Elucidating Predictors of Obesity Hypoventilation Syndrome in a Large Bariatric Surgery Cohort

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Abstract

Rationale: Although understanding predictors of obesity hypoventilation syndrome (OHS), a condition associated with increased morbidity and mortality, is of key importance for risk prediction, existing characterization is limited.

Objectives: We hypothesize that OHS patients referred for bariatric surgery have more severe obstructive sleep apnea and metabolic derangements compared with their eucapnic counterparts.

Methods: A total of 1,718 patients undergoing polysomnography with end-tidal CO_2 monitoring prior to bariatric surgery at Cleveland Clinic from September 2011 to September 2018 were included. OHS was defined by body mass index (BMI) $\geq$ 30 kg/m^2 and either polysomnography-based end-tidal $CO_2 \geq$ 45 mm Hg or serum bicarbonate levels $\geq$ 27 mEq/L based on the updated European Respiratory Society guidelines. Unadjusted and multivariable logistic regression models (odds ratio; 95% confidence interval) were used to examine OHS predictors consisting of factors in domains of patient characteristics, polysomnography (cardiorespiratory and sleep architecture), laboratory, and metabolic parameters.

Results: The analytic sample comprised 1,718 patients with the following characteristics: age of 45.3 $\pm$ 12.1 years, 20.7% were male, BMI = 48.6 $\pm$ 9 kg/m^2, and 63.6% were white individuals. OHS prevalence was 68.4%. Unadjusted analyses revealed a 1.5% increased odds of OHS (1.01; 1.00–1.03) per 1-unit BMI increase, 1.7% (1.02; 1.01–1.02) per 1% increase in sleep time $Sa_{O_2} < 90\%$, 12% increase (1.12; 1.03–1.22) per 1-U increase in hemoglobin A1c, and 3.4% increased odds (1.03; 1.02–1.05) per 5-U increase in apnea–hypopnea index. The association of apnea–hypopnea index with OHS persisted after adjustment for age, sex, race, and BMI and its comorbidities (1.02; 1.01–1.04).

Conclusions: OHS was highly prevalent in patients referred for bariatric surgery by more than two-thirds. Even after consideration of confounders including obesity, obstructive sleep apnea remained a strong OHS predictor, as were increasing age, male sex, nocturnal hypoxia, and impaired long-term glucose control. These findings can inform OHS risk stratification in bariatric surgery and set the stage for experimental studies to examine sleep-related respiratory and metabolic contributions to hypoventilation.

Keywords: obesity hypoventilation syndrome; bariatric surgery; obstructive sleep apnea

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Obesity hypoventilation syndrome (OHS) is a type of sleep-related hypoventilation that results in an increased likelihood of postoperative mechanical ventilation, leading to longer hospitalizations and an overall increase in morbidity and mortality (1–5). It is characterized by obesity defined by a body mass index (BMI) of $\geq$30 kg/m^2, sleep disordered breathing, and daytime hypercapnia defined by arterial blood gas (Pa_{CO_2}) of $\geq$45 mm Hg at sea level in the absence of any other cause for

hypoventilation (6). Daytime hypercapnia in OHS occurs in large part because of a balance of multiple factors, including increased mechanical load on the respiratory system and inherent ventilatory response to CO_2 production. Surrogates for arterial blood gas Pa_{CO_2} levels include end-tidal CO_2 (ET_{CO_2}) or transcutaneous CO_2 (7). OHS has been associated with chronic upregulation of systemic inflammation (8), right-sided heart failure (2, 9, 10), and metabolic derangements, including insulin resistance and resting metabolic rate (10–12), and it confers adverse effects on quality of life (13, 14). With the ongoing obesity epidemic, the prevalence of OHS is projected to also rise. As the majority of patients are not formally diagnosed with OHS until later in life in the context of clinical presentation with respiratory failure, early detection is of high importance.

The prevalence of OHS in the general population is not precisely known, but some studies have shown a prevalence of approximately 10–20% in patients with obstructive sleep apnea (OSA) and an overall prevalence estimate of 0.6% (5, 15–19). Among the bariatric surgery population, the prevalence of OSA has been well established; however, the actual prevalence and underlying factors contributing to OHS remains less clear. According to the American Society for Metabolic and Bariatric Surgery guidelines, patients referred for bariatric surgery are recommended to undergo screening for OSA and OHS to reduce perioperative complications. Typically, a BMI of $\geq$40 kg/m^2 would qualify for bariatric surgery; however, the diagnosis of OSA or OHS is considered to be a severe obesity-related comorbidity that may qualify a patient with a lower BMI of $\geq$35 kg/m^2 for bariatric surgery (20).

Few studies have examined OHS in the setting of bariatric surgery. In a large registry of bariatric surgery patients ($n > 36$ K), the prevalence of OHS was 2% and was associated with a greater than twofold higher odds of postsurgical serious adverse events (21). However, systematic assessment of OHS was not part of the routine evaluation for the vast majority of these patients, likely resulting in a substantial degree of underestimation of OHS. As diagnostic sleep testing for bariatric surgery patients and ET_{CO_2} monitoring occur standardly at our center, this allows the ability to universally assess for not only OSA but also sleep-related hypoventilation. We chose to leverage these data to address existing knowledge gaps in terms of characterizing prevalence and determinants or characteristics of OHS specific to the bariatric surgery population. The objective of this study was to evaluate the prevalence of OHS in the bariatric surgery population and to determine clinical, laboratory, metabolic, and polysomnographic characteristics inherent to those patients with OHS. We postulate that those with OHS are more likely to have a greater severity of OSA and greater metabolic derangements compared with their eucapnic counterparts; i.e., apnea–hypopnea index (AHI) and diabetes mellitus are relevant predictors of OHS.

Methods

Study Population

This was a retrospective examination of data collection from the Cleveland Clinic electronic medical record (EMR) and Polysmith software. The sample population included patients who underwent an in-lab attended polysomnogram (PSG) prior to bariatric surgery from September 2008 to September 2018. Exclusion criteria included age less than 18 years, BMI $<$ 30 kg/m^2, sleep studies performed after bariatric surgery, a home sleep apnea test instead of a diagnostic PSG or split-night study as their method of sleep study, and other potential causes for their hypoventilation, including chronic obstructive pulmonary disorder and neuromuscular disorder.

Data Collection

Relevant covariates and comorbidities. Patient characteristics collected at the time of the sleep study included age, sex, and race, along with anthropometric measurements including BMI. Medications used at the time of the sleep study, specifically sedatives, and comorbid conditions such as chronic obstructive pulmonary disorder, neuromuscular disease, diabetes mellitus, hypertension, coronary artery disease, and metabolic syndrome were obtained through the medical record. EMR data was used to extract data pertaining to history of congestive heart failure as well as ejection fraction (left ventricular ejection fraction, percentage) and right ventricular systolic pressure (millimeter of mercury) from available echocardiograms. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and the FEV_1/FVC ratio data were obtained from pulmonary function tests using the American Thoracic Society and European Respiratory Society (ERS) spirometry reproducibility criteria (22).

Relevant laboratory data, including arterial blood gas, serum bicarbonate levels, lipid panel, fasting glucose, and glycated hemoglobin (HgbA1c), were also obtained via EMR, with the values collected closest to time of the sleep study. Patient-reported outcome data including Epworth Sleepiness Scale, Functional Outcomes Sleep Questionnaire, Insomnia Severity Index, and Patient Health Questionnaire-9 were collected at the time of the sleep study visit through EMR review of the Knowledge Program (23).

This study was Institutional Review Board approved, and consent was waived because of the observational nature of the study (18–1316).

PSG. All patients underwent attended in-laboratory PSG at the Cleveland Clinic Sleep Disorders center in accordance with the American Academy of Sleep Medicine guidelines (24) using Polysmith software (Nihon Kodhen). Data from both PSGs and the diagnostic portion of split night studies were included. Standard 10–20 electroencephalogram, electrocardiogram, electromyography of the chin and bilateral anterior tibialis muscle, electrooculography, and pulse oximetry were monitored. Oral and nasal airflow were measured with a thermistor and nasal cannula. CO_2 was measured with ET_{CO_2} monitoring. Patients' respiratory efforts were measured with plethysmography bands at the chest and abdomen, including summation channel. Sleep staging was classified into awake, non–rapid eye movement sleep with stages N1, N2, N3, and rapid eye movement sleep (stage R sleep). Episodes of apnea were defined as decrease in airflow by $\geq$90% for $\geq$10 seconds and further classified as obstructive, central, or mixed according to the presence or absence of breathing efforts with thoracoabdominal paradox. Episodes of hypopnea were defined as decrease in airflow by $\geq$30% for $\geq$10 seconds along with a decrease in oxygen saturation of $\geq$3% or arousals or $\geq$4% as dictated by insurer. The ET_{CO_2} samples were obtained through oronasal cannulas (Salter Labs) with sidestream technology using a sampling flow

of 75 ml/min with calibrated Nonin RespSense devices. Total system response time (including delay and rise times) was 4 seconds, and the sampling rate for the capnograph tracing was 4 Hz.

Measurements and Definitions

The AHI was determined by the frequency of these respiratory events per hour of the patients' total sleep time. Other PSG data included sleep architecture variables such as sleep efficiency, number of awakenings, sleep latency, rapid eye movement latency, stage shift count, total sleep time, and time of wake after sleep onset. Respiratory variables included mean oxygen saturation (Sa_{O_2}), Sa_{O_2} nadir, sleep time spent with $Sa_{O_2} < 90\%$, wake supine ET_{CO_2}, and time spent with an $ET_{CO_2} \geq 50$ mm Hg, along with the minimum, maximum, and average heart rate.

We defined OHS as BMI $\geq$ 30 kg/m^2 and either a sleep study–based awake $ET_{CO_2} \geq 45$ mm Hg or daytime serum bicarbonate level $\geq$27 mmol/L to be consistent with the ERS task force report stage II–IV (25). The staging classification is based on the notion that earlier stages of hypoventilation solely occur during sleep and more advanced stages involve daytime hypercapnia and comorbidity concordant with disease progression. Stages I and II are characterized by hypoventilation (intermittent hypercapnia) during sleep differentiated by a serum bicarbonate level of $<$27 or $\geq$27 mmol/L, respectively. Stage III is defined as obesity hypoventilation without comorbidities and stage IV as obesity hypoventilation syndrome with established cardiometabolic comorbidities (25). OSA was defined by AHI of $\geq$5 and further classified as mild (AHI, 5–14), moderate (AHI, 15–29), and severe (AHI, $\geq$30).

Statistical Analysis

Continuous variables are presented as mean and standard deviation or medians, whereas categorical variables are presented as percentages. Comparisons between the OHS and non-OHS groups for continuous variables were made with a two-sample *t* test or Wilcoxon rank-sum test based on distribution, whereas Pearson's chi-square test or Fisher's exact test was used for categorical variables. OHS and variables of interest are presented, including demographics (age, sex, and race), metabolic factors (BMI, fasting glucose, HgbA1c, triglyceride levels, high-density lipoprotein, low-density lipoprotein, total cholesterol, and serum bicarbonate levels), pulmonary factors (FVC, FEV_1, and FVC/FEV_1), cardiac factors (left ventricular ejection fraction, right ventricular systolic pressure, and heart rate minimum, maximum, and average), and polysomnographic variables (AHI, Sa_{O_2} mean and nadir, time spent with $Sa_{O_2} < 90\%$, wake supine ET_{CO_2}, and time spent with $ET_{CO_2} \geq 50$ mm Hg). Logistic regression was used to assess the relationship between our main predictors of interest, i.e., AHI and diabetes mellitus, in a hierarchical modeling strategy as follows: age, sex, and race (model 1); age, sex, race, and BMI (model 2); and age, sex race, BMI, and hypertension (model 3). Secondary analyses were conducted to examine age dichotomized at 50 years as a surrogate for menopausal state to assess for age-threshold differences of OHS in women by examining the statistical interaction and conducting a subgroup analysis. Sensitivity analyses were conducted as above excluding data from the diagnostic portion of split night studies. All data were imported into SAS 9.4 (The SAS Institute) for analysis, and analyses were based on 0.05 level of significance.

Results

Of the 2,449 patients, who met initial criteria, 119 patients were excluded because of home sleep apnea test, 577 were excluded for having the sleep study performed after bariatric surgery, 10 were excluded for age $<$18 years, and 25 were excluded for BMI $<$ 30 kg/m^2 (Figure 1). The final analytic sample was composed of 1,718 patients. The

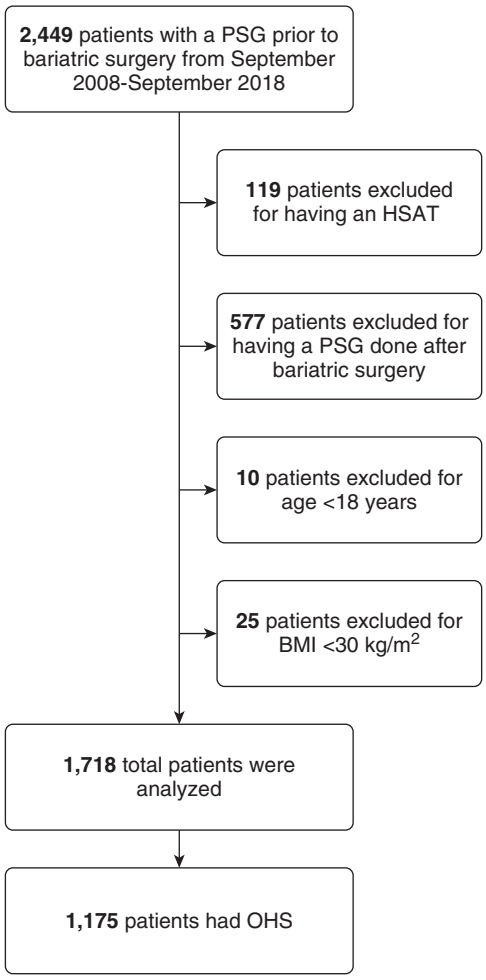

Figure 1. Study inclusion flowchart. BMI = body mass index; HSAT = home sleep apnea test; OHS = obesity hypoventilation syndrome; PSG = polysomnogram.

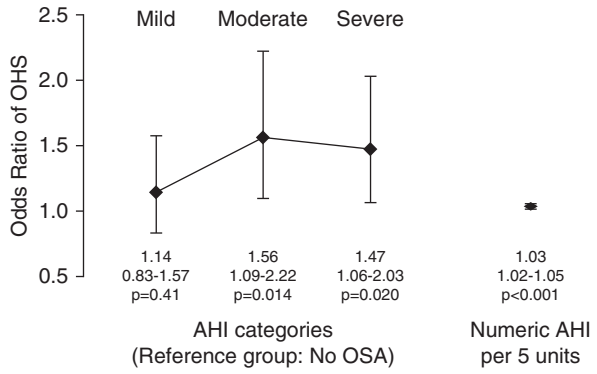

Figure 2. Univariable logistic regression of obesity hypoventilation by apnea–hypopnea index. AHI = apnea–hypopnea index; OHS = obesity hypoventilation syndrome; OSA = obstructive sleep apnea.

majority were white (62.6%), and 20.7% were male, with an average age of 45.3 ± 12.1 years. Average BMI at the time of the sleep study was 48.6 ± 9.0 kg/m^2. Of the 1,718 patients, OHS was observed in 1,175 patients (68.4%). Patients with OHS compared with those without OHS were older (45.8 ± 11.9 years versus 44.3 ± 12.4 years; $P = 0.023$), with a greater prevalence of males (22.2% versus 17.3%; $P = 0.020$), a higher AHI (17.1 [7.7–43.0] versus 13.8 [6.1–34.0]; $P \leq 0.001$), and more time with $Sa_{O_2} < 90\%$ (2.2 [0.30–11.7] versus 0.70 [0.10–5.6]; $P < 0.001$). They also had a higher HgbA1c (6 [5.6–7.0] versus 5.8 [5.5–6.4]; $P < 0.001$), along with diagnoses of diabetes (31.2% versus 23.2%; $P = <0.001$) and hypertension (57.5% versus 49.7%; $P = 0.002$). There was no difference in the patient-reported outcomes questionnaires. The central apnea index was low and similar between both groups, with the overall AHI driven by obstructive events (Table 1).

Unadjusted univariable logistic regression analysis revealed the odds of OHS increased by 5% (1.05; 1.01–1.10) per 5-year increase in age, 7% (1.07; 1.01–1.14) per 5-U increase in BMI, 9% (1.09; 1.05–1.12) per 5% increase in sleep time $Sa_{O_2} < 90\%$, and 12% (1.12; 1.03–1.22) per 1-U increase in HgbA1c. The odds of OHS were 36% higher in males versus females (1.36; 1.05–1.77), 50% higher in those with diabetes (1.50; 1.19–1.90), and 37% higher in those with hypertension (1.37; 1.12–1.68) (Table 2).

In terms of main predictors of interest, for every 5-U increase in the AHI, the odds of OHS increased by 3.4% (1.03; 1.02–1.05). When categorized by severity, there was no significant difference in those with mild OSA; however, those with moderate or severe OSA did have increased OHS odds of 56% and 47%, respectively (Table 3) (Figure 2). Both AHI and diabetes mellitus remained statistically significant in multivariable logistic regression after adjustments for age, sex, race, BMI, and hypertension (Tables 4 and 5).

Secondary age-specific analyses in women revealed lack of a statistically significant interaction of sex and age group (age <50 versus ⩾50) in the logistic model of OHS. Although not statistically significant (perhaps because of the lower percentage of men in the analytic sample), the direction of the test of the interaction suggested little difference of OHS in men ⩾50 versus <50 years of age as opposed to more OHS in women ⩾50 versus <50 years of age. A subgroup analysis for females was performed to assess the effect of age; women of ⩾50 years of age had 40% higher odds of OHS than those <50 years of age (1.40 [1.10–1.78]). With adjustment of age group and covariates (race, baseline BMI, and hypertension), AHI retained a significant relationship with OHS in females (1.03 [1.01–1.05]). A total of 1,100 patients were included in the analytic sample for the secondary sensitivity analysis, which excluded split night studies. Of those 1,100 patients, OHS was observed in 719 patients (65.4%). Findings were consistent with primary results after excluding split night studies, including older age, higher AHI, more time with $Sa_{O_2} < 90\%$, higher HgbAlc, and diagnoses of diabetes and hypertension as significant predictors of OHS. BMI was not significantly different between the two groups in the secondary analysis, with an average BMI of 47.8 ± 8.4 in the OHS group and 47.7 ± 9 in the non-OHS group (Table 6).

Discussion

We report findings from a cohort undergoing bariatric surgery with the most detailed phenotyping to date of nocturnal surrogate arterial partial pressure of carbon dioxide (P_{CO_2}) monitoring during PSG. First, we identify a high prevalence of OHS (68.4%). Second, we identify that OSA severity defined by AHI at moderate to severe levels was associated with OHS, and AHI remained a significant predictor of OHS after consideration of confounding influences of age, sex, race, BMI, and hypertension. Of note, the association of OHS with AHI was driven mainly by OSA and not central sleep apnea. Third, we observe diabetes as a significant predictor of OHS in adjusted analyses, including accounting for BMI, such that the diagnosis of diabetes was associated with a 34% increased odds of OHS (odds ratio, 1.34; 1.04–1.72). These findings were further corroborated by HgbA1c values associated with a 12% increased odds of OHS (odds ratio, 1.12; 1.03–1.22). Other notable individual OHS predictors included increasing age, male sex, increasing sleep time with Sa_{O_2} <90%, and comorbid hypertension.

AHI as a predictor of OHS has been noted in literature, though not consistently (16, 18, 26–28). One particular study evaluated the AHI as a clinical predictor to help identify patients with OHS characterized by a threshold AHI of 100, which had a sensitivity of 45% and a specificity of 86%. Most of our patients did not have an AHI in that range; however, similar to the patient population in this report, the mean BMI was >40 kg/m^2 (18). Yet another study showed that though patients with OHS had more severe OSA, there was no difference once corrected for BMI (17). In contrast, our study showed that the BMI remains a significant OHS contributor in multivariable analyses. There may be shared risk factors between the two disorders, including obesity, or perhaps the underlying blunted ventilatory response leading to CO_2 retention represents a unifying factor contributing to the association of OSA and OHS. Prolonged apneas and hypopneas and shorter duration between events can lead to nocturnal hypercapnia (29). This may lead to an altered ventilatory response and the chronicity of hypercapnia. In addition to

Table 1. Subject characteristics

	Overall (*N* = *1,718*)		Non-OHS (*n* = *543*)		OHS (*n* = *1,175*)	
	N	**Statistics**	***n***	**Statistics**	***n***	**Statistics**
Age	1,718	45.3 ± 12.1	543	44.3 ± 12.4	1,175	45.8 ± 11.9
Male sex	1,718	355 (20.7)	543	94 (17.3)	1,175	261 (22.2)
Race	1,718		543		1,175	
White	—	1,092 (63.6)	—	363 (66.9)	—	729 (62.0)
Black	—	489 (28.5)	—	143 (26.3)	—	346 (29.4)
Other	—	137 (8.0)	—	37 (6.8)	—	100 (8.5)
BMI before sleep study	1,718	48.6 ± 9.0	543	47.8 ± 8.8	1,175	49.0 ± 9.1
Days from sleep study to surgery	1,718	154.0 [91.0–281.0]	543	150.0 [92.0–262.0]	1,175	156.0 [91.0–297.0]
Record type	1,718		543		1,175	
PSG	—	1,100 (64.0)	—	381 (70.2)	—	719 (61.2)
SPLIT	—	618 (36.0)	—	162 (29.8)	—	456 (38.8)
Polysomnographic data						
Sleep time, min	1,718	336.0 [287.0–378.0]	543	329.0 [284.0–369.0]	1,175	340.0 [289.0–381.0]
Sleep efficiency, %	1,718	79.4 [69.2–87.5]	543	78.8 [68.2–87.1]	1,175	79.7 [69.5–87.7]
Sleep latency, min	1,714	18.5 [9.0–35.0]	542	21.0 [10.5–38.5]	1,172	18.0 [8.5–34.0]
REM latency, min	1,694	127.0 [80.0–198.0]	534	124.0 [80.0–192.0]	1,160	127.5 [80.0–202.0]
Arousal index	1,717	22.7 [15.0–34.8]	543	22.0 [14.3–34.1]	1,174	23.0 [15.2–35.1]
Central apnea index	1,715	0.00 [0.00–0.00]	542	0.00 [0.00–0.00]	1,173	0.00 [0.00–0.00]
AHI	1,717	16.1 [7.2–39.5]	543	13.8 [6.1–34.0]	1,174	17.1 [7.7–43.0]
AHI categories	1,717		543		1,174	
No OSA (0–4)	—	230 (13.4)	—	86 (15.8)	—	144 (12.3)
Mild OSA (5–14)	—	583 (34.0)	—	200 (36.8)	—	383 (32.6)
Moderate OSA (15–29)	—	350 (20.4)	—	97 (17.9)	—	253 (21.6)
Severe OSA (⩾30)	—	554 (32.3)	—	160 (29.5)	—	394 (33.6)
Oxygen saturation mean, %	1,717	93.0 [92.0–95.0]	543	94.0 [92.0–95.0]	1,174	93.0 [92.0–95.0]
Sleep time oxygen saturation below 90%, %	1,679	1.7 [0.20–9.7]	531	0.70 [0.10–5.6]	1,148	2.2 [0.30–11.7]
ET_{CO_2}, mm Hg	1,268	49.0 [45.0–53.0]	224	42.0 [40.0–43.0]	1,044	51.0 [47.0–54.0]
Sleep time $ET_{CO_2} \geqslant 45$ mm Hg, %	614	13.1 [1.3–34.9]	92	0.00 [0.00–5.4]	522	17.4 [3.2–38.8]
Sleep time $ET_{CO_2} \geqslant 50$ mm Hg, %	1,556	0.00 [0.00–1.1]	463	0.00 [0.00–0.00]	1,093	0.20 [0.00–3.2]
Heart rate average, bpm	1,718	72.0 [65.0–79.0]	543	72.0 [65.0–79.0]	1,175	71.0 [65.0–79.0]
Pulmonary data						
FVC	163	3.1 ± 0.97	43	3.4 ± 0.88	120	3.1 ± 0.99
FEV_1	163	2.5 ± 0.79	43	2.7 ± 0.78	120	2.4 ± 0.78
FEV_1:FVC	163	80.2 [76.7–83.8]	43	80.2 [77.1–83.2]	120	80.4 [76.4–84.2]
D_{LCO}	53	18.4 [15.3–22.2]	11	17.7 [15.3–24.7]	42	18.5 [15.1–22.2]
Cardiac data						
LVEF, %	679	60.0 [56.0–64.0]	198	60.0 [56.0–64.0]	481	60.0 [56.0–64.0]
RVSP	68	35.0 [28.0–39.5]	15	36.0 [27.0–39.0]	53	34.0 [29.0–40.0]
Laboratory data						
ABG pH	86	7.4 [7.4–7.4]	23	7.4 [7.3–7.4]	63	7.4 [7.4–7.4]
ABG P_{CO_2}	95	42.0 [38.0–47.0]	29	42.0 [38.0–49.0]	66	42.0 [37.6–46.4]
ABG P_{O_2}	86	82.4 [69.0–116.0]	23	87.0 [69.0–150.0]	63	82.1 [69.0–113.0]
ABG HCO_3	86	25.1 ± 3.8	23	23.4 ± 3.7	63	25.7 ± 3.6
Serum HCO_3	1,679	25.0 ± 2.7	538	23.7 ± 2.0	1,141	25.6 ± 2.8
Total cholesterol	1,569	175.0 [154.0–199.0]	493	173.0 [153.0–195.0]	1,076	176.0 [154.0–202.0]
Hemoglobin A1c, %	1,337	5.9 [5.6–6.8]	426	5.8 [5.5–6.4]	911	6.0 [5.6–7.0]
Glucose fasting	87	94.0 [88.0–118.0]	28	92.0 [88.5–118.5]	59	94.0 [87.0–118.0]
Questionnaire data						
ESS	1,102	6.0 [4.0–11.0]	347	6.0 [3.0–10.0]	755	6.0 [4.0–11.0]
FOSQ	880	18.0 [16.0–20.0]	272	19.0 [16.0–20.0]	608	18.0 [16.0–20.0]
ISI	761	10.0 [4.0–15.0]	249	9.0 [3.0–15.0]	512	10.0 [5.0–15.0]
PHQ9	1,164	4.0 [1.00–9.0]	375	4.0 [1.00–10.0]	789	4.0 [1.00–9.0]
Comorbidities						
Atrial fibrillation	1,718	48 (2.8)	543	16 (2.9)	1,175	32 (2.7)
Heart failure	1,718	35 (2.0)	543	11 (2.0)	1,175	24 (2.0)
Diabetes	1,718	493 (28.7)	543	126 (23.2)	1,175	367 (31.2)
Hypertension	1,718	946 (55.1)	543	270 (49.7)	1,175	676 (57.5)

Definition of abbreviations: ABG = arterial blood gas; AHI = apnea–hypopnea index; BMI = body mass index; bpm = beats per minute; D_{LCO} = diffusing capacity of lung for carbon monoxide; ESS = Epworth Sleepiness Scale; ET_{CO_2} = end-tidal CO_2; FEV_1 = forced expiratory volume in 1 second; FOSQ = functional outcomes of sleep questionnaire; FVC = forced vital capacity; HCO_3 = serum bicarbonate; ISI = insomnia severity index; LVEF = left ventricular ejection fraction; OHS = obesity hypoventilation syndrome; OSA = obstructive sleep apnea; P_{CO_2} = partial pressure of carbon dioxide; PHQ9 = patient health questionnaire; P_{O_2} = partial pressure of oxygen; PSG = polysomnogram; REM = rapid eye movement; RVSP = right ventricular systolic pressure; SPLIT = PSG with titration.
Statistics presented as mean ± standard deviation, median [P25–P75], or *n* (column %).

Table 2. Univariable logistic regression models of obesity hypoventilation syndrome

Variable	*N*	OR (95% CI)	*P* Value
Age	1,718	1.01 (1.00–1.02)	***0.023***
Sex: M vs. F	1,718	1.36 (1.05–1.77)	***0.020***
Race	1,718		0.14
White vs. Black		0.83 (0.66–1.05)	0.12
Other vs. Black		1.12 (0.73–1.71)	0.61
BMI	1,718	1.01 (1.00–1.03)	***0.015***
Polysomnographic data			
AHI (per 1 U)	1,717	1.01 (1.00–1.01)	***<0.001***
Arousal index	1,717	1.00 (1.00–1.01)	0.68
Central apnea index	1,715	0.91 (0.82–1.00)	***0.044***
Oxygen saturation mean, %	1,717	0.87 (0.83–0.91)	***<0.001***
Sleep time oxygen saturation <90%	1,679	1.02 (1.01–1.02)	***<0.001***
Sleep time $ET_{CO_2} \geqslant 45$ mm Hg, %	614	1.06 (1.04–1.08)	***<0.001***
Sleep time $ET_{CO_2} \geqslant 50$ mm Hg, %	1,556	1.03 (1.02–1.04)	***<0.001***
Heart rate average, bpm	1,718	1.00 (0.99–1.01)	0.35
Pulmonary data			
FVC	163	0.71 (0.49–1.02)	0.063
FEV_1	163	0.65 (0.41–1.01)	0.055
FEV_1:FVC	163	1.00 (0.96–1.05)	0.83
Cardiac data			
LVEF, %	679	1.01 (0.99–1.04)	0.22
RVSP	68	1.00 (0.95–1.06)	0.92
Laboratory data			
ABG P_{CO_2}	86	0.98 (0.94–1.02)	0.27
ABG P_{O_2}	95	1.00 (0.99–1.01)	0.53
ABG HCO_3	86	1.17 (1.02–1.34)	***0.021***
Total cholesterol	1,569	1.00 (1.00–1.00)	0.19
Hemoglobin A1c, %	1,337	1.12 (1.03–1.22)	***0.007***
Glucose fasting	87	1.00 (0.99–1.01)	0.53
Questionnaire data			
ESS	1,102	1.03 (1.00–1.05)	***0.050***
FOSQ	880	1.00 (0.95–1.05)	0.92
ISI	761	1.01 (0.99–1.03)	0.45
PHQ9	1,164	1.00 (0.98–1.02)	0.90
Comorbidities			
Diabetes	1,718	1.50 (1.19–1.90)	***<0.001***
Hypertension	1,718	1.37 (1.12–1.68)	***0.003***

Definition of abbreviations: ABG = arterial blood gas; AHI = apnea–hypopnea index; BMI = body mass index; bpm = beats per minute; ESS = Epworth Sleepiness Scale; ET_{CO_2} = end-tidal CO_2; FEV_1 = forced expiratory volume in 1 second; FOSQ = functional outcomes of sleep questionnaire; FVC = forced vital capacity; HCO_3 = serum bicarbonate; ISI = insomnia severity index; LVEF = left ventricular ejection fraction; PHQ9 = patient health questionnaire; P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen; RVSP = right ventricular systolic pressure.
Bold and italicized *P* values are statistically significant.

reduced chest wall compliance from obesity, it is possible that OSA, in itself, is a risk factor for OHS. However, the lack of consistency in AHI findings relative to OHS among studies suggests further investigation may be needed (16, 18, 26–28).

The odds of OHS was 50% higher in those with diabetes mellitus in the current study. Prolonged hyperglycemia measured by elevated HgbA1c levels has been shown to be associated with an increase in basal metabolic rate in OHS through mechanisms of increased gluconeogenesis and lipid oxidation (11, 12). A high resting metabolic rate had a significant relation with abnormal levels of HgbA1c but not with high fasting glucose, thereby indicating more of a long-term effect of poor glucose control compared with short-term effects (11). This is consistent with our results, as HgbA1c was significantly associated with OHS, but fasting glucose was not. This notable HgbA1c finding was also observed in a smaller-scale study ($n = 53$) focused on examination of endothelial dysfunction and systemic inflammation in those with OHS (8). Patients with OHS were compared with those with obesity who were eucapnic, with results demonstrating higher levels of HgbA1c in those with versus without OHS (7.3 ± 4.3 versus 6.1 ± 1.7, respectively) along with greater usage of antihypertensive medications (8).

Other notable factors associated with OHS identified in our study include age, male sex, race, and percentage of sleep time with $Sa_{O_2} < 90\%$. Neither age nor sex have been recognized as an associated factor or notable predictor in the development of OHS; however, these characteristics are associated with OSA, the latter observed in approximately 90% of patients with OHS (9). It is recognized that increasing age is associated with increasing OSA prevalence (30). Although large magnitude sex-specific differences in hypoxic ventilatory responses have been observed—findings not seen with hypercapnic ventilatory response—it remains unclear whether this represents an explanatory factor of our findings of male sex as a predictor of OHS (31). Other studies have shown that there is actually higher prevalence of OHS in females, particularly postmenopausal females. Results of our subgroup analyses showing higher odds of OHS in women >50 versus <50 years of age support this observation. The withdrawal of progesterone may contribute to the decrease in the hypercapnic ventilatory response along with decreased muscle tone in the upper airway. Another proposed mechanism is a higher level of leptin resistance in females, as there is also a higher level of leptin in females with obesity versus males with obesity (32, 33). Although the majority of our cohort were female, most were likely not yet postmenopausal, as the

Table 3. Univariable logistic regression models of obesity hypoventilation syndrome by apnea–hypopnea index ($N = 1,717$)

Variable	OR (95% CI)	*P* Value
AHI per 5 U	1.03 (1.02–1.05)	***<0.001***
AHI categories		***0.020***
Mild vs. no OSA	1.14 (0.83–1.57)	0.41
Moderate vs. no OSA	1.56 (1.09–2.22)	***0.014***
Severe vs. no OSA	1.47 (1.06–2.03)	***0.020***

Definition of abbreviations: AHI = apnea–hypopnea index; CI = confidence interval; OR = odds ratio; OSA = obstructive sleep apnea.
Bold and italicized P values are statistically significant.

Table 4. Logistic regression models of obstructive sleep apnea as a predictor of obesity hypoventilation syndrome ($N = 1,717$)

Model	Variable	OR (95% CI)	*P* Value
Model 1	AHI per 5 U	1.03 (1.01–1.05)	***0.002***
	Age	1.01 (1.00–1.02)	0.064
	Sex: M vs. F	1.18 (0.89–1.57)	0.25
	Race		*0.032*
	White vs. Black	0.77 (0.60–0.97)	*0.026*
	Other vs. Black	1.10 (0.72–1.68)	0.67
Model 2	AHI per 5 U	1.02 (1.01–1.04)	***0.015***
	Age	1.01 (1.00–1.02)	*0.020*
	Sex: M vs. F	1.20 (0.91–1.60)	0.20
	Race		*0.041*
	White vs. Black	0.78 (0.61–0.98)	*0.035*
	Other vs. Black	1.11 (0.72–1.70)	0.64
	BMI before	1.01 (1.00–1.03)	*0.031*
Model 3	AHI per 5 U	1.02 (1.004–1.04)	***0.018***
	Age	1.01 (1.00–1.02)	0.10
	Sex: M vs. F	1.17 (0.88–1.56)	0.27
	Race		*0.049*
	White vs. Black	0.78 (0.62–0.99)	*0.042*
	Other vs. Black	1.12 (0.73–1.71)	0.62
	BMI before	1.01 (1.00–1.03)	*0.045*
	Hypertension	1.21 (0.97–1.51)	0.089

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CI = confidence interval; OR = odds ratio.
Bold and italicized *P* values are statistically significant.

average age was 45 years; however, our data is limited. Our results show that white individuals are less likely to develop OHS compared with Black patients. There are limited data focused on examination of race in OHS; however, in OSA prevalence, middle-aged Black patients are comparable with other race groups, although there appear to be differing underlying contributing risk factors. Moreover, a higher prevalence has been identified in Black individuals younger than 25 years or older than 65 years (34, 35). Our cohort consisted mainly of middle-aged white males and females. Candidate factors potentially playing a role in race-based differences included BMI and anatomical factors that could influence airway sizes and lung volumes and/or underlying genetic susceptibilities.

Table 5. Logistic regression models of diabetes mellitus as a predictor of obesity hypoventilation syndrome ($N = 1,717$)

Model	Variable	OR (95% CI)	*P* Value
Model 1	Diabetes mellitus	1.40 (1.09–1.78)	***0.007***
	Age	1.01 (1.00–1.02)	0.10
	Sex: M vs. F	1.33 (1.02–1.73)	*0.036*
	Race		0.064
	White vs. Black	0.79 (0.63–1.01)	0.055
	Other vs. Black	1.12 (0.73–1.71)	0.61
Model 2	Diabetes mellitus	1.39 (1.09–1.77)	***0.009***
	Age	1.01 (1.00–1.02)	*0.029*
	Sex: M vs. F	1.31 (1.01–1.72)	*0.045*
	Race		0.076
	White vs. Black	0.80 (0.63–1.02)	0.069
	Other vs. Black	1.13 (0.73–1.73)	0.58
	BMI before	1.02 (1.01–1.03)	*0.005*
Model 3	Diabetes mellitus	1.34 (1.04–1.72)	***0.022***
	Age	1.01 (1.00–1.02)	0.082
	Sex: M vs. F	1.29 (0.99–1.69)	0.063
	Race		0.083
	White vs. Black	0.81 (0.64–1.02)	0.076
	Other vs. Black	1.13 (0.74–1.74)	0.57
	BMI before	1.02 (1.00–1.03)	*0.008*
	Hypertension	1.15 (0.92–1.45)	0.21

Definition of abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio.
Bold and italicized *P* values are statistically significant.

Patient-reported outcome questionnaires did not demonstrate distinct differences in OHS versus non-OHS groups. Those with OHS were not noted to have more daytime sleepiness, depression, or insomnia. The findings of lack of daytime sleepiness differences are somewhat unanticipated, as those with OHS are often noted to have hypersomnia as part of their clinical presentation. Hypercapnia in itself can cause hypersomnolence via reduction of electroencephalogram activation, leading to slower electroencephalogram spectral activity (36). Coupled with sleep-disordered breathing and the cyclical respirations of apneas and hypopneas, hypoxia, and hypercapnia, it is common for patients to have daytime sleepiness. A more mild presentation of OHS, especially fairly early in the disease progression, may explain late diagnoses and, overall, underdiagnosis of OHS. This may make it difficult for the clinician to suspect the diagnosis and emphasizes the need for higher level of suspicion and clinical judgement. The clinician would not be able to differentiate on history and patient-reported symptoms alone. Because of this, it is reasonable to have clinicians rely on the official American Thoracic Society guidelines on the evaluation OHS. For patients with low to moderate suspicion of OHS, the use of serum bicarbonate threshold of <27 mmol/L can reasonably exclude the diagnosis of OHS in patients with obesity with sleep-disordered breathing and confirmation testing with Pa_{CO_2} for serum bicarbonate levels $\geqslant 27$ mmol/L (6). However, this evaluation would exclude stage I of the ERS definition spectrum of OHS, which includes patients with sleep-related hypoventilation without elevated serum bicarbonate levels of $\geqslant$27 mmol/L.

Our study has both strengths and weaknesses. We leveraged data from a large clinic-based cohort of patients undergoing bariatric surgery who, as part of routine care, obtain comprehensive sleep medicine evaluations inclusive of PSG with routine ET_{CO_2} monitoring. Our large sample size also allowed for consideration of multiple

Table 6. Data summary excluding split night studies

Factor	Overall (*N* = 1,100)		Non-OHS (*n* = 381)		OHS (*n* = 719)		
	N	Statistics	*n*	Statistics	*n*	Statistics	*P* Value
Age	1,100	43.7 ± 12.0	381	42.5 ± 12.0	719	44.4 ± 12.0	***0.014****
Male	1,100	128 (11.6)	381	40 (10.5)	719	88 (12.2)	0.39†
Race	1,100		381		719		0.51†
White	—	690 (62.7)	—	244 (64.0)	—	446 (62.0)	—
Black	—	324 (29.5)	—	112 (29.4)	—	212 (29.5)	—
Other	—	86 (7.8)	—	25 (6.6)	—	61 (8.5)	—
BMI	1,100	47.8 ± 8.6	381	47.7 ± 9.0	719	47.8 ± 8.4	0.82*
Days from sleep study to surgery	1,100	151.0 [93.5–268.0]	381	160.0 [99.0–272.0]	719	150.0 [90.0–268.0]	0.33‡
Polysomnographic data							
Sleep time, min	1,100	340.0 [293.0–379.5]	381	335.0 [292.0–373.0]	719	343.0 [293.0–382.0]	0.13‡
Sleep efficiency, %	1,100	80.6 [70.7–88.5]	381	80.8 [70.9–88.5]	719	80.6 [70.6–88.6]	0.88‡
Sleep latency, min	1,098	20.0 [10.5–38.5]	380	21.5 [11.0–41.8]	718	19.5 [10.5–37.0]	0.15‡
REM latency, min	1,086	118.0 [77.0,192.0]	376	114.0 [75.0,185.5]	710	120.5 [78.0–195.0]	0.31‡
Arousal index	1,099	20.6 [14.1–31.1]	381	19.7 [13.3–30.9]	718	21.0 [14.5–31.4]	0.40‡
Central apnea index	1,099	0.00 [0.00–0.00]	381	0.00 [0.00–0.00]	718	0.00 [0.00–0.00]	0.30‡
Apnea–hypopnea index	1,100	9.8 [5.2–18.8]	381	8.9 [5.1–17.7]	719	10.6 [5.3–20.0]	***0.035***‡
AHI category	1,100		381		719		0.17‡
No OSA (0–5)	—	230 (20.9)	—	86 (22.6)	—	144 (20.0)	—
Mild OSA (5–14)	—	501 (45.5)	—	179 (47.0)	—	322 (44.8)	—
Moderate OSA (15–29)	—	242 (22.0)	—	71 (18.6)	—	171 (23.8)	—
Severe OSA (⩾30)	—	127 (11.5)	—	45 (11.8)	—	82 (11.4)	—
Oxygen saturation mean, %	1,099	94.0 [93.0–95.0]	381	94.0 [93.0–95.0]	718	94.0 [92.0–95.0]	***<0.001***‡
Sleep time oxygen saturation below 90%	1,071	0.70 [0.10–3.6]	373	0.40 [0.00–2.2]	698	0.90 [0.10–4.4]	***<0.001***‡
ET_{CO_2}, mm Hg	802	49.0 [45.0–53.0]	155	42.0 [40.0–43.0]	647	51.0 [47.0–54.0]	***<0.001***‡
Sleep time ET_{CO_2} ⩾ 45 mm Hg, %	391	14.7 [1.1–49.1]	69	0.00 [0.00–6.0]	322	24.9 [3.0–55.6]	**<0.001**‡
Sleep time ET_{CO_2} ⩾ 50 mm Hg, %	1,013	0.00 [0.00–0.80]	336	0.00 [0.00–0.00]	677	0.20 [0.00–1.8]	***<0.001***‡
Heart rate average, bpm	1,100	72.0 [65.0–79.0]	381	73.0 [66.0–79.0]	719	72.0 [65.0–78.0]	0.081‡
Pulmonary data							
FVC	99	3.2 ± 0.94	38	3.4 ± 0.89	61	3.1 ± 0.96	0.18*
FEV_1	99	2.5 ± 0.79	38	2.7 ± 0.79	61	2.5 ± 0.78	0.22*
FEV_1:FVC	99	80.8 [77.4–83.5]	38	80.3 [77.1–83.3]	61	81.1 [77.7–83.8]	0.75‡
D_{LCO}	31	16.9 [11.6–19.8]	10	17.1 [15.3–24.7]	21	16.9 [9.5–18.4]	0.19‡
Cardiac data							
LVEF, %	406	60.0 [56.0–64.0]	130	60.5 [56.0–64.0]	276	60.0 [57.0–65.0]	0.87‡
RVSP	44	33.0 [29.0–39.0]	11	37.0 [31.0–43.0]	33	33.0 [29.0–39.0]	0.33‡
Laboratory data							
ABG pH	42	7.4 [7.4–7.4]	10	7.3 [7.3–7.4]	32	7.4 [7.4–7.4]	***0.010***‡
ABG P_{CO_2}	49	42.0 [37.6–49.0]	15	46.0 [38.0–55.0]	34	41.6 [37.0–46.0]	0.39‡
ABG P_{O_2}	42	89.0 [74.8–131.0]	10	81.5 [62.0–110.0]	32	89.4 [76.0–131.0]	0.29‡
ABG HCO_3	42	24.7 ± 3.9	10	22.6 ± 4.6	32	25.4 ± 3.4	***0.046****
Serum HCO_3	1,078	24.7 ± 2.6	377	23.7 ± 2.0	701	25.3 ± 2.7	**<0.001***
Total cholesterol	1,007	177.0 [154.0–200.0]	343	175.0 [154.0–196.0]	664	177.0 [155.0–203.0]	0.38‡
Hemoglobin A1c, %	856	5.8 [5.5–6.5]	293	5.7 [5.4–6.2]	563	5.9 [5.6–6.7]	**<0.001**‡
Glucose fasting	74	93.5 [88.0–113.0]	23	92.0 [85.0–113.0]	51	94.0 [88.0–115.0]	0.62‡
Questionnaire data							
ESS	701	6.0 [3.0–10.0]	240	6.0 [4.0–10.0]	461	6.0 [3.0–10.0]	0.65‡
FOSQ	537	19.0 [16.0–20.0]	182	19.0 [16.0–20.0]	355	19.0 [16.0–20.0]	0.48‡
ISI	482	9.0 [4.0–15.0]	171	9.0 [3.0–15.0]	311	9.0 [4.0–15.0]	0.92‡
PHQ9	738	4.0 [1.00–10.0]	264	4.0 [1.00–10.0]	474	4.0 [1.00–9.0]	0.96‡
Comorbidities							
Atrial fibrillation	1,100	20 (1.8)	381	8 (2.1)	719	12 (1.7)	0.61†
Heart failure	1,100	19 (1.7)	381	5 (1.3)	719	14 (1.9)	0.44†
Diabetes	1,100	275 (25.0)	381	74 (19.4)	719	201 (28.0)	***0.002***†
Hypertension	1,100	547 (49.7)	381	172 (45.1)	719	375 (52.2)	***0.027***†

Definition of abbreviations: ABG = arterial blood gas; AHI = apnea–hypopnea index; BMI = body mass index; bpm = beats per minute; D_{LCO} = diffusing capacity of lung for carbon monoxide; ESS = Epworth Sleepiness Scale; ET_{CO_2} = end-tidal CO_2; FEV_1 = forced expiratory volume in 1 second; FOSQ = functional outcomes of sleep questionnaire; FVC = forced vital capacity; HCO_3 = serum bicarbonate; ISI = insomnia severity index; LVEF = left ventricular ejection fraction; OHS = obesity hypoventilation syndrome; OSA = obstructive sleep apnea; P_{CO_2} = partial pressure of carbon dioxide; PHQ9 = patient health questionnaire; P_{O_2} = partial pressure of oxygen; REM = rapid eye movement; RVSP = right ventricular systolic pressure.
Statistics presented as mean ± standard deviation, median [P25–P75], or *n* (column %). Bold and italicized P values are statistically significant.
*Two-sample *t* test.
†Pearson's chi-square test.
‡Kruskal-Wallis test.

factors, including lung function testing via pulmonary function tests and cardiac function indices via echocardiogram. However, this was a retrospective study, which limited the analysis to incomplete and/or noncontemporaneous data (pulmonary, cardiac, and laboratory factors). The monitoring of CO_2 was through ET_{CO_2}, which only serves as a surrogate for P_{CO_2}. ET_{CO_2} tends to underestimate P_{CO_2}, and the lack of direct arterial P_{CO_2} levels may contribute to measurement error, particularly in patients with obesity and OSA (37). This may lead to an overall underestimation to the prevalence of OHS found in this study. The cross-sectional nature of the study precludes inferences of causality. There was variability between timing of the sleep study relative to bariatric surgery, i.e., ranging from 3 to 9 months; however, the focus of our study was examination of factors collected concordant with the sleep study, such as metabolic and cardiorespiratory measures. Our patient population consisted of young patients with severe obesity who were considered suitable for bariatric surgery; as such, our findings would not be generalizable to all those with OHS. Other important covariates that were not factored into our study include smoking, alcohol consumption, and central obesity. Future studies including these factors should be considered.

OHS is a severe obesity–related comorbidity that has many negative health consequences. It leads to adverse pulmonary, cardiovascular, and metabolic abnormalities. Most patients are not diagnosed until they develop respiratory failure or symptoms of cor pulmonale. The index of suspicion must be high to make an early diagnosis and start appropriate treatment to prevent all the negative health consequences. The bariatric surgery population is at risk for OHS, and, as our study showed, two-thirds of this population met criteria for stages II–IV OHS. A major predictive factor is AHI severity and, along with long-term glucose intolerance, male sex, and older age, informs and reinforces the need for future studies assessing OHS in the bariatric surgery population. Better understanding of the underlying mechanisms of these abnormalities would better inform the pathophysiology of OHS and its management. Further studies focused on examination of early detection of OHS treatment and the rate of perioperative complications and postoperative bariatric surgery outcomes are also needed. Further breakdown of the differences between the ERS stages would also be helpful to examine the progression of the OHS spectrum. A high clinical suspicion of OHS, especially in the bariatric surgery population, with assessment of risk factors will help with facilitating diagnosis and therefore treatment. ■

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