Unmasking the cloak of comorbidities in OSA-association and their severity – a prospective observational study [version 1; peer review: awaiting peer review]

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Abstract

Background: Obstructive sleep apnoea (OSA) is a common sleep disorder with high prevalence in the community but highly underreported. It is also seen that a significant number of cases with OSA are associated with various comorbidities. The study objective was to estimate and assess the specific type and proportion of various comorbidities seen in association with OSA and association of severity of OSA with comorbidities.

Methods: The study was a hospital-based descriptive study of 85 patients with OSA. Descriptive statistics were used to analyse the data and Chi-square test was done to find out the association.

Results: The most common comorbidity associated with OSA was obesity (60%). Around half of the patients (49.4%) had severe OSA based on Apnea Hypopnea Index (AHI) scores. Statistically significant association was seen between presence of comorbidities, like diabetes and hypertension, and risk of OSA based on the snoring, tiredness, observed apnea, blood pressure (S.T.O.P) questionnaire.

Conclusions: In our study, a significant proportion (73%) of patients with OSA had associated comorbidities at the time of initial diagnosis. This indicates a delayed diagnosis as OSA is diagnosed only after multiple and irreversible comorbidities have developed. A majority (49%) had a severe OSA on initial presentation. This combination of multiple comorbidities and severe OSA at the time on diagnosis is reflective of a huge problem that is peculiar to OSA at large at a community level.

Keywords
OSA, Comorbidities, Polysomnography, STOP questionnaire
**Introduction**

Obstructive sleep apnea (OSA) is defined as “repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction occurring during sleep. These events often result in reductions in blood oxygen saturation and are usually terminated by brief arousals from sleep.” In 2007, the World Health Organization (WHO) conducted a study to find the prevalence of OSA in the world. The numbers came close to 100 million. However, a recent study in 2018 suggested that the numbers are almost ten times the previous findings.

The prevalence is increasing with the increase of non-communicable diseases and the aging population. According to a study published in 2006, the prevalence of OSA in India was 13.7%. In contrast, recent literature quotes the prevalence of 34% in males and 17% in females in the United States of America. OSA is associated with many comorbidities such as diabetes mellitus, hypertension, thyroid disease, and gastroesophageal reflux disease (GERD).

OSA is a disease of growing concern because of its association with comorbidities, mortality, and morbidity, which can be prevented by early diagnosis and treatment of OSA. Early detection and effective therapy can reduce the subsequent complications and possibly avoid the progression to irreversible comorbidities. Presently, the majority of the OSA cases are diagnosed only after single or multiple comorbidities have been established. Clinically, when such patients with comorbidities are screened, OSA is suspected and eventually diagnosed. Some critical factors in this nexus between the OSA and comorbidities beg to be studied in greater detail. First is the onset of comorbidity to the initial diagnosis of OSA. Second is the severity of OSA and its association with comorbidities. There is little data in the scientific domain on the association between the severity of OSA with specific comorbidities and temporal association between OSA and development of comorbidities.

This study aims at determining the

1. Prevalence of various comorbidities with OSA
2. Stratification of OSA severity at the time of initial presentation and diagnosis
3. To assess the severity of OSA to the presence of specific comorbidities.

**Methods**

**Ethics and consent**

Ethical approval was received for this study on 10 April 2019 by the Institutional Ethics Committee Kasturba Medical College, Mangaluru (no. ECR/54/Inst/KA/2014/RR-17). Written informed consent was taken from participants prior to recruitment.

**Participants**

The study was conducted in a tertiary care teaching hospital in Mangalore, India. The study was conducted after obtaining approval from the institutional ethics committee (IEC).

Assuming 39% prevalence of hypertension in patients with obstructive sleep apnea (OSA) to attain the significant results with 95% confidence interval at 80% power, a modified sample size of 80 was calculated.

Inclusion criteria were: 1. Subjects screened by pulmonologists and diagnosed to have likely OSA based on clinical grounds and sleep questionnaire. 2. Subjects willing to undergo overnight polysomnography in sleep lab. 3. Subjects in the age group of 18-80 years.

Exclusion criteria were: 1. Those with hemodynamic instability (checked by the research team). 2. Subjects with acute disease states which are a contraindication for overnight polysomnography (e.g., patients with acute myocardial infarction, acute mental illness, acute exacerbation of chronic obstructive pulmonary disease and critically ill patients). 3. Patients with respiratory failure on room air with PaO2 of < 60 mm of Hg. 4. Poor quality report polysomnography due to low sleep efficiency. 5. Patient on sedatives and not on steady long-term dosing.

**Procedure**

The study was a hospital-based descriptive study that included all the patients who visited the hospital with OSA symptoms. The software used was ALICE 5 sleep study machine by Philips. After proper patient preparation (abstain from sedatives, caffeine, and alcohol prior to the study) patients were taken up for sleep study and recording was done from 10:30pm - 6am and the parameters viz. EEG (electroencephalography), EOG (electrooculography) right and left,
ECG (electrocardiography), chin and leg EMG (electromyography), nasal pressure, abdominal and thoracic movement, snoring (with snoring microphone) and saturation monitoring were conducted. A total of 120 patients who underwent screening polysomnography were included in the study and analysis was done on patients who met the inclusion and exclusion criteria after taking written informed consent from them. The study was carried out from April 2019 to September 2019. Clinical details of the patients’ demographic profile, sleep-related complaints past and current, and medical history were collected.

The S.T.O.P questionnaire was administered to all patients before polysomnography. Patients were classified for OSA risk based on their scores obtained from the S.T.O.P questionnaire. Patients with a score of 0-2 categorized as low risk of OSA and those with a score >2 were categorized as high risk of OSA. Apnea-Hypopnea index (AHI) from the Polysomnography report were collected. OSA Patients were categorized based on Apnea-Hypopnea index (AHI) as follows: no OSA (<5), mild OSA (≥ 5 to < 15 events/hour), moderate OSA (≥ 15 to < 30 events/hour), and severe OSA (≥ 30 events/hour).

Statistical methods
Non-probability sampling (Convenient sampling) was used in this study. Data analysis was done using SPSS ver. 20.0. Data were summarized using mean and standard deviation (SD), and percentages. A Chi-square test was used to find the association. P<0.05 was considered as statistically significant.

Results
In our study, 120 patients were screened during a period April 2019-September 2019 out of which 5 patients refused consent, and 30 patients were excluded later in view of poor sleep efficiency. The majority of the study group were male (67%). The median age of the study group is 50 (range 39.5, 57). The majority of the patients had a higher body mass index (BMI), in the range of 30-34.99 (29.4%). Only 27.1% of the study group did not have any comorbidities. Among those with comorbidities, the most common observed include obesity (60%), hypertension (42%), and diabetes (32%). The most common symptoms of OSA observed are snoring (84%), excessive fatigue (77%), and excessive weight gain (52%) (Table 1).

Table 1. Baseline characteristics of study participants (N=85) (IQR: interquartile range; BMI: body mass index; N: number of patients; GERD: gastroesophageal reflux disease).

| Patient details               | N (%)   |
|------------------------------|---------|
| Median (IQR) age in years    | 50.0(39.5,57) |
| Gender                       |         |
| Male                         | 57(67%) |
| Female                       | 28(33%) |
| BMI                          |         |
| 18.50-24.99                  | 14(16.5%) |
| 25-29.99                     | 20(23.5%) |
| 30-34.99                     | 25(29.4%) |
| 35-39.99                     | 18(21.2%) |
| ≥40.00                       | 8(9.4%)  |
| Presence of comorbidities    |         |
| Obesity                      | 51(60%) |
| Hypertension                 | 36(42.4%) |
| Diabetes                     | 27(31.8%) |
| Hypercholesterolemia         | 16(18.8%) |
| Rhinitis                     | 12(14.1%) |
| GERD                         | 12(14.1%) |
| Hypothyroidism               | 8(9.4%)  |
| Others                       | 17(20%)  |
| No comorbidity               | 23(27.1%) |
Based on AHI scores, 49.4% of participants were suggested to have severe OSA (≥ 5 to < 15 events/hour), followed by 24% of the group having mild OSA (≥ 5 to < 15 events/hour). 18.8% of the group had moderate OSA (≥ 15 to < 30 events/hour) while 8% had scores not indicating OSA (<5) (Table 2).

As per the S.T.O.P questionnaire, 51% of the study group had a higher risk of OSA while 49% had a low risk of OSA.

On analysis by Chi-square test, the association between the comorbidities and the severity of OSA by AHI scores was made. Association with diabetes was not statistically significant (p value-0.059). No comorbidity showed any association with the severity of OSA as per the AHI scores (Table 3).

Table 2. The severity of OSA based on AHI scores from polysomnography studies (N=85)(AHI: apnea hypopnea index; N: number of patients).

| AHI SCORES               | Frequency N (%) |
|--------------------------|-----------------|
| No (0-4/hr.)             | 7(8.2%)         |
| Mild (5-14/hr.)          | 20(23.5%)       |
| Moderate (15-29/hr.)     | 16(18.8%)       |
| Severe (≥30/hr.)         | 42(49.4%)       |

Based on AHI scores, 49.4% of participants were suggested to have severe OSA (≥ 5 to < 15 events/hour), followed by 24% of the group having mild OSA (≥ 5 to < 15 events/hour). 18.8% of the group had moderate OSA (≥ 15 to < 30 events/hour) while 8% had scores not indicating OSA (<5) (Table 2).

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Table 3. Association of comorbidities with the severity of OSA based on AHI index (N=85)(N: number of patients; COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal reflux disease; CAD: coronary artery disease; CHF: congestive heart failure).

| Variable          | No to Mild OSA N (%) | Moderate to Severe OSA N (%) | P-value |
|-------------------|----------------------|------------------------------|---------|
| No comorbidities  | 8(34.7%)             | 15(65.2%)                    | .454    |
| Hypertension      |                      |                              | .331    |
| Yes               | 10(27.7%)            | 26(72.2%)                    |         |
| No                | 17(34.6%)            | 32(65.3%)                    |         |
| Diabetes          |                      |                              | .059    |
| Yes               | 5(18.5%)             | 22(81.4%)                    |         |
| No                | 22(37.9%)            | 36(62.06%)                   |         |
| Asthma            |                      |                              | .511    |
| Yes               | 2(40%)               | 3(60%)                       |         |
| No                | 25(31.2%)            | 55(68.7%)                    |         |
| COPD              |                      |                              | .408    |
| Yes               | 2(22.2%)             | 7(77.7%)                     |         |
| No                | 25(32.8%)            | 51(67.1%)                    |         |
| GERD              |                      |                              | .429    |
| Yes               | 3(25%)               | 9(75%)                       |         |
| No                | 24(32.8%)            | 49(67.1%)                    |         |
| Hypercholesterolemia |                  |                              | .197    |
| Yes               | 7(43.75%)            | 9(56.25%)                    |         |
| No                | 20(28.9%)            | 49(71%)                      |         |
| Thyroid           |                      |                              | .496    |
| Yes               | 3(37.5%)             | 5(62.5%)                     |         |
| No                | 24(31.1%)            | 53(68.8%)                    |         |
| CAD               |                      |                              | .379    |
| Yes               | 2(50%)               | 2(50%)                       |         |
| No                | 25(30.8%)            | 56(69.1%)                    |         |
On analysis by Chi-square test, the association between the comorbidities and the risk of OSA by S.T.O.P questionnaire was studied. Association with diabetes and hypertension with the severity of OSA with the S.T.O.P questionnaire was found to be significant (hypertension p value-0, diabetes p value-0.003) (Table 4).

On analysis by Chi-square test, the association between the BMI and severity of OSA by AHI index did not show any statistical significance.

On analysis by Chi-square test, the association between the comorbidities and the risk of OSA by S.T.O.P questionnaire was studied. Association with diabetes and hypertension with the severity of OSA with the S.T.O.P questionnaire was found to be significant (hypertension p value-0, diabetes p value-0.003) (Table 4).

Table 3. Continued

| Variable | No to Mild OSA N (%) | Moderate to Severe OSA N (%) | P-value |
|----------|----------------------|-----------------------------|---------|
| CHF      |                      |                             | .621    |
| Yes      | 1(25%)               | 3(75%)                      |         |
| No       | 26(32%)              | 55(68%)                     |         |
| Depression |                    |                             | 0.682   |
| Yes      | 0 (0)                | 1(100%)                     |         |
| No       | 27(32.1%)            | 57(67.9%)                   |         |

Table 4. Analysis of the comorbidities to the severity of OSA based on S.T.O.P questionnaire (N=85) (N: number of patients; COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal reflux disease; CAD: coronary artery disease; CHF: congestive heart failure).

| Variable               | 0-2 N (%) | >2 N (%) | P   |
|------------------------|-----------|----------|-----|
| Hypertension           |           |          | .000|
| Yes                    | 9(25%)    | 27(75%)  |     |
| No                     | 33(55%)   | 27(45%)  |     |
| Diabetes               |           |          | .003|
| Yes                    | 7(25.9%)  | 20(74.1%)|     |
| No                     | 35(60.3%) | 23(39.7%)|     |
| Asthma                 |           |          | .489|
| Yes                    | 3(60%)    | 2(40%)   |     |
| No                     | 39(48.7%) | 41(51.2%)|     |
| COPD                   |           |          | .230|
| Yes                    | 6(66.6%)  | 3(33.3%) |     |
| No                     | 36(47.3%) | 40(52.7%)|     |
| GERD                   |           |          | .605|
| Yes                    | 6(50%)    | 6(50%)   |     |
| No                     | 36(49.3%) | 37(50.7%)|     |
| Hypercholesterolemia   |           |          | .090|
| Yes                    | 5(31.2%)  | 11(68.7%)|     |
| No                     | 37(53.6%) | 32(47.4%)|     |
| Rhinitis               |           |          | .187|
| Yes                    | 4(33.3%)  | 8(66.6%) |     |
| No                     | 38(52%)   | 35(48%)  |     |
| Thyroid                |           |          | .140|
| Yes                    | 2(25%)    | 6(75%)   |     |
| No                     | 40(51.9%) | 37(48.1%)|     |
Discussion

OSA is a common sleep disorder with a worldwide prevalence that is on the rise. The prevalence of OSA in the general population has not been accurately documented and is a tip of the iceberg phenomenon due to the subtle nature of its symptoms, poor self-reporting, and lack of robust diagnostics in healthcare. OSA is also associated with certain crucial risk factors which play a vital role in its natural history of evolution. Studies have revealed that OSA contributes to several non-communicable diseases such as hypertension, cardiovascular diseases, and impaired glucose metabolism. The association of OSA with comorbidities is quite complex and confounding. Obesity and certain comorbidities like hypothyroidism are known to be definite risk factors for the subsequent development of OSA. However, metabolic comorbidities have a more complex causality. It is explained physiologically that diabetes mellitus and hypertension can develop as a complication of OSA and in turn may accentuate the OSA severity and progression.

OSA is a disease that is often diagnosed late and rarely diagnosed before the onset of metabolic complications and comorbidities. It is a common observation among clinicians that OSA is diagnosed after end-organ damage has resulted in cardiovascular and neurological events. On presentation and initial diagnosis, it is often severe OSA that is diagnosed and often with the development of multiple and irreversible comorbidities. This study probes in greater detail the spectrum comorbidities suffered by OSA patient, their prevalence, and the association of comorbidities to the severity state of OSA if any.

Risk factors for OSA include age, gender, race, BMI, and lifestyle habits associated comorbidities. In our study, the median age of the patients is 50.0(39.5, 57), with a majority of them being male, similar to other studies.

In our study, we used the AHI score from polysomnography reports and the S.T.O.P questionnaire to assess the severity of OSA. As per AHI scores, 42(49%) of patients had severe OSA with AHI scores of more than 30/hr, followed by 20 patients (23.5%) who had mild OSA with scores of 5-14/hr. These are in line with a study done in Brazil where the majority of the population had severe OSA. A severe form of OSA as confirmed by AHI during the initial diagnosis is an important outcome of our study. This finding suggests that OSA is often diagnosed late and only after comorbidities and metabolic complications set in. The reasons for late presentation and subsequent diagnosis could be multifactorial like lack of awareness of the disease amongst the general population and even among the treating physicians. The subtle nature of symptoms in OSA and lack of high quality, easily available diagnostics may also be other compounding reasons. This finding in our study is critical as there is a huge scope for an early diagnosis that might modify and prevent progression to comorbidities.

As per the S.T.O.P questionnaire, 43 (50%) of the sample had a high risk of OSA. This finding is significant as it reinforces the belief that a simple questionnaire in the form of S.T.O.P questionnaire has good sensitivity in an accurate early screening and diagnosis of OSA thereby preventing complications and onset of metabolic comorbidities. In settings where diagnostic polysomnography is a luxury, the S.T.O.P questionnaire is a good alternative at least as a screening tool.

In our study, a total of 62 OSA patients (73%) had any one of the comorbidities. The most common comorbidity observed in our study was obesity (51(60%)), while hypertension (39%) followed by obesity (34%) were the most common comorbidities observed by Jose Antonio Pinto et al. The Indian study done by Surendra K. Sharma et al. showed that patients with obesity also had four times more risk of having OSA, an observation similar to our study.
In our study diabetes is seen in 31.8% of the patients suffering from OSA. On assessing the severity of OSA symptoms in patients who had diabetes using the S.T.O.P questionnaire, it was found that among the people with diabetes, the majority of them (74%) had a high risk of OSA, and the data was found to be statistically significant. On using AHI scores, it was observed that among diabetics, the majority of them had moderate to severe OSA (72%). However, this was not of statistical significance. One possible reason is that OSA leads to obesity which further increases the risk of diabetes. Whether the patients with OSA become more obese than those who do not is uncertain.\textsuperscript{32–35} Another theory is decreased sleep may increase appetite.\textsuperscript{17} In one of the studies, it has been discussed that patients with OSA had high levels of leptin, which suggested the association between OSA and leptin resistance.\textsuperscript{18} Diabetes may be the cause of OSA and studies have found that diabetic patients had more propensities to OSA than those without diabetes.\textsuperscript{19} Autonomic dysfunction in diabetic patients also may lead to OSA due to leptin resistance/deficiency causing depressed respiratory control.\textsuperscript{20–25} However, we could not deduce if diabetes was the cause or effect of OSA as the sample size was not large enough. These results might imply that early screening, diagnosis and treatment of OSA may prevent the subsequent development or modify the progression of diabetes.

The next commonly associated comorbidity with OSA is hypertension (42%). On assessing the severity association between the patients having hypertension and OSA using AHI, it was seen that around 72% of the hypertensive patients had moderate to severe OSA. As per the S.T.O.P questionnaire, 75% of the hypertensives had moderate to severe risk of OSA. 55% of non-hypertensive patients had no to mild risk of OSA. This data was statistically significant. Many hypotheses for the causal association between them have been stated, but the exact underlying mechanisms have not been clearly understood.\textsuperscript{26} Many theories such as recurrent and temporary negative intrathoracic pressure during apnoeic spells, recurrent hypoxemia, or hypercapnia, which cause sympathetic system stimulation, may lead to hypertension.\textsuperscript{27–29} A study showed that use of continuous positive airway pressure (CPAP) has helped to better control blood pressure in hypertensive patients.\textsuperscript{30–32}

The link between the severe form of OSA and comorbidities was explored. Occurrence of diabetes and hypertension with the severe form of OSA by S.T.O.P questionnaire reached statistical significance while only hypertension showed a significant correlation with severe OSA as graded by AHI score.

There was no association among other comorbidities with the severity of OSA. These findings emphasize the fact that diabetes and hypertension are perhaps the two most significant comorbidities that need to be addressed in OSA patients. These comorbidities are often encountered with a severe form of OSA. This suggests that these two comorbidities may accentuate the progression of OSA into more severe and refractory diseases. Alternatively, the presence of diabetes and hypertension in OSA patients may be a harbinger of a severe disease state and suggests the need for active intervention to prevent end-organ complications, often seen with these two serious comorbidities.

Overweight or obese people are strongly linked with OSA.\textsuperscript{11,33} It is often difficult to establish which is the cause or effect among them, hence the disease progression is difficult to establish. In our study, at least 80% of the study population were overweight or obese. The most common comorbidity with OSA was obesity which was seen in 60% of the patients. On assessing the association between these two, it was seen that among the obese, 60% of them had moderate to severe OSA compared to other groups. Obesity manifests as a change in certain anatomical features such as the increase in neck circumference that might narrow the airway.\textsuperscript{34,35} Obesity is known to cause reduced lung volume\textsuperscript{36} which may lead to an increased risk of oropharyngeal collapse during sleep (due to decreased strength of airways),\textsuperscript{37,38} which increase CPAP requirements,\textsuperscript{39} and greater severity of OSA.\textsuperscript{40} Secondly, the risk of collapse of the upper airway is higher in obese individuals.\textsuperscript{41} Other theories include the imbalance of carbohydrate and lipid metabolism.\textsuperscript{42–44} Reduction in body weight is an effective strategy for treating sleep apnea.\textsuperscript{41,45,46}

Our study had a few limitations. Probing in detail the duration of onset of each specific comorbidity to the onset of OSA would have given vital data on the predilection and causality of the comorbidities with OSA. This complex exercise was not captured in our study data due to technical shortcomings. The findings of our study should be substantiated with a study involving a larger population and probably a multicentric study for more representative data.

Conclusion
In our study, a significant proportion (73%) of patients with OSA at the time of diagnosis had comorbidities. This is indicative of a delayed presentation in OSA patients and that OSA is often diagnosed only after multiple and irreversible comorbidities have set in.

Among the spectrum of comorbidities encountered in our study, the most common were obesity, hypertension, and diabetes, among many others (dyslipidemia, GERD, asthma, COPD). It was seen that there was an association between
the comorbidities and the severity of OSA as graded by the S.T.O.P questionnaire for both diabetes and hypertension and hypertension alone when graded by AHI scores. There was no association among other comorbidities with the severity of OSA. This crucial data implies that among the basket of comorbidities often seen with OSA, diabetes and hypertension are probably the most significant of the comorbidities. Both these may have a disease-modifying role in OSA and lead to a severe form of OSA and vice-versa. This finding needs to be validated with larger studies and the pathophysiological link needs a more comprehensive exploration too.

Another disconcerting finding from our study was the skewed presentation of OSA at the time of initial diagnosis. A majority (49%) had a severe form of OSA at the time of diagnosis. This, combined with multiple comorbidities at diagnosis, is reflective of a huge problem that is peculiar to OSA at large on a community level. OSA as a disease entity has poor awareness in the community and is seldom screened early in primary health care, thereby leading to suboptimal early intervention and care. There is strong evidence that early detection of OSA can benefit the patient by preventing the development of irreversible comorbidities. The inverse is also true. More importantly, due to late diagnosis and delayed intervention of OSA more often, these subjects present with multiple comorbidities that result in end-organ damage due to progression of these comorbidities (e.g., uncontrolled hypertension or diabetes leading to ischaemic heart disease or stroke). Early identification of OSA has a critical role in preventing the development of comorbidities in some patients, progression of comorbidities in majority and preventing complications arising out of the comorbidities in many.

Data availability

Underlying data

figshare: Unmasking the cloak of comorbidities in OSA-association and their severity – A Prospective observational study. https://doi.org/10.6084/m9.figshare.19571365

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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