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Preoperative Risk and the Association between Hypotension and Postoperative Acute Kidney Injury

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Abstract

Background: Despite the significant healthcare impact of acute kidney injury, little is known regarding prevention. Single-center data have implicated hypotension in developing postoperative acute kidney injury. The generalizability of this finding and the interaction between hypotension and baseline patient disease burden remain unknown. The authors sought to determine whether the association between intraoperative hypotension and acute kidney injury varies by preoperative risk.

Methods: Major noncardiac surgical procedures performed on adult patients across eight hospitals between 2008 and 2015 were reviewed. Derivation and validation cohorts were used, and cases were stratified into preoperative risk quartiles based upon comorbidities and surgical procedure. After preoperative risk stratification, associations between intraoperative hypotension and acute kidney injury were analyzed. Hypotension was defined as the lowest mean arterial

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Competing Interests

The authors declare no competing interests.

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pressure range achieved for more than 10 min; ranges were defined as absolute (mmHg) or relative (percentage of decrease from baseline).

Results: Among 138,021 cases reviewed, 12,431 (9.0%) developed postoperative acute kidney injury. Major risk factors included anemia, estimated glomerular filtration rate, surgery type, American Society of Anesthesiologists Physical Status, and expected anesthesia duration. Using such factors and others for risk stratification, patients with low baseline risk demonstrated no associations between intraoperative hypotension and acute kidney injury. Patients with medium risk demonstrated associations between severe-range intraoperative hypotension (mean arterial pressure less than 50 mmHg) and acute kidney injury (adjusted odds ratio, 2.62; 95% CI, 1.65 to 4.16 in validation cohort). In patients with the highest risk, mild hypotension ranges (mean arterial pressure 55 to 59 mmHg) were associated with acute kidney injury (adjusted odds ratio, 1.34; 95% CI, 1.16 to 1.56). Compared with absolute hypotension, relative hypotension demonstrated weak associations with acute kidney injury not replicable in the validation cohort.

Conclusions: Adult patients undergoing noncardiac surgery demonstrate varying associations with distinct levels of hypotension when stratified by preoperative risk factors. Specific levels of absolute hypotension, but not relative hypotension, are an important independent risk factor for acute kidney injury.

Worldwide, over 300 million surgeries requiring anesthesia care are performed annually.[1] Despite focused efforts to improve perioperative care, postoperative complications continue to pose a substantial threat to public health. Among general surgery patients, over 30% experience a complication.[2] Acute kidney injury (AKI) constitutes a large burden of these complications: international data demonstrate that AKI occurs in 13% of patients undergoing major surgery and is associated with a six-fold increased risk of mortality.[3–5] AKI increases hospital length of stay, cost, and mortality.[5,6] As a result, the development of AKI has been studied through predictive modeling in both the cardiac[7–9] and noncardiac surgery literature.[3,4,10–16]

Treatment of AKI remains largely supportive,[17] making AKI prevention a critical focus of investigation. Nearly all pharmacologic attempts to prevent development of AKI have been unsuccessful.[3,18] However, single-center studies have demonstrated an association between intraoperative hypotension and AKI.[14,19,20] The frequency of hypotension revealed by these studies is striking; among patients undergoing noncardiac surgery, up to 40% of cases demonstrate a mean arterial pressure (MAP) of less than 65 mmHg for at least 10 to 12 min.[13,14,19,21] In these cases, it is proposed that the risk-adjusted association between hypotension and AKI may be explained by a hypotension-induced disruption in renal perfusion leading to injury.[21] Consequently, optimizing blood pressure management during the intraoperative period has emerged as a promising nascent area of investigation.[22,23] Current single-center studies of postoperative AKI and hypotension propose nonspecific blood pressure targets across a broad range of patients that largely ignore the clinical realities of variable underlying patient risk. An individualized solution to blood pressure management has been recently explored by one small prospective trial targeting relative hypotension thresholds in a high-risk patient population.[24] However, no study has analyzed the association between hypotension and AKI in the context of underlying patient risk,

across a broadly representative surgical population to bring clinical relevance to findings of previous underpowered studies.

We performed a multicenter study examining risk factors for postoperative AKI after noncardiac surgery among a generalizable cohort of adult patients from private and academic medical centers nationally. We hypothesized that measures of intraoperative hypotension were independently associated with postoperative AKI, when adjusted for all available preoperative factors comprising a multicenter AKI prediction model. Additionally, we hypothesized that by using preoperative characteristics to risk-stratify patients undergoing noncardiac surgical procedures, hypotension ranges independently associated with AKI—and varying by preoperative risk—could be derived and validated. These data could inform the design of future prospective interventional trials targeting AKI prevention.

Materials and Methods

Study Design

Institutional review board approval for this multicenter, retrospective observational study (HUM24166, Ann Arbor, Michigan) was obtained. Similar approval was obtained at participating institutions (appendix 2). Because no care interventions were involved and all protected health information except date of service and extremes of age (more than 89 yr) were removed before analysis, patient consent was waived. Study outcomes, data collection, and statistical methods were established *a priori* and presented and approved at a multicenter peer-review forum before data analyses.[25] The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the Transparent Reporting of a multivariable Prediction model for Individual prognosis or diagnosis (TRIPOD) guidelines were followed throughout this study (Supplemental Digital Content, STROBE checklist, http://links.lww.com/ALN/C131; and TRIPOD checklist, http://links.lww.com/ALN/C132).[26]

Study Population

Surgical procedures performed at eight academic and private centers nationally between July 1, 2008, and December 1, 2015 (appendix 2), were reviewed. Institutions and dates chosen were based upon availability of complete data as relevant to this study. Adult (at least 18 yr old) patients with a creatinine level collected within 30 days before surgery were included. A baseline creatinine level was defined as the preoperative serum creatinine level collected closest to the start of surgery. Cases with extremely low baseline risk (outpatient and nonoperative procedures), unique operative physiology (liver transplantation, cardiac surgery), and urologic surgeries directly affecting renal function were excluded (fig. 1). Patients without a postoperative creatinine within 7 days, as well as patients with chronic kidney disease stage 5 (preoperative estimated glomerular filtration rate less than 15 ml · min^{-1} · 1.73 m^{-2}), were excluded from primary analysis. The Chronic Kidney Disease Epidemiology Collaboration creatinine equation was used for estimated glomerular filtration rate calculation.[27]

Study Outcomes

Our primary outcome was AKI (any stage), defined by the Kidney Disease: Improving Global Outcomes guidelines as a serum creatinine increase of at least 0.3 mg/dl within 48 h after surgery or an increase of at least 50% from baseline within 7 postoperative days.[28] In the case of multiple surgical procedures within a 7-day period, postoperative creatinine values were censored at the start of the subsequent surgical procedure. Secondary outcomes included stage 2 or higher AKI and stage 3 AKI, defined as at least 100% and 200% increases from baseline, respectively. Renal replacement therapy data were not available for outcome definition.

Data Source

A limited data set from the Multicenter Perioperative Outcomes Group database was extracted as applicable to this study. Within this research consortium, data from enterprise and departmental electronic health record systems are routinely uploaded to a secure, centralized database. Methods used for data input, storage, quality assurance, and extraction within the Multicenter Perioperative Outcomes Group consortium have been described elsewhere and utilized in prior studies.[29,30] In summary, each center uses a standardized set of data diagnostics to evaluate and address data quality on a monthly basis. In addition, random subsets of cases are manually audited by a clinician at each center to assess and attest to the accuracy of data extraction and source data.

Patient and Procedural Characteristics

A priori selected preoperative variables included an array of patient, procedural, and institution characteristics (Supplemental Digital Content 1, http://links.lww.com/ALN/C116). Patient medical history data was collected as classified by the Elixhauser Comorbidity Enhanced International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification algorithm.[31] Additional study variables have been previously assessed, including age,[4,16] preoperative renal function,[11,14,16,32] preoperative medications,[13,14,16] preoperative hemoglobin,[33] preinduction blood pressure,[13,14,16] American Society of Anesthesiologists (ASA) Physical Status classification,[4,5,14,32] procedure urgency,[5,10,14] and surgical procedure type,[5,10,14,16] characterized by body region on the basis of primary anesthesiology current procedural terminology code.

Intraoperative Hypotension Exposure

A priori ranges for intraoperative hypotension were selected based upon previous literature,[13,14] including absolute MAP values less than 50 mmHg, 50 to 54 mmHg, 55 to 59 mmHg, and 60 to 64 mmHg, as well as relative MAP values greater than 40%, 30 to 40%, and 20 to 30% below preinduction baseline. As similarly defined in previous studies,[14,34] preinduction MAP was determined as the MAP measured in the preoperative holding room on the date of surgery; if unavailable, preinduction MAP was defined as the first valid (*e.g.*, nonartifact) value obtained upon arrival to the operating room. In cases where MAP values were not directly measured, MAP was approximated as ($\frac{1}{3}$ · systolic blood pressure + $\frac{2}{3}$ · diastolic blood pressure).

The number of minutes of hypotension during each case was tabulated. Based upon recent primary and systematic review literature, prolonged, clinically relevant hypotension was defined as the lowest range for which more than 10 cumulative minutes were recorded.[13,21] Methods for intraoperative blood pressure measurement, signal processing, and artifact reduction have been previously published and are described in appendix 3 in greater detail.[35]

Statistical Analyses

Statistical analyses were performed using STATA/MP version 14 (StataCorp, USA) and SPSS version 24 (IBM, USA). Patients meeting selection criteria were randomly partitioned into derivation (two thirds) and validation (one third) cohorts. No statistical power calculation was conducted before the study; the sample size was based on the available data and our previous experience with this design.[10,36] Univariate analyses were completed for all covariates described in Supplemental Digital Content 1 (http://links.lww.com/ALN/C116). All continuous data that were normally distributed are reported as means and SD and analyzed using a two-tailed independent samples *t* test; all nonnormally distributed data were reported as medians and interquartile ranges and analyzed using a Mann–Whitney U test. Continuous covariates were assessed for normality using the Kolmogorov–Smirnov test; if the test indicated a *P* value less than 0.05, covariates were transformed according to the direction of the skew before modeling. Categorical data were analyzed using a Pearson chi-square or Fisher's exact test. Before all predictive modeling, collinearity among covariates was assessed using the variance inflation factor: if greater than 4, a Pearson correlation matrix was used to assess correlations. Covariates with a correlation of more than 0.70 were either reduced to a collapsed composite or selectively excluded from the model. Model discrimination was assessed using and c-statistics and net reclassification improvement.

Two separate multivariable logistic regression models were performed to develop risk quartiles for postoperative AKI (dependent variable). First, a mixed-effects multivariable logistic regression model for the derivation cohort was developed, using all covariates with less than 15% missing data as described in Supplemental Digital Content 1 (http://links.lww.com/ALN/C116). The remaining missing data were handled *via* a complete case analysis. Anonymized institution was included as a random effect; all other variables were included as fixed effects. Among cases with complete data, an AKI probability score was generated from the multivariable logistic regression model β-coefficients. The probability score incorporated both fixed and random effects, ranged from 0 to 1 per patient, and was used to stratify patients into four equal-sized preoperative risk quartiles: low, medium, high, and highest risk for developing AKI. Next, a clinically usable weighted risk score fixed effects model was developed by first grouping continuous covariates into prespecified physiologic and laboratory ranges and then normalizing model β-coefficients to approximated integer multiples.

Internal and external validation were performed to assess reproducibility of the preoperative risk model. Internal validation was performed using Somers' D on the original derivation data set with bootstrapping set to 1,000 repetitions. The Somers' D from the original derivation data set and the bootstrapped data set were then compared. External validation

was performed by comparing the c-statistic, as well as the incidence of quartile-stratified AKI between the derivation and validation cohorts.

Using the derivation cohort, any incremental improvement in model discrimination with measures of intraoperative hypotension added to the preoperative risk model was next assessed. An assessment of whether intraoperative hypotension exposures were independent predictors of AKI was also performed in the derivation cohort.

After these analyses, the risk quartile-stratified relationship between the intraoperative hypotension nadir and AKI was assessed. Within each risk quartile, a subsequent multivariable logistic regression investigating AKI as the dependent variable was developed, with hypotension ranges—adjusted for anesthesia duration included as a separate covariate—as the independent variable. A P value less than 0.05 was considered statistically significant. Measures of effect size were represented using adjusted odds ratios and 95% CI. The same techniques were used to analyze intraoperative hypotension alternatively defined by MAP ranges relative to preinduction baseline in a separate model. To assess the reproducibility of intraoperative hypotension associations, multivariable analyses of risk quartile-stratified hypotension and AKI were repeated for the validation cohort.

Preplanned Sensitivity Analyses

A preplanned sensitivity analysis was conducted, adjusting for estimated blood loss within each risk quartile for absolute and relative intraoperative hypotension definitions. Additional preplanned sensitivity analyses were performed, including: (1) cases with no postoperative creatinine available assumed to have no AKI, (2) cases restricted to 30-day index cases (defined as the first operation within a 30-day period for a given patient), and (3) missing data handled *via* multiple imputation (methods and results described in Supplemental Digital Content 2, http://links.lww.com/ALN/C117).

Post Hoc Secondary Subgroup Analyses

Several *post hoc* secondary subgroup analyses were performed in response to peer review. These included examining cases among patients receiving general anesthetics, cases with more than 20 min of invasive arterial line blood pressure monitoring, and cases among patients who underwent major high-risk surgeries. Primary anesthesiology current procedural terminology codes were used to identify surgical type; major high-risk surgeries were defined based upon the Revised Cardiac Risk Index,[37] including intraperitoneal, intrathoracic, and suprainguinal vascular procedures.

Results

Of the 499,658 surgical cases reviewed across eight institutions, 138,021 met the study inclusion criteria (fig. 1). Among these cases, 12,431 (9.0%) experienced postoperative AKI within 7 days. Among cases with complete data, 44% developed more than 10 min of absolute intraoperative hypotension of any severity, and 68% developed more than 10 min of relative intraoperative hypotension of any severity. Across eight institutions, crude AKI incidence ranged from 6.8 to 12.3%. Postoperative AKI remained evenly distributed between the derivation cohort (9.1%) and validation cohort (8.9%, $P = 0.182$).

Patient Population: Baseline Characteristics

We describe preoperative characteristics for the 138,021 cases in the entire cohort and the 91,314 cases in the derivation cohort (Supplemental Digital Content 1, http://links.lww.com/ALN/C116). Our study population had a median age of 58 yr, and 50% were men. Cases spanned a wide variety of surgical procedures, among which 13% were emergent and 87% required general anesthesia. A wide range of medical comorbidities were observed, commonly including uncomplicated hypertension (37%), chronic pulmonary disease (17%), uncomplicated diabetes (16%), and cardiac arrhythmias (16%). A majority of patients (83%) had normal or mildly decreased preoperative renal function (preoperative estimated glomerular filtration rate of at least 60 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}).

Preoperative Risk Model Derivation and Validation: Multivariable Analyses

Of the 91,314 cases within the derivation cohort, more than 95% completeness rates were observed for all but three risk adjustment variables: ASA Physical Status (93%), body mass index (87%), and preoperative serum albumin level (45%; Supplemental Digital Content 1, http://links.lww.com/ALN/C116). Excluding consideration of preoperative serum albumin levels, a total of 70,929 (78%) cases had complete data available for multivariable analysis and preoperative risk quartile derivation (Supplemental Digital Content 3, http://links.lww.com/ALN/C118). All continuous data elements demonstrated a P value of less than 0.001 for the Kolmogorov–Smirnov test and were transformed according to the direction of the skew (table 1). The variance inflation factor was less than 2 for all multivariable models; thus, no covariates were removed on the basis of collinearity.

We summarize preoperative predictors, preoperative risk quartiles, and model discrimination for the reduced, clinically usable weighted risk score model (table 1) and the full model (Supplemental Digital Content 4, http://links.lww.com/ALN/C119) here. The strongest perioperative predictors included chronic kidney disease (adjusted odds ratio [95% CI] for stage 4 = 3.89 [3.47 to 4.38], stage 3b = 2.03 [1.82 to 2.26], stage 3a = 1.45 [1.31 to 1.60]), ASA physical status 3 or greater (ASA 5 = 4.76 [3.22 to 7.05], ASA 4 = 2.52 [1.96 to 3.23], ASA 3 = 1.80 [1.41 to 2.29]), elevated risk surgery (2.31 [2.10 to 2.55]), and moderate to severe anemia (2.08 [1.92 to 2.25]). Our reduced, clinically usable weighted risk score model demonstrated good discrimination within the derivation cohort (c-statistic 0.76 [95% CI, 0.75 to 0.76]) and validation cohort (0.73 [0.72 to 0.73]). The weighted risk score model demonstrated good calibration for both the derivation and validation cohorts (Supplemental Digital Content 5A, 5B, 5C, http://links.lww.com/ALN/C120), with similar AKI incidence per quartile. Internal validation for the original derivation data set indicated good agreement among covariates: the Somers' D was 0.500 for the original derivation data set and 0.500 for the bootstrapped data set.

Among cases with complete data, AKI of at least stage 1 occurred in 8.6% of cases, at least stage 2 in 1.7% of cases, and AKI stage 3 occurred in 0.5% of cases (table 2). In the derivation cohort, the occurrence of AKI ranged from 2.0 to 20% across low baseline risk to highest baseline risk quartiles and similarly from 2.1 to 20% in the validation cohort. In both cohorts, rates of AKI of at least stage 2 and AKI stage 3 also increased with increasing preoperative risk ($P < 0.001$).

Impact of Intraoperative Hypotension as Incremental AKI Risk Modifier

In the derivation cohort, median preinduction MAP was observed to be 90 mmHg (interquartile range, 80 to 101 mmHg; Supplemental Digital Content 6, http://links.lww.com/ALN/C121). Of these cases, 43% demonstrated absolute intraoperative hypotension (any severity) for more than 10 min, and 68% demonstrated relative intraoperative hypotension (any severity) for more than 10 min. Among derivation cohort patients with severe-range absolute hypotension (MAP of less than 50 mmHg) for more than 10 min (n = 2,188, 3.1% of derivation cohort), 38.7% of such cases (n = 628) demonstrated persistent hypotension for more than 10 consecutive minutes; among such cases, 15.9% (n = 100) were ASA class 4 or 5 physical status, 8.3% (n = 52) were emergent; and 8.3% (n = 52) involved more than 1,000 ml of estimated blood loss.

In figure 2, the incidence of AKI *versus* severity of hypotension observed for each case is compared. In the derivation cohort, among patients with low preoperative risk (quartile 1), AKI incidence varied from 1.6 to 2.6% for absolute intraoperative hypotension ranges, and severity of hypotension demonstrated no significant association with AKI risk ($P = 0.20$). Conversely, among patients with the highest preoperative risk (quartile 4), AKI incidence ranged from 19.1 to 31.4%, and the severity of absolute intraoperative hypotension demonstrated a significant association with AKI risk for absolute intraoperative hypotension ($P < 0.001$). Similar findings were observed for the validation cohort. In contrast to absolute intraoperative hypotension, no associations between relative intraoperative hypotension severity and AKI incidence were replicable across derivation and validation cohorts among any risk quartile. When intraoperative hypotension measures were added to the full preoperative risk models, all ranges of absolute intraoperative hypotension for more than 10 min independently predicted AKI, whereas only severe ranges of relative intraoperative hypotension for more than 10 min were independent predictors in both the derivation and validation cohorts (Supplemental Digital Content 7, http://links.lww.com/ALN/C122). Additionally, when absolute or relative intraoperative hypotension was added to the preoperative risk models, performance was not observed to have significant improvement as assessed by c-statistic but was observed to have significant improvement as assessed by net reclassification improvement in both the derivation and validation cohorts. When examining the incidence of AKI *versus* risk quartile for each absolute and relative MAP range, AKI incidence was significantly different across risk quartiles (Supplemental Digital Content 8, http://links.lww.com/ALN/C123, $P < 0.001$ for all comparisons).

In figure 3, the association between more than 10 min of intraoperative hypotension and AKI when stratified by preoperative risk is analyzed. Among patients with low preoperative risk (quartile 1), multivariable analysis of the derivation cohort demonstrated no intraoperative hypotension ranges were associated with additional AKI risk. Among patients with medium preoperative risk (quartile 2), only severe intraoperative hypotension with a MAP range of less than 50 mmHg was independently associated with an additional AKI risk (adjusted odds ratio, 1.77; 95% CI, 1.20 to 2.61; $P = 0.004$). Finally, among patients with high and highest preoperative risk (quartiles 3 and 4), even milder intraoperative hypotension with MAP ranges of 55 to 59 mmHg (both quartiles 3 and 4) and 60 to 64 mmHg (quartile 3) were independently associated with additional AKI risk. These findings

were replicated in the validation cohort: no intraoperative hypotension range was independently associated with AKI among patients with low preoperative risk, whereas hypotension across multiple ranges of severity was independently associated with AKI among patients with the highest preoperative risk. Although weak associations between relative intraoperative hypotension (percentage of decrease from baseline) and AKI were observed in several instances, no clear pattern of relative intraoperative hypotension severity and AKI risk was observed across preoperative risk quartiles, and findings were not reproducible within the validation cohort.

Preplanned Sensitivity Analyses

Among *a priori* planned sensitivity analyses performed, an analysis of AKI and more than 10 min of intraoperative hypotension adjusted for estimated blood loss yielded similar results (Supplemental Digital Content 9, http://links.lww.com/ALN/C124). Preoperative risk models and subsequent risk quartile-stratified intraoperative hypotension models yielded similar model discrimination, independent risk factors, and intraoperative hypotension ranges among sensitivity analyses with modified AKI definitions or missing data handled *via* multiple imputation (Supplemental Digital Content 10, http://links.lww.com/ALN/C125; Supplemental Digital Content 11, http://links.lww.com/ALN/C126; Supplemental Digital Content 12, http://links.lww.com/ALN/C127).

Secondary Subgroup Analyses Performed in Response to Peer Review

Among *post hoc* secondary subgroup analyses performed in response to peer review, the incidence of AKI was determined to be 9.3% among patients receiving a general anesthetic, 13.1% among patients with more than 20 min of invasive arterial line blood pressure monitoring data, and 10.7% among patients undergoing major high-risk surgeries (intraperitoneal, intrathoracic, or suprainguinal vascular). Preoperative risk models and subsequent risk quartile-stratified intraoperative hypotension models yielded similar model discrimination, independent risk factors, and intraoperative hypotension ranges among all secondary subgroup analyses (Supplemental Digital Content 13, http://links.lww.com/ALN/C128; Supplemental Digital Content 14, http://links.lww.com/ALN/C129; Supplemental Digital Content 15, http://links.lww.com/ALN/C130).

Discussion

In this multicenter study of AKI, we report an overall AKI incidence of 9.0% among a generalizable population of major noncardiac procedures spanning U.S. academic medical centers and private hospitals. Our study builds on existing literature by providing a robust multicenter analysis of a modifiable risk factor for postoperative AKI: intraoperative hypotension.

The data presented establish the intuitive concept that the relationship between hypotension and AKI varies by underlying patient and procedural risk. Patients with low risk demonstrated no associated increased risk of AKI across all blood pressure ranges including severe (MAP of less than 50 mmHg). Conversely, patients with the highest baseline risk demonstrated (1) an association between even mild absolute intraoperative hypotension

ranges and AKI, including a 25 to 54% associated increase in AKI for a hypotension range of 55 to 59 mmHg, and (2) an amplified association between severe absolute hypotension and AKI, including a 79 to 150% associated increase in AKI for more than 10 min of hypotension of less than 50 mmHg. In addition, these data demonstrate the common nature of intraoperative hypotension, with 44% of patients experiencing at least one absolute hypotension episode of more than 10 min. Finally, we provide a multicenter analysis establishing absolute hypotension, but not relative hypotension, as a risk factor for AKI. Given the historical lack of data defining intraoperative blood pressure targets in relation to underlying patient risk, we provide evidence to support a risk-stratified approach to AKI risk reduction and prediction. These data may enable prospective clinical trials of interventions aimed to decrease hypotension-mediated AKI.

The observed AKI incidence of 9.0%, with institution-specific AKI incidences ranging from 6.8 to 12.3%, is similar to recent studies.[3,13,16,19] Variation among institutions may be attributable to institution-specific patient populations, practice variation, and postoperative surveillance differences. In contrast to previous studies, the current data describe a more generalizable and understudied noncardiac surgery population for whom therapies to prevent AKI may still be of significant benefit.

The AKI probability score developed for preoperative risk stratification yielded a predictive performance comparable with previously reported postoperative multicenter AKI prediction models.[10,15,16] Independent preoperative risk factors consistent with previous multicenter studies included gender, body mass index, estimated glomerular filtration rate, liver disease, hypertension, diabetes mellitus, anemia, preoperative renin–angiotensin–aldosterone system blockade, surgery type, and expected anesthesia duration.[10,15,16] In contrast to previous studies, we observed patient age to lack an independent association with postoperative AKI. Two possible explanations for such findings include (1) differences in patient populations and practice patterns existed across studies, and/or (2) preoperative variables correlated to age and newly evaluated in our study, including ASA physical status classification, weight loss, and coagulopathy, demonstrated stronger independent associations with postoperative AKI. Assuming the latter to be true, our findings suggest that age serves as a useful marker for the burden of preoperative comorbidities, when more granular data are not available for AKI risk prediction.

The risk-adjusted association of absolute intraoperative hypotension on AKI was reproducible in the derivation and validation cohorts (Supplemental Digital Content 7A, 7C, http://links.lww.com/ALN/C122). Our study provides validated blood pressure targets for prospective trials investigating individualized hypotension management for AKI risk reduction, a promising potential practice standard.[24] Just as importantly, without these data presented, the clinician has little to guide management of the majority of patients undergoing surgical procedures on a daily basis. These data establish that among low-risk patients, there are no associations with hypotension as low as MAP of 50 mmHg for 10 or more minutes (fig. 3). These data should not be interpreted that hypotension at this threshold is innocuous for low risk patients; an association was not observed for the studied AKI outcome and specific population. Prudent observation and management of mild hypotension (MAP of less

than 60 mmHg) for high-risk patients is supported by our data in the primary and multiple sensitivity analyses.

Although our data demonstrate the risk-adjusted relationship between hypotension and AKI, the optimal treatment of hypotension remains controversial. As shown in our study, the association between hypotension and AKI varies by clinical context; however, it remains understudied whether specific interventions to treat hypotension can reduce AKI risk and whether the effectiveness of such interventions vary by clinical context as well. In a randomized trial of 292 high-risk, elderly patients, Futier *et al.*[24] demonstrated that maintaining systolic blood pressure within 10% of preoperative baseline using norepinephrine *versus* allowing patients to experience systolic intraoperative hypotension of 80 mmHg (or within 40% of preoperative baseline) and treatment using ephedrine boluses decreased a composite morbidity outcome, including AKI, from 63 to 46%. The study included a controversial definition of "standard care," observed a remarkably high primary event rate, did not observe a mortality difference, was focused on very high-risk patients and only evaluated one aspect of hypotension management. In addition to treatment *via* vasoconstrictors, anesthesiologists may also treat the hypotensive patient using fluid resuscitation, inotropic support, or a decrease in cardiovascular depressant sedative, analgesic, or anesthetic agents. In each case, the putative mechanism for reducing AKI risk is a restoration of renal blood flow; indeed, prior studies have shown that alterations in renal blood flow are associated with AKI.[38,39] However, given these varied mechanisms by which normotension can be achieved, the relationship between restoration of normotension and restored renal blood flow is not straightforward. Although our data cannot establish the value of restoring normotension, it demonstrates that in low-risk patients, maneuvers to increase blood pressure may offer little benefit, given the lack of relationship observed between intraoperative hypotension and AKI.

In addition to correction of hypotension, studies investigating other hemodynamic goals to direct therapies are well established; they include measurements of fluid responsiveness using dynamic waveform indices,[40–42] stroke volume,[43] cardiac index,[41,42] and central venous oxygen saturation.[41] Additionally, in two recent prospective interventional trials, implementation of a care bundle, which included goal-directed advanced hemodynamic monitoring, successfully reduced postoperative AKI incidence in high-risk patients.[44,45] However, these studies are limited by dependence upon infrequently used and heterogeneous surrogate measures for perfusion. Measurement of blood pressure remains a universal standard of perioperative care as set forth by professional guidelines.[46]

Study Limitations

The data and analysis must be viewed in the context of several limitations. The AKI outcome definition did not include postoperative renal replacement therapy or urine output per complete guidelines because these data were unavailable; creatinine values alone were relied upon.[28] For uncomplicated surgical procedures, postoperative creatinine values were occasionally not measured, and the exclusion of such cases likely led to an overestimation of AKI. Although measures were taken to maximize data quality, including careful participating site selection and artifact reduction algorithms, our analysis and results

remained subject to a level of data quality derived from routine clinical care rather than a controlled experimental setting. Specifically, a lack of minute-to-minute MAP recordings among patients monitored solely with intermittent noninvasive blood pressure measurements or monitored *via* invasive arterial blood pressure measurements that were periodically interrupted (*e.g.*, arterial blood gas sampling) may have limited an ability to provide precise risk estimates. Additionally, it is possible that preinduction MAP values obtained on the date of surgery were not truly reflective of "baseline" MAP; other MAP values such as those obtained during preoperative clinic or primary care visits were not available for study. However, such blood pressure measurements obtained on the date of surgery have been previously demonstrated as similar to preoperative and primary care blood pressure values, with a mean bias of only 2 to 5 mmHg greater than preoperative clinic values.[47] Furthermore, the pragmatic nature of this observational study, limited to health data routinely available to providers, including intermittent MAP recordings and lack of a computed average baseline MAP, favors results generalizable to real-world settings.

Additionally, associations between intraoperative hypotension and AKI within preoperative risk strata were conditional on the accuracy of risk model; although good preoperative risk model discrimination was observed, the true preoperative risk of AKI remains not fully elucidated. Given these findings, we recommend further study to elucidate the complex relationships between preoperative risk, hypotension severity, and AKI. Despite these limitations, we present a robust multicenter study— across academic and nonacademic hospitals—assessing the association between potentially modifiable intraoperative hypotension and AKI *via* a nuanced approach accounting for preoperative risk derived from a wide array of risk factors.

Conclusions

In summary, we describe a 9.0% incidence of AKI for patients undergoing inpatient noncardiac surgical procedures across eight institutions. Major factors identifying patients at risk for AKI included anemia, estimated glomerular filtration rate, elevated risk surgery, ASA Physical Status, and expected anesthesia duration. Such factors and others can be used to stratify patients by preoperative risk of AKI. We observed that high-risk patients are sensitive to hypotension as mild as MAP of less than 65 mmHg, levels routinely tolerated in perioperative or critical care settings. Given the lack of effective therapies for AKI, prevention of hypotension in high-risk patients may be a modifiable process of care. Our study informs further investigations targeting a risk-stratified approach to intraoperative hypotension monitoring (*e.g.*, decision to use arterial line) and management (*e.g.*, treatment interventions), potentially impacting clinical decisions made for the millions of patients undergoing major noncardiac surgery each year. Our findings represent a call to action for more routine assessment of preoperative AKI risk and preoperative risk-stratified intraoperative hypotension vigilance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix 3.: Intraoperative Blood Pressure Monitoring, Signal Processing, and Arterial Blood Pressure Artifact Reduction Algorithm

We used arterial line waveform data and noninvasive blood pressure–monitoring data for the study; when simultaneous values were recorded, the higher of the two MAP values was used. When blood pressure monitoring was noncontinuous during a case (*e.g.*, noninvasive blood pressure measurements or arterial line disconnected), blood pressure was assumed to be constant and equal to the previous measurement if within 5 min from the most recent measurement; if 5 min or greater from any blood pressure measurement value, blood pressure was presumed to be unknown and treated as missing data for analysis purposes. To minimize the impact of blood pressure–monitoring artifact, we used an artifact reduction algorithm, which is shown in the following table.

Artifact Elimination Strategy	Rules/Logic
Provider marked artifacts	Marked as artifact in real time by the provider
Artifact from arterial line	SBP > 200 and PP < 50
clamping, damping, or flushing; or cuff under external pressure	SBP > 150 and SBP ≤200 and PP < 30
	SBP ≥ 100 and SBP ≤ 150 and PP < 15
	SBP < 100 and PP < 10
Artifact from arterial line or cuff transducing signal but disconnected from patient	SBP ≤ 10 or DBP ≤ 10
	SBP = DBP = MAP
	MAP < 0
	MAP ≥ 140
	If any BP is marked as artifact, then all BP measurements for that time will be marked

Artifact Elimination Strategy	Rules/Logic
	as artifact

If artifact other than provider-marked, is detected for SBP, DBP, or MAP for a specific reading, then all three blood pressure values are marked as an artifact. BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure (SBP – DBP); SBP, systolic blood pressure.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Acute kidney injury occurs in 13% of patients undergoing major surgery and is associated with a six-fold increased risk of mortality.
- Single-center studies have demonstrated an association between intraoperative hypotension and acute kidney injury.

What This Article Tells Us That Is New

- In a large cohort of noncardiac surgical patients, the incidence of acute kidney injury was 9%.
- Major factors identifying patients at risk for acute kidney injury included anemia, estimated glomerular filtration rate, elevated risk surgery, American Society of Anesthesiologists Physical Status, and expected anesthesia duration.
- The relationship between hypotension and acute kidney injury varied by underlying patient and procedural risk. Patients with low risk demonstrated no associated increased risk of acute kidney injury across all blood pressure ranges, whereas patients with the highest baseline risk demonstrated an association between even mild absolute intraoperative hypotension ranges and acute kidney injury.

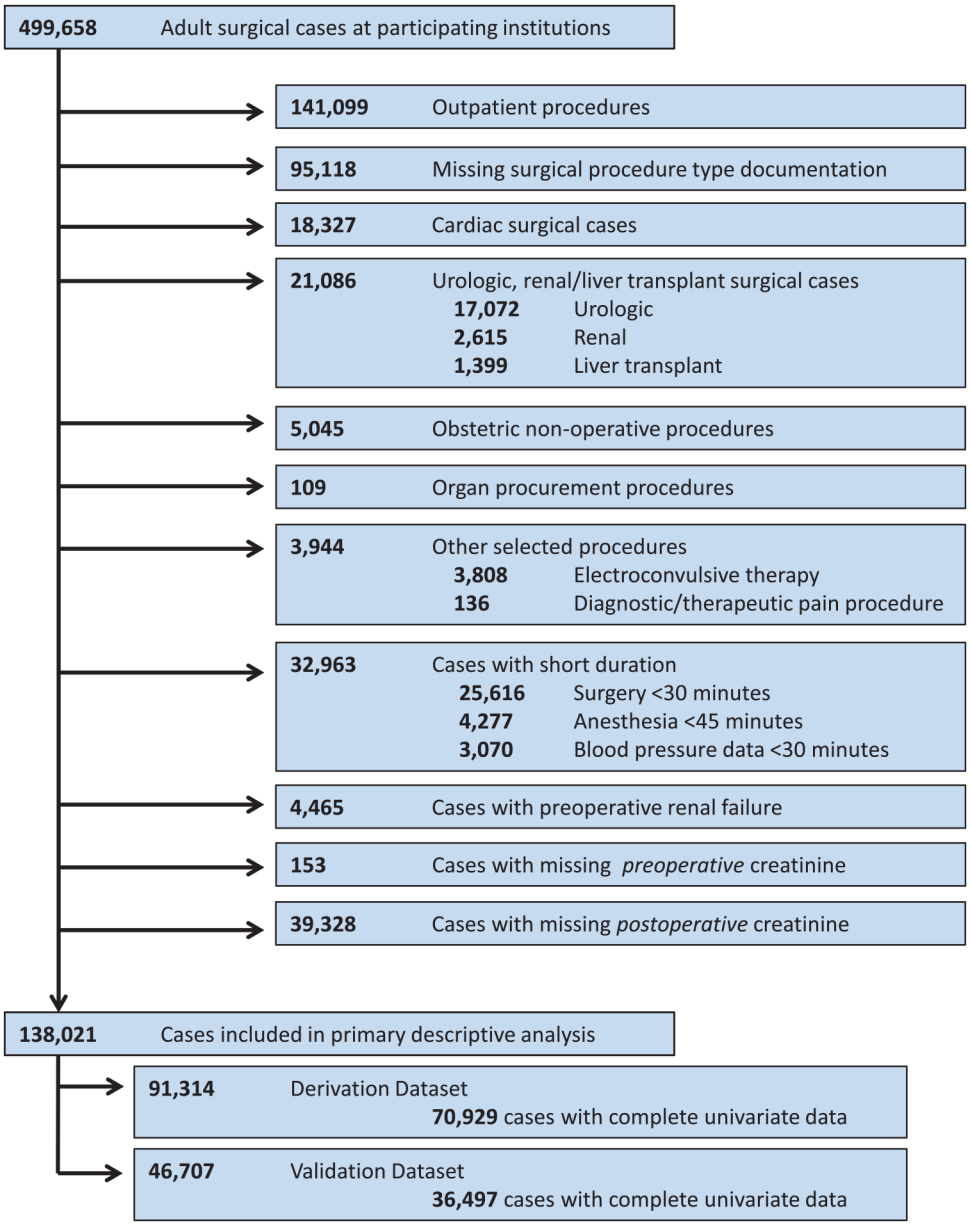


Fig. 1.
Study inclusion/exclusion criteria.

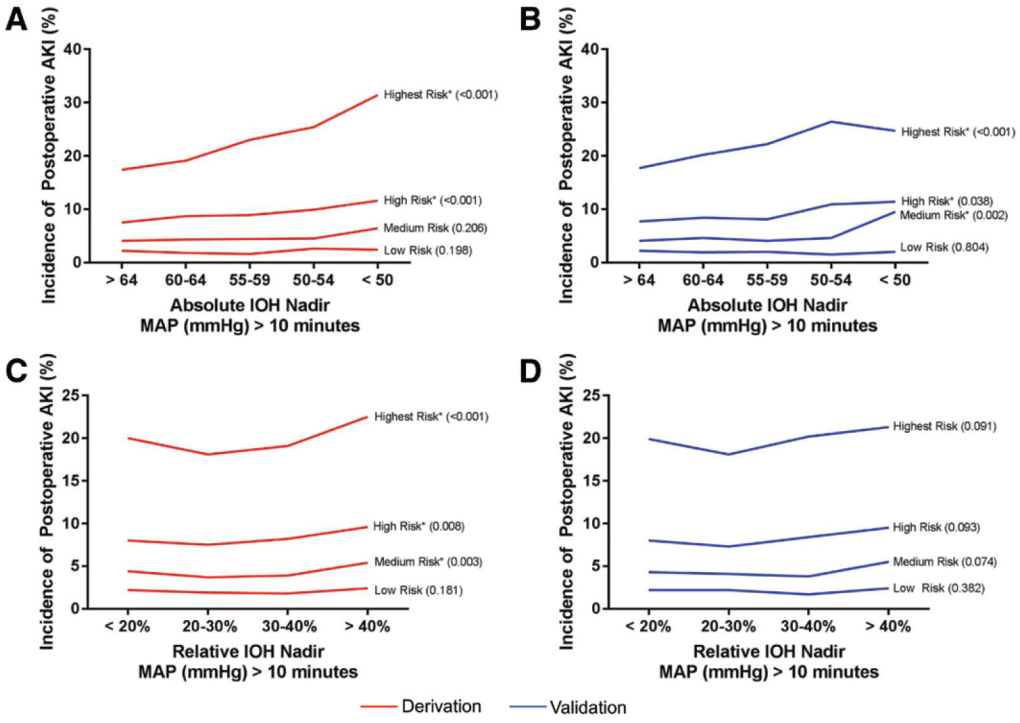
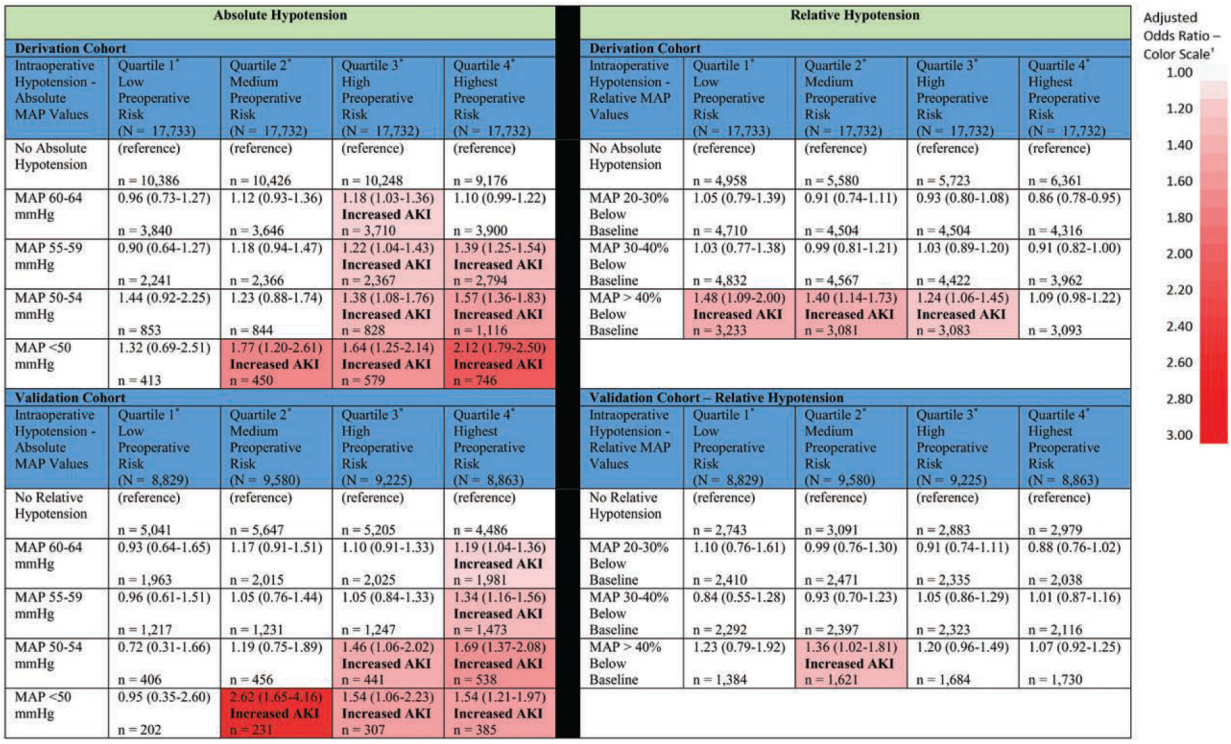


Fig. 2.

Relationship between acute kidney injury (AKI) incidence and intraoperative hypotension (IOH), stratified by preoperative risk quartile. Quartiles with *asterisks* indicate statistically significant within-quartile differences among mean arterial pressure (MAP) ranges ($P < 0.05$). (*A*) and (*B*) represent compare absolute IOH ranges for each quartile in the derivation and validation cohorts, respectively; (*C*) and (*D*) compare relative IOH ranges for each quartile in the derivation and validation cohorts, respectively.



Absolute Hypotension

Derivation Cohort

Intraoperative Hypotension - Absolute MAP Values	Quartile 1* Low Preoperative Risk (N = 17,733)	Quartile 2* Medium Preoperative Risk (N = 17,732)	Quartile 3* High Preoperative Risk (N = 17,732)	Quartile 4* Highest Preoperative Risk (N = 17,732)
No Absolute Hypotension	(reference) n = 10,386	(reference) n = 10,426	(reference) n = 10,248	(reference) n = 9,176
MAP 60-64 mmHg	0.96 (0.73-1.27) n = 3,840	1.12 (0.93-1.36) n = 3,646	1.18 (1.03-1.36) **Increased AKI** n = 3,710	1.10 (0.99-1.22) n = 3,900
MAP 55-59 mmHg	0.90 (0.64-1.27) n = 2,241	1.18 (0.94-1.47) n = 2,366	1.22 (1.04-1.43) **Increased AKI** n = 2,367	1.39 (1.25-1.54) **Increased AKI** n = 2,794
MAP 50-54 mmHg	1.44 (0.92-2.25) n = 853	1.23 (0.88-1.74) n = 844	1.38 (1.08-1.76) **Increased AKI** n = 828	1.57 (1.36-1.83) **Increased AKI** n = 1,116
MAP <50 mmHg	1.32 (0.69-2.51) n = 413	1.77 (1.20-2.61) **Increased AKI** n = 450	1.64 (1.25-2.14) **Increased AKI** n = 579	2.12 (1.79-2.50) **Increased AKI** n = 746

Validation Cohort

Intraoperative Hypotension - Absolute MAP Values	Quartile 1* Low Preoperative Risk (N = 8,829)	Quartile 2* Medium Preoperative Risk (N = 9,580)	Quartile 3* High Preoperative Risk (N = 9,225)	Quartile 4* Highest Preoperative Risk (N = 8,863)
No Relative Hypotension	(reference) n = 5,041	(reference) n = 5,647	(reference) n = 5,205	(reference) n = 4,486
MAP 60-64 mmHg	0.93 (0.64-1.65) n = 1,963	1.17 (0.91-1.51) n = 2,015	1.10 (0.91-1.33) n = 2,025	1.19 (1.04-1.36) **Increased AKI** n = 1,981
MAP 55-59 mmHg	0.96 (0.61-1.51) n = 1,217	1.05 (0.76-1.44) n = 1,231	1.05 (0.84-1.33) n = 1,247	1.34 (1.16-1.56) **Increased AKI** n = 1,473
MAP 50-54 mmHg	0.72 (0.31-1.66) n = 406	1.19 (0.75-1.89) n = 456	1.46 (1.06-2.02) **Increased AKI** n = 441	1.69 (1.37-2.08) **Increased AKI** n = 538
MAP <50 mmHg	0.95 (0.35-2.60) n = 202	2.62 (1.65-4.16) **Increased AKI** n = 231	1.54 (1.06-2.23) **Increased AKI** n = 307	1.54 (1.21-1.97) **Increased AKI** n = 385

Relative Hypotension

Derivation Cohort

Intraoperative Hypotension - Relative MAP Values	Quartile 1* Low Preoperative Risk (N = 17,733)	Quartile 2* Medium Preoperative Risk (N = 17,732)	Quartile 3* High Preoperative Risk (N = 17,732)	Quartile 4* Highest Preoperative Risk (N = 17,732)
No Absolute Hypotension	(reference) n = 4,958	(reference) n = 5,580	(reference) n = 5,723	(reference) n = 6,361
MAP 20-30% Below Baseline	1.05 (0.79-1.39) n = 4,710	0.91 (0.74-1.11) n = 4,504	0.93 (0.80-1.08) n = 4,504	0.86 (0.78-0.95) n = 4,316
MAP 30-40% Below Baseline	1.03 (0.77-1.38) n = 4,832	0.99 (0.81-1.21) n = 4,567	1.03 (0.89-1.20) n = 4,422	0.91 (0.82-1.00) n = 3,962
MAP > 40% Below Baseline	1.48 (1.09-2.00) **Increased AKI** n = 3,233	1.40 (1.14-1.73) **Increased AKI** n = 3,081	1.24 (1.06-1.45) **Increased AKI** n = 3,083	1.09 (0.98-1.22) n = 3,093

Validation Cohort – Relative Hypotension

Intraoperative Hypotension - Relative MAP Values	Quartile 1* Low Preoperative Risk (N = 8,829)	Quartile 2* Medium Preoperative Risk (N = 9,580)	Quartile 3* High Preoperative Risk (N = 9,225)	Quartile 4* Highest Preoperative Risk (N = 8,863)
No Relative Hypotension	(reference) n = 2,743	(reference) n = 3,091	(reference) n = 2,883	(reference) n = 2,979
MAP 20-30% Below Baseline	1.10 (0.76-1.61) n = 2,410	0.99 (0.76-1.30) n = 2,471	0.91 (0.74-1.11) n = 2,335	0.88 (0.76-1.02) n = 2,038
MAP 30-40% Below Baseline	0.84 (0.55-1.28) n = 2,292	0.93 (0.70-1.23) n = 2,397	1.05 (0.86-1.29) n = 2,323	1.01 (0.87-1.16) n = 2,116
MAP > 40% Below Baseline	1.23 (0.79-1.92) n = 1,384	1.36 (1.02-1.81) **Increased AKI** n = 1,621	1.20 (0.96-1.49) n = 1,684	1.07 (0.92-1.25) n = 1,730

Adjusted Odds Ratio – Color Scale†

1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80 3.00

Fig. 3.

Adjusted risk of acute kidney injury (AKI) associated with intraoperative hypotension nadir greater than 10 min, by preoperative risk quartile. Regression within each quartile included all four blood pressure ranges and operative duration log transformed. Values presented as adjusted odds ratio and 95% confidence interval. *Patients were stratified by risk of postoperative AKI using the full-fit multivariable model. †Color scale used only for adjusted odds ratios demonstrating statistically significant associations. MAP, mean arterial pressure.

Table 1.

Independent Preoperative Predictors of Acute Kidney Injury from the Derivation Cohort of 70,929 Patients: Weighted Risk Score Multivariable Logistic Regression Model

Risk Factor	β-Coefficient	aOR (95% CI)	Points in Model*
Medical factors			
Patient age (yr)			
18–30	Reference		0
31–40	−0.001	1.00 (0.86–1.16)	
41–50	−0.029	0.97 (0.85–1.12)	
51–60	0.090	1.09 (0.96–1.24)	
61–70	0.065	1.07 (0.94–1.22)	
71–80	0.028	1.03 (0.89–1.19)	
> 80	0.070	1.07 (0.91–1.26)	
BMI (kg/m^2, by WHO Classification)			
Underweight (< 18.5)	0.010	1.01 (0.85–1.20)	0
Normal weight (18.5–24.9)	Reference		
Overweight (25.0–29.9)	0.078	1.08 (1.00–1.17)	
Class I obesity (30.0–34.9)	0.235	1.27 (1.16–1.38)	1
Class II obesity (35.0–39.9)	0.344	1.41 (1.27–1.56)	
Class III obesity (> 40.0)	0.426	1.53 (1.39–1.69)	
Male gender	0.215	1.24 (1.17–1.31)	
Patient medical history†			
Liver disease	0.427	1.53 (1.40–1.68)	1
Coagulopathy	0.369	1.44 (1.32–1.59)	1
Hypertension, complicated	0.264	1.30 (1.18–1.44)	1
Diabetes, complicated	0.293	1.34 (1.15–1.57)	1
Weight loss	0.220	1.25 (1.14–1.36)	1
Pulmonary circulation disorders	0.160	1.17 (1.05–1.31)	1
AIDS/HIV	0.547	1.73 (1.02–2.92)	2
Congestive heart failure	0.034	1.04 (0.94–1.14)	0
Cardiac arrhythmias	0.104	1.11 (1.03–1.20)	0

Peripheral vascular disorders	0.062	1.06 (0.98–1.15)	0
Chronic pulmonary disease	0.009	1.01 (0.94–1.09)	0
Hypertension, uncomplicated	0.023	1.02 (0.96–1.10)	0
Diabetes, uncomplicated	0.051	1.05 (0.98–1.13)	0
Lymphoma	0.113	1.12 (0.92–1.36)	0
Paralysis/other neurologic disorders	0.106	1.12 (1.01–1.23)	0
Metastatic cancer	0.013	1.01 (0.92–1.12)	0
Psychoses	−0.077	0.93 (0.73–1.18)	0
Valvular disease	0.003	1.00 (0.90–1.12)	0
Drug abuse	−0.042	0.96 (0.81–1.14)	0
Rheumatoid arthritis/collagen vascular diseases	−0.067	0.94 (0.81–1.08)	0
Peptic ulcer disease excluding bleeding	0.028	1.03 (0.85–1.25)	0
Solid tumor	−0.014	0.99 (0.91–1.07)	0
Hypothyroidism	−0.135	0.87 (0.80–0.96)	0
Alcohol abuse	−0.155	0.86 (0.75–0.99)	0
Preoperative chronic medications			
ACEI/ARB	−0.016	0.98 (0.91–1.07)	0
β-Blocker	−0.114	0.89 (0.83–0.96)	0
Anemia (hemoglobin range, g/dl)			
Normal (> 12.0, females; > 13.0, males)	Reference		0
Mild (10.1–12.0, females; 10.1–13.0, males)[≠]	0.523	1.69 (1.57–1.81)	2
Moderate to severe (≤ 10.0)[≠]	0.731	2.08 (1.92–2.25)	2
CKD severity (eGFR range, ml · min^{-1} · 1.73 m^{-2})			
Stage 1 (≥ 90)[§]	Reference		0
Stage 2 (60–89[§]	0.085	1.09 (1.01–1.17)	2
Stage 3a (45–59)[§]	0.371	1.45 (1.31–1.60)	3
Stage 3b (30–44)[§]	0.706	2.03 (1.82–2.26)	
Stage 4 (15–29)[§]	1.357	3.89 (3.47–4.38)	4
Preinduction baseline mean arterial pressure range (mmHg)[//]			
Hypotensive (< 70)	0.283	1.33 (1.21–1.45)	1

Normotensive (70–107)	Reference		0
Stage 1 hypertension (108–120)	0.135	1.15 (1.04–1.26)	
Stage 2 hypertension (> 120)	0.348	1.42 (1.22–1.65)	1
Surgical factors			
Surgical body region			
Elevated risk (all regions except below)	0.839	2.31 (2.10–2.55)	3
Low Risk (ENT, upper extremity, spine)	Reference		0
Emergent surgery	0.253	1.29 (1.18–1.41)	1
Anesthetic factors			
ASA class			
ASA class 1	Reference		0
ASA class 2	−0.019	0.98 (0.77–1.25)	
ASA class 3	0.586	1.80 (1.41–2.29)	3
ASA class 4	0.924	2.52 (1.96–3.23)	4
ASA class 5	1.561	4.76 (3.22–7.05)	5
Expected anesthesia duration > 1 h	0.077	1.08 (1.07–1.09)	(h/4)[#]
General anesthesia	0.395	1.49 (1.36–1.63)	1
Institutional factors			
Nonuniversity hospital	0.195	1.22 (1.09–1.36)	1
Weighted risk score model c-statistic (95% CI)		0.76 (0.75–0.76)	

Preoperative Risk Quartiles	**Points in Model**	**Number of Cases, n (%)**	**observed AKI Proportion (%)**
Quartile 1 (low risk)	1–7	14,521 (20)	1.7
Quartile 2 (medium risk)	8–10	20,372 (29)	4.6
Quartile 3 (high risk)	11–12	15,255 (22)	7.8
Quartile 4 (highest risk)	≥ 13	20,781 (29)	17.8

[*] Fixed-effects model excluding anonymized institution identifier; continuous variables transformed to ordinal/interval scales. Weighted risk score values were derived using β-coefficients normalized to approximated integer multiples for clinical simplification.

[†] As determined by Elixhauser Comorbidity Enhanced ICD-9-CM/ICD-10 CM algorithm.

[‡] Classification of anemia as by WHO definition and other studies.[48,49]

[§] As determined by CKD–EPI formula, indexed by body surface area; classification of chronic kidney disease stage by the Kidney Disease: Improving Global Outcomes 2012 practice guidelines.[48]

[//] Classification of hypertension ranges by Seventh Report of the Joint National Committee,[50] and hypotension range as defined by the National Heart, Lung, and Blood Institute's Health Information for the Public.[51]

[#] One point for every 4 h.

ACEI, angiotensin converting enzyme inhibitor; AIDS, autoimmune deficiency syndrome; AKI, acute kidney injury; aOR, adjusted odds ratio; ARB, angiotensin receptor blocker; ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CKD–EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ENT, ear/nose/throat; HIV, human immunodeficiency virus; WHO, World Health Organization.

Table 2.

Acute Kidney Injury Risk Quartiles by Preoperative Characteristics: Multivariable Models

AKI Stage	Cohort Patients with Complete Data, n (%)	Quartile 1 Low Preoperative Risk, n (%)	Quartile 2 Medium Preoperative Risk, n (%)	Quartile 3 High Preoperative Risk, n (%)	Quartile 4 Highest Preoperative Risk, n (%)
Derivation					
N	70,929	17,733	17,732	17,732	17,732
Any stage	6,077 (8.6)	363 (2.0)	755 (4.3)	1,453 (8.2)	3,506 (20)
≥ Stage II	1,207 (1.7)	56 (0.3)	150 (0.8)	290 (1.6)	711 (4.0)
Stage III	327 (0.5)	16 (0.1)	39 (0.2)	84 (0.5)	188 (1.1)
Validation					
N	36,497	8,829	9,580	9,225	8,863
Any stage	3,117 (8.5)	185 (2.1)	415 (4.3)	757 (8.2)	1,760 (20)
≥ Stage II	647 (1.8)	43 (0.5)	76 (0.8)	171 (1.9)	357 (4.0)
Stage III	174 (0.5)	10 (0.1)	18 (0.2)	48 (0.5)	98 (1.1)

AKI, acute kidney injury.