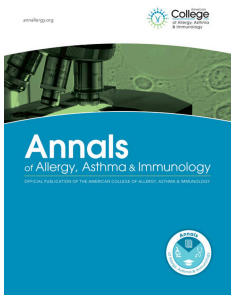

Association of obstructive sleep apnea with severity of patients hospitalized for acute asthma

Shojiro Oka, MD, Tadahiro Goto, MD, MPH, Atsushi Hirayama, MD, MPH, Mohammad Kamal Faridi, MPH, Carlos A. Camargo, Jr., MD, DrPH, Kohei Hasegawa, MD, MPH

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Association of obstructive sleep apnea with severity of patients hospitalized for acute asthma

Shojiro Oka, MD[1]; Tadahiro Goto, MD, MPH[2,3,4]; Atsushi Hirayama, MD, MPH[2,5]; Mohammad Kamal Faridi[2], MPH; Carlos A. Camargo, Jr., MD, DrPH[2]; and Kohei Hasegawa, MD, MPH[2]

Affiliations:

1. Department of Emergency Medicine, Okinawa Prefectural Chubu Hospital, Okinawa, Japan
2. Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA, USA
3. Graduate School of Medical Sciences, University of Fukui, Fukui, Japan
4. Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan
5. Department of Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan

Email addresses:

Shojiro Oka: oka_shojiro@hosp.pref.okinawa.jp

Tadahiro Goto: tag695@mail.harvard.edu

Atsushi Hirayama: ath877@mail.harvard.edu

Mohammad Kamal Faridi: mkfaridi1@mgh.harvard.edu

Carlos A. Camargo, Jr.: CCAMARGO@PARTNERS.ORG

Kohei Hasegawa: KHASEGAWA1@PARTNERS.ORG

Corresponding Author: Dr. Tadahiro Goto, Graduate School of Medical Sciences, University of Fukui, Matsuoka-shimoaizuki, Eiheiji, Yoshida, Fukui, 910-1193, Japan; and Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA, 02114-1101, USA. Email: tag695@mail.harvard.edu

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Abbreviations:

CI, confidence interval

HCUP, Healthcare Cost and Utilization Project

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification

LOS, length-of-stay

OR, odds ratio

OSA, Obstructive sleep apnea

SID, State Inpatient Databases

Key words: Obstructive sleep apnea; acute asthma; hospitalization; severity; positive pressure ventilation; length-of-stay

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Background: Studies suggest that obstructive sleep apnea (OSA) is associated with suboptimal disease control and worse chronic severity of asthma. However, little is known about the relations of OSA with acute asthma severity in hospitalized patients.

Objective: To investigate the association of OSA with acute asthma severity. Methods: This is a retrospective cohort study using State Inpatient Databases from eight geographically-diverse US states, 2010-2013. The outcomes were markers of acute severity—mechanical ventilation use, hospital length-of-stay (LOS), and inhospital mortality. To determine the association of interest, we fit multivariable logistic regression models adjusting for age, sex, race/ethnicity, primary insurance, household income, patient residence, comorbidities, hospital state, and hospitalization year. We repeated the analysis for children aged 6-17 years.

Results: Among 73,408 adult patients hospitalized for acute asthma, 10.3% had OSA. Coexistent OSA was associated with a significantly higher risk of non-invasive positive pressure ventilation (NIPPV) use (14.9% vs. 3.1%; unadjusted OR 6.48 [95%CI 5.88-

7.13]; adjusted OR 5.20 [95%CI 4.65-5.80]), while coexistent OSA was not significantly associated with the risk of invasive mechanical ventilation use. Patients with OSA had 37% longer hospital LOS (unadjusted incidence rate ratio [IRR] 1.37 [95%CI 1.33-

1.40]); this significant association persisted in the multivariable model (IRR 1.13 [95%CI 1.10-1.17]). The in-hospital mortality did not significantly differ between groups. These findings were consistent in both obesity and non-obesity groups, and in 27,935 children.

Conclusion: Among patients hospitalized for acute asthma, OSA was associated with a higher risk of NIPPV use and longer LOS compared to those without OSA.

Association of obstructive sleep apnea with severity of patients hospitalized for acute asthma

INTRODUCTION

Asthma is a common inflammatory disease of the airways, affecting approximately 27 million Americans in 2016.[1] Although asthma mortality has declined,[2] the acute morbidity remains substantial. Indeed, acute asthma accounts for approximately 340,000 hospitalizations in the U.S. each year.[3] In parallel, obstructive sleep apnea (OSA) is another common chronic respiratory condition. Recent studies have indicated that OSA affects approximately 20% of the U.S. population[4] and coexists in 8% to 50% of patients with asthma.[5,6]

Increasing evidence indicates that, among patients with asthma, coexistent OSA is associated with poor disease control.[4,7-9] For example, observational studies have reported that, compared to the patients without OSA, those with coexistent OSA have a higher Asthma Control Questionnaire score,[8] more severe daytime and nighttime symptoms,[10] worse quality of life,[10,11] and more frequent exacerbations.[7,11] In addition, another study has also reported that the patients with both asthma and OSA have increased healthcare utilization (e.g., higher hospital charges).[12] [13,14] While the literature has demonstrated the link between OSA and chronic morbidity of asthma, the relationship between OSA and acute severity measures among patients hospitalized for acute asthma remains to be elucidated. Hospitalized asthma patients are an important population with high morbidity and large healthcare burden.[6]

To address this knowledge gap in the literature, we analyzed a large, population-based dataset from eight racially/ethnically- and geographically-diverse U.S. states to investigate the association of coexistent OSA with acute asthma severity. We hypothesized that patients with

OSA who were hospitalized for acute asthma have a higher risk of non-invasive or invasive positive pressure ventilation use, longer hospital length-of-stay (LOS), and in-hospital mortality when compared to those without OSA.

METHODS

Study Design and Setting

We conducted a retrospective cohort study using data from the 2010-2013 State Inpatient Databases (SIDs) of eight US states (Arkansas, California, Florida, Iowa, Nebraska, New York, Utah, and Washington). The SID is a component of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare and Research Quality. The HCUP data are the largest collection of longitudinal hospital care data in the U.S. with all-payer, encounter-level information. The HCUP SID encompass approximately 97 percent of all U.S. community hospital discharges, and contain all inpatient discharges from short-term, acute-care, non-federal, general, and other specialty hospitals—regardless of payers, source of hospitalization, or disposition—in the participating states. Additional details of the SID may be found elsewhere.[15] These eight states were selected for their geographic distribution and high data quality. The institutional review board of Massachusetts General Hospital approved this study.

Study Sample

We identified all unplanned hospitalizations made by patients aged 18-54 years with a primary discharge diagnosis of asthma (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes: 493.xx).[16-18] Then, we further identified patients with OSA by using a concurrent diagnosis of OSA (*ICD-9-CM* codes: 327.23, 780.53, and 780.57) in any diagnosis field, according to prior literature.[19,20] We also analyzed data focusing on children

aged 6-17 years since asthma and OSA are prevalent in this population. The lower cut-off value of age was determined according to the Global Initiative for Asthma (GINA) guidelines since no tests diagnose asthma with certainty in children 5 years and younger.[21] We included only the first hospitalization for acute asthma for each patient during the study period.

Measurements

The SID contains the information on patient demographics (age, sex, and race/ethnicity), primary insurance, estimated household income, urban-rural status, patient comorbidities, hospital state, hospitalization year, *ICD-9-CM* diagnoses, procedures, and disposition. The cut-offs for the estimated income quartile designation were determined using ZIP code-demographic data. The urban–rural status of the patient residence was defined according to the National Center for Health Statistics guidelines.[22]

Outcomes

The primary outcomes were the use of non-invasive mechanical ventilation (NIPPV; *ICD-9-CM* procedure code 93.90) or invasive positive pressure ventilation (codes 96.04 and 96.70-96.72) during the hospitalization, hospital length-of-stay (LOS), and in-hospital mortality.[17,23]

Statistical Analysis

First, we examined the patient characteristics at the hospitalization for acute asthma. Next, to examine the association between OSA and each outcome, we fit unadjusted and multivariable logistic regression models using generalized estimating equations to account for

patient clustering within hospitals. In the multivariable models, we adjusted for age (18-39 and 40-54 years for adults), sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian or Pacific Islander, Native American, and others), primary insurance (Medicare, Medicaid, private, no insurance, and others), quartiles for median household income, patient residence (metropolitan and non-metropolitan residence), 28 Elixhauser comorbidity measures[24] as well as arrhythmia,[25] hospital state, and hospitalization year, based on biological plausibility and *a priori* knowledge.[17,18,23,26] For the hospital LOS outcome, we constructed two models—1) logistic regression model using the hospital LOS as a dichotomous variable (LOS ≤3 days vs. LOS ≥4 days based on the median LOS in the data) and 2) negative binomial model fitting the LOS as a count variable.

To determine the robustness of our inference, we also performed a series of sensitivity analyses. First, we repeated the analysis with the stratification by the concurrent diagnosis of obesity (*ICD-9-CM* codes: 278.00, 278.01, v85.31-v85.39, and v85.41-85.45) because obesity exists in 70% of patients with OSA.[17,26] Second, we repeated the analysis with a stratification by age (18-39 vs. 40-54 years) and sex (male vs. female). Third, we used the stabilized inverse probability weighting (IPW) method to estimate the effect of OSA on the outcomes in this observational study.[27] Weighting subjects by an inverse probability to have the exposure (OSA) creates a synthetic sample in which the exposure is independent from measured baseline covariates—i.e., in the synthetic sample, OSA and non-OSA patients are exchangeable with regard to the risk factors for the outcomes. Although conventional IPW enables us to obtain unbiased estimates of average effects of OSA on each outcome, patients with a very low or high probability of having the exposure can increase the variability of the estimated effects. In contrast, the stabilized IPW method addresses this problem and directly estimates both the main

93 effect and its variance using conventional regression models.[27] All analyses were performed
94 using STATA 14.1 (StataCorp, College Station, TX). All P-values were two-tailed, with $P<0.05$
95 considered statistically significant.

RESULTS

Patient Characteristics

During the 4-year study period, we identified 73,408 adult patients hospitalized for acute asthma across the eight U.S. states. Overall, the median age was 44 years (interquartile range [IQR] 33-49 years), 70% were women, and 45% were non-Hispanic white. Of these, 7,564 patients (10.3%) had a concurrent OSA. The patients with OSA were older and more likely to be male, non-Hispanic white, and Medicare beneficiaries, compared to those without OSA (all, P<0.001; **Table 1**). These patients with OSA were also more likely to have comorbidities, such as hypertension, diabetes, and congestive heart failure (all P<0.001).

OSA and Severity Outcomes

Figure 1 and **Supplemental Table 1** summarize the unadjusted and adjusted associations of OSA with each outcome. Patients with a concurrent diagnosis of OSA had a significantly higher risk of NIPPV use compared to those with non-OSA (14.9% vs. 3.1%; unadjusted OR 6.48 [95%CI 5.88-7.13]; adjusted OR 5.20 [95%CI 4.65-5.80]) in the patients with OSA, while there was no significant association of OSA with the risk of invasive mechanical ventilation use. Similarly, the patients with OSA had a higher risk of prolonged hospital LOS (i.e., LOS ≥4 days) compared to those without OSA (66.0% vs. 47.9%; unadjusted OR 2.06 [1.96-2.17]; adjusted OR 1.39 [95%CI 1.31-1.48]). Likewise, in the analysis using the hospital LOS as a count variable, the patients with OSA had a 37% longer hospital LOS (unadjusted incidence rate ratio [IRR] 1.37; 95%CI 1.33-1.40). This significant association also persisted after adjusting for the potential confounders and patient clustering (adjusted IRR 1.13; 95%CI 1.10-1.17). By contrast, there was no statistically significant difference in in-hospital mortality (0.15% vs. 0.16%;

unadjusted OR 0.93 [95%CI 0.49-1.77]; adjusted OR 0.46 [95%CI 0.21-1.01]) between the patients with OSA and those without.

OSA and Severity Outcomes in children

The associations between OSA and acute asthma severity persisted in the analysis of 27,935 children aged 6-17 years with acute asthma. Overall, 395 (1.4%) had a diagnosis of coexistent OSA. Patient characteristics are shown in **Supplemental Table 2**. Children with OSA were likely to be older and to have public health insurance (Medicaid). Among the children with acute asthma, similar to the findings in adults, coexistent OSA was associated with a significantly higher risk of NIPPV use and longer hospital LOS (both P<0.001; **Supplemental Table 3**).

Sensitivity Analysis

Table 2 summarizes the associations between OSA and acute severity of acute asthma, according to obesity status. In this sensitivity analysis, and similar to the main findings, concurrent OSA was associated with a significantly higher risk of NIPPV use both in the non-obesity (adjusted OR 4.98; 95%CI 4.23-5.88) and obesity (adjusted OR 5.49; 95%CI 4.73-6.36) groups. Likewise, OSA was associated with a longer hospital LOS both in the non-obesity (adjusted IRR 1.14; 95%CI 1.08-1.20) and obesity (adjusted IRR 1.14; 95%CI 1.09-1.18) groups. In the stratified analysis by age (**Supplemental Table 4**), the associations between OSA and outcomes were similar to the main findings, while the magnitude of the association with the use was perhaps amplified in the older patients (age 40-54 years). Likewise, in the sensitivity analysis stratified by sex (**Supplemental Table 5**), OSA was associated with a significantly

higher risk of NIPPV use and longer hospital LOS in both men and women. Furthermore, all of these associations remained significant in the sensitivity analysis using the stabilized IPW method (**Supplemental Table 6**).

DISCUSSION

In this population-based study of 73,408 adult patients and 27,935 children hospitalized for acute asthma in eight U.S. states, we found that concurrent OSA was associated with a significantly higher risk of NIPPV use. In addition, these patients with coexistent OSA had an approximately 40% longer hospital LOS compared to those without OSA. By contrast, concurrent OSA and asthma was not associated with significantly higher inpatient mortality. All of these associations persisted after stratifying by obesity status. Furthermore, the observed associations persisted across several different analytic assumptions (i.e., the stratification by age and sex, and analysis using stabilized IPW).

The literature has shown that OSA (diagnosed by symptoms or polysomnography) is not only prevalent in patients with asthma[9,28-31] but also contributes to chronic morbidity of asthma.[5-8,32] For example, in a single-center study of 472 adults with asthma, a higher Sleep Apnea scale of the Sleep Disorders Questionnaire score was associated with a higher risk of poorly-controlled asthma—defined by the Asthma Control Questionnaire score of ≥1.5.[8] This finding was validated by an analysis of 401 subjects (255 patients with asthma and 146 health controls) who are enrolled in the Severe Asthma Research Program (SARP) II, which also reported the associations with more severe asthma symptoms, more frequent short-acting β-agonist use and healthcare utilization, and worse quality of life.[7] Furthermore, studies reported that coexistent OSA is associated with higher frequencies of acute asthma.[13,14] Another study using nationally-representative inpatient data also showed that patients with coexistent asthma and OSA had higher total hospital charges (while the cost information was not available).[12] The present study builds on these prior reports, and extends them by comprehensively demonstrating the relations

of OSA with increased severity of acute asthma—i.e., the higher risk of NIPPV use and prolonged hospital LOS—among patients hospitalized for acute asthma.

In the current study, comorbid OSA was not significantly associated with the risk of invasive mechanical ventilation use, whereas a previous study using US nationally-representative inpatient data reported increased respiratory therapy including invasive positive pressure ventilation use in asthma patients with OSA.[12] The apparent discrepancy in the results between the earlier and our studies may be attributable to the difference in the definition of outcome measure (i.e., intubation or respiratory therapy). Indeed, the previous study defined "respiratory therapy (intubation and mechanical ventilation)" using *Clinical Classification Software* (*CCS*) code of 216 in the *primary CCS*-procedure filed, which includes NIPPV use. Therefore, the positive association between OSA and intubation therapy observed in the earlier study was driven, at least partially, by the higher risk of NIPPV use—which is consistent with our findings.

Potential Limitations

The current study has several potential limitations. First, as with any study using administrative data, there may been some misclassifications (e.g., underestimation of OSA) in the current study. However, this would have increased the outcome risks preferentially in the non-OSA group, thereby biasing the inferences toward the null. In addition, the HCUP data have been validated against the National Hospital Discharge Survey. Second, the SIDs do not include some of the helpful clinical information on chronic severity measures for asthma (e.g., chronic symptoms, controller use, and pulmonary function) and OSA (e.g., polysomnography, symptoms). Third, as with any observational study, the causal inference might be confounded by unmeasured factors, such as chronic severity of asthma, severity of OSA, and institutional

variations in resource use. Yet, the observed associations between OSA and severity of acute asthma remained significant after accounting for at least hospital-level variations. Fourth, our findings are not validated using *ICD-10-CM* codes. However, the use of *ICD-9-CM* codes to identify asthma has high specificity (93%) and negative predictive value (82%) compared with the reference standard using manual chart review by a clinician,[33] supporting the validity of observed relations between two disease conditions (rather than those between *ICD*-coded diagnoses). Finally, while the study sample was comprised of racially/ethnically- and geographically-diverse patients with asthma in the eight U.S. states, our inferences might not be generalizable to patients with less-severe acute asthma (e.g., those who presented to the emergency department without a subsequent hospitalization). Nevertheless, our data remain directly relevant for 340,000 patients hospitalized for acute asthma in the US each year[3]—a population with high morbidity and large healthcare utilization.

In summary, by using large population-based data of 73,408 adult patients and 27,935 children hospitalized for acute asthma in eight U.S. states, we found that the patients with coexistent OSA had a significantly higher risk of NIPPV use and prolonged hospital LOS compared to those without OSA. These associations persisted after adjusting for potential confounders and across several different analytic assumptions. For clinicians, our findings underscore the importance of accurately identify patients at high risk, such as patients with coexistent OSA and acute asthma. For researchers, our observations should facilitate further investigations into the pathobiological mechanisms that underlie the identified OSA-acute severity association in asthma and encourage the development of targeted prevention and treatment strategies in this clinical population with high morbidity.

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297 **FIGURE LEGEND**

298 **Figure 1. Unadjusted and adjusted associations between obstructive sleep apnea and acute**
299 **severity of asthma exacerbation**

300

301 Obstructive sleep apnea (OSA) was associated with a significantly higher risk of NIPPV use. The
302 patients with OSA had a 37% longer hospital length-of-stay compared to those without OSA in
303 the unadjusted model. The association remained significant after adjusting for age, sex,
304 race/ethnicity, primary insurance, quartiles for median household income, patient residence, 28
305 Elixhauser comorbidity measures as well as arrhythmia, hospital state, and hospitalization year.

Table 1. Characteristics of patients hospitalized for acute asthma, according to coexistence of obstructive sleep apnea

Characteristics	Obstructive sleep apnea n=7,564 (10.3%)	No obstructive sleep apnea n=65,844 (89.7%)	P value
Age, median (IQR), year	47 (40-51)	43 (32-49)	<0.001
Female	5,077 (67.1)	46,215 (70.5)	<0.001
Race/ethnicity			<0.001
Non-Hispanic white	3,620 (49.6)	27,799 (44.1)	
Non-Hispanic black	2,165 (29.7)	17,534 (27.8)	
Hispanic	1,166 (16.0)	13,133 (20.9)	
Asian or Pacific Islander	84 (1.2)	1,071 (1.7)	
Native American	42 (0.6)	265 (0.4)	
Others*	218 (3.0)	3,172 (5.0)	
Primary health insurance			<0.001
Medicare	1,802 (23.8)	7,461 (11.3)	
Medicaid	2,506 (33.1)	22,721 (34.5)	
Private	2,274 (30.1)	20,462 (31.1)	
No insurance	597 (7.9)	10,822 (16.4)	
No charge	115 (1.5)	1460 (2.2)	
Others	266 (3.5)	2,882 (4.4)	
Quartiles for median household income			0.02
1 (lowest)	2,846 (39.1)	24,036 (38.7)	
2	1,811 (24.9)	15,320 (24.7)	
3	1,642 (22.5)	13,488 (21.7)	
4 (highest)	986 (13.5)	9,211 (14.8)	
Patient residence			0.70
Metropolitan	6,974 (92.5)	60,726 (92.7)	
Non-metropolitan	590 (7.7)	5,118 (7.3)	
Selected comorbidities†			
Hypertension	4,704 (62.2)	20,463 (31.1)	<0.001
Diabetes	3,041 (40.0)	9,861 (15.0)	<0.001
Congestive heart failure	1,216 (16.1)	2,400 (3.6)	<0.001
Cardiac arrhythmias	931 (12.3)	6,326 (9.6)	<0.001
Renal failure	442 (5.8)	1,249 (1.9)	<0.001

Hospital state			<0.001
Arkansas	215 (2.8)	2,088 (3.2)	
California	1,163 (15.4)	11,035 (16.8)	
Florida	2,753 (36.4)	20,741 (31.5)	
Iowa	211 (2.8)	1,343 (2.0)	
Nebraska	129 (1.7)	938 (1.4)	
New York	2,275 (30.1)	24,807 (37.7)	
Utah	127 (1.7)	991 (1.5)	
Washington	691 (9.1)	3,901 (5.9)	
Hospitalization year			0.77
2010	2,699 (35.7)	23,780 (36.1)	
2011	2,114 (28.0)	18,408 (28.0)	
2012	1,453 (19.2)	12,647 (19.2)	
2013	7,564 (17.2)	11,089 (16.7)	

Data are shown as n (%) unless otherwise specified.

* The other insurance status includes worker's compensation, unreimbursed native health, other miscellaneous.

† Selected from Elixhauser comorbidity

Table 2. Unadjusted and adjusted associations between obstructive sleep apnea and severity of acute asthma, according to obesity

Obesity status and outcomes	Obstructive sleep apnea (95% CI)	No obstructive sleep apnea (95% CI)	Unadjusted association (95% CI)	P value	Adjusted association* (95% CI)	P value
Non-obesity (n=55,307)						
Non-invasive positive pressure ventilation	12.2% (10.9%-13.7%)	3.0% (2.9%-3.2%)	5.14 (4.42-5.98)	<0.001	4.98 (4.23-5.88)	<0.001
Invasive mechanical ventilation	1.8% (1.3%-2.5%)	2.0% (1.8%-2.1%)	0.97 (0.70-1.35)	0.85	1.09 (0.94-2.13)	0.64
Hospital length-of-stay ≥4 days	61.0% (58.9%-63.1%)	45.9% (45.5%-46.3%)	1.82 (1.66-1.99)	<0.001	1.41 (1.28-1.56)	<0.001
Hospital length-of-stay as a count variable, day, median (IQR)	3 (2-5)	2 (1-4)	1.28 (1.22-1.35)†	<0.001	1.14 (1.08-1.20)†	<0.001
In-hospital mortality	0.14% (0.05%-0.44%)	0.16% (0.13%-0.20%)	0.90 (0.27-2.95)	0.86	0.37 (0.08-1.66)	0.19
Obesity (n=18,101)						
Non-invasive positive pressure ventilation	16.0% (15.0%-17.0%)	2.4% (3.1%-3.8%)	5.91 (5.15-6.79)	<0.001	5.49 (4.73-6.36)	<0.001
Invasive mechanical ventilation	1.7% (1.4%-2.1%)	1.4% (1.2%-1.6%)	1.17 (0.91-1.52)	0.23	0.98 (0.72-1.33)	0.91
Hospital length-of-stay ≥4 days	67.9% (66.7%-69.2%)	56.1% (55.2%-56.9%)	1.64 (1.53-1.75)	<0.001	1.40 (1.30-1.51)	<0.001
Hospital length-of-stay as a count variable, day, median (IQR)	3 (2-5)	3 (2-4)	1.25 (1.20-1.30)†	<0.001	1.14 (1.09-1.18)†	<0.001
In-hospital mortality	0.15% (0.07%-0.29%)	0.15% (0.10%-0.24%)	0.97 (0.42-2.25)	0.95	0.50 (0.19-1.36)	0.18

Abbreviations: CI, confidence interval; IQR, interquartile range.

Associations are indicated by odds ratio unless otherwise specified.

* Logistic regression model for the binomial outcomes and negative binomial model for the count outcome (hospital length-of-stay), adjusting for age, sex, race/ethnicity, primary insurance, household income, residential status, comorbidities, hospital state, and year.

† Incidence rate ratio.

Models	Odd ratio (95%CI)	P value
Unadjusted associations		
Non-invasive positive pressure ventilation	6.48 (5.88-7.13)	<0.001
Invasive mechanical ventilation	0.94 (0.78-1.13)	0.50
Hospital length-of-stay ≥4 days	2.06 (1.96-2.17)	<0.001
Hospital length-of-stay, as a count variable	IRR, 1.37 (1.33-1.40)	<0.001
In-hospital mortality	0.93 (0.49-1.77)	0.82
Adjusted associations		
Non-invasive positive pressure ventilation	5.20 (4.65-5.80)	<0.001
Invasive mechanical ventilation	1.00 (0.80-1.26)	0.98
Hospital length-of-stay ≥4 days	1.39 (1.31-1.48)	<0.001
Hospital length-of-stay, as a count variable	IRR, 1.13 (1.10-1.17)	<0.001
In-hospital mortality	0.46 (0.21-1.01)	0.06