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SCIENTIFIC INVESTIGATIONS

The prevalence and impact of pre-existing sleep disorder diagnoses and objective sleep parameters in patients hospitalized for COVID-19

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Study Objectives: Obstructive sleep apnea and other sleep disorders overlap with comorbidities associated with poor outcomes related to severe acute respiratory syndrome coronavirus 2 infection. However, the prevalence of obstructive sleep apnea among patients hospitalized for COVID-19 and relationship to outcomes is poorly characterized, and the relevance of other sleep disorders remains unknown. The objective of this study was to identify the prevalence of pre-existing sleep disorders and association with outcomes related to severe COVID-19 illness.

Methods: Patients with severe acute respiratory syndrome coronavirus 2 infection admitted to the University of Michigan Hospital System were included. Electronic medical records were queried for sleep disorders diagnostic codes. Data were extracted from polysomnography and home sleep testing in a subgroup with previous diagnostic testing at our center. Logistic regression was used to examine the association of sleep disorders with mechanical ventilation requirement, treatment with vasopressors, and death and Cox proportional hazards regression for time to discharge.

Results: Among n = 572 adult patients hospitalized for COVID-19, 113 (19.8%) patients had obstructive sleep apnea, 4 patients had central sleep apnea (0.7%), 5 had hypoventilation (0.9%), 63 had insomnia (11.0%), and 22 had restless legs syndrome or periodic limb movements disorder (3.9%). After adjusting for age, sex, body mass index, and race, no significant relationship was apparent between sleep disorders diagnoses or indices of sleep-disordered breathing severity and outcomes.

Conclusions: This is the first study to determine the prevalence of obstructive sleep apnea and other sleep disorders in a well-characterized cohort of patients hospitalized for COVID-19. Once hospitalized, a significant contribution of sleep disorders to outcomes was not identified. Therefore, future evaluations should focus on earlier outcomes, such as infection or clinical manifestations after exposure to severe acute respiratory syndrome coronavirus 2.

Keywords: COVID-19, sleep disorders in hospitalized patients, mechanical ventilation, mortality

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Many have hypothesized that sleep disorders, particularly obstructive sleep apnea, are relevant in patients infected with severe acute respiratory syndrome coronavirus 2 given the overlap of with comorbidities associated with worse outcomes related to COVID-19. However, objective data regarding the prevalence of sleep disorders and association with outcomes in patients hospitalized with COVID-19 are minimal.

Study Impact: Sleep disorders were common in individuals hospitalized for COVID-19 but did not contribute to mortality or other critical outcomes. Therefore, earlier outcomes such as the development of illness after exposure to severe acute respiratory syndrome coronavirus 2 or requirement of hospitalization warrant further investigation. The role of sleep disorders in COVID-19 is particularly important given the disproportionate impact of both sleep disorders and COVID-19 on individuals with unfavorable social determinants of health.

INTRODUCTION

In March of 2020, the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic.[1] Although the majority of SARS-CoV-2 infections do not produce severe symptoms,[2–9] individuals with illness that warrants hospitalization often require support in the intensive care unit, and the case fatality rate in the United States was 2% during the drafting of this manuscript.[10]

Comorbidities such as cardiovascular disease, diabetes, hypertension, chronic lung disease, chronic kidney disease, and tobacco use are associated with more severe manifestations of COVID-19 illness and increased mortality.[9,11–15] Obstructive sleep apnea (OSA)[16–22] and other sleep disorders[23–28] are common in individuals with these chronic conditions and, therefore, may have relevance for the clinical course of those infected with SARS-CoV-2.

Notably, OSA has become increasingly recognized as prevalent in hospitalized patients and may worsen acute outcomes.[29–35] For example, in individuals hospitalized for pneumonia, OSA was associated with increased intensive care unit transfers, intubation, and prolonged inpatient stay.[36] Though the prevalence

of other chronic sleep disorders such as insomnia and restless legs syndrome (RLS) in hospitalized patients is less clear, sleep disturbances from any source are associated with inpatient complications such as delirium,[37–39] failure of noninvasive ventilation,[40] prolonged ventilator weaning,[41] and poor glucose control.[42]

However, at this time, the prevalence of sleep disorders among patients hospitalized with COVID-19 is poorly characterized. In 3 small studies (n = 21–104), OSA was identified in approximately 6–29% of patients[43–45]; however, impact on COVID-19 outcomes was not evaluated in these investigations. The Coronavirus SARS-CoV-2 & Diabetes Outcomes study (CORONADO) presented an inpatient cohort of 1,317 patients with diabetes and reported that patients treated for OSA had a higher risk of death from COVID-19 (adjusted odds ratio [OR], 2.65; 95% confidence interval: 1.36, 5.19), although body mass index (BMI) was not included as a covariate in this model and details on how the categorization of "treated OSA" was derived were not provided.[46]

In a large population (n = 9,409), not isolated to inpatients, OSA (as identified by *International Classification of Diseases*, *Tenth Revision*, [ICD] code) was present in 6.3% and was associated with increased risk of COVID-19 infection, hospitalization, and respiratory failure, even after models were adjusted for BMI, diabetes, and hypertension.[47] However, another sample of patients with COVID-19 infection (n = 4,668) also used ICD codes and found OSA in 9.5% but did not observe a statistically significant association between OSA and hospitalization, death, or the composite outcome of death, mechanical ventilation, and critical care requirement after models were adjusted for BMI and other comorbidities.[48]

Therefore, the prevalence of OSA among patients with COVID-19 and, specifically, in individuals who require hospitalization for severe symptoms, and contribution to outcomes remain unclear. Furthermore, no information regarding other pre-existing sleep disorders among patients with COVID-19 is available and no studies have included objectively quantified data from diagnostic sleep studies. Thus, the objective of this study was to identify the prevalence of OSA (and other sleep-disordered breathing diagnoses), insomnia, and RLS in patients hospitalized with SARS-CoV-2 virus and explore relationships with COVID-related outcomes including the requirement for mechanical ventilation and vasopressors, length of stay, and death.

Two assessments of sleep disorders were conducted among patients admitted to the University of Michigan for care related to SARS-CoV-2 infection: (1) evaluation of diagnostic codes for sleep disorders extracted from the electronic medical record and (2) in patients who had undergone diagnostic sleep study prior to infection, evaluation of objective sleep measures from polysomnography or home sleep apnea test. With these approaches, the impact of pre-existing sleep disorders on COVID-19-related health outcomes could be examined.

METHODS

This observational study accessed the Michigan Institute for Clinical and Health Research's COVID-19 Rapid Response Registry for the clinical characterization of persons with SARS-CoV-2 infection, further described elsewhere.[49] All patients admitted to the University of Michigan Hospital System (Michigan Medicine) who tested positive for SARS-CoV-2 infection are included in this registry. Reverse-transcriptase polymerase chain reaction positive SARS-CoV-2 tests were used to confirm infection. The registry includes core items from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Clinical Characterization Protocol[50,51] and follows STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations.[52] The Institutional Review Board of the University of Michigan approved the study (HUM00180621).

Patients included in the current study were adults, admitted between March 9 to November 4, 2020. Out of a total of 893 adult patients, 321 patients who had been transferred from other hospitals were excluded from the primary analysis, as data on their clinical course were incomplete. This left 572 patients to be examined for the main analyses, and their follow-up data continued through November 25, 2020. Data analyses on the entire population of 893 patients, inclusive of transfers, was also performed and is available in the supplemental material. Four COVID-related outcomes were examined in this study: the use of mechanical ventilation after hospital admission, treatment with vasopressors, length of stay, and the occurrence of death.

To investigate the potential influence of pre-existing sleep disorders on these medical outcomes, 2 approaches were taken. The first approach searched each patient's electronic medical record for sleep disorder diagnostic codes to indicate a diagnosis of sleep-disordered breathing, insomnia, RLS, and periodic limb movement disorder (PLMD) (**Table S1** in the supplemental material contains all diagnostic codes queried). Codes were collapsed into categories of OSA, hypoventilation, central sleep apnea (CSA), insomnia, and RLS/PLMD to approximate the ICSD, third edition, disease categorizations.[53] This electronic medical record search was conducted automatically with use of the University of Michigan's Data Direct program.[54] Specifically, we included diagnostic codes used for billing purposes in the ambulatory environment within 2 years prior to COVID-19 admission to best approximate the methodology used by Jolley and colleagues[55] that validated billing codes against sleep clinic diagnoses.

The second approach consisted of identifying all patients who had completed a diagnostic sleep study at the University of Michigan's Sleep Disorder Centers prior to COVID-19 infection and extracting relevant objective measures from the sleep study records (see details below). Whenever multiple diagnostic studies were available, the data from the most recent diagnostic sleep study were used.

Diagnostic sleep study data

Diagnostic sleep studies took place in laboratory or were conducted out of center with type III portable monitoring devices. In-laboratory polysomnography (PSG) included either full night diagnostic or split-night studies (diagnostic portion followed by positive airway pressure [PAP] titration if severity criteria met during the first 2 hours of recording). All in-laboratory data were recorded on the Compumedics acquisition system

(Compumedics Limited, Victoria, Australia) and recorded signals from the following leads: frontal, central and occipital electroencephalogram, electrooculogram, submentalis electromyogram, oronasal thermocouple, nasal pressure transducer, electrocardiogram, thoracic and abdominal inductance plethysmography, right and left anterior tibialis electromyogram, snore microphone, and pulse oximetry. Out-of-center home sleep apnea tests (HSATs) were conducted with either the Somte (Compumedics Limited, Victoria, Australia), Alice PDx (Philips Respironics, Eindhoven, The Netherlands), Alice NightOne (Philips Respironics, Eindhoven, The Netherlands), or ApneaLink (ResMed, San Diego, CA) systems and recorded signal from nasal pressure transducer (airflow and snore), respiratory inductance plethysmography (respiratory effort), and pulse oximetry (oxygen saturation and heart rate).

Sleep studies were conducted in accordance with the technical specifications and scoring guidelines set for in *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*[56,57] or prior to release, the recommendations published in 2001 by the American Academy of Sleep Medicine Clinical Practice Review Committee.[58] Given the introduction of the scoring manual in 2007, all versions in publication through version 2.6 were used.[56,57]

Given the absence of electroencephalogram during HSATs and change in hypopnea scoring criteria over time, to harmonize the respiratory indices (apnea-hypopnea index [AHI] and respiratory effort index [REI]), the AHI and REI extracted used the 4% hypopnea scoring criteria. Therefore, hypopneas, regardless of derivation from PSG or HSAT, were scored in the presence of ≥ 30% decrement in airflow of at least 10 seconds in duration with resultant oxygen desaturation of 4%. Apneas are scored when airflow decreases by at least 90% for 10 seconds or more independent of oxygen desaturation. Apneas and hypopneas are designated as obstructive or central dependent on the presence or absence or respiratory effort, respectively. The AHI with use of the 4% oxygen desaturation criteria was not reported prior to 2004 in our laboratory; therefore, these studies were not considered for inclusion. In addition to the AHI (REI), the following were extracted from in laboratory PSGs and HSATs: minimum oxygen saturation (SpO_2), mean SpO_2, total sleep time with $SpO_2 \leq 88\%$, and sleep study diagnosis.

Statistical analysis

Descriptive statistics were provided overall and by sleep disorder. Frequencies and percentages were used for categorical variables and medians and interquartile ranges used for continuous variables, given nonnormal distributions. Comparisons of characteristics with and without sleep disorders were made using chi-square and Kruskal-Wallis tests. Logistic regression was used to test the association between each sleep disorder and mechanical ventilation, vasopressor treatment, and death. Length of stay was modeled as time to discharged alive using Cox proportional hazards models (as of the final data review, 4 patients were still hospitalized; deaths were treated as nonevents). Models were also adjusted for age, race, and BMI. For the subset of patients with diagnostic sleep study data, continuous sleep study measures were compared by ventilator status and survival status using Kruskal-Wallis tests. Two-sided $\alpha = 0.05$ was used to assess statistical significance. Analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 572 adult patients hospitalized for COVID-19 were included. Of these, 109 patients were mechanically ventilated (19.1%), 102 required treatment with vasopressors (17.8%), and 72 patients died (12.6%). Clinical characteristics were compared between transferred (n = 321) and nontransferred (n = 572) patients and revealed that the transferred population had significantly worse makers of disease severity and worse outcomes (**Table S3**).

Diagnostic codes in the electronic medical record indicated that 113 (19.8%) patients had OSA, 4 patients had CSA (0.7%), 5 had hypoventilation (0.9%), 63 had insomnia (11.0%), and 22 had RLS/PLMD (3.9%). Seventy-three (12.8%) of the patients had previously completed a diagnostic sleep study. The median follow-up period after admission was 224 days (range 121–239 days).

The baseline characteristic differences between those patients with and without diagnoses of OSA and insomnia are shown in **Table 1**. Baseline characteristics by sleep disorders with lower frequency (CSA, hypoventilation, and RLS/PLMD) can be found in the supplemental material (**Table S2**). Patients with OSA, as expected, had a higher BMI and overall had poorer health, including a lower estimated glomerular filtration rate (kidney function) and a trend for increased comorbid chronic cardiac disease and asthma. Patients with insomnia were more likely to be white, were older (although age did not meet statistical significance), and had comorbid asthma. Additionally, alanine aminotransferase, aspartate aminotransferase, ferritin, and white blood cell count were lower among individuals with insomnia. Patients with CSA were more likely to be male and have chronic cardiac disease and lower lactate dehydrogenase levels. Patients with hypoventilation were more likely to be black, have a higher BMI and comorbid asthma, and demonstrated lower total bilirubin levels. Patients with RLS/PLMD were more likely to be white, and have lower lymphocyte count.

Unadjusted models did not find an association between sleep disorder diagnoses and outcomes of mechanical ventilation, vasopressor requirement, length of stay, or death (**Table 2**). Analysis of the population as a whole, with inclusion of transferred patients, also did not reveal an association between sleep disorder diagnoses and outcomes (**Table S4**).

Multivariable models adjusting for age, sex, BMI, and race did not show a statistically significant impact of OSA, insomnia, or RLS/ PLMD on mechanical ventilation, vasopressor requirement, length of stay, or death. The presence of OSA and insomnia demonstrated a nearly statistically significant association with increased odds of death and vasopressor requirement respectively (OR [95% confidence interval], 1.83 [0.89, 3.75] and 1.86 [0.98, 3.56]). The small number of patients precluded inclusion of hypoventilation and CSA as predictors (**Table 3**). Analysis of the population as a whole, with inclusion

Table 1—Descriptive characteristics of 572 hospitalized patients with COVID-19 by OSA and insomnia diagnoses.

Characteristic	Overall (n = 572)	OSA		*P*	Insomnia		*P*
		Yes (n = 113)	No (n = 459)		Yes (n = 63)	No (n = 509)	
Age (years), median (IQR)	63.0 (50.0 to 73.5) (n = 572)	62.0 (52.0 to 67.0) (n = 113)	64.0 (49.0 to 74.0) (n = 459)	.17	65.0 (55.0 to 76.0) (n = 63)	62.0 (49.0 to 72.0) (n = 509)	.07
Female, n (%)	252 (44)	48 (42)	204 (44)	.17	34 (54)	218 (43)	.25
Race, n (%)				.83			.003
Black	160 (28)	32 (28)	128 (28)		15 (24)	145 (28)	
Other	81 (14)	14 (12)	67 (15)		1 (2)	80 (16)	
White	331 (58)	67 (59)	264 (58)		47 (75)	284 (56)	
BMI (kg/m^2), median (IQR)	31.0 (25.5 to 37.8) (n = 537)	35.9 (29.7 to 41.5) (n = 108)	29.4 (25.0 to 35.9) (n = 429)	< .001	31.4 (26.2 to 39.0) (n = 56)	31.0 (25.5 to 37.8) (n = 481)	.83
Temperature (°Fahrenheit), median (IQR)	98.8 (98.2 to 99.9) (n = 569)	98.7 (98.1 to 99.6) (n = 112)	98.8 (98.2 to 99.9) (n = 457)	.42	98.6 (98.2 to 99.1) (n = 61)	98.8 (98.2 to 100.0) (n = 508)	.27
Absolute lymphocyte count (10^9/L)	0.9 (0.6 to 1.3) (n = 551)	0.9 (0.6 to 1.4) (n = 111)	0.9 (0.6 to 1.3) (n = 440)	.62	1.0 (0.5 to 1.3) (n = 61)	0.9 (0.6 to 1.3) (n = 490)	.72
Alkaline phosphatase (IU/L), median (IQR)	78.0 (60.0 to 104.0) (n = 539)	81.0 (66.0 to 109.0) (n = 105)	76.5 (59.0 to 103.0) (n = 434)	.14	78.0 (56.0 to 103.0) (n = 61)	78.0 (60.0 to 104.0) (n = 478)	.85
Alanine aminotransferase (IU/L), median (IQR)	32.0 (21.0 to 54.0) (n = 542)	35.0 (23.0 to 51.0) (n = 105)	31.0 (21.0 to 54.0) (n = 437)	.48	29.0 (17.0 to 42.0) (n = 61)	32.0 (22.0 to 56.0) (n = 481)	.01
Aspartate aminotransferase (IU/L), median (IQR)	43.5 (30.0 to 66.0) (n = 542)	45.0 (33.0 to 65.0) (n = 105)	43.0 (29.0 to 66.0) (n = 437)	.26	37.0 (24.0 to 54.0) (n = 61)	44.0 (30.0 to 67.0) (n = 481)	.01
Albumin (g/dL), median (IQR)	3.7 (3.4 to 4.0) (n = 539)	3.7 (3.4 to 4.0) (n = 105)	3.7 (3.4 to 4.0) (n = 434)	.91	3.8 (3.5 to 4.1) (n = 61)	3.7 (3.4 to 4.0) (n = 478)	.11
eGFR (ml/min/1.73m^2), median (IQR)	70.0 (45.4 to 90.9) (n = 557)	67.7 (35.2 to 84.8) (n = 107)	71.1 (47.7 to 91.5) (n = 450)	.03	68.5 (47.6 to 85.4) (n = 63)	70.1 (45.3 to 91.4) (n = 494)	.75
Total bilirubin (mg/dl), median (IQR)	0.6 (0.4 to 0.9) (n = 539)	0.6 (0.4 to 0.9) (n = 105)	0.6 (0.4 to 0.9) (n = 434)	.80	0.5 (0.4 to 0.9) (n = 61)	0.6 (0.4 to 0.9) (n = 478)	.70
C-reactive protein (mg/L), median (IQR)	7.6 (3.8 to 15.1) (n = 438)	6.4 (2.8 to 12.9) (n = 89)	8.1 (3.8 to 15.6) (n = 349)	.10	5.9 (2.3 to 8.1) (n = 43)	8.1 (3.8 to 15.5) (n = 395)	.01
D-Dimer (mg/dL), median (IQR)	1.0 (0.6 to 1.9) (n = 410)	0.8 (0.6 to 1.6) (n = 81)	1.0 (0.6 to 2.0) (n = 329)	.24	0.8 (0.6 to 1.5) (n = 38)	1.0 (0.6 to 2.0) (n = 372)	.14
Ferritin (ng/mL), median (IQR)	611.1 (249.8 to 1350.2) (n = 450)	502.4 (248.9 to 1006.5) (n = 90)	636.5 (251.9 to 1417.7) (n = 360)	.18	350.7 (125.8 to 917.9) (n = 46)	637.5 (275.9 to 1417.7) (n = 404)	.004
Lactate dehydrogenase (IU/L), median (IQR)	348.0 (258.0 to 486.0) (n = 401)	374.0 (274.0 to 515.0) (n = 77)	347.0 (253.0 to 476.5) (n = 324)	.30	276.0 (234.0 to 376.0) (n = 37)	361.0 (262.0 to 497.5) (n = 364)	.003
White blood cell count (10^9/L), median (IQR)	7.0 (5.1 to 9.9) (n = 569)	7.0 (5.2 to 9.8) (n = 113)	7.0 (5.1 to 10.0) (n = 456)	.72	6.0 (4.7 to 8.8) (n = 63)	7.1 (5.2 to 10.2) (n = 506)	.04
Chronic pulmonary disease, n (%)	88 (15)	24 (21)	64 (14)	.05	10 (16)	78 (15)	.91
Chronic cardiac disease, n (%)	163 (28)	44 (39)	119 (26)	.01	25 (40)	138 (27)	.04

(continued on following page)

Table 1—Descriptive characteristics of 572 hospitalized patients with COVID-19 by OSA and insomnia diagnoses. (continued)

Characteristic	Overall (n = 572)	OSA		*P*	Insomnia		*P*
		Yes (n = 113)	No (n = 459)		Yes (n = 63)	No (n = 509)	
Chronic kidney disease, n (%)	140 (24)	36 (32)	104 (23)	.04	14 (22)	126 (25)	.66
Asthma, n (%)	88 (15)	31 (27)	57 (12)	< .001	18 (29)	70 (14)	.002
Hypertension, n (%)	357 (62)	82 (73)	275 (60)	.01	46 (73)	311 (61)	.07
Diabetes, n (%)	204 (36)	49 (43)	155 (34)	.06	22 (35)	182 (36)	.90

BMI = body mass index, eGFR = estimated glomerular filtration rate, IQR = interquartile range, OSA = obstructive sleep apnea.

of transferred patients, did not reveal an association between sleep disorder diagnoses and outcomes in the adjusted model (**Table S5**).

Objective sleep variables available in 73 patients were derived from HSAT (n = 4), full-night diagnostic PSG (n = 33), and split-night PSG (n = 6). Objective sleep variables (AHI/REI, minimum SpO_2, mean SpO_2, time $SpO_2 < 88\%$, and PLMI) were not significantly related to mechanical ventilation, vasopressor requirement, or death (**Table 4** and **Figure 1**). Analysis of the entire population, with inclusion of transferred patients who had prior HSAT, full-night or split-night PSG within our system did not demonstrate a relationship between sleep study parameters and outcomes (**Table S6** and **Figure S1**).

DISCUSSION

To our knowledge, this is the first study to systematically evaluate the prevalence of sleep-disordered breathing (OSA, CSA, and hypoventilation), insomnia, and RLS/PLMD in a cohort of patients hospitalized for COVID-19. Additionally, this work evaluated the contribution of sleep diagnoses, as well objective parameters from diagnostic sleep studies (PSG and HSAT), to outcomes in hospitalized COVID-19 patients.

Prevalence

We found that OSA, CSA, and hypoventilation diagnoses were present in 19.8%, 0.7%, and 0.9% of patients, respectively. Insomnia was observed in 11% and RLS/PLMD in 3.9% of patients.

Currently, 3 of the 4 available small studies (n = 21–124) that assessed the presence of OSA diagnoses among patients hospitalized for COVID-19 found a prevalence of 20–30%[43,44,59] with 1 outlier that identified 7.25%.[45] In a much larger population, the CORONADO cohort,[46] "treated obstructive sleep apnea" was present in 12.1% of inpatients with diabetes and COVID-19; however, no details regarding the derivation of the designation is available, so whether patients were prescribed treatment, self-reported treatment use, or were objectively confirmed to adhere to treatment (PAP-generated data) remains unclear.

Variable (and often unclear) methods of identifying which patients carried a diagnosis of OSA preclude direct comparison between our study and other investigations that cite OSA prevalence in COVID-19 inpatients. However, our predominately male (56%) population was characterized by a median age of 63 and median BMI in the obese range (31 kg/m^2); therefore, our finding that 20% of individuals hospitalized for COVID-19 were diagnosed with OSA is not unexpected. Additionally, because the odds ratios for hypertension among patients with OSA are up to 2- to 3-fold[60] and 15–30% of patients with OSA have diabetes,[18] comorbid OSA is not unexpected in our cohort, which also had a high prevalence of diabetes (39%) and hypertension (68%).

Notably the proportion OSA in our hospitalized cohort was much greater than the prevalence in populations with COVID-19 that include outpatients (< 10%).[47,48]

Table 2—Sleep disorders among 572 hospitalized patients with COVID-19: prevalence and unadjusted association with mechanical ventilation, vasopressor requirement, death, and length of stay.

Sleep Diagnosis	All* (n = 572)	Mechanical Ventilation* (n = 109)	OR [95% CI]	Vasopressor Requirement* (n = 102)	OR [95% CI]	Death* (n = 72)	OR [95% CI]	LOS† (n = 572)	HR to Discharge [95% CI]
OSA	113 (19.8)	28 (25.7)	1.54 [0.94, 2.51]	26 (25.5)	1.51 [0.91, 2.49]	16 (22.2)	1.19 [0.65, 2.16]	8 (3, 43)	0.92 [0.74, 1.15]
Insomnia	63 (11.0)	14 (12.8)	1.25 [0.66, 2.35]	16 (15.7)	1.67 [0.91, 3.01]	12 (16.7)	1.76 [0.89, 3.49]	12 (4, 76)	0.81 [0.61, 1.08]
RLS/PLMD	22 (3.9)	1 (0.9)	0.20 [0.02, 1.47]	2 (2.0)	0.45 [0.10, 1.96]	3 (4.2)	1.10 [0.32, 3.82]	10.5 (5, 42)	0.86 [0.54, 1.35]

*Values are n (%). †Values are median (interquartile range). CI = confidence interval, HR = hazard ratio, LOS = length of stay, OR = odds ratio, OSA = obstructive sleep apnea, PLMD = periodic limb movement disorder, RLS = restless legs syndrome.

Table 3—Multivariable logistic and Cox proportional-hazards regression.

Characteristic	Mechanical Ventilation, OR [95% CI]	Vasopressor Requirement, OR [95% CI]	Death, OR [95% CI]	HR to Discharge [95% CI]
OSA	1.53 [0.90, 2.59]	1.40 [0.81, 2.40]	1.83 [0.89, 3.75]	0.81 [0.64, 1.03]
Age*	1.08 [0.94, 1.24]	1.17 [1.01, 1.35]	2.46 [1.89, 3.21]	0.83 [0.79, 0.87]
Sex	1.78 [1.13, 2.81]	1.82 [1.14, 2.90]	1.43 [0.80, 2.56]	0.85 [0.71, 1.03]
Race (Black vs White)	1.29 [0.89, 1.86]	1.28 [0.88, 1.88]	1.02 [0.64, 1.65]	1.02 [0.82, 1.26]
Race (other vs White)	0.77 [0.47, 1.28]	0.75 [0.44, 1.28]	0.99 [0.53, 1.83]	1.27 [0.95, 1.70]
BMI**	1.01 [0.90, 1.15]	1.07 [0.94, 1.21]	0.92 [0.75, 1.12]	1.08 [1.03, 1.13]
Insomnia	1.44 [0.74, 2.80]	1.86 [0.98, 3.56]	1.64 [0.75, 3.57]	0.85 [0.62, 1.16]
Age*	1.07 [0.94, 1.23]	1.16 [1.00, 1.34]	2.41 [1.86, 3.12]	0.83 [0.79, 0.88]
Sex	1.82 [1.15, 2.87]	1.88 [1.18, 3.02]	1.48 [0.83, 2.63]	0.85 [0.70, 1.02]
Race (Black vs White)	1.29 [0.89, 1.86]	1.28 [0.88, 1.88]	1.03 [0.64, 1.67]	1.02 [0.82, 1.26]
Race (other vs White)	0.77 [0.47, 1.28]	0.77 [0.45, 1.31]	0.99 [0.53, 1.82]	1.28 [0.96, 1.72]
BMI**	1.03 [0.92, 1.16]	1.08 [0.96, 1.22]	0.94 [0.78, 1.14]	1.07 [1.02, 1.12]
RLS/PLMD	0.20 [0.03, 1.55]	0.46 [0.10, 2.07]	1.23 [0.32, 4.77]	0.81 [0.50, 1.32]
Age*	1.08 [0.94, 1.24]	1.17 [1.01, 1.35]	2.42 [1.87, 3.14]	0.83 [0.79, 0.87]
Sex	1.77 [1.12, 2.79]	1.81 [1.13, 2.89]	1.46 [0.82, 2.60]	0.85 [0.70, 1.02]
Race (Black vs White)	1.29 [0.89, 1.85]	1.29 [0.88, 1.88]	1.04 [0.65, 1.67]	1.01 [0.81, 1.25]
Race (other vs White)	0.74 [0.45, 1.22]	0.73 [0.43, 1.23]	0.96 [0.52, 1.77]	1.29 [0.96, 1.73]
BMI**	1.03 [0.91, 1.16]	1.08 [0.96, 1.22]	0.94 [0.78, 1.15]	1.07 [1.02, 1.12]

*Age per 10 years. **BMI in 5-kg/m^2 increments. BMI = body mass index, CI = confidence interval, HR = hazard ratio, OR = odds ratio, OSA = obstructive sleep apnea, PLMD = periodic limb movement disorder, RLS = restless legs syndrome.

In regards to sleep disturbances apart from OSA, we are unaware of available data regarding the prevalence of pre-existing CSA, hypoventilation, insomnia, or RLS/PLMD in hospitalized patients infected with COVID-19. However, insomnia symptoms increase with age, and chronic insomnia has been observed in more than 40% of individuals with underlying medical comorbidities such as hypertension and cardiovascular disease.[61,62] Similarly, an increased burden of comorbid conditions (including diabetes, hypertension, myocardial infarction, obesity, stroke, cancer, and renal disease) has been associated with increased prevalent and incident RLS.[63]

Therefore, given significant overlap between chronic comorbidities and sleep disorders, the presence of OSA and insomnia diagnoses among patients hospitalized for COVID-19, who were older, overweight, and had high prevalence of hypertension and diabetes, was not surprising.

Contribution to outcomes

We did not identify any associations between sleep-disordered breathing, insomnia, or RLS/PLMD with outcomes among hospitalized COVID-19 patients. Among the subgroup of individuals with diagnostic sleep study data, AHI (REI), minimum SpO_2, mean SpO_2, time $SpO_2 < 88\%$, and PLMI, were also unrelated to outcomes.

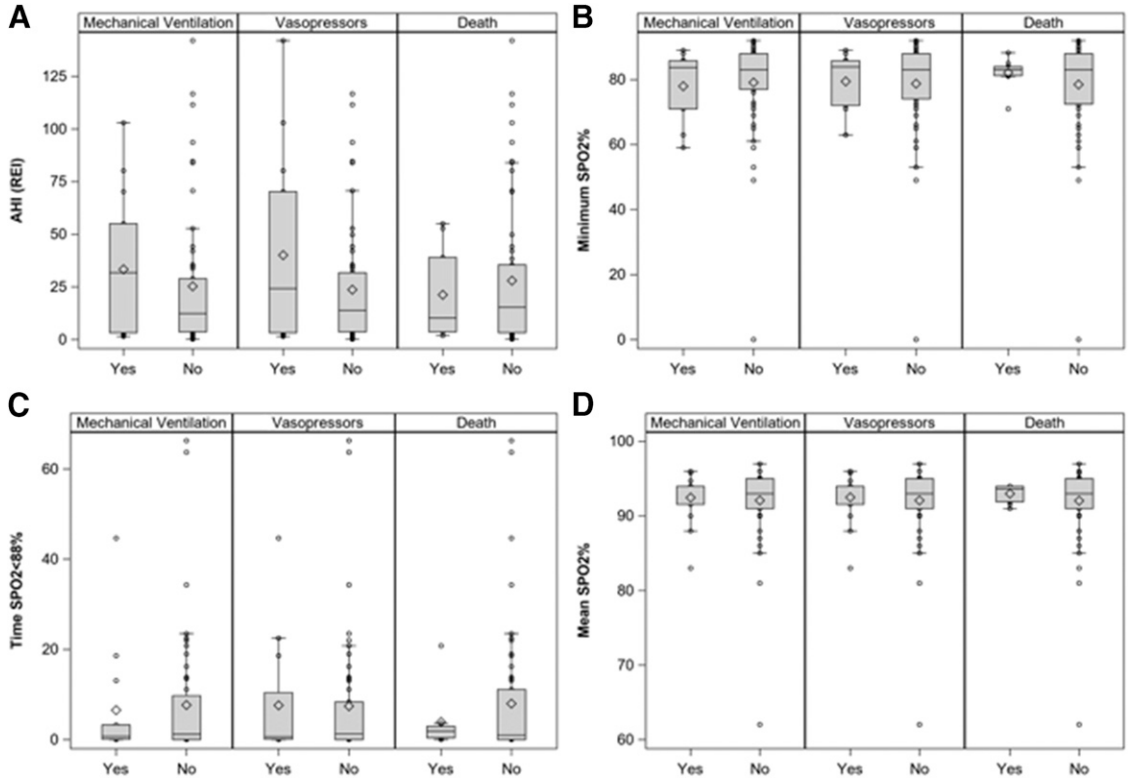
The theory that disordered sleep could worsen outcomes related to COVID-19 has been postulated by multiple investigators and potential mechanisms include: increased expression of angiotensin converting enzyme 2 (the entry receptor of

Table 4—HSAT or PSG parameters in 73 patients with available diagnostic sleep study data.

Sleep Parameter	Mechanical Ventilation		*P*	Vasopressor Requirement		*P*	Death		*P*
	Yes	No		Yes	No		Yes	No	
AHI (REI) (events/h)*			.32			.32			.89
n (missing)	15 (0)	53 (5)		14 (0)	54 (5)		9 (0)	59 (5)	
Median (IQR)	31.8 (3.2 to 55.1)	12.4 (3.6 to 29.0)		24.3 (3.2 to 70.3)	13.8 (3.6 to 31.8)		10.2 (3.7 to 39.1)	15.3 (3.2 to 35.6)	
Range	1.5 to 103.0	0.2 to 142.0		1.5 to 142.0	0.2 to 116.7		1.9 to 55.1	0.2 to 142.0	
Mean SpO_2 (%)			.97			.81			.89
n (missing)	15 (0)	58 (0)		14 (0)	59 (0)		9(0)	64 (0)	
Median (IQR)	94.0 (91.6 to 94.0)	93.0 (91.0 to 95.0)		94.0 (91.6 to 94.0)	93.0 (91.0 to 95.0)		93.7 (91.9 to 94.0)	93.0 (91.0 to 95.0)	
Range	83.0 to 96.0	62.0 to 97.0		83.0 to 96.0	62.0 to 97.0		91.0 to 94.0	62.0 to 97.0	
Minimum SpO_2 (%)			.40			.69			.97
n (missing)	15 (0)	58 (0)		14 (0)	59 (0)		9 (0)	64 (0)	
Median (IQR)	83.7 (71.0 to 85.8)	83.0 (77.0 to 88.0)		83.9 (72.0 to 85.8)	83.0 (74.0 to 88.0)		83.0 (81.1 to 84.0)	83.0 (72.4 to 88.0)	
Range	59.0 to 89.0	0.0 to 92.0		63.0 to 89.0	0.0 to 92.0		71.0 to 88.2	0.0 to 92.0	
Time SpO_2 < 88% (minutes)			.88			.88			.90
n (missing)	13 (2)	52 (6)		12 (2)	53 (6)		8 (1)	57 (7)	
Median (IQR)	0.7 (0.1 to 3.3)	1.2 (0.0 to 9.7)		0.7 (0.1 to 10.4)	1.2 (0.0 to 8.4)		1.9 (0.4 to 2.9)	1.0 (0.0 to 11.1)	
Range	0.0 to 44.7	0.0 to 66.3		0.0 to 44.7	0.0 to 66.3		0.0 to 20.8	0.0 to 66.3	
PLM index (events/h)**			.45			.62			.19
n (missing)	15(0)	54 (4)		14 (0)	55 (4)		9 (0)	60 (4)	
Median (IQR)	0.0 (0.0 to 10.6)	0.7 (0.0 to 9.6)		0.0 (0.0 to 10.6)	0.7 (0.0 to 9.6)		10.2 (0.0 to 14.9)	0.1 (0.0 to 8.0)	
Range	0.0 to 14.9	0.0 to 129.9		0.0 to 14.9	0.0 to 129.9		0.0 to 129.9	0.0 to 48.2	

*Both AHI and REI were derived with use of 4% hypopnea scoring criteria to harmonize between data extracted from HSAT and in-lab PSG. **Missing in participants with HSAT. AHI = apnea-hypopnea index, HSAT = home sleep apnea test, IQR = interquartile range, PLM = periodic limb movement, PSG = polysomnography, REI = respiratory event index, SpO_2 = oxygen saturation.

Figure 1—Respiratory parameters from PSG and HSAT in the 73 individuals with diagnostic sleep study data.



(A) Both AHI and REI were derived with use of 4% hypopnea scoring criteria to harmonize between data extracted from HSAT and in-lab PSG. **(B)** Minimum SpO_2 (%). **(C)** Time with SpO_2 < 88% (minutes). **(D)** Mean SpO_2 (%). AHI = apnea-hypopnea index, HSAT = home sleep apnea test, PSG = polysomnography, REI = respiratory event index, SpO_2 = oxygen saturation.

SARS-CoV-2) and dysregulation of renin-angiotensin system related to OSA,[64,65] hypoxemia worsened by OSA (and, if present, obesity hypoventilation syndrome),[66] and exaggeration of the cytokine storm seen in COVID-19 by the proinflammatory states of OSA and obesity.[66]

Additionally, sleep disruption is associated with proinflammatory cytokines (interleukin-6 and tumor necrosis factor-α),[67] increased viral susceptibility, resistance to the anti-inflammatory effects of corticosteroids, and in animal models, pulmonary inflammation and increased mortality in the face of septic challenges.[65,67] Therefore, sleep deprivation, independent of sleep-disordered breathing, is potentially relevant to COVID-19 pathogenesis.[67]

Despite these putative mechanisms, scant evidence is available to confirm or refute the impact of disturbed sleep on COVID-19 outcomes in hospitalized patients. In a group of 1,317 individuals with diabetes, Cariou and colleagues[46] found that treated OSA was associated with increased mortality on day 7 of admission (OR = 2.65; 95% confidence interval: 1.36, 5.19) after adjustment for age, sex, hypertension, microvascular and macrovascular complications of diabetes, heart failure, cancer, and use of beta-blockers, metformin, insulin, loop diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid-receptor antagonist. However, BMI was not included as a confounder in this model. Furthermore, how patients with "treated obstructive sleep apnea"' were identified is not detailed. Treated OSA could refer to treatment ordered, self-reported treatment use, or objectively confirmed treatment of OSA (by assessment of PAP-generated adherence data). Additionally, treatment of OSA could include PAP (CPAP or bilevel PAP), surgical interventions, hypoglossal nerve stimulation, or oral appliance use. Therefore, whether the relationship between treated OSA and death reflects a detriment of OSA itself or of the treatment for OSA remains unknown.[46] No investigations are available that report the contribution of non-OSA diagnoses or objective sleep parameters to COVID-19 outcomes.

The absence of an impact of sleep disorder diagnoses or objective sleep parameters to inpatient outcomes is perhaps not surprising in this study, given that COVID-19 illness severe enough to result in hospitalization is associated with high risk of endotracheal intubation and mechanical ventilation and death. For example, among 2,741 patients hospitalized for COVID-19 in a US cohort, 647 (23.6%) required mechanical ventilation and 24.2% died or progressed to hospice care.[11] Therefore, the role of pre-existing sleep disorders in COVID-19 may exert more of an impact in susceptibility to the virus or disease severity prior to hospitalization. In support of this hypothesis, among a large, 10 hospital integrated health care system, individuals diagnosed with OSA were more likely to become infected by SARS-CoV-2 and those with OSA and COVID-19 were more likely to progress to hospitalization (OR = 1.65; 95% confidence interval: 1.36, 2.02) and respiratory failure (OR = 1.98; 95%

confidence interval: 1.65, 2.37), despite adjustment for BMI, diabetes, and hypertension. Another large health care system study found that OSA was a risk factor for hospitalization, death, critical care requirement, and mechanical ventilation, but this finding did not persist after adjusting for BMI, hypertension, diabetes, and chronic lung disease. Notably, this investigation demonstrated effect sizes (unadjusted odds of death: OR = 1.79; 95% confidence interval: 1.31, 2.45) and odds of death adjusted for BMI and demographics (OR = 1.39; 95% confidence interval: 0.97, 1.98) not dissimilar to those reported here.[48]

Strengths

This is the first study to evaluate OSA and other sleep disorders diagnoses in a large population of well-characterized patients hospitalized for COVID-19. The identification of patients with sleep disorders was systematically extracted by mining the electronic health record for sleep disorder diagnostic codes. The use of diagnostic codes from our electronic health record database allowed for a systemic evaluation of pre-existing sleep disorders that was not dependent on provider query or patient self-report at the time of admission, which may be vulnerable to recall bias. Although one other larger study (n = 1,317) evaluated the role of OSA in COVID-19 specifically in hospitalized patients, the population was limited to diabetic patients, the designation of "treated OSA" was not well-defined, and BMI was not included in the multivariable models assessing the relationship of treated OSA with outcomes.[46] No published study to our knowledge has reported on other sleep disorders in patients hospitalized for COVID-19. Additionally, in a subgroup of patients, diagnostic sleep study data were available, which allowed us to explore objective severity measures (AHI [REI], oxygen measures, and PLMI) on COVID-19 related outcomes.

Limitations

Although novel, this study has a number of limitations that should be considered. Use of diagnosis codes may result in the coding for conditions that are suspected and not confirmed. However, an investigation of sleep disorders codes (compared to the gold standard of sleep disorder confirmed by a sleep specialist) demonstrated that ICD-9 sleep disorder codes had a positive predictive value of 89% for confirmed sleep disorders.[55] The negative predictive value of the presence of an ICD-9 sleep disorders code was 16%; therefore, of greater concern is that use of diagnostic codes may not capture all patients with sleep disorders.[55] This limitation takes place on the backdrop of a decreased reporting of sleep related symptoms in racial/ethnic minorities and the socioeconomically disadvantaged,[68] groups that are disproportionately affected by COVID-19.[14,69,70] Additionally, the time elapsed since the diagnosis was coded in the electronic health record was not appraised and could vary between individuals, although we restricted the use of the diagnosis codes to the 2 years prior to COVID-19 hospitalization.

The treatment of sleep disorders was unknown in our cohort. This may be of particular relevance in OSA, where the adherence to the most common therapeutic intervention, CPAP, is poor (nonadherence estimated in 29–83% of patients).[71,72] Additionally, CPAP adherence may be worse in groups with disparate outcomes related to COVID-19, including racial/ethnic minorities[68] and older adults with lower socioeconomic status.[73] Interestingly, in individuals who use CPAP, adherence has remained relatively stable[74] or marginally improved during shelter in place restrictions during the COVID-19 pandemic.[75]

Additionally, our sample size, although large, may have been insufficient. For example, we observed an adjusted OR of 1.83 for the impact of OSA on mechanical ventilation. If the true OR is indeed equal to 1.83, our sample of 113 OSA and 459 non-OSA patients only had 60% power to detect a statistically significant difference. This is based on the likelihood ratio test, with use of a 2-sided $\alpha = 0.05$ and assuming an event rate of 0.12 in the non-OSA group. Therefore, a sample of 191 with OSA and 775 without OSA (total n = 996) would be required for 80% power to detect a statistically significant difference (assuming the same ratio of patients with OSA to those without OSA in a subsequent population). Regarding the signal seen in the association of insomnia and death, our sample of 63 patients with insomnia and 509 without insomnia had 32% power to detect a true OR of 1.64 (assuming an event rate of 0.12 in the non-insomnia group). Therefore, a sample of 270 with insomnia and 2,182 without insomnia (2,452 total) would be required for 80% power a statistically significant difference (assuming the same ratio of insomnia to patients without insomnia in a subsequent population).

Diagnostic sleep study data were only available on a limited number of our patients (13%), potentially because sleep studies were performed outside of our health system. Given the small number, the respiratory indices to determine sleep-disordered breathing were considered together whether data were acquired from PSG (AHI) or HSAT (REI). To best harmonize these data, AHI and REI extracted used the 4% hypopnea scoring criteria. However, despite use of the 4% hypopnea scoring criteria, the accuracy of HSAT in determining sleep-disordered breathing severity may be inferior to PSG, as the REI denominator is inherently less precise (total recording time or patient reported sleep duration) and technical issues may degrade the signals acquired by out-of-center testing. Additionally, at the University of Michigan, we do not routinely report the oxygen desaturation index, which may be a marker of greater utility in determining the contribution of OSA severity to other disease states.[76,77] However, overall, the oxygen measures used in this study (minimum SpO_2, mean SpO_2, and time $SpO_2 < 88\%$) were actually more favorable in individuals with worse outcomes (though not reaching statistically significant difference); but this cannot be logically interpreted without information regarding outpatient treatment and may be irrelevant give the frequent use of supplemental oxygen in hospitalized patients.

A large proportion of our inpatient population is transferred from other hospitals and, therefore, does not have complete data regarding their disease course. However, analysis with inclusion of transfers was also conducted and did not change our conclusions based on nontransfers.

CONCLUSIONS

In this first investigation that evaluated the presence of pre-existing sleep disorders in patients hospitalized for

COVID-19, a high prevalence of OSA (20%) and insomnia (11%) were identified. However, these values might be considered lower than expected compared to population studies in individuals with similar demographic characteristics and comorbidities, which may highlight the under recognition of sleep disorders in the same underserved patient groups who may be at increased risk for poor outcomes related to COVID-19 infection.

With adjustment for relevant confounders, pre-existing sleep disorders or objective markers of sleep-disordered breathing severity were not associated with mechanical ventilation, vasopressor use, length of stay, or death among patients hospitalized for COVID-19. Therefore, future evaluations on the role of earlier outcomes, such as infection or illness after exposure to SARS-CoV-2 or hospitalization, may be beneficial. Additionally, since myocardial injury is prevalent among critically ill patients with COVID-19,[78] sleep disorders may be relevant for long-term cardiac outcomes, given their contribution to cardiovascular health. Furthermore, given the at-risk population, it remains an open question if new sleep disorders will be long-term sequelae in those who recover from severe COVID-19.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CORONADO, Coronavirus SARS-CoV-2 & Diabetes Outcomes study
CSA, central sleep apnea
HSAT, home sleep apnea test
ISARIC, International Severe Acute Respiratory and Emerging Infection Consortium
OR, odds ratio
OSA, obstructive sleep apnea
PAP, positive airway pressure
PLMD, periodic limb movement disorder
PSG, polysomnography
REI, respiratory event index
RLS, restless legs syndrome
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
SpO_2, oxygen saturation

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