PCRC Proposal Cover Sheet

Title: Anesthesia Dosing And Outcomes Among Surgical Patients Age≥65

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Approved by Mentor: Robert B. Schonberger

Type of Study: Retrospective Observational

Hypothesis:

Hypotheses 1: The administered induction dose of anesthetic (propofol, fentanyl, midazolam) in patients age>65 will be significantly higher than published recommendations.

Hypothesis 2. In patients age>65, dosing above vs. at guidelines will be associated with a higher rate of post-induction/pre-incision hypotension requiring pressor support. While the primary focus of the proposed study broadly concerns anesthesia dosing among patients age>65, the age of 40 years is frequently cited as the juncture at which the mean alveolar concentration of commonly used inhaled anesthetics for the maintenance of general anesthesia begins to decline. We will thus include patients starting at age 40 for analyses concerning dose response (e.g., hypotension) by decade of age so as to use MPOG data to initiate the establishment of an evidence base for proper age-adjustment of anesthetic induction dosing.

Exploratory hypothesis 3: We will investigate the relationship of post-induction/pre-incision hypotension to peri- and postoperative complications in patients age>65, and b) separately in patients age>80.

Number of Patients/Participants: Approximately 2.3 million.

Power Analysis: Because of the abundance of data in MPOG (over 2.3 million cases undergoing General Anesthesia with age 40 years or older), we will have sufficient number of events (i.e., post-induction pre-incision hypotension) to follow the rule of thumb of maintaining at least 10 events per variable (EPV) in developing a multivariable risk model. Therefore, model overfitting is extremely unlikely. Nevertheless, the overfitting can be detected through our model calibration process in which the calibration curve plot with a slope larger than 1 would indicate an overfit model.

Proposed statistical test/analysis:
1) Basic descriptive statistics to understand distributions, central tendency, missingness, and data quality issues among the varied institutional sources.

2) Hypothesis 1: Within each stratified group, the induction doses of three anesthetic agents - propofol, fentanyl, midazolam - will be compared to their recommended age-adjusted doses using one-sample t-test or Wilcoxon signed rank test, as appropriate. The differences of age-adjusted doses among different age groups will be compared by one-way analysis of variance (ANOVA), followed by pair-wise comparisons using two-sample t-test (or by the Kruskal-Wallis test, followed by pair-wise comparisons using a two-sample Wilcoxon rank sum test, as appropriate).

3) Hypothesis 2: Initial analysis will define hypotension as a period where there is a decrease in MAP to <=55 mmHg. We will also note the use of pressor support agents (as a yes/no variable) post induction/pre incision. The rates of hypotension among the two groups (dosing above vs. at guidelines) – and the use of pressor support - will be compared by logistic regression, controlling for pre-specified covariates. Separate sensitivity analyzes will be performed on the distinct surgical procedures (e.g. gastro-intestinal, thoracic, orthopedic), gender, and race. A prediction model of post-induction/pre-incision hypotension will then be developed on a randomly sampled 50% derivation set and then tested on the remaining 50% validation set. To aid in clinical decision-making process by anesthesiologists, we will then create a risk points-scoring system based on the final prediction model.

4) Exploratory hypothesis: The complications to be examined will include time between surgery end and anesthesia emergence, post-operative delirium, AKI, myocardial injury, and perioperative mortality. This will be modelled using a GLMM statistical framework. Choice of link functions will be based on the distributions of every complication outcome.

Resources (Brief summary of resources for data collection, personnel, financial): This proposal has received a priority score from AHRQ that is unlikely to be funded but will enable a first resubmission for consideration in Spring 2017).

Introduction

What is the significance of the clinical problem being addressed?

The US Population is Aging. Currently, 14% of the US population is over age 65, and this group *accounts for nearly 40% of the surgical procedures performed annually.*[1] By the year 2020, it is estimated that this group will increase by 25% to number 55 million people, and almost one quarter will be over age 80, making the extreme elderly the fastest growing patient group.[2] As a result, increasing numbers of surgical patients are presenting with age-related, pre-existing medical conditions that increase their risk for adverse outcomes.[3] In addition to the greater medical morbidity that accompanies aging[4,5] there are changes in metabolism, along with other factors that influence surgical risk.[6] *A critical issue for the growing elderly surgical population is the safe delivery of surgical and anesthetic services, so as to avoid complications and optimize return to previous levels of functioning after surgery*.[3]

Surgical patients age>65 have a higher incidence of perioperative complications after surgery compared to younger patients, and the risk of these complications increases by 2-4 fold after age 80.[3,5] These complications include death due to cardiac and non-cardiac causes, myocardial infarction (MI), congestive heart failure (CHF), acute kidney injury (AKI), respiratory failure, and post-operative cognitive dysfunction (POCD). For example, 40% of patients aged>70 undergoing non-cardiac surgery will develop one or more serious post-operative complications,[3,7] while 60-80% of elderly patients develop delirium postoperatively, leading to a higher incidence of complications, longer post-surgical hospital stay, and greater healthcare costs.[8] *Researchers and practitioners are therefore focusing on risk stratification models and looking for modifiable factors – among them the approach to anesthesia - that contribute to elevated risk of post-operative complications, so as to improve outcomes among elderly patients.*[9]

With aging comes a number of physiological changes that increase the effective potency of anesthetic agents. First among these is a decline in organ function, and physiologic reserve capacity, and ability to endure physiologic stress[10-12] Vascular auto-regulation is impaired[13-16], which leaves critical organs more prone to injury due to the changes in blood pressure and intravascular volume status that occur during surgery[17,18]. In addition, there is a reduction in vascular compliance – arterial stiffening - since the proportion of collagen to elastin in the blood vessels increases with advancing age[11]. The physiological consequence is an increase in afterload to the heart, widening of the pulse-pressure, and decreased coronary perfusion pressure, which together lead to compensatory cardiac hypertrophy, diastolic dysfunction, and a greater risk of hypotension under conditions – such as surgery - in which intravascular volume may quickly change.[19] *Thus a decline in overall organ function and reduction in vascular compliance among elderly surgical patients, result in both a greater effective anesthetic potency, and a narrower therapeutic window before hemodynamic effects result in significant organ injury.*

A second age related change that increases the effective potency of anesthetics is a progressively increasing disease burden. The incidence of cardiovascular disease, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, and

diabetes is higher in the elderly, and increases with increasing age.[20] Renal function declines, with glomerular filtration rate (GFR) declining by 1mL/min/year after the age of 40[21,22], and together with declines in liver function and a higher overall fat to lean-body mass ratio[23], *the redistribution and clearance of several anesthetics and their metabolites are slowed*[23-25]**.** In addition, the accelerating decline in GFR with each passing year translates to decreasing renal reserve in elderly surgical patients - e.g., elderly patients increasingly approach a threshold where further declines in GFR may lead to overt renal failure. *A downward spiral can quickly develop in which anesthesia over-dosing leads to hypotension which leads to renal injury and cardiovascular dysfunction, which further impairs anesthetic clearance.*

A third age-related change concerns the central nervous system (CNS). Imaging studies have demonstrated a loss of gray and white matter, and reduced functional connectivity in brains of elderly patients as compared to young adults.[26] These and other CNS changes increase the risk of delayed anesthesia emergence and post-operative delirium, both of which are common in elderly surgical patients, with a prevalence of 44% after major surgery [27,28], and both of which are associated with significant increases in morbidity and health care costs.[29] Appropriate anesthetic management in elderly surgical patients – e.g., to prevent post-operative delirium - involves the identification of pre-morbid conditions and the control of symptoms,[30] though with the recognized prevalence and associated morbidity and mortality, better preventive approaches are being sought.[31] Age-related changes in the CNS also create a higher sensitivity to anesthetic drugs. *Indeed, it is estimated that the requirements for volatile anesthetics to induce a state of general anesthesia decline by 6-8% per decade after the age of 40.*[32]

The consequences of anesthetic overdosing can be profound and costly, and include post-operative delirium and intraoperative hypotension. A single episode of delirium is associated with major postoperative complications, prolonged hospitalization, loss of functional independence, reduced cognitive function, incomplete recovery, delayed rehabilitation, and even death.[33] In addition, intra-operative hypotension can directly cause major adverse events. For example, in one prospective observational study it was found that 1-year post-operative mortality increased 4.4% for each minute during which systolic blood pressure fell below 80mmHg[34], while others have shown that excess mortality begins 100 days post-op with only 1 minute of a systolic blood pressure below 90mmHg[35]. Another retrospective analysis of over 33,000 surgical procedures found that less than 5 minutes in a hypotensive state was associated with an 18% increased risk of AKI and a 30% increased risk of myocardial injury[36], independent of medical comorbidity, and these risks increased further as the duration of hypotension increased. It is important to note that these time frames – 1-5 minutes in a hypotensive state – challenge the ability to successfully treat the demonstrated hypotension.

Post-op AKI increases hospitalization cost as much as $20,000 per event [37]; projecting this cost to new cases of post-op AKI in patients age>65 (7.4% of 5 million annual procedures) results in nearly $1.8 billion annually, and with the growing population of patients age>65, this amount will only increase. In addition, post-surgical delirium is estimated to cost the United States healthcare system anywhere from $38 billion to $152 billion per year [38]. Even a 10% reduction in these morbid events could reduce healthcare cost by hundreds of million, if not billions of dollars annually. Thus, *attention to the issue of anesthesia dosing among elderly surgical*

patients can have profound implications, not only for the public health, but for the growing healthcare cost burden on the US economy.

Recognizing the physiological changes that accompany aging, the effects of these changes on anesthesia potency, and the compounding that older age presents for the management of intra-operative hypotension, standard textbooks and Professional Societies have issued recommendations that the dose of intravenous anesthesia induction drugs be reduced by 25-50% for surgical patients age>65[33,39-42]. It is important to note that these are merely recommendations; they are not grounded in a necessary *clinical* evidence base. These recommendations furthermore do not account for the extreme elderly - age>80 years - who are also increasingly represented among surgical patients[26]. Furthermore, *the extent to which the recommendations that do exist are followed nationwide is not known*. *Indeed, our retrospective studies of 2,660 local surgical patients found only an 11% decrease in anesthesia dose for patients age>65 on average, with many patients not decreased at all* (see Preliminary Findings and Expertise, below). It is important to note that the issue is likely not one of merely educating anesthesiologists nationwide - e.g., by disseminating the recommendations. Rather, the problem is that over-dosing - dosing above guidelines - is likely occurring because the recommendations are not evidence based. *A clear public health need is a set of evidence-based guidelines that can inform clinical anesthesia practice, so as to improve the safe delivery of surgical and anesthetic services for elderly patients.*

While the consequences of anesthesia overdosing are known to be profound, it is not known whether the failure to sufficiently age-adjust anesthetic dose contributes *explicitly* to hemodynamic instability and thence to poor outcomes (see Figure 1). The few published studies have been limited to single-centers and therefore lack generalizability. For example, one single center prospective study found an almost 2-fold higher post-surgical mortality in patients age>65 (10.3% vs 5.5%), and aside from medical comorbidity, deep anesthesia time and intra-operative hypotension were the only other predictors[34]. In another study, intra-operative hypotension, defined as a 30% decrease in mean arterial pressure (MAP), resulted in perioperative recurrent MI in 20% of patients with a prior history[43]. Another study of patients undergoing non-cardiac surgery reported cardiac complications in 19% of patients who had a 20mmHg drop in MAP of as short as 5 minutes [44]. It is thus reasonable to assume – though not yet rigorously demonstrated - that anesthetic overdosing in elderly patients can cause perioperative complications, longer post-operative hospital stays and higher medical costs. Due to the importance of surgical morbidity among the elderly and a paucity of literature to guide anesthetic dosing in this population, *it is essential to determine the causal chain from anesthesia dose to hypotension, and then on to poorer perioperative and post-operative outcomes and higher costs, specifically in elderly surgical populations.*

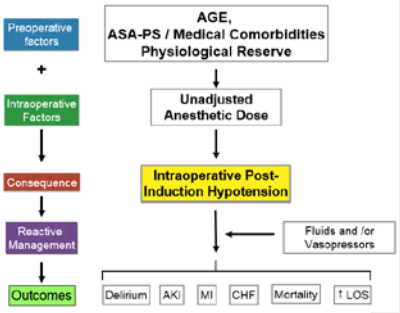

Figure 1

What current gaps exist in the understanding of this problem?

1. How stringently are the recommendations for anesthetic drug dosing in the elderly being followed in contemporary clinical practice? A number of Professional Societies have issued recommendations for reducing induction doses of anesthesia agents by 25%-50%. These recommendations have been issued in recognition of, a) the physiological changes that increase relative anesthesia potency, b) the increased medical comorbidity that accompanies aging, and thus c) the clearly associated higher risks for poorer post-operative outcomes and accompanying higher healthcare costs. Of note, there are no further recommendations for patients age>80 years. Most important, *data describing the doses of anesthetics actually administered in older patients for surgical procedures in contemporary anesthesia practice has historically not been available.* Our 2 small studies demonstrate that the recommendation of reducing anesthesia dosing for patients age>65 in clinical practice is clearly not being followed. *This represents a critical knowledge gap, in that any effort to address dosing practices must be predicated on a better understanding regarding what those practices are. This represents one of the hypotheses of the proposed study*.

2. Does anesthesia dosing among patients age>65 contribute explicitly to hemodynamic instability, and thence to poor outcomes? Anesthetic doses are clinically adjusted for severity of illness and it is generally recommended that "sicker" patients require a smaller dose of anesthetics. Among the metrics used for this dose adjustment are the American Society of Anesthesiology-Physical Status (ASA-PS) score and the Elixhauser co-morbidities.. Only a few small, single-center studies have taken this question to the issue of age and whether older patients at a given anesthetic dose are more likely to experience intra-operative hypotension than a similarly sick (e.g., same ASA-PS or Charlson score) younger person. Furthermore, it is not known if the response of a less sick older patient (ASA-PS score of I or II) to a particular anesthetic dose is significantly different - clinically and statistically - than that of an older patients who is sicker (e.g., ASA-PS score of III or IV). Lastly, it is not known if intra-operative hypotension differentially affects outcomes among older vs. younger surgical patients. *Thus a key healthcare safety and public health issue concerns the effect of anesthesia dose on intra-operative hemodynamic instability – e.g., hypotension - specifically among older surgical patients. This represents a second Specific Aim of the proposed study*.

3. What is the relationship of post-induction/intraoperative hypotension to complications and hospital length of stay? Perioperative hypotension has been associated with poor peri- and post-operative outcomes. While many studies do not differentiate between anesthetic induced hypotension (potentially modifiable through clinical practice) and other causes of hypotension, the hypotension that develops immediately after induction is potentially preventable through improved anesthetic practice. No study to date has addressed the specific relationship of hypotension occurring post-anesthesia induction but pre-surgical incision, to outcomes such as delirium, myocardial injury/infarction, AKI, hospital length of stay and healthcare costs, and related outcomes in patients age>65. *The frequency of this specific modifiable clinical practice and its impact on perioperative outcomes represents a third aim of the proposed study*.

4. Can an evidence base be developed to better guide clinical anesthesia practice for the surgical population age>65, and can this be done to accommodate differences by gender and race/ethnicity? Can this evidence base be extended to patients age>80? As noted, the imperative to reduce anesthesia dose by 25%-50% for patients' age>65 is a clinical recommendation that has been published by Professional Societies. As a recommendation, it does not rise to the standard of an evidence base, a fact that may in part contribute to what we have found in 2 small studies to be an apparent clinical practice failure on the part of anesthesiologists. Given the vast array of surgical sub-specialties and procedures, and the likelihood of both gender and race/ethnicity based differences, any effort to establish an evidence base for anesthesia dosing as a function of age - whether >65 alone, or for those age>80 as well - becomes a daunting task. *In this study we propose to clearly determine failures in anesthesia age-adjustment nationwide, the consequences of these failures, and initiate efforts toward the establishment of an evidence base to better guide clinical practice.*

How will this project address this gap and advance clinical care and/or research knowledge?

We propose to use the MPOG database to determine: 1) the extent to which anesthetic dosing is adjusted for elderly patients in clinical practice, and 2) the relationship of age-related dosing to hypotension and perioperative outcomes. We will then, 3) develop models for proper age-adjustment of anesthesia dosing by decade of age. By demonstrating the pervasiveness of the failure among anesthesiologists to age adjust anesthesia dose, and that this failure leads to treatment-requiring hypotension and costly medical complications, we will highlight a clear target for making healthcare safer among older patient groups, while also contributing to the establishment of evidence based guidelines for age-adjusting anesthesia doses.

IRB statement

The Yale Human Investigations Committee has determined that the limited national dataset can be accessed without local IRB approvals in addition to any U of M approvals that have already been obtained. Should the study receive funding from AHRQ, the Yale HIC has requested resubmission to ensure that the studies are concordant with the funding for the proposed research.

Study type

Observational. Our study will be conducted in accordance with the STROBE guidelines.

Primary outcome

Hypothesis 1 primary outcome: The administered dose of anesthesia (propofol, fentanyl, midazolam) in patients age>65 will be significantly higher than recommendations.

Hypothesis 2 co-primary outcome: In the patients from hypothesis 1, dosing above vs. at guidelines will be associated with a higher rate of post-induction/pre-incision hypotension (MAP <=55mmHg) or any blood pressure requiring pressor support by the judgement of the attending anesthesiologist. This hypotheses will be tested separately for, a) distinct classes or surgical

procedures b) for different levels of medical comorbidity, and c) different gender and race/ethnicity groups.

Hypothesis 2 co-primary outcome: A prediction model of post-induction/pre-incision hypotension (MAP<=55mmHg) will be developed on a randomly sampled 50% derivation set and then tested on the remaining 50% validation set. Discrimination and calibration of the model will be assessed. To aid in clinical decision-making process by anesthesiologists, we will then create a risk points-scoring system based on the final prediction model.

Hypothesis 2 co-primary outcome: We will facilitate the generation of more precise thresholds to guide anesthesia practice by modeling the relationship of anesthesia dose to hypotension risk according to 10-year age increments for each surgical class and medical comorbidity level, and by gender and race/ethnicity, starting at age 40. This will be accomplished by graphing the dosages reported (x-axis) against the report of hypotension that occurs post-induction/pre-incision (y-axis). Thus for each decade, we anticipate a range of dosages and a range of hypotension frequency. We assume that the reported dosage was sufficient to induce the required sedation. The resulting graphs will then visually display the dose threshold at which hypotension frequency (hence likelihood) begins to rise. This threshold will thereby indicate in large samples a more useful marker of proper dosage for the given age group.

Secondary outcome(s), where applicable

Exploratory Outcome: The relationship of post-induction/pre-incision hypotension to peri- and postoperative complications in patients age>65, and b) separately in patients age>80.

Patient inclusion criteria

1) Age≥40 years (while a primary focus of the proposed study broadly concerns anesthesia dosing among patients age>65, the age of 40 years is frequently cited as the juncture at which the mean alveolar concentration of commonly used inhaled anesthetics for the maintenance of general anesthesia begins to decline. We will thus include patients starting at age 40 for analyses concerning post-induction hypotension so as to initiate the establishment of an evidence base for proper age-adjustment of anesthesia induction dosing.

2) Surgery was performed under general endotracheal anesthesia.

3) Patients who received a propofol-dominated induction (defined as receiving a bolus dose of at least 0.5 mg/kg of propofol between anesthesia start and intubation AND where intubation occurred prior to surgical incision).

Patient exclusion criteria

Patient related factors:

1) Hypotension at presentation (defined as systolic blood pressure<90mmHg) or normotension requiring ongoing inotropic/vasopressor support.

2) Intubation at presentation.

3) Patients with uncontrolled hypertension at presentation (Defined as systolic blood pressure ≥220mHg or diastolic blood pressure ≥110 mmHg).

4) Patients with acute coronary syndrome in the 6 weeks prior to surgery.

5) Patients with preoperative diagnosis of pulmonary hypertension and/or right ventricular failure.

Surgery/Anesthesia related factors:

6) Patients who undergo transplant surgery.

7) Patients who are undergoing a second surgery within 30 days of a prior anesthetic.

8) Patients who did not receive primary propofol based inductions (as defined in inclusion criteria above). These include; a) patients who were primarily induced with inhalational anesthetics; b) patients who receive a combination of intravenous anesthetic agents (ketamine, etomidate, thiopental, methohexital with or without propofol) at induction; or c) receive less than 0.5 mg/kg of propofol at induction, suggesting either use of higher doses of other anesthetic agents (high dose opioids, midazolam or combination of inhalational and intravenous induction doses).

9) Patients who receive combined neuro-axial and general anesthesia.

10) ASA physical status 6 patients.

Data source

MPOG database

Statistical analysis

Descriptives: The first step in the analysis will be to delineate descriptive characteristics, including sample size for surgery types, gender, race/ethnicity groups, age groups, and anesthetic agent groups. Continuous data elements will be assessed for normality by investigating P-P plots as well as reporting a test statistic for Gaussian distribution via the Kolmogorov-Smirnov Test. Following the tests for normality, descriptive statistics (e.g., mean, standard deviation, median, interquartile range, minimum and maximum) will be compared by two sample t-test or Wilcoxon rank sum test, as appropriate. Categorical data will be compared using Chi-square or Fisher's exact test, as appropriate. If there is skewness or non-normality, logarithm or other transformations will be considered based on the statistical inference needs. These preliminary analyses will guide the optimal groupings of patients for hypothesis testing and exploratory analyses to insure adequate sample sizes and appropriate covariate control. These preliminary analyses will also help determine whether there are important variations in key variables as a function of such factors as institution and hospital size.

Hypotheses 1: **The administered dose of anesthesia (propofol, fentanyl, midazolam) in patients age>65 will be significantly higher than published recommendations.** Patients

will be divided into 3 age groups (<65, 65-79 and ≥80 years) and then further stratified by ASA-PS status (ASA 1-2 vs. ASA 3-5). Within each stratified group, the doses of three anesthetic agents - propofol, fentanyl, midazolam - will be will be compared to their recommended age-adjusted doses using one-sample t-test or Wilcoxon signed rank test. If data are normal and are not heteroscedastic (i.e. unequal variance), the differences of age-adjusted doses among different age groups will be compared by one-way analysis of variance (ANOVA), followed by pair-wise comparisons using two-sample t-test. If data are not normal, they will be compared using Kruskal-Wallis test, followed by pair-wise comparisons using two-sample Wilcoxon rank sum test. This hypothesis will be tested separately for distinct classes or surgical procedures.

Hypothesis 2. In patients age >65, dosing above vs. at guidelines will be associated with a higher rate of post-induction/pre-incision hypotension requiring pressor support. For these analyses, several indices of post-induction/pre-incision hypotension will be computed, including percent and absolute change in mean arterial pressure (MAP), and percent and absolute change in systolic blood pressure. Initial tests will define hypotension as a period post induction and pre incision where the MAP<=55mmHg per Walsh, et al.. We will also note the use of pressor support agents post induction/pre incision. The rates of hypotension among the two groups (dosing above vs. at guidelines) – and the use of pressor support - will be compared by logistic regression, controlling for pre-specified covariates. Separate sensitivity analyzes will be performed on the distinct surgical procedures, gender, and race.

A prediction model of post-induction/pre-incision hypotension will then be developed on a randomly sampled 50% derivation set and then tested on the remaining 50% validation set. Collinearity (variance Inflation factor for continuous variables and cross-tabulations for categorical variables), the linear assumption, and the additivity assumption of the predictors will be checked, and nonlinear modeling of continuous predictors will be investigated. If collinearity is detected (variance inflation factor > 10), then a bivariate correlation matrix will be developed. Any bivariate comparison > 0.70 will be considered collinear and will be resolved by either selecting one of the two variables or combining the variables into one. Any covariate with a significant p-value will be considered an independent predictor and reported with adjusted odds ratios and 95% confidence intervals. The model's goodness of fit will be tested with the Hosmer-Lemeshow test. The model's discriminating capacity will be evaluated using a c-statistic area under the curve from the receiver operating characteristic curve.

To aid in clinical decision-making process by anesthesiologists, we will create a risk points-scoring system based on the final prediction model. Patients will be categorized into different groups based on total risk scores (e.g., very low risk, low risk, moderate risk and high risk) and incidences of hypotension among different groups will be compared by Cochran-Armitage trend test. To determine the clinical usable for the risk points-scoring system both an unweighted and weighted risk score will be developed. An unweighted risk score will assign one point for each independent predictor that was present for the patient. The weighted risk score will be based on the β coefficient of the independent predictors. The weighted score is calculated by taking the specific β coefficient for the independent predictor and dividing it by the lowest β coefficient for all independent predictors, multiplied by two and then rounded to the nearest integer. We will compare the weighted and unweighted risk scores c-statistics derived from the area under the curve from the receiver operating characteristic curve. If the 95% confidence intervals for the c-

statistics overlap with one another, the models will be considered statistically the same and the unweighted risk score will be used. Both unweighted and weighted risk scores will be applied to the derivation and validation datasets.

Hypothesis 2 continued: Modeling Anesthesia Dose to Hypotension Risk by Decade. We will facilitate the generation of more precise thresholds to guide anesthesia practice by modeling the relationship of anesthesia dose to hypotension risk according to 10-year age increments for each surgical class and medical comorbidity level, starting at age 40. This will be accomplished by graphing the dosages reported (x-axis) against the report of hypotension that occurs post-induction/pre-incision (y-axis). Thus for each decade, we anticipate a range of dosages and a range of hypotension frequency. We assume that the reported dosage was sufficient to induce the required sedation. The resulting graphs will then visually display the dose threshold at which hypotension frequency (hence likelihood) begins to rise. This threshold will thereby indicate in large samples a more useful marker of proper dosage for the given age group.

Commented [AS1]: Is 10 years too much? Should we do 5? I know all the MAC calculations are based on a 40 year old and age adjustment happens after that. I just think that maybe a 5 year age span would be more appropriate.

Exploratory Aims concern the relationship of post-induction/pre-incision hypotension to peri- and postoperative complications in patients age>65, and in patients age≥80. The complications to be examined will include time between surgery end and anesthesia emergence, AKI, myocardial injury, and in-hospital mortality. This will be modelled using the above discussed GLMM statistical framework. Choice of link functions will be based on the distributions of every complication outcome, while keeping the same process of covariate screening, selection and evaluation of model performance as described above.

Power analysis

Because of the abundance of data in MPOG (over 2.3 million surgical records, for patients age>40), we will have sufficient number of events (i.e., post-induction pre-incision hypotension) to follow the rule of thumb of maintaining at least 10 events per variable (EPV) in developing a multivariable risk model. Therefore, model overfitting is extremely unlikely. Nevertheless, the overfitting can be detected through our model calibration process in which the calibration curve plot with a slope larger than 1 would indicate an overfit model.

Variables to be collected

Management of missing data

Missing values will be carefully investigated to identify the causes and mechanisms of missing data with multiple imputation methods considered as appropriate.[45] We will omit from consideration in further analyses variables with homogenous distributions or with a high degree of missingness, and we will collapse categorical variables with underrepresented levels. Highly correlated groups of predictors will be examined and dimensionality reduced either by subject matter knowledge, principal components, or simple point scores.[46] Note that this reduction will occur without examination of the predictor-response relations which should maintain the validity of interval estimates and p-values in the final models.

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