The Effect of Obstructive Sleep Apnea on Postoperative Respiratory Complications

Scholarly report submitted in partial fulfillment of the MD Degree at Harvard Medical School

1 March 2016

Christina H. Shin

The Effect Of Obstructive Sleep Apnea on Postoperative Respiratory Complications

Primary Mentor: Matthias D. Eikermann, MD PhD
Department of Anesthesia, Critical Care and Pain Medicine
Massachusetts General Hospital, Boston, Massachusetts, USA

Secondary Mentor: Tobias Kurth, MD MSc
Institute of Public Health
Charité Universitätsmedizin, Berlin, Germany

Scholarly Project Abstract

TITLE: The effect of obstructive sleep apnea on postoperative respiratory complications

Christina H. Shin, Tobias Kurth, Matthias D. Eikermann

Purpose: Postoperative respiratory complications (PRCs) are associated with significant morbidity, mortality, and costs. Obstructive sleep apnea (OSA), which is often undiagnosed in the surgical population, may be a contributing factor.

Methods: We conducted an observational study of adult surgical patients at Partners HealthCare hospitals (2007-2014) using electronic patient and perioperative data. OSA was defined as the occurrence of an OSA diagnostic code preceded by a polysomnography procedure code. *A priori* defined variables were analyzed by multivariable logistic regression analysis to develop our score. Score validity was assessed by investigating the score's ability to predict noninvasive ventilation. Following the development of our Score for Preoperative Prediction of Obstructive Sleep Apnea (SPOSA), we assessed the effect of high OSA risk on our primary outcome, PRCs within seven postoperative days. In order to improve the clinical utility of the score, a dichotomized OSA risk scale was developed using the SPOSA cut point of 7. Propensity score matched cohorts were used to understand patient and health care outcomes among patients identified as high risk for OSA.

Results: Predictors for OSA included BMI >25 kg/m^2 and comorbidities, including hypertension, diabetes, and dyslipidemia. The score yielded an area under the curve of 0.81. Inclusion of early postoperative desaturation did not improve the score. Noninvasive ventilation was significantly associated with high OSA risk (odds ratio 1.45, 95% confidence interval 1.20-1.76, $p<0.001$), confirming the validity of the SPOSA. Using a dichotomized endpoint, 29,087 patients were identified as high risk for OSA and 7.7% of these patients experienced PRCs. OSA risk was

significantly associated with PRCs (OR 1.38, 95% CI 1.1.26-1.51, p<0.001). High OSA risk was also significantly associated with increased postoperative length of stay, increased total costs of care, and higher rates of admission to the intensive care unit, adverse discharge, and readmission within 30 days of initial discharge.

Conclusions: The SPOSA assesses OSA risk and predicts the occurrence of respiratory complications. High OSA risk is associated with adverse clinical and care outcomes. Utilization of the SPOSA will allow providers to risk stratify patients prior to admission and may help reduce perioperative consequences of OSA.

The following scholarly report submitted as partial fulfillment for the MD Degree at Harvard Medical School spans the work completed during my final two years at Harvard Medical School, including my fifth year Scholars in Medicine research fellowship year from 2014-2015. Mentored by Dr. Matthias Eikermann in the Department of Anesthesia, Critical Care and Pain Medicine at the Massachusetts General Hospital, I contributed significantly to initial study design and data collection. I performed all statistical analyses required to address our *a priori* defined objectives. Finally, I wrote the scientific manuscripts for publication of the work: I wrote the first draft and critically revised all subsequent drafts, preparing the written works for publication.

My scholarly report spans three first author manuscripts, addressing my primary research question in three phases. The research investigates the effect of high obstructive sleep apnea risk on patient-centered postoperative outcomes.

Phase 1: Develop a published protocol for prediction score methodology

The first phase of the research was to develop a protocol for publication that justifies our research question and outlines a detailed methodology for addressing the research question. In this manuscript, I explored the multifactorial nature of perioperative obstructive sleep apnea, including discussions of the contributions of body position and opiates. We aimed to meet the higher standards of clinical epidemiology studies by publishing a protocol prior to the development of the prediction score. The first manuscript has been published in *BMJ Open*.

Citation:

> Shin CH, Zaremba S, Devine S, Nikolov M, Kurth T, Eikermann M. Effects of obstructive sleep apnoea risk on postoperative respiratory complications: protocol for a hospital-based registry study. BMJ Open. Jan 2016; 6(1):e008436.

Link: http://bmjopen.bmj.com/cgi/content/full/bmjopen-2015-008436?ijkey=alQ3YkcJHKSq8zO&keytype=ref

Phase 2: Develop a novel prediction score to quantify a patient's risk for obstructive sleep apnea

The second phase was to develop a novel prediction score for quantifying a patient's risk for obstructive sleep apnea. I utilized patient data available in the electronic hospital medical record and performed multivariable logistic regression analyses with forward selection procedure to determine which patient demographic and comorbidity data were significant predictors for obstructive sleep apnea. The final score, Score for Preoperative Prediction of Obstructive Sleep Apnea (SPOSA), was validated by its predictive ability for postoperative noninvasive ventilation. This manuscript has been submitted to *Anaesthesia*.

Citation:

> Shin CH, Grabitz SD, Timm FP, Mueller N, Ladha K, Devine S, Kurth T, Eikermann M. Score for preoperative prediction of obstructive sleep apnea (SPOSA). Anaesthesia. In revision.
> *Please see full manuscript in appendix (pages 7 – 34)*

Phase 3: Assess the effect of high obstructive sleep apnea risk on postoperative outcomes

The final phase was to assess the effect of high obstructive sleep apnea risk, as quantified by SPOSA, on patient-centered postoperative outcomes, including postoperative respiratory complications, postoperative length of stay, and readmission rates. Patients in the study population were identified as high preoperative risk for obstructive sleep apnea if SPOSA >10. Population was divided into two cohorts based on low versus high preoperative risk status and risk of postoperative outcomes were analyzed using multivariable logistic regression analyses

adjusting for preoperative and intraoperative factors. This manuscript will be submitted to a surgical journal with the aim of influencing how clinicians individualize preoperative risk assessment and perioperative pathways for high-risk patients.

Please see full manuscript in appendix (pages 35-61)

APPENDIX

I. Phase 2: Score for Preoperative Prediction of Obstructive Sleep Apnea

Score for Preoperative Prediction of Obstructive Sleep Apnoea (SPOSA)

Christina H. Shin BA,[1,2] Stephanie D. Grabitz Cand med,[1] Fanny P. Timm Cand med,[1] Noomi Mueller Cand med,[1] Karim Ladha MD MSc,[3] Scott Devine PhD,[4] Tobias Kurth MD ScD,[2,5,6] and Matthias Eikermann MD PhD.[1,2,7]

[1]Department of Anesthesia, Critical Care, and Pain Medicine. Massachusetts General Hospital, Boston, Massachusetts, 02114, USA;

[2]Harvard Medical School, Boston, MA;

[3]Department of Anesthesia, Toronto General Hospital and University of Toronto, Toronto, Canada;

[4]Center for Observational and Real-World Effectiveness US Outcomes Research, Merck & Co., Inc;

[5]Institute of Public Health, Charité Universitätsmedizin Berlin, Germany;

[6]Division of Preventive Medicine, Brigham and Women's Hospital;

[7]Universitaet Duisburg-Essen, Essen, Germany

Correspondence to: Dr. Matthias Eikermann, meikermann@partners.org

SUMMARY

Postoperative respiratory complications are associated with significant morbidity, mortality, and hospital costs. Obstructive sleep apnoea (OSA), often undiagnosed in the surgical population, may be a contributing factor. Thus, we aimed to develop a novel tool, called Score for Preoperative Prediction of Obstructive Sleep Apnoea (SPOSA), based on data available in electronic medical records preoperatively. OSA was defined as the occurrence of an OSA diagnostic code preceded by a polysomnography procedure. *A priori* defined variables were analysed by multivariable logistic regression analysis to develop our score. Reclassification analysis was conducted to evaluate if post-extubation deoxygenation added important information to the prediction of OSA. Score validity was assessed by investigating the score's ability to predict noninvasive ventilation. A total of 99,353 surgical patients at Partners HealthCare hospitals (2007-2014) were studied. Predictors for OSA included BMI >25 $kg.m^{-2}$ and comorbidities, including pulmonary hypertension, hypertension, and diabetes. The score yielded an area under the curve of 0.81. Inclusion of early postoperative desaturation did not improve the score. Noninvasive ventilation was significantly associated with high OSA risk (odds ratio 1.45, 95% confidence interval 1.20-1.76). Our findings suggest that the SPOSA predicts OSA using electronic medical record-derived data. Its use will allow preoperative screening for OSA prior to admission, which may result in better coordination of individualised perioperative treatment.

INTRODUCTION

Obstructive sleep apnoea (OSA), the most common type of sleep-disordered breathing, is characterised by recurrent partial or complete collapse of the upper airway during sleep. It is associated with significant immediate and long-term morbidity, including fragmented sleep, impaired daytime functioning, and reduced quality of life.[1,2] OSA has also been associated with other medical conditions including hypertension,[3] stroke,[4] heart failure,[5,6] type 2 diabetes,[7] obesity,[8] and metabolic syndrome.[9,10]

OSA is a highly prevalent disease, affecting approximately 9 to 24% of the general population.[11,12] However, these numbers underestimate the true prevalence of the disease, as studies have shown that a significant proportion of OSA patients are undiagnosed.[13-15]

Surgical patients with OSA are particularly vulnerable to perioperative morbidity,[16] as anaesthesia and surgery affect the collapsibility of the upper airway as well as respiratory drive.[17] The American Society of Anaesthesiologists have recently updated a set of practice guidelines for providers regarding the importance of preoperative screening for OSA through comprehensive review of medical records for history of comorbidities as well as any prior sleep studies, interview with patient and/or family, and physical examination.[18] To date, several prediction scores and questionnaires have been constructed. Those that have been validated in the perioperative period include the Perioperative Sleep Apnoea Prediction Score (PSAP)[19] and the STOP-Bang score.[20] Anaesthesiologists have also used scores, such as the Mallampati Score and the ASA Checklist, to assess difficulty of intubation as related to a narrow upper airway,[21] but there is inconsistency in reported sensitivity and specificity of the Mallampati score as a predictor of OSA.[22] The currently available scores require data not routinely available from clinical databases, such as history of snoring, witnessed apnoea, and neck

circumference. As a result, there is an emphasis on patient awareness and physician suspicion, both of which may fail to detect OSA with high sensitivity and specificity.[23] Amongst surgical patients, many do not even see an anaesthesiologist prior to the day of surgery and instead are screened preoperatively via phone in order to generate or update the electronic health care record. Given the strong associations between OSA and various comorbid diseases,[24] it may be fruitful to utilise readily available data on demographics and comorbidities to make predictions regarding OSA risk.

The objective of this study was to develop a novel prediction score based on patient data available in hospital-based electronic medical records.

METHODS

This study is an analysis of prospectively collected data on file using hospital-based electronic patient data at Massachusetts General Hospital, a tertiary care facility and teaching hospital of Harvard Medical School, as well as several hospitals affiliated with Partners HealthCare in Massachusetts, USA. The protocol for this study has been previously peer-reviewed and published.[25] This project received approval from the Partners Institutional Review Board (Protocol #2014P000218).

As previously used for studies by our group, data from two clinical databases were retrieved and combined to provide de-identified pre- and postoperative information: the Research Patient Data Registry and the Anesthesia Information Management System.[26-28] The Research Patient Data Registry contains demographic and billing data regarding patient comorbidities and postoperative outcome and survival. The Anesthesia Information Management System contains physiological data from patient monitors as well as documentation of important surgery and

anaesthesia-related events, including adverse events, perioperative procedures, and drug and fluid therapy. Patient data from these databases are linked through unique patient identifiers and the variables utilised for our prediction model were abstracted to form one database. The present database spans from January 2007 to August 2014 and includes more than 145,000 surgical cases.

Subject Selection

We included all surgical patients aged 18 years or older who underwent general anaesthesia and received endotracheal intubation or airway management by supraglottic airway device at our institution between January 2007 and August 2014 and who have had removal of all airway management devices within the operating room after the procedure. Patients who underwent surgery in the four weeks prior to the study case were excluded. Finally, all patients with an intraoperative death were excluded from the study since OSA is not a biological mechanism of intraoperative death when a patient's airway is secured by an airway device.

Prediction Model Reference Standard

The reference standard for the prediction model was defined as patients with an ICD-9 OSA diagnosis following the appearance of a polysomnography procedural (CPT, Current Procedural Terminology) code in our medical databases. From this specific sequence of events, we inferred that these patients had their clinically suspected OSA diagnosis confirmed by polysomnography. Our OSA endpoint was confirmed by a chart review of 100 randomly selected patients in our study population. 50 of the 100 cases were positive for our reference standard and two study staff members performed chart review of all 100 cases blindly. If available, sleep

study results were reviewed as well as preoperative evaluation reports by anaesthesiology providers and consultation notes. Diagnoses of "obstructive sleep apnoea" and/or evidence of active use of "positive airway pressure" devices at home were considered positive for OSA.

In addition, patients who had experienced a weight loss of at least 10% of their body weight between the date of their polysomnogram and the date of surgery were identified and excluded from the study population in an effort to optimize the cohort identified as having OSA given that significant weight loss has been shown to improve the severity of OSA.

Set of Predictor Variables Analysed

Primary Objective

A number of variables have been found to be associated with an increased prevalence of OSA and are currently used for different prediction tools for OSA in surgical patients. From our clinical databases, we included the following variables in our prediction score: age, BMI, gender, ASA physical status classification, and medical comorbidities using ICD-9 diagnostic codes (supplemental table 1). All covariates included in the prediction model were present within one year prior to surgery date.

Secondary objective

In addition, we incorporated oxygen desaturation immediately after extubation as a predictor in order to attempt to increase the predictive value of our score, given the vulnerability to desaturation present amongst patients with OSA. Anaesthesiologists measure oxygen saturation after extubation and it is intuitive to assume desaturation should occur more frequently in OSA patients emerging from anaesthesia compared with patients without OSA. Post-

extubation oxygen desaturation thresholds were defined as an oxyhaemoglobin reading less than 90% and 80% for at least one minute, as measured by pulse oximetry during the first 10 minutes after extubation in the operating room.

Development of the Prediction Model

Primary objective

Continuous, normally distributed variables were expressed as mean ± standard deviation, while ordinal as median (IQR) and categorical variables as frequency (percentages) if not otherwise specified. Out of the *a priori* defined aforementioned group of predictor variables, we identified those variables that had lowest p values of ICD-9 code verified OSA and met an entry criteria of p=0.01 using a multivariable logistic regression analysis with a forward selection procedure. The Hosmer-Lemeshow test was used to determine the goodness of fit of the final prediction model, with a P-value ≥ 0.05 indicative of no significant difference between the observed and expected outcome. The odds ratio of each significant predictor was divided by the smallest odds ratio and the results were then rounded to the nearest whole number to define the score point value. The discriminative ability of the score for OSA was assessed using the c-statistic, which is equivalent to the area under the receiver operating characteristic curve (AUC).[29]

Secondary objective

Further, we evaluated if the addition of a variable that can be obtained by anaesthesiologists at the end of the surgical case, e.g. post-extubation desaturation, improved the predictive ability of the score model using risk reclassification analysis.[30,31] The net

reclassification improvement (NRI) was generated by balancing the proportion of subjects whose risk was more accurately classified using the expanded prediction model with post-extubation desaturation compared with the prediction model without post-extubation desaturation against the proportion of subjects whose risk was less accurately classified.[30] Patients were divided into four risk groups for OSA of less than 1%, 1 to <15%, 15 to <20%, and 20% or higher. We then calculated the number of participants who were reclassified into either higher or lower risk clinical categories using the expanded score rather than the score based on comorbidities and demographics alone.

Validation of Score

The prediction score was internally validated using ten-fold cross-validation approach and the root mean square error values were averaged across all estimations of the model. In addition, we calculated the derived score for each surgical case and evaluated its predictive value in the dataset using a logistic regression model. The calculated c-statistic and the estimated probabilities for OSA were determined.

As an additional assessment for the clinical predictability of our score, we performed a multivariable logistic regression analysis to predict the outcome of noninvasive ventilation. In fact, recently published data suggest that the combination of a polysomnography followed by receipt of a noninvasive ventilation device is highly specific for a true diagnosis of OSA.[32] We identified those patients with a procedure code for noninvasive ventilation within seven days of surgery and investigated its association with OSA risk, as defined by our prediction score. Statistical analyses were conducted by using the software STATA (Version 13.1, StataCorp, College Station, TX) and a two-sided p-value of <0.05 was considered statistically significant.

RESULTS

Study Cohort

A total of 146,288 surgical cases were identified. Of those a total of 46,935 cases were excluded because they either had missing values for covariates, received their care predominantly outside the main Massachusetts General Hospital, age was <18 years at the time of surgery, or did not undergo endotracheal intubation or placement of supraglottic airway device. In addition, patients with a surgical procedure within four weeks prior to the study case were excluded and only the first procedure remained in the cohort. The study flow is summarised in Figure 1.

Obstructive Sleep Apnoea and Patient Characteristics

The modelling cohort is described in Table 1. Within the entire cohort, patients were on average 54.5 ±16 years old and 56% were female. A total of 2,079 patients met our criteria for OSA based on a combination of an OSA diagnostic code preceded by occurrence of a polysomnography procedure code. Review of 100 randomly selected cases yielded a positive predictive value of 86% and a negative predictive value of 96% based on evidence of either AHI > 5 in polysomnography reports, active use of continuous positive airway pressure at home, or confirmation of OSA diagnosis in preoperative evaluation notes.

Analysis of preoperative data on body weight allowed us to identify 243 patients as having experienced significant weight loss, defined as a loss of greater than or equal to 10% of body weight, between the time of polysomnogram and time of surgery. Based on prior studies examining the association between body weight and AHI,[33,34] exclusion of these patients further optimize the final cohort identified as having OSA at the time of surgery. Compared to

patients without OSA, patients with OSA were significantly more overweight (BMI 36.4 ±9.4 vs. 28.4 ±7.0, p<0.001). Additional characteristics of the study population are described in Table 1.

Primary objective: Preoperative predictors for obstructive sleep apnoea

Based on the results of an unconditional multivariable logistic regression model with forward selection procedure, strongest predictors included BMI>25, age 18 to 70, and the following comorbidities: dyslipidemia, chronic pulmonary disease, liver disease, hypertension, congestive heart failure, pulmonary hypertension, atrial fibrillation, diabetes, hemiplegia/paraplegia, and stroke (Table 2). The final model yielded a c-statistic of 0.81. The Hosmer-Lemeshow test demonstrated a well-calibrated model (p= 0.3078).

Based on the beta coefficients for the final model, point values were assigned to the predictors and are summarised in Table 2. The summed point values of the developed score (Score for Preoperative Prediction of Obstructive Sleep Apnoea, SPOSA) ranged from 0 to 24 (median 5 -[IQR 3 to 8] points (the maximum point value achieved in this dataset was 21) and were on average higher in patients who had ICD-9 codes for OSA versus who did not (median score value 11 [IQR 8 to 14] vs. 5 [IQR 3 to 8] points, p<0.001). The score led to a c-statistic of 0.81.

Using the Youden Index,[35] we calculated a score value of 7 as cut-off for a dichotomisation that optimises the test performance of the score for the OSA. This cut point identified 28,902 (29.2%) of the population as high risk for OSA with a SPOSA range of 8 to 21 (median score value 10 [IQR 9 to 12]). Patients at low risk for OSA (SPOSA ≤ 7) had a SPOSA range of 0 to 7 (median score value 4 [IQR 3 to 6]).

In order to classify a patient as low, moderate, and high risk for OSA, our study population was divided into three equal sized groups based on the SPOSA score. A total of 38,888 patients were considered low OSA risk with a SPOSA range of 0 to 4 (median score value 3 [IQR 2 to 4]). 31,320 patients were identified as moderate OSA risk with a SPOSA range of 5 to 7 (median score value 6 [IQR 5 to 7]). Finally, 28,902 patients were classified as high OSA risk with a SPOSA range of 8 to 21 (median score 10 [IQR 9 to 12]). The highest SPOSA tertile classification coincided well with our dichotomised approach.

Secondary objective: Additive Value of Post-extubation Desaturation

The addition of the postoperative variable, post-extubation desaturation below 80% for at least one minute or greater, did not improve the predictive ability of the prediction model, compared with the model based on comorbidities and demographic data alone (Table 3). The prediction model yielded a calculated AUC of 0.81 and 0.81 with and without the inclusion of early postoperative desaturation (Figure 2). The corresponding ROC for the prediction score yielded comparable AUC values (Figure 2).

Risk reclassification analysis was performed to evaluate whether this additional postoperative variable provided clinically relevant improvements in OSA risk prediction. The addition of post-extubation desaturation did not affect the predictive ability of the score in a clinically significant fashion, as reflected by an NRI of 0.15% (p=0.00014).

Amongst 97,274 patients without OSA, 16 patients were reclassified into a higher risk category using the post-extubation desaturation variable model while 163 were reclassified into a lower risk category. Amongst 1,836 patients with OSA, none were reclassified into a lower or

higher risk category using the post-extubation desaturation variable model. Based on this result, we decided not to include post-extubation desaturation in the final model

Validation of prediction score

10-fold cross-validation was performed for internal validation of our prediction model and yielded an average mean absolute error estimate of 0.13 across ten iterations with an AUC of 0.81.

We further sought to assess the validity of our prediction score by investigating its association with the incidence of noninvasive ventilation following surgery. This approach was based on the work of McIsaac and coworkers who reported that the combination of a polysomnography procedure code followed by receipt of a noninvasive ventilation device was highly specific for a true diagnosis of OSA (specificity of 98%).[32] In our study, a total of 1,103 or 3.8% of patients at high risk of OSA (SPOSA> 7) received noninvasive ventilation without subsequent reintubation within 7 days of surgery, compared with a total of 328 or 0.50% of patients at low risk of OSA (SPOSA ≤ 7). Multivariable logistic regression analyses, which controlled for a variety of potential intraoperative confounders, resulted in a significant association between high OSA risk and the outcome of noninvasive ventilation (odds ratio 1.45, 95% confidence interval 1.20-1.76, p<0.001).

DISCUSSION

In our study, a novel prediction score for OSA based on data available in electronic medical records alone was developed. The SPOSA is a score based on demographic data and data on medical comorbidities identified as predictors for OSA. Our score yielded an AUC of

0.81 and identified 29.2% of our population as high OSA risk based on a cut point of SPOSA > 7, which was optimised based on sensitivity and specificity for the condition of OSA. This cut point of SPOSA > 7 also identified the highest tertile of OSA risk in our population. Our score was validated internally using cross validation and its clinical validity was further assessed by its prediction of noninvasive ventilation within seven days after surgery. The score was not improved by the addition of desaturation measures.

Our score is a weighted model containing comorbidity and demographic variables known to be associated with OSA, including: chronic pulmonary disease,[36] congestive heart failure,[5,6] diabetes,[7] dyslipidemia,[37,38] hypertension,[3,39] atrial fibrillation, [40,41] liver disease,[42] and pulmonary hypertension.[43,44] The association between hemiplegia/paraplegia and OSA may be related to the latter's association with acute ischemic stroke.[4,45] Male gender, high BMI, and older age have also been shown to predict OSA and are included in our model.[8,9,12,46]

Studies have demonstrated the increased vulnerability of OSA patients to perioperative complications. Recent ASA guidelines underscore the importance of preoperative detection and management of patients with OSA. While overnight polysomnography remains the gold standard for OSA diagnosis, the test is costly, inconvenient, and inaccessible to many patients. Thus, polysomnography is not an ideal screening tool but instead should be used to confirm the diagnosis in patients with high pre-test probabilities for OSA. Several scores have been developed to predict a patient's likelihood of having OSA. These scores have been developed in general surgical populations using information obtained from preoperative evaluation visits, such as history of snoring and neck circumference. Most well-known and validated scores are the STOP-Bang[20] and P-SAP scores[19]. However, to the best of our knowledge, no score for

OSA exists that has been developed from electronic medical records that does not contain information derived from direct patient encounters or physical examinations and is applicable to a surgical patient population.

Patient information available in electronic medical records and health administrative databases confer the advantage of studying large populations and screening the individual preoperative patient in a relatively inexpensive and more accessible way. Current methods of detecting OSA rely on patient-reported symptoms and physician-led examinations. However, many surgical patients opt for a phone interview with a non-anaesthesia provider instead of an in-person preoperative evaluation by an anaesthesia provider and thus many patients who may be at risk for OSA are missed in the screening process due to lack of physical exam information. Still, during these phone interviews, information on patient demographics and comorbidities are updated in the electronic record and this readily available data may be used for important screening efforts. A recent study performed amongst non-surgical patients concluded that non-symptom medical history was superior over patient-reported symptoms.[47] Using a new machine learning method (Supersparse Linear Integer Model, SLIM), authors identified the following variables as predictive for OSA in a sleep-lab referred population: older age, high BMI, diabetes, hypertension, smoker, and male gender. Compared with symptom-based features, a model based on history alone demonstrated a significantly higher AUC (0.78 vs. 0.670, $p<0.0001$).[47] The findings of Ustun and coworkers support the rationale and findings of our study as we sought to create a prediction model based on data available in the medical record. Our data add to the findings of Ustun and coworkers that an instrument composed of an optimal combination of comorbidities and BMI reliably predicts OSA risk in a surgical cohort.

The performance of the SPOSA is comparable to scores that have been developed in clinic-based settings. For example, the c-statistic for STOP-Bang and Ramachandran score are 0.81 and 0.79, respectively, for an AHI>5 compared to a c-statistic of 0.81 of the SPOSA score. Of note, the STOP-Bang and Ramachandran score require biological measurements to be taken during an exam (neck circumference, thyromental distance). The good test performance of our SPOSA – an instrument that does not utilise biomarkers (physical exam or lab information) – is consistent with other examples in which scores that do not include biomarkers perform very similarly to scores that do include such information.[48-50] For example, in cardiovascular risk prediction score with and without laboratory measurements, such as cholesterol or c-reactive protein, predictive measures have been very similar,[48,49] which is very important for applications in more general settings or in regions where laboratory data are not easily ascertainable.

Our score substantially adds to other available scores and allows providers to identify patients at increased risk of OSA from existing preoperative data resources. Of note, in an important study by McIsaac and colleagues, the authors demonstrate that OSA specific billing codes alone are insufficient to identify patients with OSA.[32] Therefore, in our study, we utilised a different approach: we use a combination of available data on OSA associated comorbidities and other known predictors such as BMI, age, and gender. Our data show that a substantially high proportion of our cohort (about one third) presents with high risk of OSA whereas only 2.1% carried the OSA specific billing codes. Our study supports the view of McIsaac and colleagues that OSA-associated billing codes administrative data alone fails to capture the underdiagnosed.

Strengths and limitations

Strengths of our study include a large study cohort and a large number of patients with ICD9 codes for OSA, allowing us to robustly develop a prediction score for OSA. Our database contains a variety of surgical procedure types and methods of anaesthesia, thus increasing the generalisability of the study results and applicability of our prediction score model. In addition, the validity of our score has been assessed by its prognostic ability – that is, its ability to predict noninvasive ventilation early after surgery, an outcome that is known to occur more frequently amongst patients with OSA.[51]

Several limitations have to be considered when interpreting our results. Our approach relies on the investigation of electronic patient data on file. Thus, our findings depend on the quality of the database, which is susceptible to measurement biases. There is potential for variability in the input of billing diagnoses and codes. This database has been used in previous studies[26-28] and demonstrated to have high specificity following verification of diagnostic codes. We have included evidence of OSA diagnosis up to one year prior to the surgical event in our study. However, one could argue that a patient with a confirmed OSA diagnosis may improve their OSA condition by significant weight loss, as suggested in prior studies investigating the association between lifestyle modifications and AHI.[33,34] To improve our definition of OSA, we excluded those patients who experienced significant weight loss in the time between their OSA diagnosis and the date of surgery. Furthermore, we have confirmed the accuracy of our unique combination of diagnostic and procedural codes in capturing patients with known OSA by medical record review. Nevertheless, it is possible that information is left out of some patients' charts and consequently, our database of our composite outcomes and independent variables.

In summary, the SPOSA allows providers to identify surgical patients at high risk of OSA with routinely available clinical information. This instrument will allow providers and anaesthesiologists to conduct further testing in high-risk groups and to individualise treatment in the perioperative period.

REFERENCES

1 Lacasse Y, Godbout C, Series F. Health-related quality of life in obstructive sleep apnoea. *European Respiratory Journal* 2002;**19**:499–503. doi:10.1183/09031936.02.00216902

2 Engleman HM, Douglas NJ. Sleep. 4: Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. *Thorax* 2004;**59**:618–22. doi:10.1136/thx.2003.015867

3 Logan AG, Perlikowski SM, Mente A, *et al*. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens* 2001;**19**:2271–7.

4 Lyons OD, Ryan CM. Sleep Apnea and Stroke. *Can J Cardiol* 2015;**31**:918–27. doi:10.1016/j.cjca.2015.03.014

5 Naughton MT. Respiratory sleep disorders in patients with congestive heart failure. *J Thorac Dis* 2015;**7**:1298–310. doi:10.3978/j.issn.2072-1439.2015.07.02

6 Stansbury RC, Strollo PJ. Clinical manifestations of sleep apnea. *J Thorac Dis* 2015;**7**:E298–310. doi:10.3978/j.issn.2072-1439.2015.09.13

7 Kent BD, Grote L, Ryan S, *et al*. Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. *CHEST* 2014;**146**:982–90. doi:10.1378/chest.13-2403

8 Isono S. Obesity and obstructive sleep apnoea: mechanisms for increased collapsibility of the passive pharyngeal airway. *Respirology* 2012;**17**:32–42. doi:10.1111/j.1440-1843.2011.02093.x

9 Coughlin SR, Mawdsley L, Mugarza JA, *et al*. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J* 2004;**25**:735–41. doi:10.1016/j.ehj.2004.02.021

10 Gruber A, Horwood F, Sithole J, *et al*. Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state. *Cardiovasc Diabetol* 2006;**5**:22. doi:10.1186/1475-2840-5-22

11 Memtsoudis SG, Besculides MC, Mazumdar M. A rude awakening--the perioperative sleep apnea epidemic. *N Engl J Med* 2013;**368**:2352–3. doi:10.1056/NEJMp1302941

12 Peppard PE, Young T, Barnet JH, *et al*. Increased prevalence of sleep-disordered breathing in adults. *American Journal of Epidemiology* 2013;**177**:1006–14. doi:10.1093/aje/kws342

13 Young T, Evans L, Finn L, *et al*. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 1997;**20**:705–6.

14 Finkel KJ, Searleman AC, Tymkew H, *et al*. Prevalence of undiagnosed obstructive sleep

apnea among adult surgical patients in an academic medical center. *Sleep Medicine* 2009;**10**:753–8. doi:10.1016/j.sleep.2008.08.007

15 Singh M, Liao P, Kobah S, *et al*. Proportion of surgical patients with undiagnosed obstructive sleep apnoea. *British Journal of Anaesthesia* 2013;**110**:629–36. doi:10.1093/bja/aes465

16 Mokhlesi B, Hovda MD, Vekhter B, *et al*. Sleep-Disordered Breathing and Postoperative Outcomes After Elective Surgery. *CHEST* 2013;**144**:903–14. doi:10.1378/chest.12-2905

17 Sasaki N, Meyer MJ, Eikermann M. Postoperative respiratory muscle dysfunction: pathophysiology and preventive strategies. *Anesthesiology* 2013;**118**:961–78. doi:10.1097/ALN.0b013e318288834f

18 American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. Anesthesiology. 2014;**120**:268–86. doi:10.1097/ALN.0000000000000053

19 Ramachandran SK, Kheterpal S, Consens F, *et al*. Derivation and validation of a simple perioperative sleep apnea prediction score. *Anesth Analg* 2010;**110**:1007–15. doi:10.1213/ANE.0b013e3181d489b0

20 Chung F, Yegneswaran B, Liao P, *et al*. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology* 2008;**108**:812–21. doi:10.1097/ALN.0b013e31816d83e4

21 Chung F, Yegneswaran B, Liao P, *et al*. Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. *Anesthesiology* 2008;**108**:822–30. doi:10.1097/ALN.0b013e31816d91b5

22 Abrishami A, Khajehdehi A, Chung F. A systematic review of screening questionnaires for obstructive sleep apnea. *Can J Anaesth* 2010;**57**:423–38. doi:10.1007/s12630-010-9280-x

23 Skomro RP, Kryger MH. Clinical presentations of obstructive sleep apnea syndrome. *Prog Cardiovasc Dis* 1999;**41**:331–40. doi:10.1053/pcad.1999.0410331

24 Eastwood PR, Malhotra A, PALMER LJ, *et al*. Obstructive Sleep Apnoea: From pathogenesis to treatment: Current controversies and future directions. *Respirology* 2010;**15**:587–95. doi:10.1111/j.1440-1843.2009.01699.x

25 Shin CH, Zaremba S, Devine S, *et al*. Effects of obstructive sleep apnoea risk on postoperative respiratory complications: protocol for a hospital-based registry study. *BMJ Open* 2016;**6**:e008436. doi:10.1136/bmjopen-2015-008436

26 McLean DJ, Diaz-Gil D, Farhan HN, *et al*. Dose-dependent Association between

Intermediate-acting Neuromuscular-blocking Agents and Postoperative Respiratory Complications. *Anesthesiology* 2015;**122**:1201–13. doi:10.1097/ALN.0000000000000674

27 Ladha K, Vidal Melo MF, McLean DJ, *et al*. Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: hospital based registry study. *BMJ* 2015;**351**:h3646. doi:10.1136/bmj.h3646

28 Brueckmann B, Villa-Uribe JL, Bateman BT, *et al*. Development and validation of a score for prediction of postoperative respiratory complications. *Anesthesiology* 2013;**118**:1276–85. doi:10.1097/ALN.0b013e318293065c

29 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;**143**:29–36. doi:10.1148/radiology.143.1.7063747

30 Pencina MJ, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;**27**:157–72–discussion207–12. doi:10.1002/sim.2929

31 Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem* 2008;**54**:17–23. doi:10.1373/clinchem.2007.096529

32 McIsaac DI, Gershon A, Wijeysundera D, *et al*. Identifying Obstructive Sleep Apnea in Administrative Data: A Study of Diagnostic Accuracy. *Anesthesiology* 2015;**123**:253–63. doi:10.1097/ALN.0000000000000692

33 Ng SSS, Chan RSM, Woo J, *et al*. A Randomized Controlled Study to Examine the Effect of a Lifestyle Modification Program in OSA. *CHEST* 2015;**148**:1193–203. doi:10.1378/chest.14-3016

34 Fredheim JM, Rollheim J, Sandbu R, *et al*. Obstructive sleep apnea after weight loss: a clinical trial comparing gastric bypass and intensive lifestyle intervention. *J Clin Sleep Med* 2013;**9**:427–32. doi:10.5664/jcsm.2656

35 Liu X. Classification accuracy and cut point selection. *Stat Med* 2012;**31**:2676–86. doi:10.1002/sim.4509

36 Soler X, Gaio E, Powell FL, *et al*. High Prevalence of Obstructive Sleep Apnea in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2015;**12**:1219–25. doi:10.1513/AnnalsATS.201407-336OC

37 Xu H, Guan J, Yi H, *et al*. Elevated low-density lipoprotein cholesterol is independently associated with obstructive sleep apnea: evidence from a large-scale cross-sectional study. *Sleep Breath* Published Online First: 30 September 2015. doi:10.1007/s11325-015-1262-3

38 Trzepizur W, Le Vaillant M, Meslier N, *et al*. Independent association between nocturnal intermittent hypoxemia and metabolic dyslipidemia. *CHEST* 2013;**143**:1584–9. doi:10.1378/chest.12-1652

39 Shahar E, Whitney CW, Redline S, *et al*. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001;**163**:19–25. doi:10.1164/ajrccm.163.1.2001008

40 Gami AS, Pressman G, Caples SM, *et al*. Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 2004;**110**:364–7. doi:10.1161/01.CIR.0000136587.68725.8E

41 Qureshi WT, Nasir UB, Alqalyoobi S, *et al*. Meta-Analysis of Continuous Positive Airway Pressure as a Therapy of Atrial Fibrillation in Obstructive Sleep Apnea. *Am J Cardiol* 2015;**116**:1767–73. doi:10.1016/j.amjcard.2015.08.046

42 Chou T-C, Liang W-M, Wang C-B, *et al*. Obstructive sleep apnea is associated with liver disease: a population-based cohort study. *Sleep Medicine* 2015;**16**:955–60. doi:10.1016/j.sleep.2015.02.542

43 Bady E, Achkar A, Pascal S, *et al*. Pulmonary arterial hypertension in patients with sleep apnoea syndrome. *Thorax* 2000;**55**:934–9. doi:10.1136/thorax.55.11.934

44 Kholdani C, Fares WH, Mohsenin V. Pulmonary hypertension in obstructive sleep apnea: is it clinically significant? A critical analysis of the association and pathophysiology. *Pulm Circ* 2015;**5**:220–7. doi:10.1086/679995

45 Johnson KG, Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. *JCSM* 2010;**6**:131–7.

46 Young T, Palta M, Dempsey J, *et al*. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;**328**:1230–5. doi:10.1056/NEJM199304293281704

47 Ustun B, Westover MB, Rudin C, *et al*. Clinical Prediction Models for Sleep Apnea: The Importance of Medical History over Symptoms. *J Clin Sleep Med* 2015.

48 Gaziano TA, Young CR, Fitzmaurice G, *et al*. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *Lancet* 2008;**371**:923–31. doi:10.1016/S0140-6736(08)60418-3

49 D'Agostino RB, Vasan RS, Pencina MJ, *et al*. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;**117**:743–53. doi:10.1161/CIRCULATIONAHA.107.699579

50 Stephan BCM, Tzourio C, Auriacombe S, *et al*. Usefulness of data from magnetic resonance imaging to improve prediction of dementia: population based cohort study. *BMJ* 2015;**350**:h2863–3. doi:10.1136/bmj.h2863

51 Lindenauer PK, Stefan MS, Johnson KG, *et al*. Prevalence, treatment, and outcomes associated with OSA among patients hospitalized with pneumonia. *CHEST* 2014;**145**:1032–8. doi:10.1378/chest.13-1544

FIGURES AND TABLES

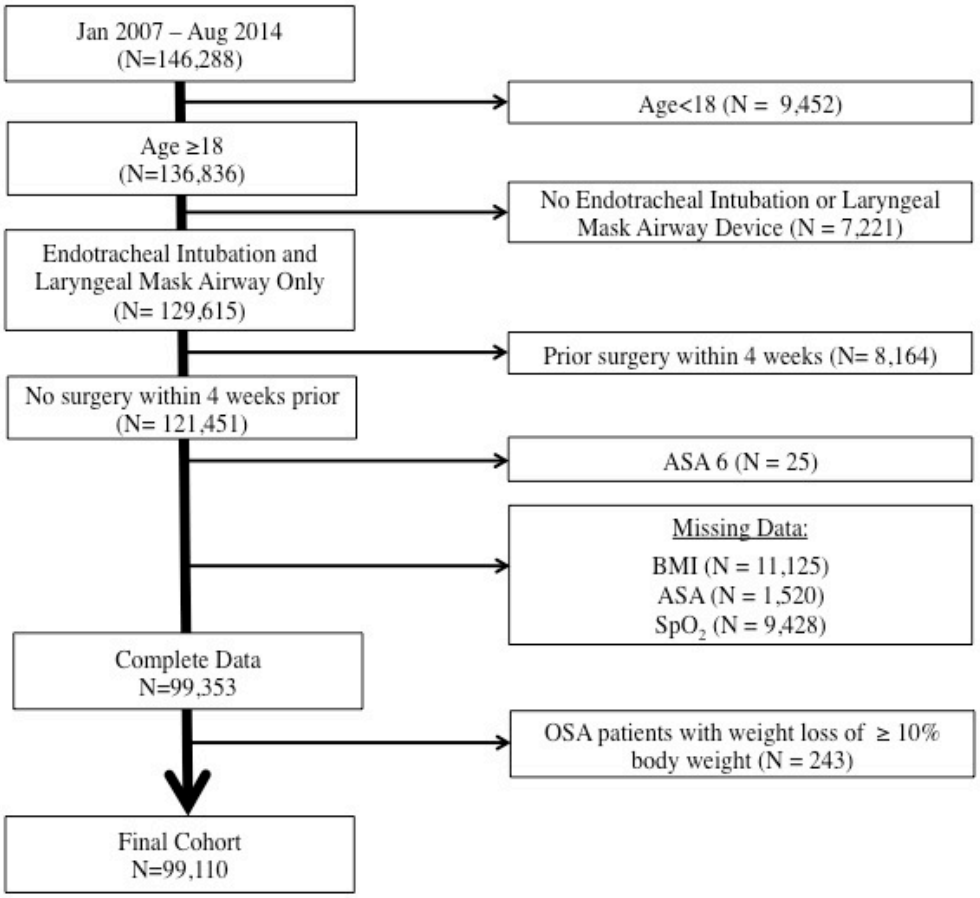

Figure 1. Study Flow Chart.

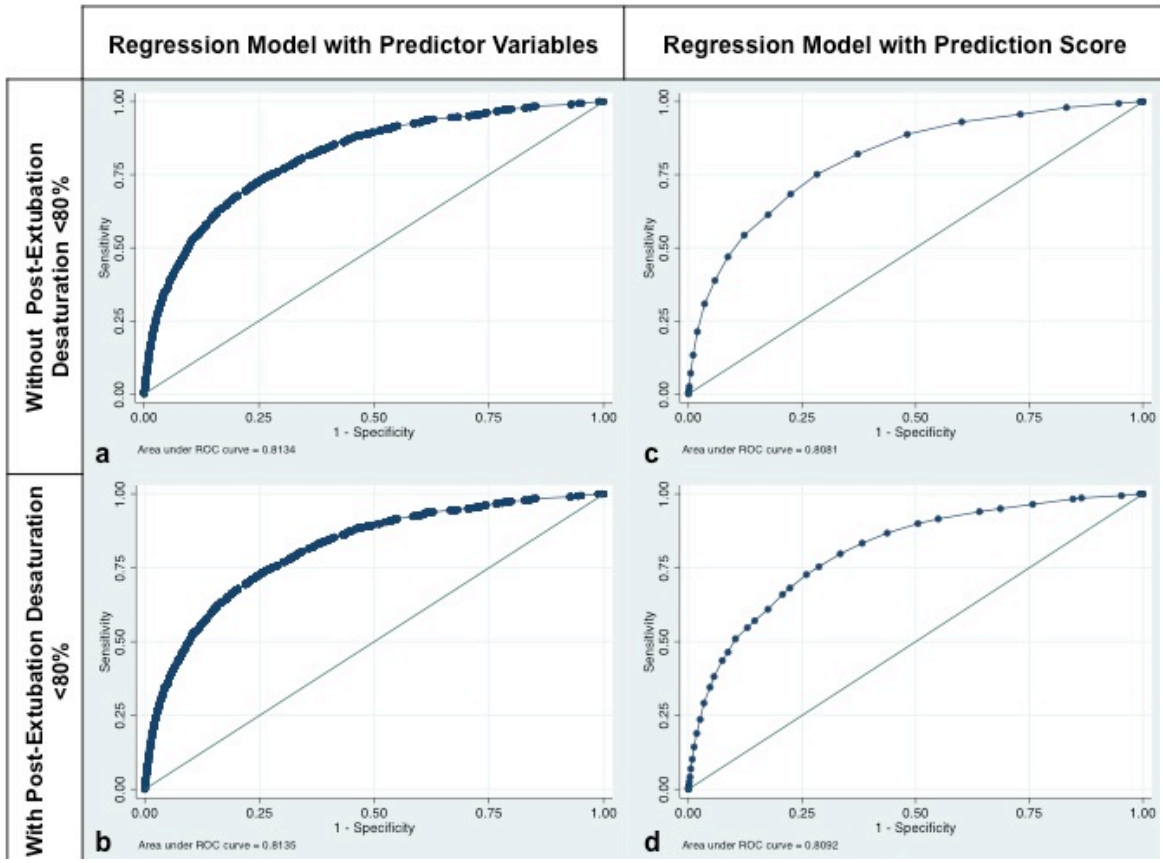

Figure 2. Receiver-operating characteristic (ROC) curve for prediction of obstructive sleep apnoea.

ROC curve was performed for the logistic regression model derived from significant independent predictors, a) without post-extubation desaturation <80% variable (AUC 0.8134) and b) with post-extubation desaturation <80% variable (AUC 0.8135). A second ROC curve was fitted based on the composite prediction score derived from our prediction model, c) without post-extubation desaturation <80% variable (AUC 0.8081) and b) with post-extubation desaturation <80% variable (AUC 0.8092).

Table 1: Characteristics of study population. Values are mean (SD) or number (proportion).

Variables	All patients (n= 99,110)	OSA patients (n=1,836)	Non-OSA patients (n=97,274)
Demographics			
Age (yrs), mean (SD)	54.5 (16.4)	55.2 (14.0)	54.5 (16.4)
Gender			
Male	43,950 (44.3%)	925 (50.4%)	43,025 (44.2%)
Female	54,249 (54.7%)	911 (49.6%)	54,249 (55.8%)
BMI ($kg.m^{-2}$), mean (SD)	28.6 (7.1)	36.4 (9.4)	28.4 (7.0)
ASA status, median [IQR]	2 [2 to 3]	2 [2 to 3]	2 [2-3]
1	9,382 (9.5%)	19 (1.0%)	9,363 (9.6%)
2	59,725 (60.3%)	942 (51.3%)	58,783 (60.4%)
3	28,542 (28.8%)	837 (45.6%)	27,705 (28.5%)
4	1,436 (1.4%)	37 (2.0%)	1,399 (1.4%)
5	25 (0.03%)	1 (0.1%)	24 (0.03%)
Comorbidities			
Acute Ischemic Stroke	2,153 (2.2%)	74 (4.0%)	2,079 (2.1%)
Arterial Hypertension	42,414 (42.8%)	1,316 (71.7%)	42,085 (43.3%)
Atrial Fibrillation	6,767 (6.8%)	251 (13.7%)	6,516 (6.7%)
Cerebrovascular Disease	7,661 (7.7%)	162 (8.8%)	7,499 (7.7%)
Chronic Pulmonary Disease	12,097 (12.2%)	525 (28.6%)	11,572 (11.9%)
Congestive Heart Failure	6,974 (7.0%)	317 (17.3%)	6,657 (6.8%)
Coronary Artery Disease	6,765 (6.8%)	261 (14.2%)	6,504 (6.7%)
Dementia	521 (0.5%)	15 (0.8%)	506 (0.5%)
Diabetes Mellitus	12,351 (12.5%)	580 (31.6%)	11,771 (12.1%)
Dyslipidemia	32,551 (32.8%)	1,144 (62.3%)	31,407 (32.3%)
Hemi/Paraplegia	2,031 (2.0%)	62 (3.4%)	1,969 (2.0%)
Liver Disease	9,698 (9.8%)	464 (25.3%)	9,234 (9.5%)
Myocardial Infarction	1,165 (1.2%)	32 (1.7%)	1,133 (1.2%)
Peptic Ulcer Disease	618 (0.6%)	19 (1.0%)	599 (0.6%)
Peripheral Vascular Disease	7,648 (7.7%)	217 (11.8%)	7,431 (7.6%)
Pulmonary Hypertension	1,590 (1.6%)	120 (6.5%)	1,439 (1.5%)
Postoperative			
Post-extubation Desaturation below 80%	1,297 (1.3%)	20 (1.1%)	1,277 (1.3%)
Post-extubation Desaturation below 90%	5,187 (5.2%)	125 (6.8%)	5,062 (5.2%)

*All values stated as number of patients (%), unless otherwise stated

Table 2. Prediction Model for Obstructive Sleep Apnoea.

Odds ratios, p-values and 95% CI are presented for those predictor variables identified as the strongest independent predictors in a multivariable binary logistic regression model for obstructive sleep apnoea. Predictors were assigned a rounded score point value in proportion to the lowest odds ratio in the model. Score values for all predictors were unchanged with or without the addition of the post-extubation desaturation <80% variable to the model.

Predictor	Odds Ratio	p-value	95% CI	Score Value
Male Gender	1.26	<0.001	1.14-1.39	1
BMI ($kg.m^{-2}$)				
25 to <30	2.22	<0.001	1.82-2.72	2
30 to <35	4.52	<0.001	3.71-5.50	4
35+	10.11	<0.001	8.37-12.20	8
Age (yr)				
18-50	2.05	<0.001	2.37-4.21	2
50-70	1.49	<0.001	1.66-2.87	1
Arterial Hypertension	1.67	<0.001	1.47-1.88	1
Atrial Fibrillation	1.44	<0.001	1.23-1.69	1
Chronic Pulmonary Disease	1.89	<0.001	1.69-2.13	2
Congestive Heart Failure	1.34	<0.001	1.15-1.55	1
Diabetes	1.20	0.001	1.08-1.35	1
Dyslipidemia	2.10	<0.001	1.88-2.35	2
Hemiplegia/Paraplegia	1.45	0.007	1.11-1.91	1
Liver Disease	1.88	<0.001	1.68-2.12	2
Pulmonary hypertension	1.68	<0.001	1.34-2.11	1
Stroke	1.40	0.01	1.08-1.80	1

Table 3. Risk Reclassification comparing the Prediction Model with and without Post-Extubation Desaturation below 80%

Prediction model without Post-Extubation Desaturation <80%	Prediction model with Post-Extubation Desaturation <80%				Total
	< 1% risk	1 to <15% risk	15 to <20% risk	>20% risk	
In 1,836 patients with OSA					
<1% risk	254	0	0	0	254
1 to <15% risk	0	1,385	0	0	1,385
15 to <20% risk	0	0	105	0	105
>20% risk	0	0	0	92	92
Total	254	1,385	105	92	1,836
In 97, 274 patients without OSA					
<1% risk	54,995	6	0	0	55,001
1 to <15% risk	149	41,278	2	0	41,429
15 to <20% risk	0	9	458	4 8	475
>20% risk	0	2	3	364	369
Total	55,144	41,295	463	372	97,274

Supplemental Table 1: Diagnostic (ICD-9) and Procedural (CPT) codes used to generate predictor and outcome variables.			
Variable	**Diagnostic or Procedure Name**	**Code Type**	**Code**
Reference Standard Outcome for Prediction Model of Aim 1			
Obstructive Sleep Apnoea	Obstructive sleep apnoea (adult or pediatric)	ICD-9	327.23
	Unspecified sleep apnoea	ICD-9	780.57
Polysomnography	Sleep study, simultaneous recording of ventilation, respiratory effort, ECG or heart rate, oxygen saturation, attended by a technologist	CPT	95807
	Any age, sleep staging with 1-3 additional parameters of sleep, attended by a technologist	CPT	95808
	Age 6 years or older, sleep staging with 4 or more additional parameters of sleep, attended by a technologist	CPT	95810
	Age 6 years or older, sleep staging with 4 or more additional parameters of sleep, with continuous positive airway pressure therapy or bi-level ventilation, attended by a technologist	CPT	95811
Medical Comorbidities			
Arterial	Malignant Essential Hypertension	ICD-9	401.0

	Benign essential hypertension	ICD-9	401.1
	Unspecified essential hypertension	ICD-9	401.9
	Other malignant secondary hypertension	ICD-9	405.09
	Other benign secondary hypertension	ICD-9	405.19
	Other unspecified secondary hypertension	ICD-9	405.99
Pulmonary Hypertension		ICD-9	416.0
Coronary Artery Disease	Coronary atherosclerosis of unspecified type of vessel native or graft	ICD-9	414.00
	Coronary atherosclerosis of native coronary artery	ICD-9	414.01
	Coronary atherosclerosis of autologous vein bypass graft	ICD-9	414.02
	Coronary atherosclerosis of nonautologous biological bypass graft	ICD-9	414.03
	Coronary atherosclerosis of artery bypass graft	ICD-9	414.04
	Coronary atherosclerosis of unspecified bypass graft	ICD-9	414.05
	Coronary atherosclerosis of native coronary artery of transplanted heart	ICD-9	414.06
	Coronary atherosclerosis of bypass graft (artery) (vein) of transplanted heart	ICD-9	414.07
	Aneurysm of heart (wall)	ICD-9	414.10
	Aneurysm of coronary vessels	ICD-9	414.11
	Dissection of coronary artery	ICD-9	414.12
	Other aneurysm of heart	ICD-9	414.19
	Chronic total occlusion of coronary artery	ICD-9	414.20
	Coronary atherosclerosis due to lipid rich plaque	ICD-9	414.30
	Coronary atherosclerosis due to calcified coronary lesion	ICD-9	414.40
	Other specified forms of chronic ischemic heart disease	ICD-9	414.80
	Chronic ischemic heart disease unspecified	ICD-9	414.90

Dyslipidemia	Pure hypercholesterolemia	ICD-9	272.0
	Pure hyperglyceridemia	ICD-9	272.1
	Mixed hyperlipidemia	ICD-9	272.2
	Hyperchylomicronemia	ICD-9	272.3
	Other and unspecified hyperlipidemia	ICD-9	272.4
	Other disorders of lipoid metabolism	ICD-9	272.8
Ischemic Stroke	Acute ischemic stroke or cerebral infarction	ICD-9	434.91
	Embolic Stroke	ICD-9	434.11
	Thrombotic Stroke	ICD-9	434.01
Atrial Fibrillation		ICD-9	427.31
The following medical comorbidities are derived from ICD9 Codes, as defined by the Deyo Charlson Comorbidity Index[26]: Myocardial Infarction, Congestive Heart Failure, Peripheral Vascular Disease, Cerebrovascular Accident, Dementia, Chronic Pulmonary Disease, Mild Liver Disease, Moderate to Severe Liver Disease, Diabetes with Chronic Complications, Diabetes without Chronic Complications, Hemiplegia or Paraplegia, Peptic Ulcer Disease, Renal Disease, Any Malignancy including Leukemia and Lymphoma but excluding malignant neoplasm of skin, Metastatic Solid Tumor, AIDS/HIV, Rheumatic Disease			
Noninvasive Ventilation	Continuous positive airway pressure ventilation	CPT	94660
	Respiratory Therapy	ICD-9	93.9

II. Phase 3: The effect of Obstructive Sleep Apnea risk on Postoperative Outcomes

Effect of Obstructive Sleep Apnea risk on Postoperative Outcomes: an observational study

Christina H. Shin BA[1,2], Stephanie D. Grabitz Cand med[1], Fanny P. Timm Cand med, Karim Ladha MD MSc[3], Scott Devine PhD[4], Tobias Kurth MD, ScD[2,5,6], and Matthias Eikermann MD, PhD[1,2,7]

[1]Department of Anesthesia, Critical Care, and Pain Medicine. Massachusetts General Hospital, Boston, MA 02114, USA; [2]Harvard Medical School, Boston, MA; [3]Department of Anesthesia, Toronto General Hospital and University of Toronto, Toronto, Canada; [4]Center for Observational and Real-World Effectiveness US Outcomes Research, Merck & Co., Inc; [5]Institute of Public Health, Charité - Universitätsmedizin Berlin, Germany; [6]Division of Preventive Medicine, Brigham and Women's Hospital; [7]Universitaet Duisburg-Essen, Essen, Germany

Correspondence to: Dr. Matthias Eikermann, meikermann@partners.org

ABSTRACT

Objective: To assess the effect of high obstructive sleep apnea (OSA) risk on postoperative respiratory outcomes (PRC)

Background: PRCs are associated with significant morbidity, mortality, and hospital costs. OSA, which is often undiagnosed in the surgical population, may be a contributing factor.

Methods: Observational study of 99,816 surgical patients at Partners HealthCare hospitals (2007-2014). Patients were classified as high, moderate, and low risk for OSA using the Score for Preoperative Prediction of Obstructive Sleep Apnea (SPOSA). Multivariable logistic regression analyses were performed to analyze the effect of OSA risk on our primary endpoint, PRCs within 7 days of surgery. In order to improve the clinical utility of the score, a dichotomized risk scale was developed using the SPOSA cut point of 7. Propensity score matched cohorts were used for additional analyses aimed at understanding clinical and health care economic outcomes among patients identified as high risk for OSA.

Results: PRCs occurred in 7.7%, 5.5%, and 3.6% of those identified as high, moderate, and low risk for OSA. OSA risk was significantly associated with incidence of PRC in unadjusted analyses and analyses adjusted for patient comorbidities and procedure-specific variables. Using a dichotomized endpoint, the significant association between high OSA risk and PRCs remained stable (adjusted OR 1.38, 95% CI 1.26-1.51, $p<0.001$). Within propensity score matched cohorts, high OSA risk was significantly associated with increased postoperative length of stay, increased total costs of care, and higher rates of admission to the intensive care unit, adverse discharge, and readmission within 30 days of initial discharge.

Conclusions: High risk of OSA is associated with the occurrence of respiratory complications as well as adverse discharge and readmission within 30 days. Utilization of SPOSA may allow providers to individualize perioperative treatment.

INTRODUCTION

Approximately 45 million procedures are performed every year in hospitals across the United States.[1] Complications arising from surgical procedures are costly, both in terms of patient lives and hospital resources. There has been widespread interest in measuring and improving quality of care delivered. Quality improvement efforts often focus on patient-centered outcomes, including patient satisfaction, length of stay, costs of care, and readmission rates. A number of national databases, including the National Surgical Quality Improvement Project (NSQIP), have been utilized to better understand postoperative complications and its broader financial impact.[2-5] Much of these studies find wide variation in quality across providers and hospitals, a finding that has driven many institutions to improve quality of care as a response to payers' initiatives to identify and selectively refer patients to higher quality hospitals.[6] Furthermore, the rise of episode-based bundled payments, in which lump reimbursements for inpatient surgery are provided as a single payment to hospitals and caregivers, motivates providers to work together to improve cost-effective care.[6]

Within general surgery, adverse outcomes have been largely attributed to high baseline risk, a function of surgical complexity and patient preoperative risk factors.[7,8] One study proposed that more than the quality of care delivered, patient illness and risk factors are the driving force behind high rates of adverse outcomes.[9] To that end, new value-based care reimbursement requires identification of high-risk patients prior to surgery. A number of professional societies have recommended screening for specific risk factors that would make patients vulnerable to perioperative complications. American Society of Anesthesiology has recently put forth guidelines for preoperative screening of obstructive sleep apnea, a widely prevalent disease characterized by the repetitive collapse of the upper airway. However,

evidence supporting such guidelines have been inconsistent – for example, some studies report an increased length of stay and in-hospital mortality among OSA patients while others find the opposite effect.[2,3,10-13]

Though the most common sleep-related breathing disorder in the general population,[14,15] it is likely that the true prevalence of obstructive sleep apnea is underestimated.[16] Obesity, a significant driving force of OSA, has increased in the last decade[17] and studies have shown that OSA is frequently undiagnosed, including among the surgical population. [16,18]

Surgical patients with OSA are particularly vulnerable to perioperative morbidity,[3] as anesthesia and surgery affect the collapsibility of the upper airway as well as respiratory drive.[19] In order to identify such high-risk patients, our group has developed a novel screening tool that relies solely on patient data routinely available in the electronic medical record. This tool, called Score for Preoperative Prediction of Obstructive Sleep Apnea (SPOSA), assesses the surgical patient's risk for preoperative OSA based on the presence of specific comorbidities. The SPOSA is distinct from other perioperative questionnaires because it does not rely on a clinical exam, which often does not occur immediately prior to day of surgery. In our previous study, we have identified a cut-point of 10 as high risk for OSA. Identifying patients at high preoperative risk for OSA will permit providers to better assess the risk of postoperative complications, which will ultimately improve quality and cost of health care delivered.

In this study, we use SPOSA to identify patients in our institution's large database at high risk of OSA and characterize the impact of high OSA risk on important clinical endpoints, including postoperative respiratory complications (PRCs), adverse discharge, hospital

readmission rates, length of stay and total costs of care. We hypothesize that patients at high risk of OSA will also have higher risk of adverse postoperative outcomes.

METHODS

This study is an analysis of prospectively collected data on file using hospital-based electronic patient data at Massachusetts General Hospital, a tertiary care facility and teaching hospital of Harvard Medical School, as well as several hospitals affiliated with Partners HealthCare in Massachusetts, USA.

As previously used for studies by our group, data from three clinical databases were retrieved and combined to provide de-identified pre- and postoperative information: the Research Patient Data Registry, Anesthesia Information Management System, and an administrative database EPSi. The Research Patient Data Registry contains demographic and billing data regarding patient comorbidities and postoperative outcome and survival. The Anesthesia Information Management System contains physiological data from patient monitors as well as documentation of important surgery and anesthesia-related events, including adverse events, perioperative procedures, and drug and fluid therapy. EPSi contains administrative data on admission and discharge dates, hospital length of stay, and total care costs. Patient data from these databases are linked through unique patient identifiers and the variables utilized for our prediction model were abstracted to form one database. The present database spans from January 2007 to August 2014 and includes more than 145,000 surgical cases.

Subject Selection

We included all surgical patients aged 18 years or older who underwent general anesthesia and received endotracheal intubation or airway management by supraglottic airway device at our institution between January 2007 and August 2014 and who have had removal of all airway management devices within the operating room after the procedure. Because reintubation is a component of our composite outcome of PRC, we only included those patients who had removal of all airway management devices within the operating room after the procedure. Surgical procedures followed by reintubation for an additional scheduled surgical procedure in the operating room after initial extubation or removal of airway device were excluded from the study. Patients who underwent surgery in the four weeks prior to the study case were excluded. Finally, all patients with an intraoperative death were excluded from the study since OSA is not a biological mechanism of intraoperative death when a patient's airway is secured by an airway device.

Exposure Variables

Our primary exposure variable of interest was OSA risk, as defined by our previously developed prediction score, Score for Preoperative Prediction of Obstructive Sleep Apnea (SPOSA) [ref]. The surgical population was divided into three equal-sized groups based on increasing SPOSA score. Patients were categorized as low (SPOSA 0 to 4; n=39,204), moderate (SPOSA 5 to 7; n=31,525), and high (SPOSA 8+; n=29,087) risk for OSA. In addition, a dichotomized OSA risk classification approach was investigated as a means to develop a clinically relevant tool that could be easily implemented by providers. The SPOSA cut point of 7, such that low risk would be SPOSA 0 to 7 and high risk would be SPOSA 8+, was determined

using the Youden Index.[20] This cut-point has previously been shown to optimize sensitivity and specificity of our score.[SPOSA citation]

Outcome Variables

The primary outcome was a composite outcome, postoperative respiratory complications (PRCs), defined as the incidence of reintubation, pulmonary edema, pneumonia and respiratory failure within the first seven postoperative days. The primary outcome has been previously used and validated by chart review.[51,66] Events were identified by ICD-9 diagnostic and CPT procedural codes obtained from the Research Patient Data Registry database (Supplemental Table 1). Secondary outcomes included the aforementioned individual outcomes as well as postoperative hospital length of stay and in-hospital mortality. Additional exploratory endpoints included adverse discharge, readmission within 30 days, postoperative acute kidney injury, and total hospital care costs. Adverse discharge was defined as discharge to a skilled nursing facility, long term care, or in-hospital death. With the exception of postoperative acute kidney injury, secondary and exploratory outcomes were obtained from our institution's EPSi administrative database. Postoperative acute kidney injury was defined as either an increase from a baseline creatinine value by 50% or by 0.3 mg/dL within 48 hours of surgery or the occurrence of an ICD-9 diagnostic code for acute renal failure within three days of surgery. Of note, all patients with previous history of dialysis were not considered to have new acute kidney injury following surgery.

Statistical Analysis: Primary Outcome

We first aimed to understand the effect and impact of OSA risk by investigating its association with the incidence of PRCs following surgery. We performed unadjusted logistic regression analyses as well as analyses adjusted for demographic variables, comorbidities, and procedure-related variables. Variables included in our adjusted model were the following: age, gender, BMI, ASA physical status classification, Charlson Comorbidity Index, duration of the surgical procedure, admission type, emergency status, duration of hypotension, procedure relative value units, volume of intraoperative fluids, dose of anesthesia (median dose of anesthetic agents corrected for age), opioids (calculated as total morphine equivalent dose), vasopressors, sedatives, neuromuscular blocking agents, neostigmine use, units of packed red blood cell transfusion, and median values for plateau and peep pressures. Variables were selected based on *a priori* knowledge about association patterns between covariates, OSA, and PRCs. Results are presented as an age- and multivariable-adjusted odds ratio with 95% confidence intervals.

Statistical Analysis: Secondary and Exploratory Outcomes

We were also interested in understanding the health economic impact of a population identified as having sleep apnea. To that end, we created propensity score matched cohorts of patients. We used a logistic regression model with high OSA risk, as defined by the dichotomized SPOSA cut point of 10, as the dependent variable and procedure-related variables as independent variables to account for variation in surgical procedures. The procedure-related variables included duration of surgery, work relative value units, surgical service, and units of packed red blood. On the basis of calculated propensity scores, we matched patients using a

greedy algorithm without replacement that first identifies matched pairs within a closeness range of 0.00001 of the propensity score, then if no more individuals can be found, the program identifies matched pairs in a range of 0.0001, and so on up to a closeness range of 0.1. Using the matched cohorts, we performed logistic regression analyses with high OSA risk as the independent variable and postoperative respiratory complications, adverse discharge, readmission within 30 days, ICU admission rate, in-hospital mortality, and postoperative acute kidney injury as dependent variables. For postoperative length of stay and total cost of care, we performed zero-truncated negative binomial regression analyses and report outcomes as incidence rate ratios (IRR) with 95% confidence intervals (CI).

Statistical analyses were conducted by using the software STATA (Version 13.1, StataCorp, College Station, TX) and a two-sided p-value of <0.05 was considered statistically significant.

RESULTS

Study Cohort

A total of 146,288 surgical cases were identified. Of those, a total of 46,472 cases were excluded because they either had missing values for covariates, age was <18 years at the time of surgery, did not undergo endotracheal intubation or placement of supraglottic airway device, or underwent cardiac surgery. In addition, patients with a surgical procedure within four weeks prior to the study case were excluded and only the first procedure remained in the cohort. The study flow is summarized in Figure 1.

Primary Outcome: Postoperative Respiratory Complications

A total of 5,375 (5.4%) patients experienced a postoperative respiratory complication within 7 days of surgery. The breakdown of individual respiratory complications was as follows: 3,569 (3.6%) pulmonary edema, 1,324 (1.3%) pneumonia, 1,796 (1.8%) respiratory failure, and 362 (0.4%) reintubation. Clinical characteristics of our study cohort by the occurrence of our primary endpoint are described in Table 1. Increasing OSA risk, as characterized by groups of increasing SPOSA scores, was significantly associated with higher odds of PRCs in an unadjusted model (Table 2). This association remained stable after adjustments (Table 2).

A total of 2,224 patients (7.7%) of patients identified as high OSA risk experienced PRCs within 7 days following surgery, while a total of 3,151 (4.5%) of low OSA risk patients were positive for this primary outcome. In unadjusted and adjusted analyses, high OSA risk was significantly associated with PRCs (unadjusted OR 1.78, 95% CI 1.68-1.88, $p<0.001$; adjusted OR 1.38, 95% CI 1.26-1.51, $p<0.001$). Of the individual respiratory complications, this effect seemed to be driven largely by pulmonary edema (adjusted OR 1.50, 95% CI 1.35-1.66, $p<0.001$). A summary of our multivariable regression analyses is provided in Table 2.

Secondary outcomes: postoperative length of stay, in-hospital mortality

Mean ± SD postoperative length of stay for high and low OSA risk groups were 4.3 ± 5.1 days and 3.9 ± 5.1 days, respectively. Using propensity score matched cohorts (Table 3), we found OSA risk to be associated with increased postoperative length of stay (IRR 1.06, 95% CI 1.03-1.09, $p<0.001$).

In-hospital death occurred in 105 (0.4%) patients at high risk for OSA and in 102 (0.4%) patients at low risk for OSA. There was no significant association between in-hospital mortality and OSA risk (OR 1.03, 95% CI 0.78-1.35, p=0.831).

A summary of the regression analyses using our propensity score matched cohorts is provided in Table 4.

Exploratory outcomes: postoperative acute kidney injury, ICU admission, adverse discharge, readmission within 30 days, total cost of care

A total of 1,608 (5.6%) high OSA risk patients and 873 (3.0%) low OSA risk patients experienced acute kidney injury within 2-3 days after surgery. High OSA risk was significantly associated with increased risk of postoperative acute kidney injury (OR 1.89, 95% CI 1.74-2.06, p<0.001).

A total of 1,138 (3.9%) high OSA risk patients and 907 (3.1%) low OSA risk patients were admitted to the intensive care unit (ICU) within 7 days after surgery. ICU admission was significantly associated with high OSA risk (OR 1.27, 95% CI 1.16-1.38, p<0.001).

Patients' discharge dispositions were captured from our administrative databases and included discharge to home, rehabilitation centers, long term care, and skilled nursing facility. First time adverse discharge was defined as patient death during hospitalization or patient's first time discharge to either skilled nursing facility or long-term care. Given this definition, 2,235 (7.7%) of high OSA risk patients experienced adverse discharge dispositions, compared with a total of 1,956 (6.1%) of low OSA risk patients. There was a significant association between high OSA risk and likelihood of adverse discharge (OR 1.16, 95% CI 1.08-1.23, p<0.001).

Data on readmission rates within 30 days following discharge from index hospitalization were captured from our EPSi administrative database. Readmission within 30 days occurred in a total of 2,540 (8.8%) high OSA risk patients and 2,060 (7.1%) low OSA risk patients. High OSA risk was associated with increased readmission rates within 30 days (OR 1.26, 95% CI 1.18-1.34, $p<0.001$).

DISCUSSION

In this large observational hospital-based registry of adult surgical patients, we found that a high preoperative risk of OSA, as predicted by the SPOSA, was associated with increased odds of postoperative respiratory complications. Our results remained stable after accounting for patient comorbidities and perioperative factors, suggesting that the association between high OSA risk and postoperative respiratory complications is likely a consequence of OSA risk, rather than a consequence of OSA-associated comorbidities. In addition to respiratory complications, we aimed to understand the patient-centered and health care economic outcomes of patients who present with high preoperative risk of OSA and found that, when controlling for procedure-related variability, this subpopulation experienced higher odds of increased postoperative length of stay, ICU admission, adverse discharge, and hospital readmission.

SPOSA score is predictive of postoperative respiratory complications

OSA has been established as a risk factor for adverse perioperative outcomes. The higher propensity of patients with high risk for OSA towards PRCs is most likely multifactorial and related to a pathological imbalance of upper airway dilation and collapse. We hypothesized that surgical patients at high risk for OSA are especially vulnerable to multiple perioperative insults,

including the effects of sedatives, opioids, neuromuscular blocking agents, fluid resuscitation, and more. In order to evaluate the biological implications of high OSA risk, we performed our primary analysis and investigated the association between high OSA risk and incidence of PRCs as a composite outcome within seven days following surgery while controlling for several perioperative factors. We report a significant association between high preoperative OSA risk, as defined by increasing SPOSA values, and increased rate of PRCs in non-cardiac surgery patients. Of note, the primary driver of this association appeared to stem from a significant association between high preoperative OSA risk and pulmonary edema. High OSA risk did not appear to have a significant impact on the remaining components of our composite primary outcome: reintubation, respiratory failure, and pneumonia. Our findings are supported by other work in the literature, which have primarily associated a medical diagnosis of sleep-disordered breathing with cardiopulmonary complications. In a retrospective analysis of 530,089 patients undergoing total hip and knee arthroplasties, 8.4% had a known diagnosis for sleep apnea and this diagnosis was an independent risk factor for major postoperative pulmonary complications (OR 1.86, 95% CI 1.65-2.09).[11] In a 2014 meta-analysis of prospective and retrospective cohort studies, Gaddam et al investigated postoperative respiratory complications, which ranged in the various studies from hypoxemia, bronchospasm, respiratory failure, to pneumonia. The authors demonstrated an overall OR of 2.77 (95% CI 1.73-4.43).[21]

Emergent intubation or reintubation is a common respiratory endpoint studied in the context of OSA patients and many studies have demonstrated a significant association. [2,3] However, our findings differ in that our increased rate of reintubation observed among patients at high OSA risk was, although increased, not statistically significant. The absence of a significant association between high OSA risk and reintubation may be in part due to the significantly

increased rates of postoperative noninvasive ventilation among high OSA risk patients found in our study. Thus it is possible that the reason for a non-elevated risk of emergent reintubation is that patients at high OSA risk experience postoperative respiratory distress receive positive airway pressure as the first, and often successful, intervention. While the authors of a meta-analysis of the association between OSA and postoperative outcomes did not specifically investigate noninvasive ventilation, they also found a non-significant association between reintubation and OSA patients, consistent with our findings.[22] This finding was confirmed by an updated meta-analysis where the combined association was OR 1.37, 95% CI 0.65-2.91.[21]

Biological Implications

Consistent with several studies in the literature, we found that high preoperative risk of OSA increases the risk of developing respiratory complications within seven days following surgery. This association was stable across numerous methods of SPOSA categorization. Strikingly, the significant association between high OSA risk and PRCs appears to be in part driven by the high rate of pulmonary edema in this vulnerable group of patients following surgery. There is limited epidemiological data in the literature regarding this association among surgical patients. Prompted by anecdotal evidence, one group found that pulmonary edema develops after recurrent obstructive apneas in intubated, anesthetized dogs.[23] Two recent cases of postoperative negative pressure pulmonary edema have been described in patients as the etiology of their severe postoperative noncardiogenic pulmonary edema requiring mechanical ventilation. [24,25] In each case, NPPE was attributed to laryngospasm and bronchospasm, respectively. Though a preoperative diagnosis of OSA was not present in either case, we can apply a similar mechanism by which NPPE formed in the setting of airway obstruction. Strong

inspiratory efforts in the setting of obstruction generates highly negative intrathoracic and intrapleural pressures, increasing venous return to the right atrium with a subsequent increase in pulmonary blood volume and fluid shifts from vessel to pulmonary interstitium.[26] Also contributing to increased edema formation are disruptions in the alveolar epithelium and pulmonary microvascular membranes from mechanical stress and inflammation.[26] Another potential driving force of pulmonary edema formation is the phenomenon of overnight rostral fluid shifts. Redolfi et al measured leg fluid volumes and performed overnight polysomnography in healthy non-obese men.[27] The authors found that overnight changes in leg fluid volume were significantly correlated with AHI ($r= -0.773$, $p<0.001$) and changes in neck circumference ($r= -0.588$, $p=0.003$). This correlation was thought to be primarily driven by changes in position: time spent sitting during the day was significantly correlated with changes in leg fluid volume when patients were supine and asleep ($r= -0.588$, $p=0.003$). In the context of our study, we may presume that surgical patients likely find themselves spending more of their time in the supine position and flat in their hospital bed during the postoperative recovery period. This is in contrast to their preoperative state where during the daytime, patients are likely more mobile and more often in the sitting or standing positions. Thus, not only are our patients with high preoperative SPOSA scores at risk for perioperative airway obstruction but rostral fluid shifts secondary to the positioning of patients during surgery and in the hospital may significantly contribute to adverse outcomes. An additional component contributing to PRC risk in the high OSA risk patient is postoperative delirium and other sources of cognitive impairment. Postoperative delirium, an acute state of fluctuating impairment in cognition, occurs frequently in the surgical population, particularly affecting elderly patients.[28] Bateman et al have posited various mechanisms behind the demonstrated associations between postoperative delirium and OSA, including chronic

intermittent hypoxia and disrupted sleep as triggers of delirium as well as a hyperinflammatory state.[28] Patients at high risk of OSA with impaired cognition in the immediate postoperative period are then particularly vulnerable to additional postoperative complications, such as aspiration resulting in pneumonitis, respiratory distress, pulmonary edema, and a need for non-invasive and/or invasive ventilation therapy.

SPOSA score is predictive of adverse outcomes of care

As a highly prevalent disease and an established perioperative risk factor, OSA has become an important focus of discussions centered on patient outcomes and health care utilization. In order to evaluate the clinical implications of patients who have been identified as high risk for OSA, we developed propensity score matched cohorts, accounting only for procedure-specific variation. In so doing, we were interested in drawing conclusions about the high risk OSA patient as a whole – the perioperative course such patients faced and how their patterns of health care utilization differed from low OSA risk patients. In other words, we were interested in assessing the impact of preoperative OSA risk on patients' adverse outcomes of care. Our analyses were notable for an association between high OSA risk and increased postoperative length of stay. However, no significant effect was observed on in-hospital mortality. Investigations into both length of stay and in-hospital mortality have produced mixed results in the literature. Kaw et al studied 1,759 patients undergoing elective non-cardiac surgery and found that among patients with a history of an AHI>5 on a polysomnography within 3 years of surgery, there was a risk of longer hospital stay.[10] In analyses of the Nationwide Inpatient Sample, Mokhlesi et al found increased length of stay among patients undergoing elective orthopedic surgery but decreased length of stay among patients undergoing elective abdominal,

cardiovascular, and bariatric surgery. [2,3] Griffin et al also analyzed the NIS and out of a cohort of 22,988 patients undergoing total shoulder arthroplasty or hemiarthroplasty, 5.9% had OSA and this group demonstrated a shorter hospital length of stay compared with non-OSA patients.[12] This same group also found no significant association between OSA and in-hospital mortality, similar to the findings of our study.[12] Focusing on a group of 304,515 bariatric surgery patients in the NIS from 2006 to 2008, Nguyen et al found that sleep apnea was not a significant predictor of in-hospital mortality.[29] In contrast, Mokhlesi et al also used the NIS database to examine elective bariatric, abdominal, prostate, cardiovascular and orthopedic surgical patients and found that across all but the prostate surgery subtype, sleep disordered breathing was significantly associated with decreased in-hospital death.[2,3]

We also found an increased risk for ICU admission, higher hospital care costs, adverse discharge, and readmission within 30 days. Our findings are supported by studies in the literature on health care utilization patterns by surgical patients with OSA. Memtsoudis et al found significantly higher number of ICU transfers and total costs among OSA patients undergoing orthopedic surgery compared with their non-OSA counterparts.[11] We add to the findings of Memtsoudis et al by expanding our population to both elective and non-elective non-cardiac surgeries, increasing the generalizability of the results. Consistent with our findings, Kaw et al found an increased risk of ICU transfers among elective non-cardiac surgical patients with OSA as previously diagnosed on polysomnography.[30] Regarding readmission rates, a prospective observational study of 24,662 patients undergoing bariatric surgery found that OSA, among a number of other complications, was a significant predictor for hospital readmission (OR 1.5, 95% CI 1.1-1.9).[31] In an era where more and more patients are discharged from the hospital to various levels of acute “step-down” care, we sought to also characterize the discharge disposition

of patients and classify some as adverse or favorable health outcomes. We considered an adverse discharge as transfer of a patient to a skilled nursing facility, evidence that the patient persistently required high levels of acute care. We found that high OSA risk predicted the likelihood of an adverse discharge and to our knowledge, this is the first report of such an association.

Clinical Implications

Screening for OSA has increasingly been recommended as part of routine preoperative evaluation,[32] efforts which were largely driven by the frequently observed adverse outcomes among patients with OSA. Consistent with the work of others, our findings demonstrate the adverse care outcomes associated with high risk of OSA. We find that such a population has increased costs of care, longer postoperative length of stay, adverse discharge, and higher rates of ICU admission and readmission. To our knowledge, we are the first to report on the outcome of adverse discharge. Furthermore, unlike much of the studies utilizing the NIS and NSQIP, we were able to control rigorously for intraoperative confounders in our regression models examining the impact of OSA risk on postoperative outcomes.

In contradiction to a few studies, [2,3] we found no significant association in in-hospital mortality among patients identified as high risk for OSA. One possible explanation for the difference in findings may lie in the populations studied. Nearly half of the NIS populations studied by Mokhlesi et al were composed of patients receiving care at non-academic practices. In contrast, our study population is derived solely from a large academic institution and its two close affiliates in Boston, Massachusetts. In addition to differences in institutional practice, variations in hospital volumes may also drive the observed differences in in-hospital mortality.

Pieper et al, along with many others, have extensively studied the volume-outcome relationship, concluding that high volume hospitals, compared with low volume counterparts, experience improved survival and complication rates.[33]

Our findings of increased adverse outcomes among patients identified as high risk of OSA have important implications for all members of the perioperative team. The SPOSA can be utilized as a key preoperative tool in identifying patients at risk for OSA, prompting further diagnostic evaluation prior to surgery as well as any planned treatment interventions including continuous positive airway therapy.[34]

REFERENCES

1 Weiser TG, Regenbogen SE, Thompson KD, *et al*. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008;**372**:139–44. doi:10.1016/S0140-6736(08)60878-8

2 Mokhlesi B, Hovda MD, Vekhter B, *et al*. Sleep-disordered breathing and postoperative outcomes after bariatric surgery: analysis of the nationwide inpatient sample. *OBES SURG* 2013;**23**:1842–51. doi:10.1007/s11695-013-0991-2

3 Mokhlesi B, Hovda MD, Vekhter B, *et al*. Sleep-Disordered Breathing and Postoperative Outcomes After Elective Surgery. *CHEST* 2013;**144**:903–14. doi:10.1378/chest.12-2905

4 Dimick JB, Weeks WB, Karia RJ, *et al*. Who pays for poor surgical quality? Building a business case for quality improvement. *ACS* 2006;**202**:933–7. doi:10.1016/j.jamcollsurg.2006.02.015

5 Hospital costs associated with surgical complications: A report from the private-sector National Surgical Quality Improvement Program. 2004;**199**:531–7. doi:10.1016/j.jamcollsurg.2004.05.276

6 Birkmeyer JD, Gust C, Dimick JB, *et al*. Hospital quality and the cost of inpatient surgery in the United States. *Annals of Surgery* 2012;**255**:1–5. doi:10.1097/SLA.0b013e3182402c17

7 Schilling PL, Dimick JB, Birkmeyer JD. Prioritizing Quality Improvement in General Surgery. *Journal of the American College of Surgeons* 2008;**207**:698–704. doi:10.1016/j.jamcollsurg.2008.06.138

8 Davenport DL, Henderson WG, Khuri SF, *et al*. Preoperative risk factors and surgical complexity are more predictive of costs than postoperative complications: a case study using the National Surgical Quality Improvement Program (NSQIP) database. *Annals of Surgery* 2005;**242**:463–8–discussion468–71. doi:10.1097/01.sla.0000183348.15117.ab

9 Aust JB, Henderson W, Khuri S, *et al*. The impact of operative complexity on patient risk factors. *Annals of Surgery* 2005;**241**:1024–7–discussion1027–8. doi:10.1097/01.sla.0000165196.32207.dd

10 Kaw R, Pasupuleti V, Walker E, *et al*. Postoperative complications in patients with obstructive sleep apnea. *CHEST* 2012;**141**:436–41. doi:10.1378/chest.11-0283

11 Memtsoudis SG, Stundner O, Rasul R, *et al*. The Impact of Sleep Apnea on Postoperative Utilization of Resources and Adverse Outcomes. *Anesth Analg* 2014;**118**:407–18. doi:10.1213/ANE.0000000000000051

12 Griffin JW, Novicoff WM, Browne JA, *et al*. Obstructive sleep apnea as a risk factor after shoulder arthroplasty. *J Shoulder Elbow Surg* 2013;**22**:e6–9. doi:10.1016/j.jse.2013.06.003

13 Weingarten TN, Flores AS, McKenzie JA, *et al*. Obstructive sleep apnoea and perioperative

complications in bariatric patients. *British Journal of Anaesthesia* 2011;**106**:131–9. doi:10.1093/bja/aeq290

14 Memtsoudis SG, Besculides MC, Mazumdar M. A rude awakening--the perioperative sleep apnea epidemic. *N Engl J Med* 2013;**368**:2352–3. doi:10.1056/NEJMp1302941

15 Peppard PE, Young T, Barnet JH, *et al*. Increased prevalence of sleep-disordered breathing in adults. *American Journal of Epidemiology* 2013;**177**:1006–14. doi:10.1093/aje/kws342

16 Finkel KJ, Searleman AC, Tymkew H, *et al*. Prevalence of undiagnosed obstructive sleep apnea among adult surgical patients in an academic medical center. *Sleep Medicine* 2009;**10**:753–8. doi:10.1016/j.sleep.2008.08.007

17 Flegal KM, Carroll MD, Kit BK, *et al*. Prevalence of Obesity and Trends in the Distribution of Body Mass Index Among US Adults, 1999-2010. *JAMA* 2012;**307**:491–7. doi:10.1001/jama.2012.39

18 Singh M, Liao P, Kobah S, *et al*. Proportion of surgical patients with undiagnosed obstructive sleep apnoea. *British Journal of Anaesthesia* 2013;**110**:629–36. doi:10.1093/bja/aes465

19 Sasaki N, Meyer MJ, Eikermann M. Postoperative respiratory muscle dysfunction: pathophysiology and preventive strategies. *Anesthesiology* 2013;**118**:961–78. doi:10.1097/ALN.0b013e318288834f

20 Liu X. Classification accuracy and cut point selection. *Stat Med* 2012;**31**:2676–86. doi:10.1002/sim.4509

21 Gaddam S, Gunukula SK, Mador MJ. Post-operative outcomes in adult obstructive sleep apnea patients undergoing non-upper airway surgery: a systematic review and meta-analysis. *Sleep Breath* 2014;**18**:615–33. doi:10.1007/s11325-013-0925-1

22 Kaw R, Chung F, Pasupuleti V, *et al*. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome. *British Journal of Anaesthesia* 2012;**109**:897–906. doi:10.1093/bja/aes308

23 Fletcher EC, Proctor M, Yu J, *et al*. Pulmonary edema develops after recurrent obstructive apneas. *Am J Respir Crit Care Med* 1999;**160**:1688–96. doi:10.1164/ajrccm.160.5.9810003

24 Krodel DJ, Bittner EA, Abdulnour R, *et al*. Case scenario: acute postoperative negative pressure pulmonary edema. *Anesthesiology* 2010;**113**:200–7. doi:10.1097/ALN.0b013e3181e32e68

25 Krodel DJ, Bittner EA, Abdulnour R-EE, *et al*. Negative pressure pulmonary edema following bronchospasm. *CHEST* 2011;**140**:1351–4. doi:10.1378/chest.11-0529

26 Krodel DJ, Bittner EA, Abdulnour R, *et al*. Case scenario: acute postoperative negative pressure pulmonary edema. *Anesthesiology* 2010;**113**:200–7.

doi:10.1097/ALN.0b013e3181e32e68

27 Redolfi S, Yumino D, Ruttanaumpawan P, *et al*. Relationship between overnight rostral fluid shift and Obstructive Sleep Apnea in nonobese men. *Am J Respir Crit Care Med* 2009;**179**:241–6. doi:10.1164/rccm.200807-1076OC

28 Bateman BT, Eikermann M. Obstructive sleep apnea predicts adverse perioperative outcome: evidence for an association between obstructive sleep apnea and delirium. *Anesthesiology* 2012;**116**:753–5. doi:10.1097/ALN.0b013e31824b96e1

29 Nguyen NT, Masoomi H, Laugenour K, *et al*. Predictive factors of mortality in bariatric surgery: data from the Nationwide Inpatient Sample. *Surgery* 2011;**150**:347–51. doi:10.1016/j.surg.2011.05.020

30 Kaw R, Pasupuleti V, Walker E, *et al*. Postoperative complications in patients with obstructive sleep apnea. *CHEST* 2012;**141**:436–41. doi:10.1378/chest.11-0283

31 Dorman RB, Miller CJ, Leslie DB, *et al*. Risk for hospital readmission following bariatric surgery. *PLoS ONE* 2012;**7**:e32506. doi:10.1371/journal.pone.0032506

32 American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. Anesthesiology. 2014;**120**:268–86. doi:10.1097/ALN.0000000000000053

33 Pieper D, Mathes T, Neugebauer E, *et al*. State of evidence on the relationship between high-volume hospitals and outcomes in surgery: a systematic review of systematic reviews. *Journal of the American College of Surgeons* 2013;**216**:1015–8. doi:10.1016/j.jamcollsurg.2012.12.049

34. Zaremba S, Shin CH, Hutter MM, Malviya S, Grabitz SD, MacDonald T, Diaz-Gil D, Ramachandran SK, Hess D, Malhotra A, Eikermann M. Continuous positive airway pressure mitigates opioid-induced worsening of sleep-disordered breathing early after bariatric surgery. Anesthesiology. 2016. Accepted.

FIGURES AND TABLES

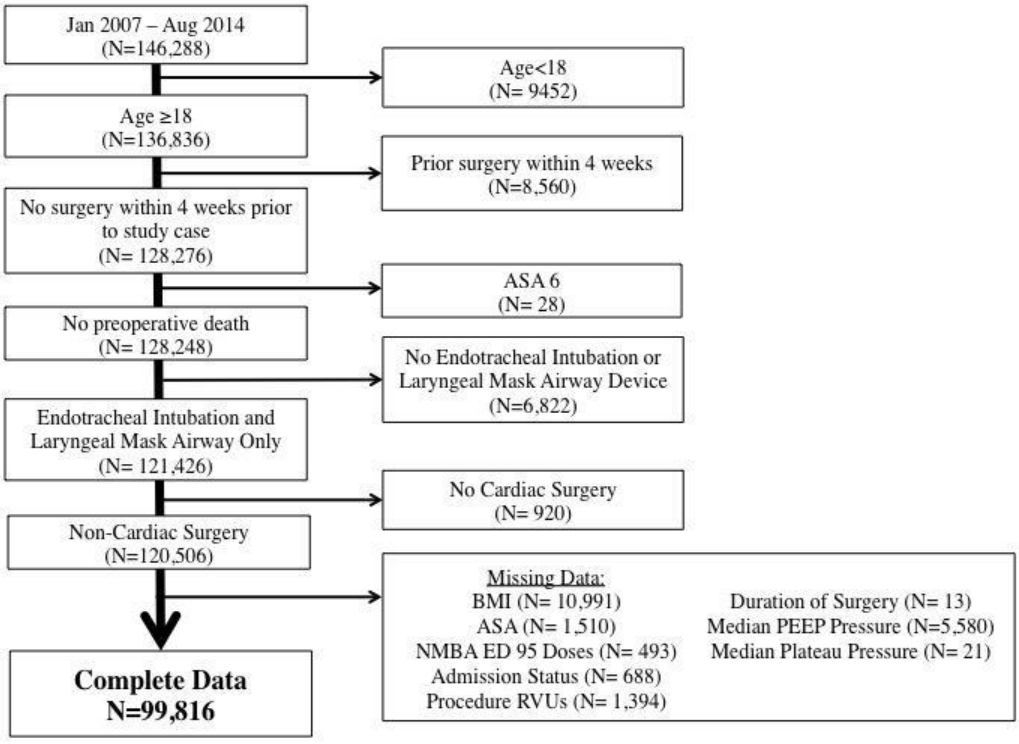

Figure 1. Study Flow

Table 1: Clinical Characteristics of Study Population by Incidence of Postoperative Respiratory Complications (PRC) within 7 days after surgery

Clinical Covariates used for Confounder Control		No PRC (n=94,150) N (%)	PRC (n=5,666) N (%)	Total Population (99,816) N (%)
Gender	Male	41,342 (43.9%)	2,783 (49.1%)	44,125 (44.2%)
	Female	53,099 (56.4%)	2,592 (45.7%)	55,691 (55.8%)
Age, years (categorized)	18 to <50	35,644 (37.9%)	882 (15.6%)	36,526 (36.6%)
	50 to <70	41,892 (44.5%)	2,502 (44.2%)	44,394 (44.5%)
	70 to <80	12,084 (12.8%)	1,274 (22.5%)	13,358 (13.4%)
	80+	4,821 (5.1%)	717 (12.7%)	5,538 (5.5%)
ASA Score	1	9,550 (10.1%)	67 (1.2%)	9,617 (9.6%)
	2	58,549 (62.2%)	1,682 (29.7%)	60,231 (60.3%)
	3	25,344 (26.9%)	3,235 (57.1%)	28,579 (28.6%)
	4	975 (1.0%)	389 (6.9%)	1,364 (1.4%)
	5	23 (0.0%)	2 (0.0%)	25 (0.0%)

Charlson Comorbidity Index, median (IQR)		1 (0-2)	3 (2-8)	1 (0-3)
BMI, kg/m2 (categorized)	<18	1,881 (2.0%)	203 (3.6%)	2,084 (2.1%)
	18 to <25	29,469 (31.3%)	1,662 (29.3%)	31,131 (31.2%)
	25 to <30	31,367 (33.3%)	1,670 (29.5%)	33,037 (33.1%)
	30 to <35	17,441 (18.5%)	1,006 (17.8%)	18,447 (18.5%)
	35+	14,283 (15.2%)	834 (14.7%)	15,117 (15.1%)
Emergency Status	Non-Emergent	90,793 (96.4%)	4,964 (87.6%)	95,757 (95.9%)
	Emergent	3,648 (3.9%)	411 (7.3%)	4,059 (4.1%)
Intraop Fluid Volume, mL (Quintiles)	0 to <750	20,002 (21.2%)	1,007 (17.8%)	21,009 (21.0%)
	750 to <1000	21,445 (22.8%)	835 (14.7%)	22,280 (22.3%)
	1000 to <1500	15,847 (16.8%)	754 (13.3%)	16,601 (16.6%)
	1500 to <2500	19,492 (20.7%)	1,075 (19.0%)	20,567 (20.6%)
	2500+	17,655 (18.8%)	1,704 (30.1%)	19,359 (19.4%)
NMBA ED95 Dose, mg (quintiles)	0 to <0.44	19,337 (20.5%)	638 (11.3%)	19,975 (20.0%)
	0.44 to <2.03	19,315 (20.5%)	669 (11.8%)	19,984 (20.0%)
	2.03 to <2.86	19,349 (20.6%)	940 (16.6%)	20,289 (20.3%)
	2.86 to <4.17	18,434 (19.6%)	1,191 (21.0%)	19,625 (19.7%)
	4.17+	18,006 (19.1%)	1,937 (34.2%)	19,943 (20.0%)
Age-Adjusted MAC (Quintiles)	0 to <0.66	18,514 (19.7%)	1,450 (25.6%)	19,964 (20.0%)
	0.66 to <0.82	18,713 (19.9%)	1,250 (22.1%)	19,963 (20.0%)
	0.82 to <0.94	18,884 (20.1%)	1,079 (19.0%)	19,963 (20.0%)
	0.94 to <1.07	19,101 (20.3%)	862 (15.2%)	19,963 (20.0%)
	1.07+	19,229 (20.4%)	734 (13.0%)	19,963 (20.0%)
Admission Type	Inpatient	23,438 (24.9%)	120 (2.1%)	23,558 (23.6%)
	Same Day Admit	55,030 (58.4%)	3,339 (58.9%)	58,369 (58.5%)
	Ambulatory	15,973 (17.0%)	1,916 (33.8%)	17,889 (17.9%)
Duration of Hypotension, min (categorized)	0 to 10	91,962 (97.7%)	4,882 (86.2%)	96,844 (97.0%)
	11 to 20	1,494 (1.6%)	313 (5.5%)	1,807 (1.8%)
	21+	985 (1.0%)	180 (3.2%)	1,165 (1.2%)
Morphine Equivalent Dose, mg (Categorized)	0 to <3	37,713 (40.1%)	2,769 (48.9%)	40,482 (40.6%)
	3 to <6	15,264 (16.2%)	650 (11.5%)	15,914 (15.9%)
	6 to <10	19,148 (20.3%)	774 (13.7%)	19,922 (20.0%)
	10+	22,316 (23.7%)	1,182 (20.9%)	23,498 (23.5%)
Units of Blood Transfusion (Categorized)	0 to <1	91,741 (97.4%)	4,716 (83.2%)	96,457 (96.6%)
	1 to <3	2,197 (2.3%)	498 (8.8%)	2,695 (2.7%)
	3+	503 (0.5%)	161 (2.8%)	664 (0.7%)
Duration of Surgery, hr (categorized)	0 to <1	8,160 (8.7%)	203 (3.6%)	8,363 (8.4%)
	1 to <2	27,192 (28.9%)	991 (17.5%)	28,183 (28.2%)
	2 to <3	22,613 (24.0%)	1,119 (19.7%)	23,732 (23.8%)
	3 to <4	15,565 (16.5%)	918 (16.2%)	16,483 (16.5%)

	4+	20,911 (22.2%)	2,144 (37.8%)	23,055 (23.1%)
Vasopressor Infusion Rate (mg/hr) (categorized)	0	38,032 (40.4%)	674 (11.9%)	38,706 (38.8%)
	0 to <0.01	14,715 (15.6%)	573 (10.1%)	15,288 (15.3%)
	0.01 to <0.05	14,249 (15.1%)	1,018 (18.0%)	15,267 (15.3%)
	0.05 to <0.12	14,206 (15.1%)	1,072 (18.9%)	15,278 (15.3%)
	0.12 +	13,239 (14.1%)	2,038 (36.0%)	15,277 (15.3%)
Neostigmine use	No	37,611 (39.9%)	1,501 (26.5%)	39,112 (39.2%)
	Yes	56,830 (60.4%)	3,874 (68.4%)	60,704 (60.8%)
Procedure Relative Value units, mean (SD)		16.5 (10.5)	21.4 (13.6)	16.8 (10.7)
Median Plateau Pressure, mean (SD)		19.1 (4.9)	20.2 (4.9)	19.2 (4.9)
Median PEEP Pressure, mean (SD)		4.1 (2.2)	4 (2.2)	4.1 (2.2)

Table 2. Frequency and Odds Ratios (OR) of Postoperative Respiratory Complications in patients with low vs. moderate vs. high OSA risk

OSA Risk	**Frequency of PRC (%)**	**Unadjusted OR (95% CI), p-value**	**Adjusted OR (95% CI), p-value**
Three Tier Classification			
Low (SPOSA 0 to 4; n=39,204)	1,419 (3.6%)	1	1
Moderate (SPOSA 5 to 7; n=31,525)	1,732 (5.5%)	1.55 (1.44-1.66), p<0.001	1.32 (1.21-1.45), p<0.001
High (SPOSA 8+; n=29,087)	2,224 (7.7%)	2.20 (2.06-2.36), p<0.001	1.74 (1.55-1.95), p<0.001
Dichotomized Classification			
Low (SPOSA 1 to 7; n=70,729)	3,151 (4.5%)	1	1
High (SPOSA 8+; n=29,087)	2,224 (7.7%)	1.78 (1.68-1.88), p<0.001	1.38 (1.26-1.51), p<0.001

Table 3. Characteristics of Propensity Score Matched Cohorts

Procedure Specific Variables		**Low OSA Risk SPOSA ≤ 7 N=28,961 N (%)**	**High OSA Risk SPOSA > 7 N=28,961 N (%)**	**Total N=57,922 N (%)**
Duration of Surgery (categorized)	0 to <1 hr	2,277 (7.9%)	2,296 (7.9%)	4,573 (7.9%)
	1 to <2 hrs	7,467 (25.8%)	7,423 (25.6%)	14,890 (25.7%)
	2 to <3 hrs	7,038 (24.3%)	6,826 (23.6%)	13,864 (23.9%)
	3 to <4 hrs	5,169 (17.8%)	5,311 (18.3%)	10,480 (18.1%)
	4+ hrs	7,010 (24.2%)	7,105 (24.5%)	14,115 (24.4%)
Units of Blood Transfusion	0 to <1	27967 (96.6%)	27967 (96.6%)	55934 (96.6%)
	1 to <3	796 (2.7%)	801 (2.8%)	1597 (2.8%)

(Categorized)	3+	198 (0.7%)	193 (0.7%)	391 (0.7%)
Procedure Relative Value Units, mean (SD)		16.8 10.4	17.3 10.7	17 10.5
Surgical Service	Anesthesiology	51 (0.2%)	50 (0.2%)	101 (0.2%)
	Bronchoscopy	413 (1.4%)	390 (1.3%)	803 (1.4%)
	Burn	266 (0.9%)	215 (0.7%)	481 (0.8%)
	Endoscopy	1,257 (4.3%)	1244 (4.3%)	2501 (4.3%)
	General	6,939 (24.0%)	8268 (28.5%)	15207 (26.3%)
	Gynecology	1,970 (6.8%)	1938 (6.7%)	3908 (6.7%)
	Neurosurgery	2,216 (7.7%)	2088 (7.2%)	4304 (7.4%)
	Oral/Maxillofacial	545 (1.9%)	313 (1.1%)	858 (1.5%)
	Orthopedic	6,175 (21.3%)	5760 (19.9%)	11935 (20.6%)
	Plastic	1,428 (4.9%)	1102 (3.8%)	2530 (4.4%)
	Radiology	243 (0.8%)	280 (1.0%)	523 (0.9%)
	Thoracic	1,421 (4.9%)	1387 (4.8%)	2808 (4.8%)
	Transplant	304 (1.0%)	310 (1.1%)	614 (1.1%)
	Urology	2,600 (9.0%)	2592 (8.9%)	5192 (9.0%)
	Vascular	2,205 (7.6%)	2053 (7.1%)	4258 (7.4%)
	Wound	927 (3.2%)	969 (3.3%)	1896 (3.3%)

Table 4. Frequency and Odds Ratios of Secondary and Exploratory Postoperative Outcomes in Propensity Score-matched Patients with high OSA risk (SPOSA >7) and with low OSA risk (SPOSA ≤7) according to the Score for Preoperative Prediction of Obstructive Sleep Apnea

Outcome		**High OSA Risk (SPOSA >7) (n=28,961) N (%)**	**Low OSA Risk (SPOSA ≤7) (n=28,961) N (%)**	**Odds Ratio (95% CI)**
Secondary Endpoints	Postoperative Length of Stay, days (mean ± SD)	4.2±5.1	4.1±5.0	1.06 (1.03-1.09), p<0.001
	In-hospital mortality	105 (0.4%)	102 (0.4%)	1.03 (0.78-1.35), p=0.831
Exploratory Endpoints	Postoperative Acute Kidney Injury	1,608 (5.6%)	873 (3.0%)	1.89 (1.74-2.06), p<0.001
	ICU Admission	1,138 (3.9%)	907 (3.1%)	1.27 (1.16-1.38), p<0.001
	Adverse Discharge	2,235 (7.7%)	1,956 (6.8%)	1.16 (1.08-1.23), p<0.001
	Readmission within 30d	2,540 (8.8%)	2,060 (7.1%)	1.26 (1.18-1.34), p<0.001
	Total Cost of Care			1.06 (1.03-1.09), p<0.001