemia | 2,565 (4.4) | 5,134 (3.6) | 1,110 (2.0) | 3,538 (2.7) |
| Congestive heart failure | 1,119 (1.9) | 8,747 (6.1) | 1,159 (2.1) | 10,172 (7.7) |
| Previous myocardial infarction | 165 (0.3) | 1,502 (1.0) | 167 (0.3) | 2,879 (2.2) |
| Chronic pulmonary disease | 9,796 (16.7) | 31,206 (21.7) | 5,645 (10.2) | 23,755 (17.9) |
| Diabetes (complicated) | 372 (0.6) | 1,466 (1.0) | 336 (0.6) | 1,861 (1.4) |
| Diabetes (uncomplicated) | 4,695 (8.0) | 22,314 (15.5) | 3,967 (7.2) | 24,101 (18.2) |
| Hypertension (complicated) | 517 (0.9) | 5,314 (3.7) | 559 (1.0) | 6,017 (4.5) |
| Hypertension (uncomplicated) | 12,911 (22.0) | 80,163 (55.7) | 13,378 (24.2) | 78,388 (59.2) |
| Metastatic cancer | 6,041 (10.3) | 22,478 (15.6) | 6,059 (11.0) | 23,201 (17.5) |
| Neurologic disorders | 5,459 (9.3) | 12,528 (8.7) | 5,971 (10.8) | 13,031 (9.8) |
| Obesity | 17,255 (29.5) | 31,651 (22.0) | 9,339 (16.9) | 23,100 (17.4) |
| Peripheral vascular disease | 2,199 (3.8) | 11,313 (7.9) | 2,306 (4.2) | 16,284 (12.3) |
| Solid tumor without metastasis | 10,644 (18.2) | 37,953 (26.3) | 9,781 (17.7) | 40,206 (30.4) |
| Glomerular filtration rate category | | | | |
| 1 (≥ 90 ml · min$^{-1}$ · 1.73m$^{-2}$) | 44,817 (76.5) | 45,719 (31.7) | 42,801 (77.4) | 48,499 (36.6) |
| 2 (60–89) | 12,323 (21.0) | 74,953 (52.0) | 11,019 (19.9) | 67,618 (51.1) |
| 3a (45–59) | 893 (1.5) | 16,809 (11.7) | 867 (1.6) | 12,102 (9.1) |
| 3b (30–44) | 284 (0.5) | 5,235 (3.6) | 311 (0.6) | 3,171 (2.4) |
| 4 (15–29) | 168 (0.3) | 1,145 (0.8) | 205 (0.4) | 862 (0.7) |
| 5 (< 15) | 100 (0.2) | 186 (0.1) | 100 (0.2) | 195 (0.1) |
| Anesthesia base units* ≥ 5 | 53,267 (90.9) | 134,299 (93.2) | 46,605 (84.3) | 121,979 (92.1) |
| Surgical characteristics, median [interquartile range] | | | | |
| Surgery duration (min) | 144 [88–235] | 137 [89–219] | 151 [92–242] | 143 [91–232] |
| Crystalloids equivalent volume (ml) | 1,750 [1,050–2,856] | 1,700 [1,000–2,777] | 1,900 [1,100–3,180] | 1,900 [1,100–3,100] |
| Estimated blood loss (ml) | 50 [10–200] | 100 [20–250] | 100 [15–250] | 100 [20–300] |
| Perioperative medications, n (%) | | | | |
| Propofol | 25,204 (43.0) | 68,501 (47.6) | 23,177 (41.9) | 60,342 (45.6) |
| Celecoxib | 810 (1.4) | 3,448 (2.4) | 679 (1.2) | 2,763 (2.1) |
| Etomidate | 87 (0.2) | 442 (0.3) | 182 (0.3) | 528 (0.4) |
| Ketamine | 5,245 (9.0) | 11,130 (7.7) | 5,866 (10.6) | 10,975 (8.3) |
| Ketorolac | 2,650 (4.5) | 6,191 (4.3) | 2,152 (3.9) | 4,710 (3.6) |
| Ibuprofen | 56 (0.1) | 120 (0.1) | 59 (0.1) | 123 (0.1) |
| Outcome, n (%) | | | | |
| AKI | 2,190 (3.7) | 9,320 (6.5) | 3,289 (5.9) | 11,010 (8.3) |
| AKI stage | | | | |
| None | 56,395 (96.3) | 134,727 (93.5) | 52,014 (94.1) | 121,437 (91.7) |
| 1 | 1,657 (2.8) | 7,475 (5.2) | 2,627 (4.8) | 9,210 (7.0) |
| 2 | 356 (0.6) | 1,408 (1.0) | 436 (0.8) | 1,354 (1.0) |
| 3 | 177 (0.3) | 437 (0.3) | 226 (0.4) | 446 (0.3) |
| In-hospital mortality | | | | |
| Unknown | 2,964 (5.1) | 7,337 (5.1) | 2,444 (4.4) | 6,054 (4.5) |
| No | 55,212 (94.2) | 134,604 (93.4) | 52,300 (94.6) | 123,819 (93.5) |
| Yes | 409 (0.7) | 2,106 (1.5) | 559 (1.0) | 2,574 (1.9) |

*Each anesthesia code is assigned a base unit value by the ASA and used for the purpose of establishing fee schedule allowances. Base units take into account the complexity, risk, and skill required to perform the service.

AKI, acute kidney injury; ASA, American Society of Anesthesiology.

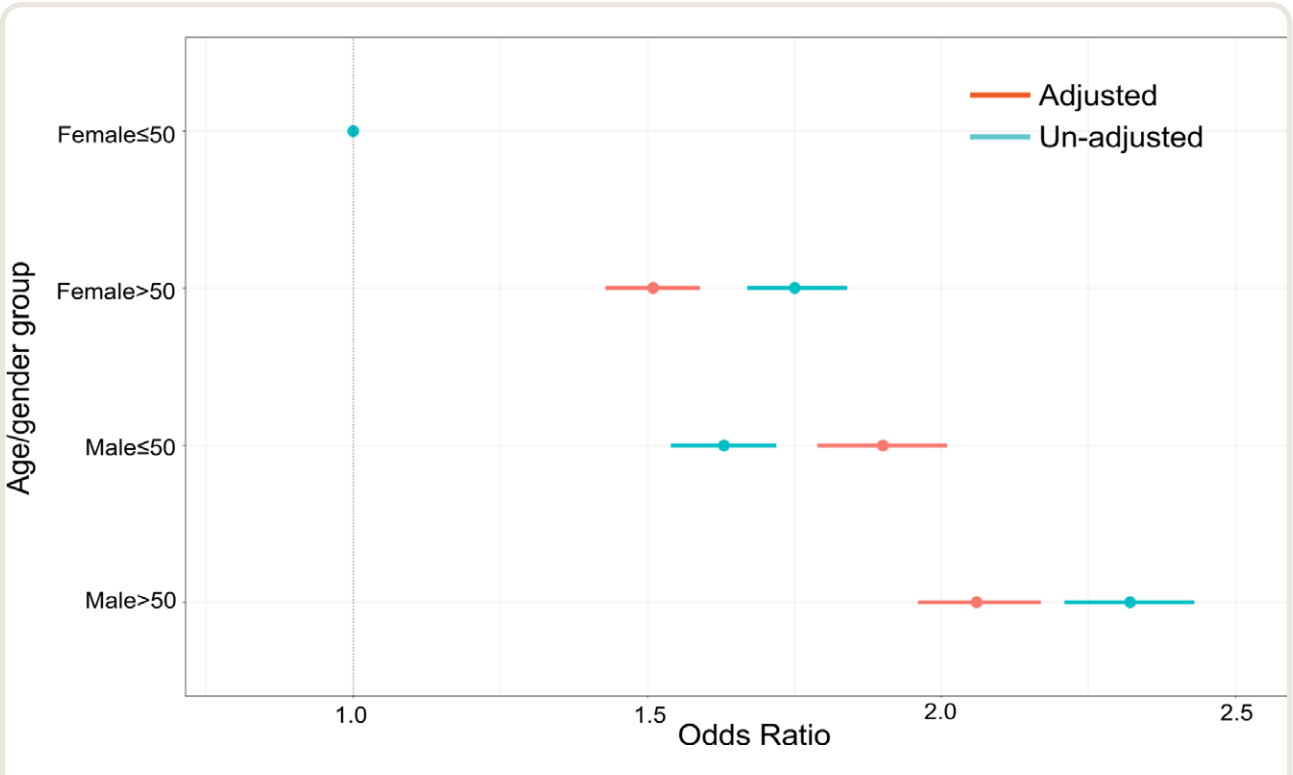


**Fig. 2.** Association of age and sex with postoperative acute kidney injury development based on age cutoff of 50 yr: women 50 yr or younger display a lower risk of postoperative acute kidney injury. *Dot* demonstrates odds ratio, and *line* displays 95% CI.

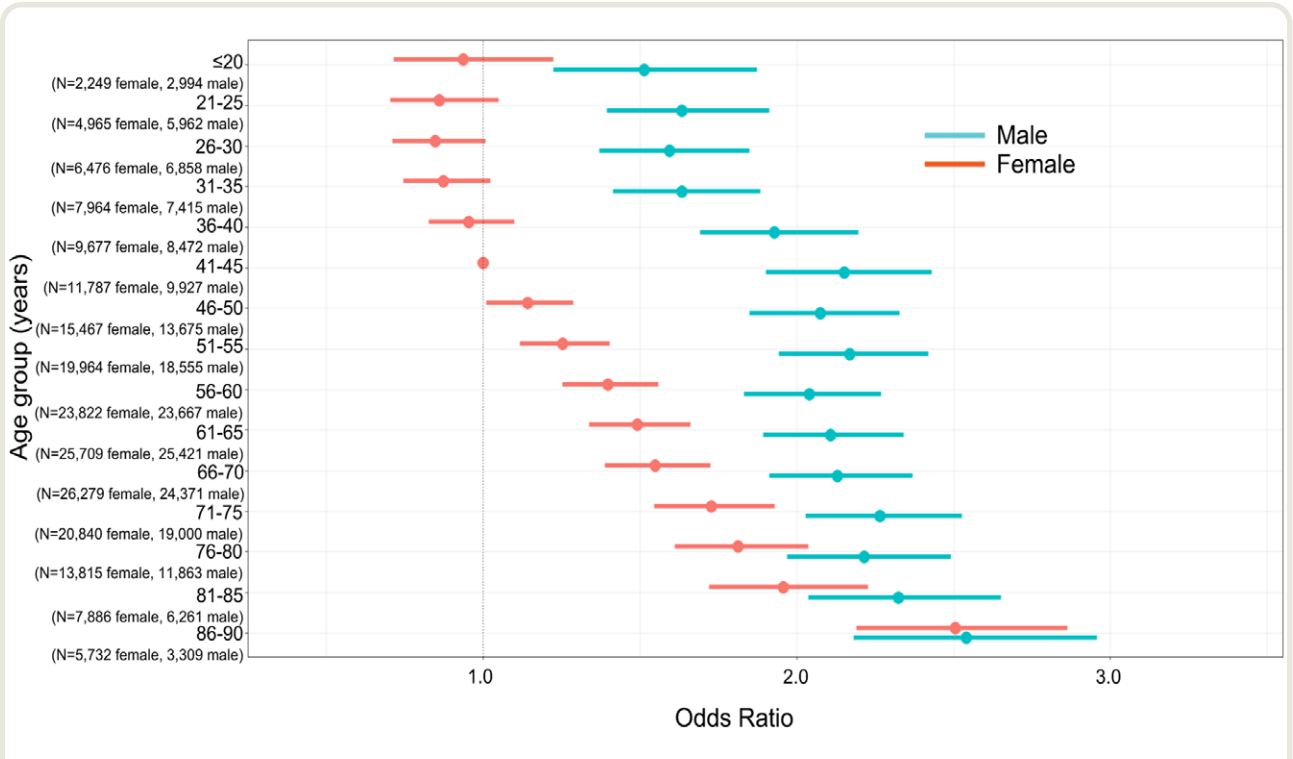


**Fig. 3.** Association of age and sex with odds of postoperative acute kidney injury based on ascending age groups. *Dot* demonstrates odds ratio, and *line* displays 95% CI.

**Table 2.** Association of Hormone Replacement Therapy on Postoperative AKI Risk

| | Patients with Home Medications Hormone Replacement Therapy | Matched Controls | *P* Value | Odds Ratio (95% CI) |
|---|---|---|---|---|
| | Estrogen only (n = 489) | Matched controls (n = 1,467) | | |
| AKI | 26 (5.3%) | 68 (4.6%) | 0.601 | 1.13 (0.71–1.82) |
| | Estrogen + progesterone (n = 146) | Matched controls (n = 438) | | |
| AKI | 5 (3.4%) | 27 (6.2%) | 0.214 | 0.54 (0.20–1.43) |
| | Estrogen + progesterone + testosterone (n = 85) | Matched controls (n = 255) | | |
| AKI | 2 (2.4%) | 3 (1.2%) | 0.444 | 2.02 (0.33–12.32) |
| | Estrogen + testosterone (n = 118) | Matched controls (n = 354) | | |
| AKI | 3 (2.5%) | 10 (2.8%) | 0.685 | 0.75 (0.19–3.00) |
| | Progesterone only (n = 546) | Matched controls (n = 1,638) | | |
| AKI | 19 (3.5%) | 64 (3.9%) | 0.651 | 0.89 (0.53–1.49) |

AKI, acute kidney injury.

a gradual increase in AKI risk. Taken together, our data demonstrate an age-dependent effect of sex on AKI risk after noncardiac surgery.

Sex is a controversial risk modifier for AKI. Studies in both surgical and nonsurgical patients have identified female sex as a risk factor for AKI, including after administration of contrast,[26] aminoglycosides,[27] rhabdomyolysis,[28] and cardiothoracic surgery.[29] Because of these studies, the current Kidney Disease Improving Global Outcomes clinical practice guideline lists female sex as a susceptibility factor for AKI.[21] In contrast to these referenced studies and the Kidney Disease Improving Global Outcomes guideline, our results here show that females are not more susceptible to postoperative AKI. The results of our study are in line with multiple studies in noncardiac surgical patients, which have shown that sex is not a significant risk factor for AKI.[2,4,12,14,30] Moreover, another study and a meta-analysis in hospitalized patient cohorts have reported that hospitalized men were much more likely to develop hospital-associated AKI and AKI requiring dialysis than were women.[22,31] One explanation for these conflicting findings is that many of the referenced studies that identified female sex as a risk factor for AKI did not examine the influence of age on sex, and its association with AKI. Indeed, the patient populations of these studies would have consisted almost entirely of women older age,[26,27,29] except for a study examining risk factors for rhadomyolysis.[28] Thus, our results and these other studies appear to indicate that female sex is not a risk factor for AKI, especially when examined in the context of age.

An age-dependent effect of sex to influence patient outcomes has been demonstrated in other clinical settings. For example, in septic shock and trauma, younger females appear to have a significant mortality benefit compared to males.[32,33] In line with this, our data here show that females gradually lose protection from postoperative AKI as they age. These results could imply that females lose protective factors and/or acquire detrimental factors as they age. Possible hypotheses are that female sex hormones are protective, and they are lost as women progress through menopause; or that females gradually produce more free androgens as they age, and androgens are detrimental. Preclinical studies in animals indicate that either is possible, with studies showing that estrogen is protective, and that testosterone is detrimental.[15–20] It should be noted that these preclinical studies would have mostly been performed in young animals. Nevertheless, based on our results and the aforementioned preclinical studies, we attempted to assess whether older females who were taking preoperative hormone replacement therapy at the time of surgery would show risk modification for postoperative AKI. We were unable to show significant risk modification for any analyzed sex hormone replacement therapy in our exploratory analyses; however, the low numbers of patients who had these medications on their home medication list limited our power to detect a difference. Thus, it remains to be determined whether estrogen, progesterone, and/or androgens modify AKI risk in the perioperative setting, although very recent studies in patients undergoing gender-affirming hormone therapy report that estrogen therapy might be protective against AKI.[34] Future epidemiologic studies examining the effect of sex hormone modulation would help to answer this question.

Our study has a few important limitations. First, the retrospective nature of our study increases the risk of unrecognized bias and residual confounding; however, a randomized controlled trial was not feasible for our study question. Second, it should be noted that a large number of patients needed to be excluded due to lack of surgical Current Procedural Terminology codes, which could have caused selection bias; however, we did perform multiple sensitivity analysis to limit this source of bias. We also excluded about 10 to 12% of patients in the initial cohort due to additional missing covariates, the most common being body mass index, followed by ASA Physical Status and Elixhauser comorbidities (all important AKI risk factors). We did run additional analyses excluding these covariates, which did not change our conclusions (see tables, Supplemental Digital

Content 6, http://links.lww.com/ALN/C968). We believe the risk of bias due to not adjusting for these covariates outweighs the risk of excluding 10 to 12% of patients with missing data. Moreover, the mechanism of missingness is data missing completely at random, which should induce the least bias. Third, it should also be noted that other sex-related factors could influence postoperative AKI beyond the loss of sex hormones during menopause. Other sex-related differences that could modify AKI risk include known sexual dimorphism in cellular metabolism, mitochondrial function, genomic instability, levels of other nonsex hormones such as insulin, and the microbiome.[35–37] Fourth, regarding sex hormones, our secondary analysis examining the effect of home medication hormone replacement therapy on postoperative AKI was underpowered due to low numbers of patients having these medications on their home medication list, a potential source of informational bias. As such, we were unable to determine an effect of specific sex hormones on AKI risk attenuation, and these findings should be interpreted with caution. Fifth, a further limitation of our study is measurement error in that we did not include oliguria as a criterion for Kidney Disease Improving Global Outcomes AKI due to limitations of the Multicenter Perioperative Outcomes Group database. However, it should be noted that incorporating oliguria into the diagnostic criteria for AKI increases the detection of AKI. Last, our study specifically focused on postoperative AKI in noncardiac surgery; thus, caution should be taken in extrapolating results to other hospitalized patient populations. Nevertheless, we do believe the significant association we showed on the impact of age and sex groups with postoperative AKI should inform future investigations to account for age when they assess the influence of sex on AKI.

In conclusion, females less than 50 yr of age had lower odds of postoperative AKI compared to men, but this difference was gradually lost in women of increasing age groups. Further epidemiologic studies should be undertaken to identify if a specific sex hormone modifies AKI risk, which, if found, would inform future clinical trials of hormone therapy to mitigate postoperative AKI.

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## Competing Interests

The authors declare no competing interests. The authors report the following not related to the current manuscript: K08-GM132689 from National Institutes of Health - National Institute of General Medical Sciences (Bethesda, Maryland) and R01-DK131065 from National Institutes of Health - National Institute of Diabetes and Digestive and Kidney Diseases (Dr. Privratsky); a past financial relationship with the American Board of Obstetrics (Dr. Price); and K01-HL141701 from National Institutes of Health - National Heart, Lung, and Blood Institute and R01-DK133226 from National Institutes of Health - National Institute of Diabetes and Digestive and Kidney Diseases (Dr. Mathis).

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## Supplemental Digital Content

Supplemental Digital Content 1: Multivariable model of age, sex, and acute kidney injury, http://links.lww.com/ALN/C963

Supplemental Digital Content 2: Sensitivity analysis with 55-yr-old age cutoff, http://links.lww.com/ALN/C964

Supplemental Digital Content 3: Association of age and sex on odds of postoperative acute kidney injury between increasing age groups of males and females, http://links.lww.com/ALN/C965

Supplemental Digital Content 4: Acute kidney injury risk by age and sex-restricted cubic spline, http://links.lww.com/ALN/C966
Supplemental Digital Content 5: Interaction analysis of continuous age and sex on postoperative acute kidney injury risk, http://links.lww.com/ALN/C967
Supplemental Digital Content 6: Sensitivity analysis for missing data, http://links.lww.com/ALN/C968

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