

ORIGINAL RESEARCH

Obstructive Sleep Apnea and Adverse Outcomes in Surgical and Nonsurgical Patients on the Wards

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BACKGROUND: Obstructive sleep apnea (OSA) has been associated with clinical deterioration in postoperative patients and patients hospitalized with pneumonia. Paradoxically, OSA has also been associated with decreased risk of inpatient mortality in these same populations.

OBJECTIVES: To investigate the association between OSA and in-hospital mortality in a large cohort of surgical and nonsurgical ward patients.

DESIGN: Observational cohort study.

SETTING: A 500-bed academic tertiary care hospital in the United States.

PATIENTS: A total of 93,676 ward admissions from 53,150 unique adult patients between November 1, 2008 and October 1, 2013.

INTERVENTION: None.

MEASUREMENTS: OSA diagnoses and comorbidities were identified by International Classification of Diseases, Ninth Revision, Clinical Modification codes. Logistic regression was used to control for patient characteristics, location prior

to ward admission, and admission severity of illness. The primary outcome was in-hospital death. Secondary outcomes included rapid response team (RRT) activation, intensive care unit (ICU) transfer, intubation, and cardiac arrest on the wards.

MAIN RESULTS: OSA was identified in 5,625 (10.6%) patients. Patients with OSA were more likely to be older, male, and obese, and had higher rates of comorbidities. OSA patients had more frequent RRT activations (1.5% vs 1.1%) and ICU transfers (8% vs 7%) than controls ($P < 0.001$ for both comparisons), but a lower inpatient mortality rate (1.1% vs 1.4%, $P < 0.05$). OSA was associated with decreased adjusted odds for ICU transfer (odds ratio [OR]: 0.91 [0.84-0.99]), cardiac arrest (OR: 0.72 [0.55-0.95]), and in-hospital mortality (OR: 0.70 [0.58-0.85]).

CONCLUSIONS: After adjustment for important confounders, OSA was not associated with clinical deterioration on the wards and was associated with significantly decreased in-hospital mortality. *Journal of Hospital Medicine* 2015;10:592-598. © 2015 Society of Hospital Medicine

Obstructive sleep apnea (OSA) is an increasingly prevalent condition characterized by intermittent airway obstruction during sleep, which leads to hypoxemia, hypercapnia, and fragmented sleep. The current prevalence estimates of moderate to severe OSA (apnea-hypopnea index ≥ 15 , measured as events/hour) in middle-aged adults are approximately 13% in men and 6% in women.¹ OSA is a well-described independent risk factor for long-term neurocognitive, cardiovascular, and cerebrovascular morbidity and mortality.²⁻⁶

Recent studies have also identified OSA as an independent risk factor for adverse perioperative out-

comes, including endotracheal intubation, intensive care unit (ICU) transfer, and increased length of stay.⁷⁻¹¹ Paradoxically, despite an increase in the risk of complications, several of these studies did not find an association between in-hospital death and OSA even after controlling for potential confounders.⁹⁻¹¹ Furthermore, a recent study of patients hospitalized for pneumonia reported increased rates of clinical deterioration and mechanical ventilation, but also lower odds of inpatient mortality in patients with OSA.¹²

These studies may have been limited by the absence of physiologic data, which prevented controlling for severity of illness. It is also unclear whether these previously described associations between OSA and adverse clinical outcomes hold true for general hospital inpatients. OSA may be worsened by medications frequently used in hospitals, such as narcotics and benzodiazepines. Opiate use contributes to both central and obstructive sleep apneas,^{13,14} and benzodiazepines are known to produce airway smooth muscle relaxation and can cause respiratory depression.¹⁵ In fact, the use of benzodiazepines has been implicated in the unmasking of OSA in patients with previously

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undiagnosed sleep-disordered breathing.¹⁶ These findings suggest mechanisms by which OSA could contribute to an increased risk in hospital ward patients for rapid response team (RRT) activation, ICU transfer, cardiac arrest, and in-hospital death.

The aim of this study was to determine the independent association between OSA and in-hospital mortality in ward patients. We also aimed to investigate the association of OSA with clinical deterioration on the wards, while controlling for patient characteristics, initial physiology, and severity of illness.

MATERIALS AND METHODS

Setting and Study Population

This observational cohort study was performed at an academic tertiary care medical center with approximately 500 beds. Data were obtained from all adult patients hospitalized on the wards between November 1, 2008 and October 1, 2013. Our hospital has utilized an RRT, led by a critical care nurse and respiratory therapist with hospitalist and pharmacist consultation available upon request, since 2008. This team is separate from the team that responds to a cardiac arrest. Criteria for RRT activation include “tachypnea,” “tachycardia,” “hypotension,” and “staff worry,” but specific vital sign thresholds are not specified.

The study analyzed deidentified data from the hospital’s Clinical Research Data Warehouse, which is maintained by the Center for Research Informatics at The University of Chicago. The study protocol was approved by the University of Chicago Institutional Review Board (IRB #16995A).

Data Collection

Patient age, sex, race, body mass index (BMI), and location prior to ward admission (ie, whether they were admitted from the emergency department, transferred from the ICU, or directly admitted from clinic or home) were collected. Patients who underwent surgery during their admission were identified using the hospital’s admission-transfer-discharge database. In addition, routinely collected vital signs (eg, respiratory rate, blood pressure, heart rate) were obtained from the electronic health record (Epic, Verona, WI). To determine severity of illness, the first set of vital signs measured on hospital presentation were utilized to calculate the cardiac arrest risk triage (CART) score, a vital-sign–based early warning score we previously developed and validated for predicting adverse events in our population.¹⁷ The CART score ranges from 0 to 57, with points assigned for abnormalities in respiratory rate, heart rate, diastolic blood pressure, and age. If any vital sign was missing, the next available measurement was pulled into the set. If any vital sign remained missing after this change, the median value for that particular location (ie, wards, ICU, or emergency department) was imputed as previously described.^{18,19}

TABLE 1. Diagnosis Codes and Prevalence of Obstructive Sleep Apnea

Diagnosis Code	Description	% of Sleep Apnea Diagnoses*
327.23	Obstructive sleep apnea	65.6
780.57	Unspecified sleep apnea	19.4
780.53	Hypersomnia with sleep apnea, unspecified	11.7
780.51	Insomnia with sleep apnea, unspecified	1.5
327.2	Organic sleep apnea, unspecified	0.2
278.03	Obesity hypoventilation syndrome	1.7

*Percentages add to >100% as a small number of patients carried more than 1 sleep apnea diagnosis.

Patients with OSA were identified by the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes using inpatient and outpatient medical records: 278.03, 327.20, 327.23, 327.29, 780.51, 780.53, and 780.57 (Table 1). Data on other patient comorbidities, including coronary artery disease, congestive heart failure, arrhythmias, uncomplicated and complicated diabetes mellitus, hypertension, and cerebrovascular disease were collected using specific ICD-9-CM codes from both inpatient and outpatient records. Information on insurance payer was also collected from the hospital’s billing database. Insurance payers were grouped into the following categories: private payer, Medicare/Medicaid, and no insurance. Patients with both public and private payers were counted as being privately insured.

Outcomes

The primary outcome of the study was in-hospital mortality. Secondary outcomes included length of stay, RRT activation, transfer to the ICU, endotracheal intubation, cardiac arrest (defined as a loss of pulse with attempted resuscitation) on the wards, and a composite outcome of RRT activation, ICU transfer, and death. Because cardiac arrests on the wards result either in death or ICU transfer following successful resuscitation, this variable was omitted from the composite outcome. Cardiac arrests were identified using a prospectively validated quality improvement database that has been described previously.²⁰ ICU transfer was identified using the hospital’s admission-transfer-discharge database. Only the index cardiac arrest, intubation, RRT, or ICU transfer for each admission was used in the study, but more than 1 type of outcome could occur for each patient (eg, a patient who died following an unsuccessful resuscitation attempt would count as both a cardiac arrest and a death).

Statistical Analysis

Patient characteristics were compared using Student *t* tests, Wilcoxon rank sum tests, and χ^2 statistics, as appropriate. Unadjusted logistic regression models

were fit to estimate the change in odds of each adverse event and a composite outcome of any event for patient admissions with OSA compared to those without OSA. Adjusted logistic regression models were then fit for each outcome to control for patient characteristics (age, sex, BMI, insurance status, and individual comorbidities), location immediately prior to ward admission, and admission severity of illness (as measured by CART score). In the adjusted model, CART score, age, and number of comorbidities were entered linearly, with the addition of squared terms for age and CART score, as these variables showed nonlinear associations with the outcomes of interest. Race, surgical status, insurance payer, location prior to ward, and BMI (underweight, <18.5 kg/m²; normal weight, 18.5–24.9 kg/m²; overweight, 25.0–29.9 kg/m²; obese, 30–39.9 kg/m²; and severely obese, ≥40 kg/m²) were modeled as categorical variables.

Given that an individual patient could experience multiple hospitalizations during the study period, we performed a sensitivity analysis of all adjusted and unadjusted models using a single randomly selected hospitalization for each unique patient. In addition, we performed a sensitivity analysis of all patients who were not admitted to the ICU prior to their ward stay. Finally, we performed subgroup analyses of all unadjusted and adjusted models for each BMI category and surgical status.

All tests of significance used a 2-sided *P* value <0.05. Statistical analyses were completed using Stata version 12.0 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

During the study period, 93,676 patient admissions from 53,150 unique patients resulted in the occurrence of 1,069 RRT activations, 6,305 ICU transfers, and 1,239 in-hospital deaths. Within our sample, 40,034 patients had at least 1 inpatient record and at least 1 outpatient record. OSA diagnosis was present in 5,625 patients (10.6% of the total sample), with 4,748 patients having an OSA diagnosis code entered during a hospitalization, 2,143 with an OSA diagnosis code entered during an outpatient encounter, and 877 with both inpatient and outpatient diagnosis codes. These patients identified as having OSA contributed 12,745 (13.6%) hospital admissions.

Patients with an OSA diagnosis were more likely to be older (median age 59 years [interquartile range 49–68] vs 55 years [38–68]), male (49% vs 42%), overweight or obese (88% vs 62%), and more likely to carry diagnoses of diabetes (53.8% vs 25.5%), hypertension (45.3% vs 18.2%), arrhythmias (44.4% vs 26.7%), coronary artery disease (46.8% vs 23.5%), heart failure (35.8% vs 13.5%), and cerebrovascular disease (13.5% vs 8.1%) than patients without an OSA diagnosis (all comparisons significant, *P* < 0.001) (Table 2).

TABLE 2. Patient Characteristics for Admissions With and Without OSA Diagnosis

Characteristic	Patient Admissions With OSA Diagnoses, n = 12,745	Patient Admissions Without OSA Diagnoses, n = 80,931	<i>P</i> Value
Age, y, median (IQR)	59 (49–68)	55 (38–68)	<0.001
Female, n (%)	6,514 (51%)	47,202 (58%)	<0.001
Race, n (%)			<0.001
White	4,205 (33%)	30,119 (37%)	
Black/African American	7,024 (55%)	38,561 (48%)	
Asian	561 (4.4%)	3,419 (4.2%)	
American Indian or Native Alaskan	20 (0.2%)	113 (0.1%)	
More than 1 race	127 (1%)	843 (1%)	
Race unknown	808 (6%)	7,876 (10%)	
Insurance status, n (%)			<0.001
Private	4,484 (35%)	32,467 (40%)	
Medicare/Medicaid	8,201 (64%)	42,208 (58%)	
Uninsured	53 (0.4%)	1,190 (1%)	
Unknown	4 (<0.1%)	16 (<0.1%)	
Location prior to wards, n (%)			<0.001
ICU	1,400 (11%)	8,065 (10%)	
Emergency department	4,633 (36%)	25,170 (31%)	
Ambulatory admission	6,712 (53%)	47,696 (59%)	
Body mass index, kg/m ² , n (%)			<0.001
Normal (18.5–25)	1,431 (11%)	26,560 (33%)	
Underweight (<18.5)	122 (1%)	4,256 (5%)	
Overweight (25–30)	2,484 (20%)	23,761 (29%)	
Obese (30–40)	4,959 (39%)	19,132 (24%)	
Severely obese (40)	3,745 (29%)	7,171 (9%)	
Initial cardiac arrest risk triage score, median (IQR)	4 (0–9)	4 (0–9)	<0.001
Underwent surgery, n (%)	4,482 (35%)	28,843 (36%)	0.3
Comorbidities			
Number of comorbidities, median (IQR)	2 (1–4)	1 (0–2)	<0.001
Arrhythmia	5,659 (44%)	21,581 (27%)	<0.001
Diabetes mellitus	6,855 (54%)	20,641 (26%)	<0.001
Hypertension	5,777 (45%)	14,728 (18%)	<0.001
Coronary artery disease	5,958 (47%)	18,979 (23%)	<0.001
Cerebrovascular accident	1,725 (14%)	6,556 (8%)	<0.001
Congestive heart failure	4,559 (36%)	10,919 (13%)	<0.001

NOTE: Abbreviations: ICU, intensive care unit; IQR, interquartile range; OSA, obstructive sleep apnea.

Complications and Adverse Outcomes

In the unadjusted analyses, the overall incidence of adverse outcomes was higher among patient admissions with a diagnosis of OSA compared to those without OSA (Table 3). Those with OSA were more likely to experience RRT activation (1.5% vs 1.1%), ICU transfer (8% vs 7%), and endotracheal intubation (3.9% vs 2.9%) than those without OSA diagnoses (*P* < 0.001 for all comparisons). There was no significant difference in the incidence of cardiac arrest between the 2 groups, nor was there a significant difference in length of stay. Unadjusted inpatient mortality for OSA patient admissions was lower than that for non-OSA hospitalizations (1.1% vs 1.4%, *P* < 0.05). A diagnosis of OSA was associated with increased unadjusted odds for RRT activation (odds ratio [OR]: 1.36 [1.16–1.59]) and ICU transfer (OR: 1.28 [1.20–1.38]). However, after controlling for

TABLE 3. Unadjusted Outcomes for Patient Admissions With and Without OSA Diagnosis

Characteristic	Patient Admissions With OSA Diagnoses, n = 12,745	Patient Admissions Without OSA Diagnoses, n = 80,931	P Value
Outcomes, n (%)			
Composite outcome*	1,137 (9%)	5,792 (7%)	<0.001
In-hospital death	144 (1.1%)	1,095 (1.4%)	0.04
Rapid response team call	188 (1.5%)	881 (1.1%)	<0.001
ICU transfer	1,045 (8%)	5,260 (7%)	<0.001
Cardiac arrest	413 (0.5%)	73 (0.6%)	0.36

NOTE: Abbreviations: ICU, intensive care unit; OSA, obstructive sleep apnea.

*Experiencing rapid response team call, ICU transfer, or in-hospital death.

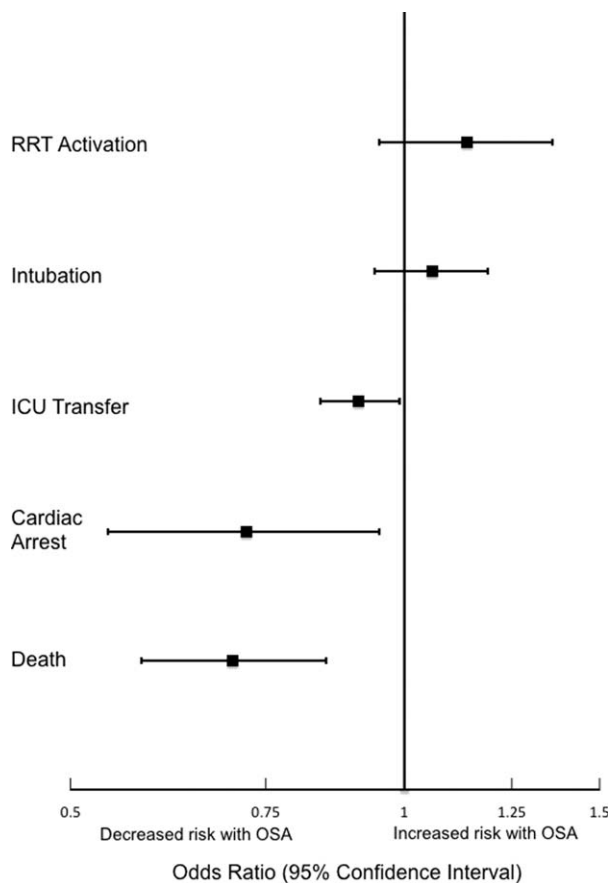


FIG. 1. Adjusted models for the association of OSA with clinical deterioration outcomes. Odds of RRT activation, intubation, ICU transfer, cardiac arrest, and in-hospital death for patient admissions with OSA diagnosis as compared to patient admissions without OSA diagnosis. Abbreviations: ICU, intensive care unit; OSA, obstructive sleep apnea; RRT, rapid response team.

confounders, OSA was not associated with increased odds for RRT activation (OR: 1.14 [0.95-1.36]) or intubation (OR: 1.06 [0.94-1.19]), and was associated with slightly decreased odds for ICU transfer (OR: 0.91 [0.84-0.99]) (Figure 1). Those with OSA had decreased adjusted odds of cardiac arrest (OR: 0.72 [0.55-0.95]) compared to those without OSA.

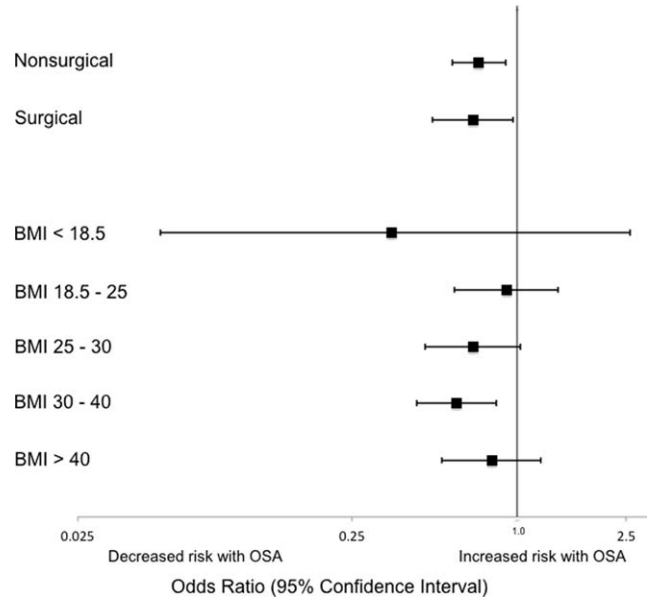


FIG. 2. Adjusted models for the association of OSA with death, by surgical status and BMI. Odds of in-hospital death for patient admissions with OSA diagnosis as compared to patient admissions without OSA diagnosis, stratified by surgical status and BMI. Abbreviations: BMI, body mass index; OSA, obstructive sleep apnea.

OSA was also associated with decreased odds of in-hospital mortality before (OR: 0.83 [0.70-0.99]) and after (OR: 0.70 [0.58-0.85]) controlling for confounders.

Sensitivity Analyses

The sensitivity analysis involving 1 randomly selected hospitalization per patient included a total of 53,150 patients. The results were similar to the main analysis, with adjusted odds of 1.01 (0.77-1.32) for RRT activation, 0.86 (0.76-0.96) for ICU transfer, and 0.69 (0.53-0.89) for inpatient mortality. An additional sensitivity analysis included only patients who were not admitted to the ICU prior to their ward stay. This analysis included 84,211 hospitalizations and demonstrated similar findings, with adjusted odds of 0.70 for in-hospital mortality (0.57-0.87). Adjusted odds for RRT activation (OR: 1.12 [0.92-1.37]) and ICU transfer (OR: 0.88 [0.81-0.96]) were also similar to the results of our main analysis.

Subgroup Analyses

Surgical and Nonsurgical Patients

Subgroup analyses of surgical versus nonsurgical patients (Figure 2) revealed similarly decreased adjusted odds of in-hospital death for OSA patients in both groups (surgical OR: 0.69 [0.49-0.97]; nonsurgical OR: 0.72 [0.58-0.91]). Surgical patients with OSA diagnoses had decreased adjusted odds for ICU transfer (surgical OR: 0.82 [0.73-0.92]), but this finding was not seen in nonsurgical patients (OR: 1.03 [0.92-1.15]).

Patients Stratified by BMI

Examination across BMI categories (Figure 2) showed a significant decrease in adjusted odds of death for OSA patients with BMI 30 to 40 kg/m² (OR: 0.60 [0.43-0.84]). A nonsignificant decrease in adjusted odds of death was seen for OSA patients in all other groups. Adjusted odds ratios for the risk of RRT activation and ICU transfer in OSA patients within the different BMI categories were not statistically significant.

DISCUSSION

In this large observational single-center cohort study, we found that OSA was associated with increased odds of adverse events, such as ICU transfers and RRT calls, but this risk was no longer present after adjusting for demographics, comorbidities, and presenting vital signs. Interestingly, we also found that patients with OSA had decreased adjusted odds for cardiac arrest and mortality. This mortality finding was robust to multiple sensitivity analyses and subgroup analyses. These results have significant implications for our understanding of the short-term risks of sleep-disordered breathing in hospitalized patients, and suggest the possibility that OSA is associated with a protective effect with regard to inpatient mortality.

Our findings are in line with other recent work in this area. In 2 large observational cohorts of surgical populations drawn from the nationally representative Nationwide Inpatient Sample administrative database, our group reported decreased odds of in-hospital postoperative mortality in OSA patients.^{10,11} Using the same Nationwide Inpatient Sample, Lindenauer et al. showed that among inpatients hospitalized with pneumonia, OSA diagnosis was associated with increased rates of clinical deterioration but lower rates of inpatient mortality.¹² Although these 3 studies have identified decreased inpatient mortality among certain surgical populations and patients hospitalized with pneumonia, they are limited by using administrative databases that do not provide specific data on vital signs, presenting physiology, BMI, or race. Another important limitation of the Nationwide Inpatient Sample is the lack of any information on RRT activations and ICU transfers. Moreover, the database does not include information on outpatient diagnoses, which may have led to a significantly lower prevalence of OSA than expected in these studies. Despite the important methodological differences, our study corroborates this finding among a diverse cohort of hospitalized patients. Unlike these previous studies of postoperative patients or those hospitalized with pneumonia, we did not find an increased risk of adverse events associated with OSA after controlling for potential confounders.

The decreased mortality seen in OSA patients could be explained by these patients receiving more vigilant care, showing earlier signs of deterioration, or display-

ing more easily treatable forms of distress than patients without OSA. For example, earlier identification of deterioration could lead to earlier interventions, which could decrease inpatient mortality. In 2 studies of postsurgical patients,^{10,11} those with OSA diagnosis who developed respiratory failure were intubated earlier and received mechanical ventilation for a shorter period of time, suggesting that the cause of respiratory failure was rapidly reversible (eg, upper airway complications due to oversedation or excessive analgesia). However, we did not find increased adjusted odds of RRT activation or ICU transfer for OSA patients in our study, and so it is less likely that earlier recognition of decompensation occurred in our sample. In addition, our hospital did not have standardized practices for monitoring or managing OSA patients during the study period, which makes systematic early recognition of clinical deterioration among the OSA population in our study less likely.

Alternatively, there may be a true physiologic phenomenon providing a short-term mortality benefit in those with OSA. It has been observed that patients with obesity (but without severe obesity) often have better outcomes after acute illness, whether by earlier or more frequent contact with medical care or heightened levels of metabolic reserve.^{21,22} However, our findings of decreased mortality for OSA patients remained even after controlling for BMI. An additional important possibility to consider is ischemic preconditioning, a well-described phenomenon in which episodes of sublethal ischemia confer protection on tissues from subsequent ischemia/reperfusion damage.²³ Ischemic preconditioning has been demonstrated in models of cardiac and neural tissue²⁴⁻²⁶ and has been shown to enhance stem cell survival by providing resistance to necrosis and lending functional benefits to heart, brain, and kidney models after transplantation.²⁵⁻³¹ The fundamentals of this concept may have applications in transplant and cardiac surgery,^{32,33} in the management of acute coronary syndromes and stroke,^{32,34,35} and in athletic training and performance.^{35,36} Although OSA has been associated with long-term cardiovascular morbidity and mortality,²⁻⁶ the intermittent hypoxemia OSA patients experience could actually improve their ability to survive clinical deterioration in the short-term (ie, during a hospitalization).

Limitations of our study include its conduction at a single center, which may prevent generalization to populations different than ours. Furthermore, during the study period, our hospital did not have formal guidelines or standardized management or monitoring practices for patients with OSA. Additionally, practices for managing OSA may vary across institutions. Therefore, our results may not be generalizable to hospitals with such protocols in place. However, as mentioned above, similar findings have been noted in studies using large, nationally representative administrative databases. In

addition, we identified OSA via ICD-9-CM codes, which are likely insensitive for estimating the true prevalence of OSA in our sample. Despite this, our reported OSA prevalence of over 10% falls within the prevalence range reported in large epidemiological studies.^{37–39} Finally, we did not have data on polysomnograms or treatment received for patients with OSA, so we do not know the severity of OSA or adequacy of treatment for these patients.

Notwithstanding our limitations, our study has several strengths. First, we included a large number of hospitalized patients across a diverse range of medical and surgical ward admissions, which increases the generalizability of our results. We also addressed potential confounders by including a large number of comorbidities and controlling for severity of presenting physiology with the CART score. The CART score, which contains physiologic variables such as respiratory rate, heart rate, and diastolic blood pressure, is an accurate predictor of cardiac arrest, ICU transfer, and in-hospital mortality in our population.⁴⁰ Finally, we were able to obtain information about these diagnoses from outpatient as well as inpatient data.

In conclusion, we found that after adjustment for important confounders, OSA was associated with a decrease in hospital mortality and cardiac arrest but not with other adverse events on the wards. These results may suggest a protective benefit from OSA with regard to mortality, an advantage that could be explained by ischemic preconditioning or a higher level of care or vigilance not reflected by the number of RRT activations or ICU transfers experienced by these patients. Further research is needed to confirm these findings across other populations, to investigate the physiologic pathways by which OSA may produce these effects, and to examine the mechanisms by which treatment of OSA could influence these outcomes.

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