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ORIGINAL ARTICLE

The clinical characteristics and hospital and post-hospital survival of patients with the obesity hypoventilation syndrome: analysis of a large cohort

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Summary

Objective

The worldwide prevalence of obesity has reached epidemic proportions. Obesity hypoventilation syndrome (OHS) is a common yet largely undiagnosed and mistreated condition that likely carries a high mortality. The aim of this study was to determine the clinical characteristics, hospital outcome, outcome following hospital discharge and predictors of death in a large cohort of patients hospitalized with OHS. OHS is an important condition as many patients with this syndrome are misdiagnosed and receive inappropriate treatment.

Methods

We reviewed the electronic medical records of patients with unequivocal OHS admitted to a 525-bed tertiary-care teaching hospital over a 5-year period. Demographic and clinical data as well as hospital disposition were recorded. In order to determine the patients' post-discharge status, we linked our database to the database of death certificates of the State Registrar of Vital Records.

Results

We identified 600 patients who met the inclusion criteria for this study. The patients' mean age was 58 ± 15 years with a mean body mass index of $48.2 \pm 8.3\ kg\ m^{-2}$; 64% were women. Thirty-seven percent had a history of diabetes and 43% had been misdiagnosed as having chronic obstructive pulmonary disease, while none had been previously diagnosed with OHS. The most common admission diagnoses were respiratory failure, heart failure and sepsis. Ninety (15%) patients died during the index hospitalization. The patients' age, S-creatinine, respiratory failure, sepsis and admission to the ICU were independent predictors of hospital mortality. The hospital survivors were followed for a mean of $1{,}174 \pm 501$ d (3.2 ± 1.3 years) from the index hospitalization. On follow-up, 98 of the 510 (19%) hospital survivors died, with an overall cumulative mortality of 31.3%. The patients' age, S-creatinine and admission to the ICU were independent predictors of post-hospital mortality.

Conclusion

Obesity hypoventilation syndrome is a common disease that is frequently misdiagnosed and mistreated and carries a 3-year morality, which is significantly worse than that for most cancers combined. Considering the high mortality of this disease, all patients with a body mass index $> 35\ kg\ m^{-2}$ should be screened for OHS; those patients with both early and established OHS should be referred to a pulmonary and/or sleep specialist for evaluation for non-invasive positive pressure ventilation, to a dietician for dietary counseling and lifestyle modification and to a bariatric surgeon for evaluation for bariatric surgery.

Keywords: Mortality, obesity, obesity hypoventilation syndrome, sleep discorded breathing.

Obesity has become a global health problem and a major cause of death and disability (1). Obesity independently affects the development and progression of cardiac, cerebrovascular and renal disease (2–4). Recently there has been increased recognition of the respiratory complications of obesity including the obesity hypoventilation syndrome (OHS), sleep disordered breathing, acute on chronic hypercapnic respiratory failure and the recently described malignant obesity hypoventilation syndrome (MOHS) (5–7). OHS is defined as the combined presence of obesity (body mass index [BMI] $> 30\,kg\,m^{-2}$) and daytime arterial hypercapnia ($PaCO_2 > 45$ mmHg) in the absence of other causes of hypoventilation (5,8,9). Lung function tests in patients with OHS demonstrate a restrictive pattern. OHS is distinguished from the 'overlap syndrome', which is the term used to describe the association of chronic obstructive pulmonary disease (COPD), obesity and obstructive sleep apnea (OSA) (10). OHS was classically described as 'Pickwickian Syndrome' in a 1956 case report by Burwell (11). This patient resembled a character depicted by Dickens in his story, *The Posthumous Papers of the Pickwick Club,* because both were obese with excessive hypersomnolence

Daytime hypercapnia is the distinguishing feature of OHS that separates it from simple obesity and OSA. Hypercapnia in these patients is entirely due to hypoventilation given that a short course of non-invasive positive pressure therapy improves hypercapnia without any significant changes in body weight, carbon dioxide production or volume of the dead space (12). It has been postulated that altered respiratory mechanics leading to a marked increase in the work of breathing with a 'resetting' of the hypothalamic respiratory center is the major factor leading to hypoventilation (13). Additionally, it is likely that insulin and leptin resistance may play a role in the pathophysiology of OHS. (5,8,14–17)

The precise prevalence of OHS is unknown, and it is likely that most patients remain undiagnosed; it is estimated to be present in between 20% and 30% of obese patients with OSA and between 0.15% and 0.3% of the general population (13,18,19). As obesity is associated with multiple serious medical disorders, it is likely that the prevalence of OHS is higher in hospitalized patients. Furthermore, as the prevalence of obesity is increasing, it is likely that the number of hospitalized patients with OHS will increase. Patients with OHS usually have other obesity-associated end-organ dysfunction. We have previously described a multi-system disease related to obesity and have coined the term the 'malignant obesity hypoventilation syndrome' to describe this entity (6). The clinical characteristics, outcomes and prognostic factors of patients with OHS have been poorly described and usually only in small studies. The goal of this study was to determine the clinical characteristics, hospital outcome, outcome following hospital discharge and predictors of death in a cohort of patients hospitalized with the OHS.

Methods

This was a retrospective study of existing data in the electronic medical record (EMR) of the Sentara Norfolk General Hospital (SNGH), located in Norfolk Virginia. The Sentara Norfolk General Hospital is a 525-bed tertiary-care facility and the major teaching hospital and referral center for the Hampton Roads area with a population in excess of 1.6 million. We queried our EMR (EPIC, Verona, WI, USA) from January 1, 2009 to December 31, 2013 to identify adult patients meeting the following criteria: (i) age > 18 and < 90 years; (ii) a BMI $\geq 40\,kg\,m^{-2}$; (iii) a daytime $PaCO_2 > 45$ mmHg and (iv) an admission $HCO_3 > 28\,mEq\,L^{-1}$. Patients were excluded if they had (i) intrinsic lung disease, (ii) thoracic musculoskeletal/neuromuscular disease, (iii) a greater than 20-pack year smoking history or (iv) evidence of obstructive lung disease on pulmonary function testing. The patients' clinical and demographic data including age, sex, race, major admitting diagnoses, comorbidities, previous diagnosis of COPD, OHS and OSA, ICU admission status, length of hospital stay and laboratory data were abstracted from the EMR. For patients with multiple hospital admissions during the study period, only data from the first admission were abstracted. The hospital disposition from the first hospitalization was recorded. We identified patients who had bariatric surgery by searching for the string 'bariatric surgery' in any of the diagnoses codes; in addition, we searched each patient's entire electronic medical record for the Current Procedural Terminology codes for bariatric surgery (43770, 73775, 43644, 43645, 43845, 43846 and 43847).

The patient's full name and date of birth were provided to the State Registrar of Vital Records for the states of Virginia and North Carolina in January 2015 via secured e-mail for comparison with their database of death certificates on file. The merged database with follow-up alive/dead status as per the state's vital records was de-identified by Sentara Information Technology specialists. The final data set was provided in an Excel spreadsheet (Microsoft, Redmond, WA, USA) without any personal health identifiers. Statistical analysis was performed using NCSS 10 (Kaysville, UT, USA). Summary statistics were generated to describe the clinical data (mean and standard deviation, ranges and percentages). Chi-squared analysis with Fisher's exact test (when appropriate) and Student's *t*-test (Mann–Whiney *U*-test for non-normal distributions) were used to compare data

between survivors and non-survivors. Logistic regression and Cox regression analysis was performed to determine the independent predictors of hospital and post-hospital survival with odds ratios and 95% confidence intervals. Spearman's test was used to determine the correlation between variables. Unless otherwise stated, all data are expressed as mean ± SD, with statistical significance declared for probability values of 0.05 or less. The study was approved by the Institutional Review Board of the Eastern Virginia Medical School and Sentara Health Systems (#14-050WC0095).

Results

We identified 600 patients who met all of the inclusion and none of the exclusion criteria. The patients' mean age was 58 ± 15 years with a mean BMI of 48.2 ± 8.3 kg m^{-2}; 64% of patients were women, 45% were Caucasian and 45% were African–American. Thirty-seven percent had a history of diabetes mellitus, 28% had hypertension and 14% had been diagnosed with OSA. Forty-three percent of patients had erroneously been diagnosed with having COPD. The mean presenting $PaCO_2$ was 55.6 ± 9.8 mmHg while the S-creatinine was 1.59 ± 1.73 mg dL^{-1}. The BMI correlated poorly with the $PaCO_2$ ($r = 0.14$) and S-creatinine ($r = -0.05$). None of the patients had a preadmission diagnosis of OHS; 61 (10%) patients had 'obesity hypoventilation syndrome' listed as a diagnosis on the hospital discharge summary; these 61 patients had all been admitted to the ICU. Ninety (15%) patients expired during the index hospital admission with 370 (62%) being discharged home and 84 (14%) being discharged to a subacute nursing facility. The clinical characteristics of the entire cohort by stratification according to hospital outcome are listed in Table 1 together with univariate predictors of outcome. S-creatinine was 1.3 ± 1.5 mg dL^{-1} in those patients who survived to hospital discharge compared with 2.8 ± 2.1 mg dL^{-1} in those who died ($p < 0.001$); the BMI and $PaCO_2$ did not predict hospital outcome. The hospital survivors were followed for a mean of 1,174 ± 501 d (3.2 ± 1.3 years) from the index hospitalization (range 380–2,186 d). On follow-up, 98 of the 510 (19%) hospital survivors died, with an overall cumulative mortality of 31.3%. The clinical characteristics of the hospital survivors stratified by post-discharge survival status are listed in Table 2. The independent predictors of hospital and post-discharge survival are listed in Table 3. A single patient underwent bariatric surgery (gastric band procedure) during the observation period (January 2009 to January 2015).

Table 1 Clinical characteristics of the cohort of patients with obesity hypoventilation syndrome stratified by hospital survival

	All ($n = 600$)	Survivors ($n = 510$)	Died ($n = 90$)	p-value[†]
Age	58.4 ± 15.2	57.2 ± 14.9	65.6 ± 14.7	<0.001
Sex: male (*n*, %)	216 (36%)	181 (36%)	35 (39%)	NS
Race				
Caucasian	270 (45%)	225 (44%)	45 (50%)	
African–American	272 (45%)	231 (45%)	41 (46%)	NS
BMI (kg m^{-2})	48.2 ± 8.3	48.3 ± 8.6	47.6 ± 6.6	NS
S-creatinine (mg dL^{-1})	1.59 ± 1.73	1.3 ± 1.5	2.8 ± 2.1	<0.001
HbA1C (%) ($n = 192$)	7.3 ± 1.9	7.3 ± 2.0	7.1 ± 1.2	NS
$PaCO_2$ (mmHg)	55.6 ± 9.8	54.8 ± 9.3	56.7 ± 12.5	NS
Comorbidities (*n*, %)				
Diabetes mellitus	223 (37%)	192 (38%)	31 (34%)	NS
Hypertension	167 (28%)	140 (27%)	27 (30%)	NS
OSA	74 (14%)	66 (13%)	8 (8.8%)	NS
Admission diagnosis (*n*, %)				
Respiratory failure	376 (63%)	300 (59%)	76 (84%)	<0.001
Heart failure	235 (39%)	198 (39%)	37 (41%)	NS
Infection	250 (41%)	190 (37%)	60 (67%)	<0.001
Pneumonia	124 (20%)	91 (18%)	33 (37%)	<0.001
Cellulitis	37 (6%)	33 (6%)	4 (4%)	NS
Decubitus ulcer	21 (3.5%)	15 (2.9%)	6 (6.6%)	NS
DVT/PE	33 (6%)	26 (5%)	7 (8%)	NS
ARF	120 (20%)	87 (17%)	33 (37%)	<0.001
ICU admission (*n*, %)	370 (61%)	296 (58%)	74 (82%)	<0.001
Hospital LOS (days)	9.7 ± 11.1	9.6 ± 11.1	10.1 ± 10.7	NS

[†]Comparison of survived vs. died.

ARF, acute renal failure; DVT, deep venous thrombosis; OSA, obstructive sleep apnea; PE, pulmonary embolism.

Table 2 Clinical characteristics of the cohort of patients with obesity hypoventilation syndrome stratified by post-discharge survival

	Survivors ($n = 412$)	Died ($n = 98$)	p-value[†]
Age	55 ± 14	62 ± 14	<0.001
Sex: male (n, %)	153 (37%)	28 (29%)	
Race			
Caucasian	174 (42%)	51 (52%)	
African–American	192 (46%)	39 (39%)	NS
BMI (kg m^{-2})	48.3 8.4	48.1 9.3	NS
S-creatinine (mg dL^{-1})	1.2 ± 1.3	1.8 ± 2.1	<0.001
HbA1C (%) ($n = 154$)	7.3 ± 2.0	7.4 ± 2.0	NS
$PaCO_2$ (mmHg)	54.6 ± 9.8	55.5 ± 8.0	
Comorbidities (n, %)			
Diabetes mellitus	156 (38%)	36 (37%)	NS
Hypertension	115 (28%)	25 (26%)	NS
OSA	60 (15%)	6 (6%)	0.03
Admission diagnosis (n, %)			
Respiratory failure	229 (55%)	71 (72%)	0.002
Infection	139 (33%)	51 (52%)	<0.001
ARF	61 (15%)	26 (26%)	0.005
ICU admission (n, %)	212 (51%)	84 (85%)	<0.001

[†]Comparison of survived vs. died.
ARF, acute renal failure; DVT, deep venous thrombosis; OSA, obstructive sleep apnea; PE, pulmonary embolism.

Table 3 Independent predictors of hospital and post-discharge mortality

Hospital mortality	
Age	1.04 (1.02–1.06)[†]
S-creatinine	1.49 (1.3–1.7)
ICU admission	2.02 (1.05–3.9)
Infection	2.63 (1.53–4.53)
Respiratory failure	3.22 (1.6–6.4)
Post-discharge mortality	
S-creatinine	1.26 (1.09–1.44)
Age	1.03 (1.01–1.05)
ICU admission	5.77 (3.05–10.94)

[†]Odds ratio and 95% confidence interval.

Discussion

Our study, which included 600 patients, represents the largest published series of patients with OHS. In a systematic review of the literature, Chau *et al*. identified 47 studies that included 1,077 patients with OHS (13). The 'large' number of patients with OHS admitted to our hospital over a 5-year period is quite alarming and is likely an epiphenomenon of the obesity pandemic. We only included patients with unequivocal severe OHS who had a BMI > 40 kg m^{-2} with an elevated $PaCO_2$, who were non-smokers or had a <20-pack year smoking history and had no evidence of intrinsic pulmonary disease. Patients with 'early' OHS (20,21), those with the overlap syndrome (10), and those with OHS in whom blood gas analysis was not performed were not included in our cohort, suggesting that the true number of patients with OHS admitted to our hospital during this time period was significantly larger. However, by using a restrictive definition of OHS, we selected a homogenous sample of OHS patients (22). It is widely believed that there is a wide spectrum of severity among patients with OHS with the prognosis and response to therapy varying according to the severity of disease (22–24). In our previous series, we included patients with a BMI > 40 kg m^{-2} and chronic hypercapnia (6,7). Similarly, in our current series, we included patients with a BMI > 40 kg m^{-2} rather than 30 kg m^{-2} who had evidence of chronic hypercapnia in order to exclude patients with mild OHS, to be sure that we were dealing with patients with 'real Pickwickian syndrome' (22).

The hospital and/or post-hospital survival of patients with OHS have been previously evaluated in eight studies. Two small studies ($n = 7$ and $n = 22$) performed in the 1970s reported an in-hospital mortality of 43% (25,26). In the largest study to date, Carrillo *et al*. evaluated the effects of non-invasive positive pressure ventilation (NIPPV) on the outcome of 173 patients with OHS (27). Similar to our cohort, 40% of patients had diabetes; they were elderly (74 ± 11 years) with 77% being female and only 9% had been previously treated with NIPPV for OSA. The hospital mortality was 6% with 85% of patients being alive at 1 year. Budweiser and colleagues conducted a retrospective analysis of 126 patients with OHS who were treated with NIPPV and reported 1-, 2- and 5-year survival rates of 97%, 92% and 70%, respectively (28). In a recently published study, Castro-Anon and colleagues compared the long-term outcome of 110 patients with OHS with 220 patients with OSA (22). The 5-year morality rates were 15.5% in OHS compared with 4.5% in the OSA cohort. It should be noted that the mean BMI of the patients with OHS was 42.2 ± 8.0 kg m^{-2} in this cohort compared with 48.2 ± 8.3 kg m^{-2} in our cohort. Furthermore, these authors evaluated the long-term outcome of these patients, which excluded hospital mortality. In a previous study, these authors reported the outcome of 54 patients with OHS who were admitted to their hospital over a 7-year period (29). Twenty-two (41%) of the patients were admitted with hypercapnic respiratory failure. Forty-two (77%) of the patients had comorbid diseases and 87% OSA. Ten patients (18.5%) died during follow-up (mean of 50 months). In this study, seven of 15 (46%) patients who refused long-term treatment with NIPPV died as compared with two of 54 (3.7%) patients treated with NIPPV. It is noteworthy that in this study, no significant weight loss was observed at the end of the follow-

up period and only two (3.7%) patients underwent weight loss surgery.

Nowbar and colleagues screened 4,332 patients admitted to a medicine service over a 6-month period for the presence of OHS (30). In this study, 47 (1%) patients were considered to have OHS, while 103 (2.3%) had eucapnic obesity. At 18 months following hospital discharge, the mortality was 23% in the OHS group as compared with 9% in the obese patients without daytime hypercarbia (hazard ratio = 4.0; 95% confidence interval, 1.5 to 10.4). In this study, most patients in the OHS group were discharged without NIPPV. Gursel *et al*. studied 29 patients with OHS admitted to hospital with hypercapnic respiratory failure (31). In this study, two (7%) patients died during their hospitalization. Bulbul *et al.* studied the causes and demographic characteristics of a cohort of 118 patients admitted to hospital with chronic alveolar hypoventilation (32). In this cohort, most patients with chronic hypercapnia were diagnosed with COPD (59%) while 27 (23%) have OHS. The mean age of the patients with OHS was 64.3 ± 11.2 years with a BMI of 42.7 ± 9.4 kg m^{-2} and a $PaCO_2$ of 59.7 ± 16.2. In this study, OHS was misdiagnosed as COPD in 48% of patients and heart failure in 20%; only 17.2% had been correctly diagnosed as OHS.

It is noteworthy that 64% of the patients in our cohort were women with the vast majority being post-menopausal. The increased prevalence of OHS in post-menopausal women may be explained by the impact of menopause (less progesterone) on hormone-related respiratory drive (33). The preponderance of post-menopausal female patients is a major distinguishing factor between OSA and OHS (34). Many of our patients were admitted with pneumonia, cellulitis (mostly of the lower legs), decubitus ulcers and thromboembolic disease; these are expected complications in obese, poorly ambulatory patients with cor pulmonale.

The high overall mortality of patients with OHS in our study is alarming. The 3-year mortality for OHS in our cohort is worse than the current 5-year survival in the USA for breast cancer, colon cancer and prostate cancer and similar to that for all cancers combined (35). We have previously coined the term‘ malignant obesity hypoventilation syndrome’ to describe a particularly lethal form of OHS (6). A number of factors likely contributed to the high mortality of patients in our current study; however, the misdiagnosis of OHS with inappropriate therapy likely played a major role. Only 61 (10%) patients were specifically diagnosed with OHS. Similar to other studies, a large proportion of patients were misdiagnosed as having COPD or left heart failure and likely received inappropriate therapy (including systemic steroids and inhalers) (36). Sin *et al*. demonstrated that while obese patients have a greater risk of self-reported asthma and greater use of bronchodilators than non-obese patients, the obese patients have a lower risk of significant airflow obstruction as determined by objective pulmonary function testing. Collins *et al*. determined the association between BMI and spirometric evidence of airflow obstruction in 5,493 veterans who were diagnosed with COPD (36). In this study, 52% of patients had objective evidence of airflow obstruction with the proportion of patients having airflow obstruction decreasing significantly with increasing BMI (36). Remarkably, those obese patients without airflow obstruction were more likely to remain on bronchodilator therapy than the non-obese patients. These studies support the observation that dyspneic obese patients are frequently misdiagnosed with asthma or COPD and treated with inappropriate pharmacologic agents (37). Furthermore, although approximately 90% of patients with OHS have OSA (38), only 14% of our patients had been diagnosed with OSA and treated with NIPPV. The lower mortality of our patients diagnosed with OSA may be related to the use of NIPPV in these patients. An elevated serum creatinine was an independent predictor of both hospital and post-discharge mortality and may be a useful marker for the initiation of aggressive management in these patients. The $PaCO_2$ was similar in both short-term and long-term rvivors compared with those who died. This suggests that obesity-related organ dysfunction rather than the degree of alveolar hypoventilation may be the major determinant of mortality.

Non-invasive positive pressure ventilation is considered an important therapeutic intervention in patients with OHS (5). The benefits of NIPPV include an improvement in gas exchange, lung volumes and central respiratory drive to carbon dioxide (13,27,28,39,40). NIPPV may reduce the short-term mortality of OHS (5,29). Oxygen therapy is potentially hazardous in patients with OHS as it may cause hyperoxia, which will promote further hypercapnia (41–43). Priou *et al*. demonstrated that supplemental oxygen therapy was an independent predictor of mortality in patients with OHS (44). As OHS is frequently misdiagnosed as COPD or ‘chronic asthma’ and the vast majorities of patients never undergo formal polysomnography (which is required for NIPPV therapy in the US), it is likely that many patients are inappropriately treated with supplemental oxygen and corticosteroids while few are treated with NIPPV (30,32,45).

Treating patients with OHS without achieving significant weight loss is unlikely to have any impact on the substantial long-term morbidity and mortality associated with this disorder. Weight loss is usually very difficult to achieve and maintain by medical management alone. Bariatric surgery is the most effective approach to

achieve substantial weight loss and to maintain this loss over extended periods of time (46). Furthermore bariatric surgery results in improvement in OSA (47,48), improved alveolar ventilation, oxygenation and lung function (47–50), resolution of pulmonary hypertension (51), reversal of cardiac hypertrophy (52,53), improvement or remission of type 2 diabetes (54–57), resolution of fatty liver (58) and improvement in renal function (59) with an overall decreased risk of death (46). In a recent meta-analysis which included 161,756 patients, the perioperative mortality of bariatric surgery was 0.08% while the 30-d mortality was 0.31% (60), which is substantially less than the short-term risk of dying from OHS. Bariatric surgery therefore appears to be the treatment of choice for patients with OHS. This recommendation is in keeping with the National Institutes of Health Consensus Development Conference, which recommends bariatric surgery for patients with a BMI of $\geq 40\,kg\,m^{-2}$ or a BMI $\geq 35\,kg\,m^{-2}$ in patients with high-risk conditions such as OSA, OHS, obesity-related cardiomyopathy or severe diabetes mellitus (61).

Our study has several strengths. To our knowledge, this is the largest study evaluating the characteristics and outcomes of patients with OHS. We used stringent criteria to ensure we only evaluated patients who unequivocally had OHS. We were able to link our database to the state's death registry, thereby ensuring that the deaths of all patients included in our database were recorded. Our study also has several limitations. We were unable to determine the number of patients treated with NIPPV and their compliance with such therapy; however, we suspect that very few patients received such therapy. As this was not a prospective study, we were unable to screen all hospital admissions for OHS, and it is likely that many patients with this diagnosis were not included in our cohort. Furthermore, we were unable to obtain lung function tests on these patients; however, with our strict inclusion and exclusion criteria, it is extremely unlikely that patients with COPD or other intrinsic lung disease were included in this cohort. Finally, we were unable to obtain the exact date of death or cause of death of our patients.

In conclusion, OHS is a common disease that is frequently misdiagnosed and mistreated and carries a high mortality (62). Serum bicarbonate greater than $27\,mmol\,L^{-1}$ is a sensitive and inexpensive marker of established OHS as well as 'early' OHS; all patients with a BMI $> 35\,kg\,m^{-2}$ should be screened for OHS using this simple test (5,18,21,62,63). Patients with OHS should be referred to a pulmonary and/or sleep specialist for evaluation for NIPPV, to a dietician for dietary counseling and lifestyle modification and to a bariatric surgeon for evaluation for bariatric surgery.

Conflict of Interest Statement

No conflict of interest was declared.

Author Contributions

Both authors were responsible for the design of the study, analysis of the data, writing this manuscript, reviewing the final version and approving it for publication.

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