Title:	**Influence of preoperative risk on the association between hypotension and postoperative acute kidney injury: a national multicenter observational study**
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Type of Study:	Retrospective observational – descriptive study
IRB Number / Status:	HUM24166 / Accepted
Aims:	**We aim to describe the influence of preoperative risk on the association between intraoperative hypotension (IOH) and postoperative acute kidney injury (AKI).** **H1**: Among patients with low preoperative risk for AKI, the relationship between IOH and AKI is weak; and a wide range of IOH – including severe range – are tolerated (i.e. no associated increased risk of AKI). **H2**: Among patients with highest preoperative risk for AKI, the relationship between IOH and AKI is strong; and a limited range of IOH – including mild ranges – are not tolerated (i.e. associated with significantly increased risk of AKI).
Patients/Participants:	**Inclusions:** Adult patients undergoing non-cardiac surgery at MPOG instititutions with complete data for analysis, from 2008-2015. **Exclusions**: Cases with low baseline risk (short or minor procedures), unique operative physiology (e.g. cardiac cases), renal/urologic surgeries directly affecting renal function, patients with pre-existing renal failure.
Power Analysis:	This study will include a convenience sample of all eligible patients with MPOG data. We estimate that approximately 100,000 patients may be available for analysis.
Proposed statistical test/analysis:	Random partitioning of data into deriviation (2/3) and validation (1/3) cohorts. Univariate analyses, with continuous data that were normally distributed analyzed using a Student's t-test; non-normally distributed data analyzed using a Mann-Whitney U test; Categorical data analyzed using a Pearson chi-square or Fisher's exact test. Preoperative risk quartiles for AKI will be developed using a mixed effects multivariable logistic regression model for the derivation cohort; all covariates treated as fixed effects except for institution ID, treated as a random effect. Internal validation performed using Somers' D on the derivation dataset and bootstrapped dataset set to 1,000 repetitions. External validation performed by comparing c-statistic of derivation and validation cohorts. Risk-quartile stratified relationships between IOH nadir and AKI analyzed via multivariable logistic regression with p-value <0.05 considered statistically significant. Effect size measures reported using adjusted odds ratios and 95% confidence intervals. Sensitivity analyses as described in proposal.
Resources:	Perioperative records query from MPOG-participating institutions, performed via IT support. Financial support as per departmental funding at participating sites.

INTRODUCTION

Surgical and anesthesia care remain essential components to a functional and responsive health system, and over 300 million surgeries are performed annually worldwide.[1 2] Despite focused efforts to improve perioperative care access and quality, postoperative complications continue to pose a substantial public health threat, with 30% of general surgery patients experiencing a complication.[3 4] 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.[5-7] AKI increases hospital length of stay, cost, and mortality.[7-9] As a result, the development of AKI has been studied through predictive modelling in both cardiac[10-14] and noncardiac surgery literature.[5 6 15-22]

Treatment of AKI remains largely supportive,[23] making AKI prevention a critical focus of investigation. Nearly all pharmacologic attempts to prevent development of AKI have been unsuccessful.[5 24 25] However, single-center studies have demonstrated an association between intraoperative hypotension (IOH) and AKI.[22 26] The frequency of IOH revealed by these studies is striking – among patients undergoing noncardiac surgery, up to 40% of cases demonstrate a mean arterial pressure (MAP) <65 mmHg for at least 10-12 minutes.[20 22 26] Given these findings, optimal blood pressure management during the intraoperative period is a promising nascent area of investigation.[27-30] Current single-center studies of postoperative AKI and hypotension propose monolithic blood pressure targets, largely ignoring 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.[31] However, no study has analyzed the association between hypotension and AKI in the context of underlying patient risk, across a broadly representative surgical population in order to bring clinical relevance to findings of previous underpowered studies.

We aim to perform a multicenter study examining risk factors for postoperative AKI following noncardiac surgery among a generalizable cohort of adult patients from private and academic medical centers nationally. We hypothesize that by using preoperative characteristics to risk-stratify patients undergoing noncardiac surgical procedures, we will be able to derive and validate variant hypotension ranges predicting increased risk of postoperative AKI.

METHODS

Study Design

We have obtained Institutional Review Board approval for this multicenter, retrospective observational study (HUM24166, Ann Arbor, Michigan). Similar approval will be obtained at participating institutions with complete data. As no care interventions will be involved and all protected health information except date of service will be removed prior to analysis, patient consent will be waived. We plan to follow the TRIPOD statement checklist for reporting observational studies throughout this study.

Study Population

We will review surgical procedures performed at MPOG centers with complete data from July 1st 2008 to December 1st 2015. We will include adult (≥18 years) patients with a baseline creatinine level collected within 30 days prior to surgery. We will exclude cases with extremely low baseline risk, unique operative physiology (liver transplantation, cardiopulmonary bypass), as well as urologic surgeries directly affecting renal function. Patients without a postoperative creatinine within seven days, as well as patients with chronic kidney disease (CKD) Stage 5 (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2), will be excluded from primary analysis. We will utilized the CKD Epidemiology Collaboration creatinine equation for eGFR calculation; among cases with race data unavailable, race will be assumed non-black.[33]

Study Outcomes

Our primary outcome is AKI (any stage), defined by the Kidney Disease – Improving Global Outcomes (KDIGO) guidelines as a serum creatinine increase of ≥0.3 mg/dl within 48 hours following surgery or an increase of ≥50% from baseline within seven postoperative days.[34] In the case of multiple surgical procedures within a seven-day period, postoperative creatinine values will be censored at the start of the subsequent surgical procedure. Secondary outcomes will include ≥Stage 2 and Stage 3 AKI, defined as ≥100% and ≥200% increases from baseline, respectively.

Data Source

We will extract a limited dataset from the Multicenter Perioperative Outcomes Group (MPOG) database as applicable to this study. Within this research consortium, data from enterprise and departmental electronic health record (EHR) systems are routinely uploaded to a secure, centralized database. Methods used for data input, storage, quality assurance, and extraction within the MPOG consortium have been described elsewhere and utilized in prior studies.[36-39] 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 reviewed by a clinician to assess and attest to accuracy of data extraction and source data.

Patient and Procedural Characteristics

A priori selected preoperative variables will include an array of patient, procedural, and institution characteristics (Table 1). We will collect patient medical history data as classified by the Elixhauser Comorbidity Enhanced ICD-9-CM/ICD-10 CM Algorithm.[40-42] Additional study variables have been previously assessed, including age,[6 43] preoperative renal function,[17 22 43 44] preoperative medications,[20 22 43] preoperative blood pressure,[20 22 43] American Society of Anesthesiologists physical status classification,[6 7 22 44] procedure urgency,[7 15 22] and surgical procedure type[7 15 22 43] characterized by body region on the basis of primary Anesthesiology Current Procedural Terminology (CPT) code.

Table 1: Preoperative Patient Characteristics

Category	Characteristic
Anthropometric Data	Age ¥
	Body Mass Index ¥
	Gender (Male)
Patient Medical History*	Congestive Heart Failure
	Cardiac Arrhythmias
	Valvular Disease
	Pulmonary Circulation Disorders
	Peripheral Vascular Disorders
	Hypertension, Uncomplicated
	Hypertension, Complicated
	Paralysis/Other Neurological Disorders
	Chronic Pulmonary Disease
	Diabetes, Uncomplicated
	Diabetes, Complicated
	Hypothyroidism
	Liver Disease
	Peptic Ulcer Disease Excluding Bleeding
	AIDS/HIV
	Lymphoma/Metastatic Cancer/Solid Tumor
	Rheumatoid Arthritis / Collagen Vascular Diseases
	Coagulopathy
	Weight Loss
	Alcohol Abuse
	Drug Abuse
	Psychoses
Preoperative Medications	Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker
	Beta Blocker
Preoperative Laboratory Values	Preoperative Serum Hemoglobin Level ¥
Preoperative eGFR (mL/min/1.73 m^2)**	≥ 90
	60-89
	45-59
	30-44
	15-29
Preoperative Blood Pressure	Mean Arterial Pressure (mmHg)
Surgical Characteristics	Emergent Procedure
Surgical Procedure Type / Body Region (Anesthesia CPT Code)	Head (0100-00222)
	Neck (00300-00352)
	Thorax - chest wall & shoulder girdle (00400-00474)
	Thorax - intrathoracic (00500-00580)
	Spine and spinal cord (00600- 00670)
	Upper abdomen (00700-00797)
	Lower abdomen (00800-00882)

	Perineum (00902-00952)
	Pelvis, except hip (01112-01190)
	Upper leg, except knee (01200-01274)
	Knee and popliteal area (01320-01444)
	Lower leg, ankle, and foot (01462-01522)
	Shoulder and axilla (01610-01682)
	Upper arm and elbow (01710-01782)
	Forearm, wrist, and hand (01810-01860)
	Radiological procedure (01916-01936) ***
	Burn excisions or debridement (01951-01953)
	Obstetric (01958-01969)
Anesthetic Characteristics	General Anesthetic Used
	Anesthetic Duration, min ¥
ASA Physical Classification	ASA 1
	ASA 2
	ASA 3
	ASA 4
	ASA 5
Institution Characteristics	Non-University Hospital
	Anonymized Institution ID

*As determined by Elixhauser Comorbidity Enhanced ICD-9-CM/ICD-10 CM Algorithm; excluding renal failure, obesity, and fluid/electrolyte disorders.

** As determined by CKD-EPI formula, indexed by body surface area; stratified by Kidney Disease Improving Global Outcomes chronic kidney disease guidelines.

*** Including procedures with and without intravenous contrast

¥ = non-parametric data presented as median [25th to 75th percentile]

ASA = American Society of Anesthesiologists; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CPT = Common Procedural Terminology; eGFR = estimated glomerular filtration rate

Intraoperative Hypotension Exposure

We will select *a priori* ranges for IOH based upon previous literature,[20 22] including absolute MAP values <50 mmHg, 50-54 mmHg, 55-59 mmHg, and 60-64 mmHg, as well as relative MAP values >40%, 30-40%, and 20-30% below preoperative baseline. The number of minutes of IOH during each case will be tabulated; clinically relevant IOH will be defined as the lowest range for which >10 cumulative minutes were recorded.[20] Methods for intraoperative blood pressure measurement, signal processing, and artifact reduction have been previously utilized, and are described in Appendix 1.[45 46]

Statistical Analyses

We will perform statistical analyses using STATA/MP version 14 (StataCorp) and SPSS version 24 (IBM). Patients meeting selection criteria will be randomly partitioned into derivation (two-thirds) and validation (one-third) cohorts. We will compelte univariate analyses for all covariates described in Table 1. All continuous data that are normally distributed will be analyzed using a Student's t-test; all non-normally distributed data will be analyzed using a Mann-Whitney U test. Continuous covariates will be assessed for normality using the Kolmogorov-Smirnov test; if the test indicates a p-value <0.05, covariates will be transformed according to the direction of the skew prior to modeling. Categorical data will be analyzed using a Pearson chi-square or Fisher's exact test. Prior to all predictive modeling, collinearity among covariates will be assessed using the variance inflation factor: if greater than 4, a Pearson correlation matrix will be used to assess correlations. Any covariate with a correlation >0.70 was not used in the model. We will assess model discrimination using a c-statistic.

We will perform two separate multivariable logistic regression models to develop risk quartiles for postoperative AKI (dependent variable). First, we will develop a mixed effects multivariable logistic regression model for the derivation cohort, with all covariates included as described in Table 1. Anonymized institution will be included as a random effect; all other variables will be included as fixed effects. Among cases with complete data, we will generate an AKI probability score from the

multivariable logistic regression model beta coefficients. The probability score will range from 0-1 per patient, and will be used to stratify patients into four equal-sized preoperative risk quartiles: low, medium, high, and highest risk for developing AKI. We will next develop a clinically usable weighted risk score by first grouping continuous covariates into pre-specified physiologic and laboratory ranges, and then normalizing model beta coefficients to approximated integer multiples.

We will perform internal and external validation to assess reproducibility of the preoperative risk model. Internal validation will be performed using Somers' D on the original derivation dataset with bootstrapping set to 1000 repetitions. The Somers' D from the original derivation dataset and the bootstrapped dataset will then be compared. External validation will be 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, we will assess any incremental improvement in model discrimination with measures of IOH added to the preoperative risk model. We will also assess whether IOH exposures were independent predictors of AKI in the derivation cohort.

Following these analyses, we will investigate the risk quartile-stratified relationship between IOH nadir and AKI. Within each risk quartile, we will develop a multivariable logistic regression investigating AKI as the dependent variable, and IOH ranges – adjusted for case duration included as a separate covariate – as the dependent variable. A p-value <0.05 will be considered statistically significant. Measures of effect size will be represented using adjusted odds ratios (aORs) and 95% confidence intervals (CIs). We will use the same techniques to analyze IOH alternatively defined by MAP ranges *relative to preoperative baseline* in a separate model. To assess reproducibility of IOH associations, we will repeat multivariable analyses of risk quartile-stratified IOH and AKI for the validation cohort.

We will conduct a sensitivity analysis, adjusting for estimated blood loss within each risk quartile for absolute and relative IOH definitions. We will perform additional sensitivity analyses, including: (i) cases with no postoperative creatinine available assumed to have no AKI, (ii) cases restricted to 30-day index cases (defined as the first operation within a 30-day period for a given patient), and (iii) missing data handled via multiple imputation (methods described in Appendix 2).

Limitations

- Complete data describing renal replacement therapy and urine output beyond the intraoperative period, will be unavailable for describing our primary outcome, AKI, as per complete KDIGO guidelines.[34]

- For uncomplicated surgical procedures, postoperative creatinine values will be occasionally not measured, and the exclusion of such cases will lead to an overestimation of AKI.

- A sensitivity analysis performed assuming that such patients did not develop AKI may underestimate AKI incidence.

- Our study analysis and results remain subject to a level of data quality derived from routine clinical care, rather than a controlled experimental setting.

- Associations between IOH and AKI within preoperative risk strata were conditional on the accuracy of preoperative risk model developed

Appendix 1: Intraoperative Blood Pressure Monitoring, Signal Processing, and Arterial Blood Pressure Artifact Reduction Algorithm

We utilized arterial line waveform data and non-invasive 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 non-continuous during a case (e.g. non-invasive blood pressure measurements, or arterial line disconnected), blood pressure was assumed constant and equal to the previous measurement if within five minutes from the most recent measurement; if five minutes or greater from any blood pressure measurement value, blood pressure was presumed unknown and treated as missing data for analysis purposes. To minimize the impact of blood pressure monitoring artifact, we used an artifact reduction algorithm, as previously described:[1 2]

Artifact Elimination Strategy	**Rules/Logic**
Provider Marked Artifacts	Marked as artifact in real-time by the provider
Artifact from arterial line clamping, damping, or flushing; or cuff under external pressure	SBP > 200 AND PP < 50
	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 as artifact

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MAP = Mean Arterial Pressure; PP = Pulse Pressure (SBP-DBP) 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.

Appendix 2: Sensitivity Analysis – Missing Data Handled by Multiple Imputation

We performed a sensitivity analysis to determine discrimination capacity for a model handling missing data by multiple imputation for analyzing our primary outcome, postoperative AKI. All imputations were performed using STATA/MP Version 14 (StataCorp) using the "mi impute chained" command (MICE). Following are the exact steps used to perform our multiple imputation:

1. All variables to be imputed were registered. These included: body mass index, all patient-level disease-specific comorbidities, emergent surgery, and ASA status.
2. All remaining covariates were then registered as "regular" variables within STATA including our outcome variable, postoperative AKI.
3. The "mi impute chained" command was then used; the following chained commands were used to specify the type of variable to be imputed: mlogit (catergorical), logit (binary), ologit (ordinal), and regress (continuous).
4. Following the "mi impute chained" command, a specified number of imputation datasets must be documented. By a common convention of using a number of imputed datasets greater than or equal to the percentage of missing data,[3] we performed 25 imputations for our dataset containing 22% of patients with missing data.
5. A mixed effects logistic regression model was then performed on the imputed dataset, in which all covariates in Table 1 were fixed effects with the exception of institution, which was included as a random effect. Estimates were saved, to create a AKI probability score for each patient, used to assess the model's overall predictive capability.
6. Beta coefficients and 95% confidence intervals along with the p-values from the imputed dataset were provided (Supplemental Digital Content 11A). The intraclass correlation coefficient was reported for the random effect. The model's predictive capability was reported as the c-statistic.
7. Monte Carlo Error estimates (MCE) were also reviewed to ensure that the proper number of imputation datasets was selected.

a. MCE assumptions for the coefficients:

   i. The MCE should be ≤ 10% of the standard error

   ii. The MCE T-statistic should be ≤ 0.1

   iii. The MCE of the p-value should be ≤ 0.01

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