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Postoperative acute kidney injury by age and sex: a retrospective cohort association study

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Abstract

Background: Acute kidney injury (AKI) following non-cardiac 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 our study was to determine the association of age and sex groups on postoperative

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AKI. We 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 2013–2019. Participants included adult inpatients without pre-existing end-stage kidney disease undergoing index major non-cardiac, non-kidney/urologic surgeries. Our primary exposure was age and sex groups defined as females ≤50 years, females >50 years, males ≤50 years, and males >50 years. Our 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: 2190/58585 [3.7%]; females >50: 9320/144047 [6.5%]; males ≤50: 3289/55503 [5.9%]; males >50: 11010/132447 [8.3%]). When adjusted for AKI risk factors, compared to females under 50 (odds ratio 1), the odds of AKI was higher in females over 50 (odds ratio 1.51, 95% CI 1.43–1.59), males under 50 (odds ratio 1.90, 95% CI 1.79–2.01), and males over 50 (odds ratio 2.06, 95% CI 1.96–2.17).

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 following non-cardiac surgery.

Introduction

Acute kidney injury (AKI) is one of the most common forms of postoperative organ injury, occurring in 6–39% of non-cardiac 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 is 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 multi-organ 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.

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 following non-cardiac 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 (KDIGO) 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 pre-clinical

and clinical results may be due to pre-clinical studies typically being carried out in young, ovulating female animals whereas most clinical studies examining postoperative AKI in female patients are in older, post-menopausal 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 this outweighs other associated risk-factors.

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

Methods

Study Design and Database

We conducted a retrospective cohort study of the Multicenter Perioperative Outcomes Group (MPOG) 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 Institutional Review Board, and follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. Prior to data analysis, the statistical analysis plan was written, registered, and posted on Open Science Framework (https://doi.org/10.17605/OSF.IO/D5X6F).

Study Population

The study population included patients 18 years and older undergoing procedures at all participating Multicenter Perioperative Outcomes Group institutions between 01/01/ 2013 to 12/31/2019. Exclusion criteria employed by Multicenter Perioperative Outcomes Group data group prior to data release were: outpatient procedures, cardiac surgery procedures, transplant surgical procedures, urological procedures, obstetrical procedures, American Society of Anesthesiology (ASA) Class 6 (organ procurement), electroconvulsive therapy, pain procedures, cases < 60 minutes in length, existing diagnosis of Elixhauser comorbidity index renal failure, centers with missing or invalid home medication data, and previous organ transplant recipients. After MPOG exclusions, we then further applied the following exclusions (Figure 1): missing surgical Current Procedural Terminology (CPT) codes, non-surgical procedures (i.e chest radiograph), procedures that should have been excluded

(i.e. cardiac surgery, cases <60 minutes), procedures with missing creatinine values to call AKI, non-index procedures on same patient (to avoid clustering within-person and potential change in risk due to repeated procedures), missing sex, 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 cut-offs defined by the following 4 groups: females ≤ 50 years old, males ≤ 50 years old, females > 50 years old, males > 50 years old. We chose a threshold of 50 years, because 50 years is often used as a reference cut-off for menopause and therefore an age that may impact AKI risk. Secondary exposures included home medication hormone replacement therapy (estrogen, estrogen + progesterone, estrogen + progesterone + testosterone, estrogen + testosterone, progesterone alone) in females > 55 years, and ascending 5-year increment age groups over 20 years in males and females.

Primary Outcome

The a priori outcome for both primary and secondary exposures was the development of post-operative 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 within 48 hours or >1.5X baseline within first 7 days. We also categorized AKI by Kidney Disease Improving Global Outcomes stage as follows: Stage 1 AKI – creatinine rise ≥ 0.3 mg/dl within 48 hours or 1.5–1.9X baseline within first 7 days after surgery; Stage 2 AKI – creatinine rise 2.0–2.9X baseline within 7 days following surgery; and Stage 3 AKI – creatinine rise to ≥ 4.0 mg/dl or 3.0X 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 pre-computed, publicly available, MPOG-specific perioperative EHR phenotype algorithms; each MPOG 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 pre-specified 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 (COPD), diabetes mellitus, previous myocardial infarction based on medical history, peripheral vascular disease, metastatic cancer, neurological disorders, obesity, and tumor without metastasis. We also calculated estimated glomerular

filtration rate category by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 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 (<15 ml/min/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

Prior to data collection, a formal power calculation was conducted. For purposes of our study, we initially considered a 25% relative reduction in postoperative AKI rates for females < 50 years old (reference group), compared to males less than 50 years old, to be a clinically meaningful effect. Based on recent Multicenter Perioperative Outcomes Group data,[14] at a power level of 80%, we determined 1705 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 prior to data release. Analyzed data from our single institution revealed a 20% difference in AKI rates between males and females less than 50 years old. Thus, we targeted a relative minimum clinically relevant effect size to be an unadjusted 20% reduction in AKI rate between females <50 and males <50 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-squared 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 post-operative 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 class, emergent status, crystalloid equivalent volume, colloid equivalent volume, estimated blood loss, medical comorbidities, and perioperative medication use (including propofol, celecoxib, etomidate, ketamine, ketorolac, ibuprofen). Random effects for institution were included to account for clustering of patients within centers. A p-value less than .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 years instead of 50. In a second sensitivity analysis we used age groups of 5 years in males and females between ages 20 and 90. 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 score, and Elixhauser comorbidities.

In the a priori proposed secondary subgroup analyses, we used propensity-matching to examine rates of postoperative AKI in females > 55 years in the following 5 groups based on hormone replacement therapy listed in home medications: estrogen alone, estrogen + progesterone/progestin, estrogen + progesterone/progestin + testosterone, estrogen + testosterone, progesterone/progestin alone. We chose to examine our secondary outcome in females > 55 years of age to reduce confounding from endogenous sex hormones in those pre-menopausal. 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 standard deviations of the propensity score distribution. After matching, we tested the balance of the covariates by looking for the matching approach which resulted in the lowest Absolute Standardized Mean Difference (ASMD), 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; Cary, NC).

Results

After exclusions, our dataset consisted of 390,382 adult patients undergoing surgery at 46 institutions (Figure 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 years old (Table 1). Patients older than 50 (whether male or female) were more likely to present with ASA class 3 or greater, indicative of more medical co-morbidities such as congestive heart failure, COPD, diabetes mellitus, hypertension, glomerular filtration rate categories 2–4, 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 less than 50 years were more likely to present as ASA class 5 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 greater than 50 (AKI rate of 6.5%), men less than 50 (5.9%), and men greater than 50 (8.3%), females less than 50 years had lowest rate of AKI at 3.7%. In the multivariable model adjusting for covariates, the lowest odds of AKI was in females under 50 (reference category), with higher odds in women over 50 (odds ratio 1.51 [1.43, 1.59]; $p < .001$), males under 50 (odds ratio 1.90 [95% CI 1.79, 2.01]; $p < .001$) and males over 50 (odds ratio 2.06 [1.96, 2.17]; $p < .001$) (Figure 2; see table, Supplemental Digital Content 1, covariates

in multivariable model). A sensitivity analysis of our primary outcome included increasing the age cut-off to 55 years old, which resulted in similar findings as our primary analysis (see table,Supplemental Digital Content 2, association of age and sex on AKI based on age cut-off of 55). Thus, females had 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 over 20 years in both sexes. Males in age groups between 20–40 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 21–25 had similar odds as did females 31–35) (Figure 3). However, after age 40, 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 (Figure 3; see table, Supplemental Digital Content 3, association of age and sex on odds of post-operative 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 prior to age 50; although after age 50, females showed progressive acceleration of AKI risk, an effect not mirrored in males (see figure, Supplemental Digital Content 4, risk of AKI by age and sex; see table, Supplemental Digital Content 5, interaction analysis of continuous age and sex on post-operative 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 > 55 years into five separate groups based on hormone replacement drugs listed on home medications. There were 1384 females greater than 55 that were listed as taking home hormone replacement therapy amongst the five hormone replacement groups (0.3% of total 390,382 patient cohort). We pursued a propensity-matching strategy with females greater than 55 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 post-operative 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 aged females were at lower odds of post-operative AKI than are females of older age and males of all ages. Moreover, we show here that groups of females of ascending age groups experience a gradual increase in AKI risk. Taken together, our data demonstrates an age-dependent effect of sex on AKI risk following non-cardiac surgery.

Sex is a controversial risk modifier for AKI. Studies in both surgical and non-surgical patients have identified female sex as a risk factor for AKI, including following administration of contrast,[26] aminoglycosides,[27] rhabdomyolysis,[28] and cardio-thoracic 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 non-cardiac 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 either lose protective factors and/or acquire detrimental factors as they age. One possible hypothesis is 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 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 10–12% of patients in the initial cohort due to additional missing covariates, the most common being body mass index, followed by ASA score 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). We believe the risk of

bias due to not adjusting for these covariates outweighs the risk of excluding 10–12% of patients with missing data. Moreover, the mechanism of missingness is 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 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 non-sex 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 criteria 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. Lastly, our study specifically focused on postoperative AKI in non-cardiac 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 years 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary Box:

What We Already Know about This Topic:

Acute kidney injury following non-cardiac 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 aged females were at lower odds of post-operative acute kidney injury than are females of older age and males of all ages.

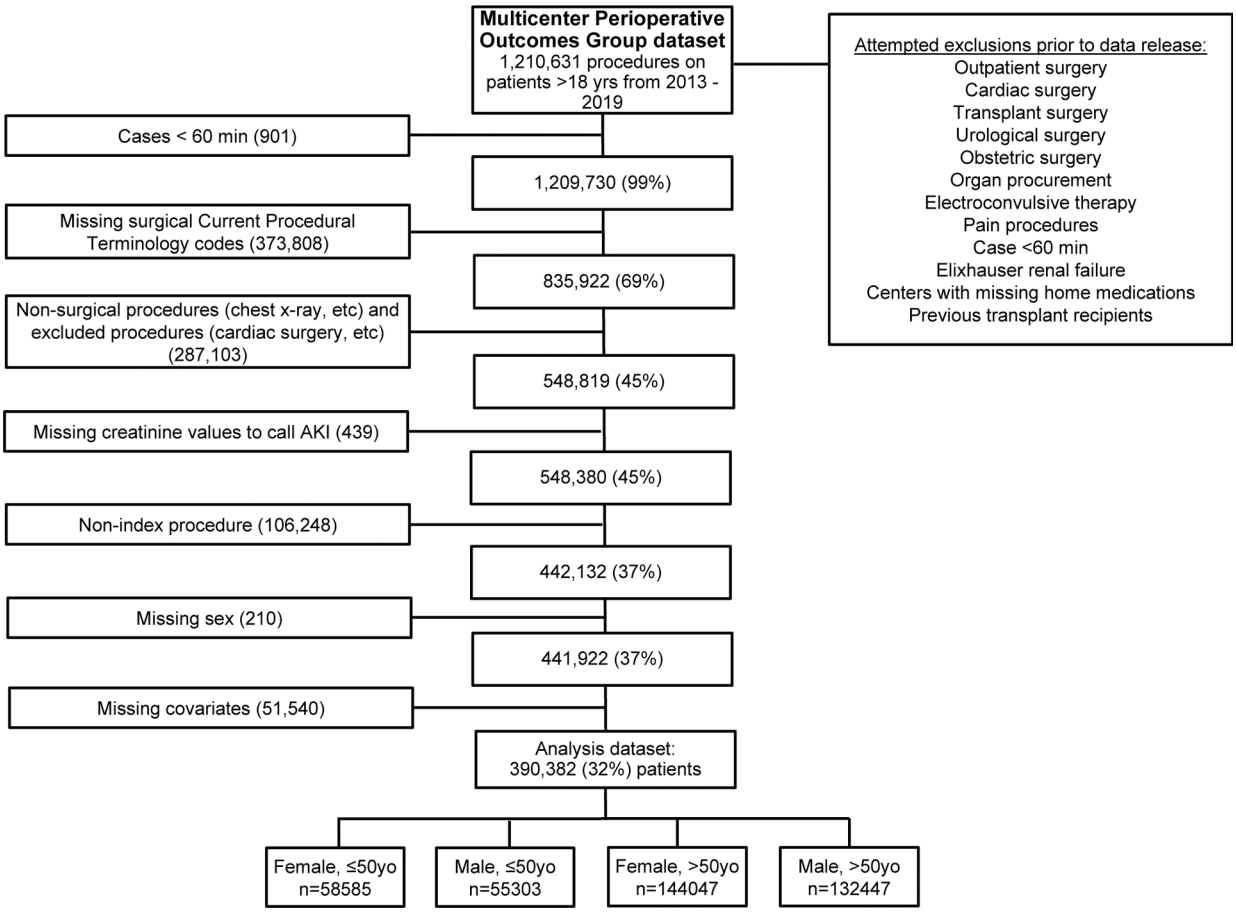

Figure 1 –.
Study design. Consort diagram of study population

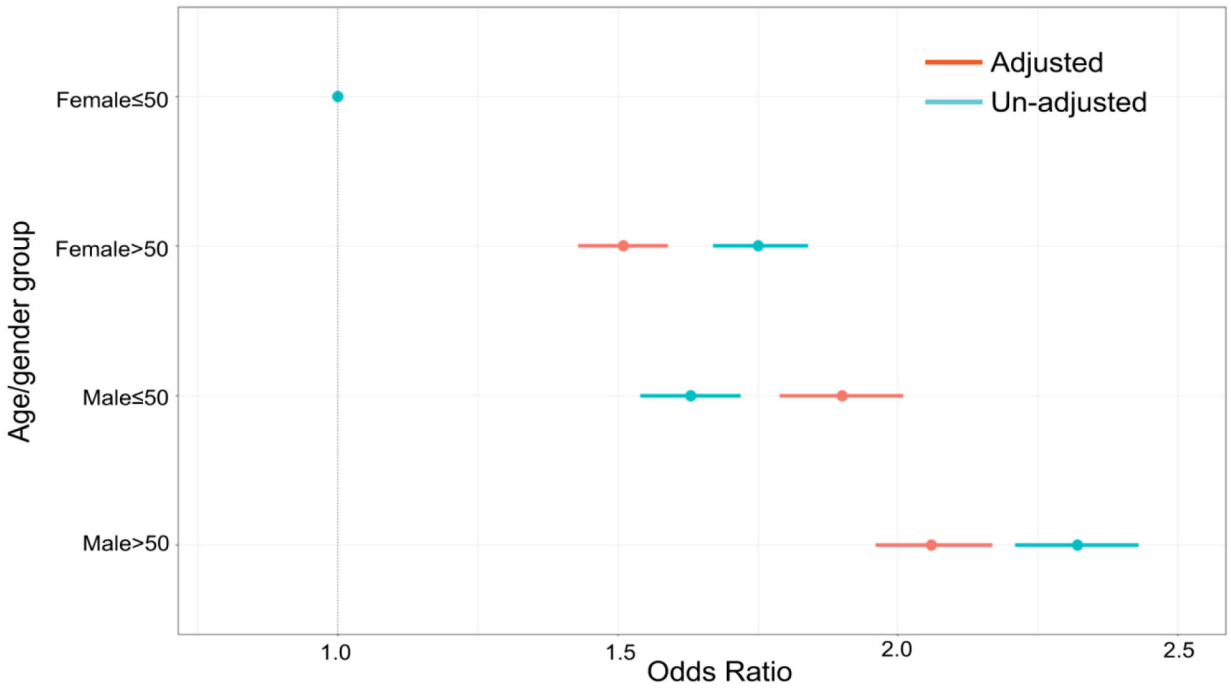

Figure 2 –.

Association of age and sex with post-operative acute kidney injury development based on age cut-off of 50: Women ≤ 50 years old display lower risk of postoperative AKI. Dot demonstrates odds ratio and line displays 95% confidence interval.

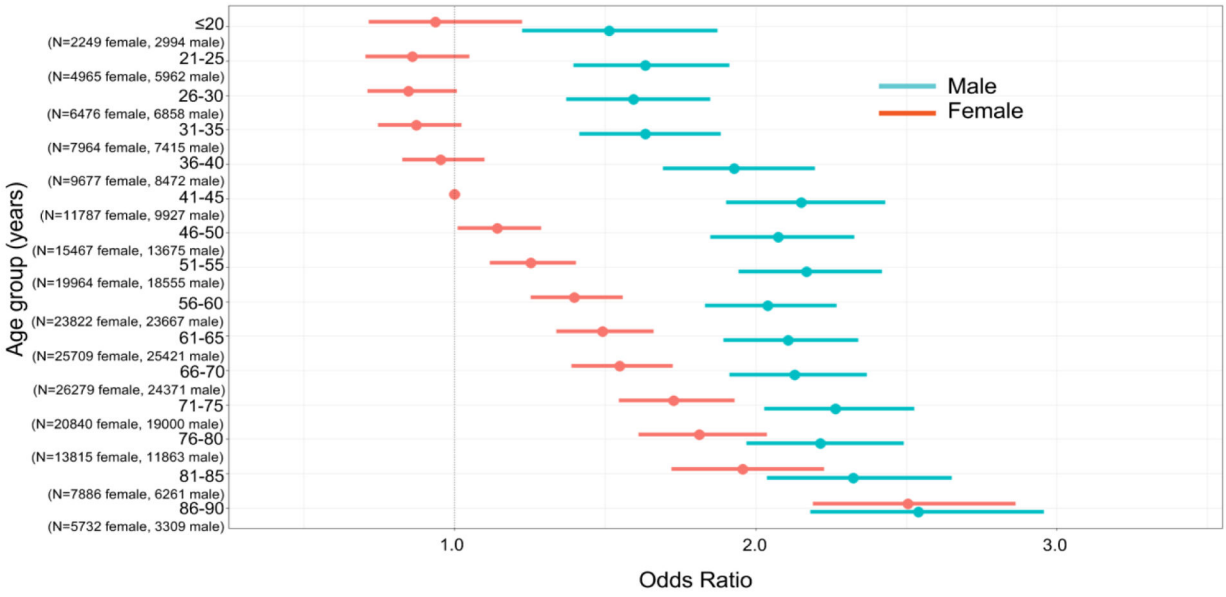

Figure 3 –.

Association of age and sex with odds of post-operative acute kidney injury based on ascending age groups. Dot demonstrates odds ratio and line displays 95% confidence interval.

Table 1:

Baseline, demographic, surgical characteristics

	Women ≤ 50 (n=58585)	**Women > 50 (n=144047)**	**Men ≤ 50 (n=55303)**	**Men > 50 (n=132447)**
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	2320 (4.0)	4178 (2.9)	2006 (3.6)	3618 (2.7)
Bi or Multi Racial	402 (0.7)	521 (0.4)	473 (0.9)	489 (0.4)
Black, not of Hispanic origin	8200 (14.0)	13405 (9.3)	6740 (12.2)	9630 (7.3)
Hispanic, Black	140 (0.2)	127 (0.1)	128 (0.2)	92 (0.1)
Hispanic, White	1123 (1.9)	1400 (1.0)	966 (1.7)	1166 (0.9)
Middle Eastern	30 (0.1)	29 (0.0)	27 (0.0)	26 (0.0)
Unknown race	6217 (10.6)	10993 (7.6)	6125 (11.1)	10163 (7.7)
White, not of Hispanic origin	39790 (67.9)	112875 (78.4)	38434 (69.5)	106756 (80.6)
ASA Class, n (%)				
1	2757 (4.7)	1111 (0.8)	4320 (7.8)	1079 (0.8)
2	25096 (42.8)	41403 (28.7)	23450 (42.4)	31611 (23.9)
3	27738 (47.3)	89953 (62.4)	23101 (41.8)	84983 (64.2)
4	2767 (4.7)	11076 (7.7)	3942 (7.1)	14120 (10.7)
5	227 (0.4)	504 (0.3)	490 (0.9)	654 (0.5)
Emergent, n (%)	5874 (10.0)	10044 (7.0)	8636 (15.6)	11217 (8.5)
Admission Type, n (%)				
Admit	14389 (24.6)	37656 (26.1)	10691 (19.3)	32836 (24.8)
Emergency	718 (1.2)	817 (0.6)	806 (1.5)	823 (0.6)
Inpatient	43257 (73.8)	105082 (72.9)	43576 (78.8)	98334 (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)	2089 (1.5)	673 (1.2)	1723 (1.3)
Iron Deficiency Anemia	2565 (4.4)	5134 (3.6)	1110 (2.0)	3538 (2.7)
Congestive Heart Failure	1119 (1.9)	8747 (6.1)	1159 (2.1)	10172 (7.7)
Previous myocardial infarction	165 (0.3)	1502 (1.0)	167 (0.3)	2879 (2.2)
Chronic Pulmonary Disease	9796 (16.7)	31206 (21.7)	5645 (10.2)	23755 (17.9)
Diabetes (complicated)	372 (0.6)	1466 (1.0)	336 (0.6)	1861 (1.4)

	Women ≤ 50 (n=58585)	Women > 50 (n=144047)	Men ≤ 50 (n=55303)	Men > 50 (n=132447)
Diabetes (uncomplicated)	4695 (8.0)	22314 (15.5)	3967 (7.2)	24101 (18.2)
Hypertension (complicated)	517 (0.9)	5314 (3.7)	559 (1.0)	6017 (4.5)
Hypertension (uncomplicated)	12911 (22.0)	80163 (55.7)	13378 (24.2)	78388 (59.2)
Metastatic Cancer	6041 (10.3)	22478 (15.6)	6059 (11.0)	23201 (17.5)
Neurological Disorders	5459 (9.3)	12528 (8.7)	5971 (10.8)	13031 (9.8)
Obesity	17255 (29.5)	31651 (22.0)	9339 (16.9)	23100 (17.4)
Peripheral Vascular Disease	2199 (3.8)	11313 (7.9)	2306 (4.2)	16284 (12.3)
Solid Tumor without metastasis	10644 (18.2)	37953 (26.3)	9781 (17.7)	40206 (30.4)
Glomerular filtration rate category				
1 (≥ 90 ml/min/1.73m^2)	44817 (76.5)	45719 (31.7)	42801 (77.4)	48499 (36.6)
2 (60–89)	12323 (21.0)	74953 (52.0)	11019 (19.9)	67618 (51.1)
3a (45–59)	893 (1.5)	16809 (11.7)	867 (1.6)	12102 (9.1)
3b (30–44)	284 (0.5)	5235 (3.6)	311 (0.6)	3171 (2.4)
4 (15–29)	168 (0.3)	1145 (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	53267 (90.9)	134299 (93.2)	46605 (84.3)	121979 (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)	1750 [1050, 2856]	1700 [1000, 2777]	1900 [1100, 3180]	1900 [1100, 3100]
Estimated Blood Loss (ml)	50 [10, 200]	100 [20, 250]	100 [15, 250]	100 [20, 300]
Perioperative Medications, n (%)				
Propofol	25204 (43.0)	68501 (47.6)	23177 (41.9)	60342 (45.6)
Celecoxib	810 (1.4)	3448 (2.4)	679 (1.2)	2763 (2.1)
Etomidate	87 (0.2)	442 (0.3)	182 (0.3)	528 (0.4)
Ketamine	5245 (9.0)	11130 (7.7)	5866 (10.6)	10975 (8.3)
Ketorolac	2650 (4.5)	6191 (4.3)	2152 (3.9)	4710 (3.6)
Ibuprofen	56 (0.1)	120 (0.1)	59 (0.1)	123 (0.1)
Outcome, n (%)				
AKI	2190 (3.7)	9320 (6.5)	3289 (5.9)	11010 (8.3)
AKI Stage				
None	56395 (96.3)	134727 (93.5)	52014 (94.1)	121437 (91.7)
1	1657 (2.8)	7475 (5.2)	2627 (4.8)	9210 (7.0)
2	356 (0.6)	1408 (1.0)	436 (0.8)	1354 (1.0)
3	177 (0.3)	437 (0.3)	226 (0.4)	446 (0.3)
In hospital mortality				
Unknown	2964 (5.1)	7337 (5.1)	2444 (4.4)	6054 (4.5)
No	55212 (94.2)	134604 (93.4)	52300 (94.6)	123819 (93.5)
Yes	409 (0.7)	2106 (1.5)	559 (1.0)	2574 (1.9)

Abbreviations: ASA-American Society of Anesthesiology, AKI-acute kidney injury

* 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.

Table 2:

Association of hormone replacement therapy on post-operative AKI risk

	Patients with Home Medications Hormone Replacement Therapy	**Matched Controls**	**p-value**	**Odds Ratio [95% CI]**
	Estrogen only (n=489)	**Matched controls (n=1467)**		
AKI	26 (5.3%)	68 (4.6%)	.601	1.13 [0.71, 1.82]
	Estrogen + Progesterone (n=146)	**Matched controls (n=438)**		
AKI	5 (3.4%)	27 (6.2%)	.214	0.54 [0.20, 1.43]
	Estrogen + Progesterone + Testosterone (n=85)	**Matched controls (n=255)**		
AKI	2 (2.4%)	3 (1.2%)	.444	2.02 [0.33, 12.32]
	Estrogen + Testosterone (n=118)	**Matched controls (n=354)**		
AKI	3 (2.5%)	10 (2.8%)	.685	0.75 [0.19, 3.00]
	Progesterone only (n=546)	**Matched controls (n=1638)**		
AKI	19 (3.5%)	64 (3.9%)	.651	0.89 [0.53, 1.49]

Abbreviations: AKI: acute kidney injury