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Original Article

Overlap of Sleep Disorders and Chronic Respiratory Diseases: An Emerging Health Dilemma

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ABSTRACT

Introduction: The burden of Overlap Syndrome (coexistence of sleep-related breathing disorders in patients with respiratory diseases) is high in developing countries, and such a phenomenon implies higher morbidity. The study was conducted to measure the prevalence of sleep-related breathing disorders in patients with Respiratory Symptom Complex and to identify factors associated with the severity of sleep-related breathing disorders.

Materials and Methods: A hospital-based cross-sectional study of 50 patients with respiratory symptom complex was conducted at BP Koirala Institute of Health Sciences. Structured proforma and Polysomnography were used for analysis.

Results: There were 24 patients (48%) with COPD, 18 (36%) with Bronchial Asthma. 6 patients (12%) with Bronchiectasis and 2 patients with Interstitial Lung Disease. 60% (n=30) patients had sleep-related breathing disorder or Overlap syndrome, 14 patients (46.67%) had mild sleep-related breathing disorder while 16 (53.33%) patients had moderate to severe type. 62.5% COPD patients, 55.55% Bronchial Asthma patients, 50% of patients with Interstitial Lung Disease and 50% Post-TB Bronchiectasis patients had a sleep-related breathing disorder. There was a significant positive correlation between the presence of sleep-related breathing disorder in patients with respiratory symptom complex and high neck circumference (0.499, p-value <0.001), waist circumference (0.293, p-value = 0.039) and hip circumference (0.371, p-value = 0.008).

Conclusions: Overlap Disorders comprising sleep disorders in patients with chronic respiratory diseases are high in developing countries. Routine sleep history and polysomnography in all patients with Respiratory Symptom Complex can detect sleep-related breathing disorders.

Keywords: Overlap Syndrome; Sleep Disorders; Respiratory Diseases

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INTRODUCTION

Chronic respiratory diseases are a leading cause of morbidity and mortality throughout the world and the burden continues to increase. In Nepal available data indicate that the proportion of people presenting with respiratory complaints is around 28%[1], and that respiratory diseases are arguably contributing to high economic burden based on disability-adjusted life years.

Sleep-related breathing disorders (SRBD) includes a spectrum of disorders characterized by an abnormal respiratory pattern, in which partial or complete cessation of breathing occurs several times during sleep. SRBD is associated with many other adverse health consequences; linked to cardiovascular disease and stroke. Various global epidemiologic studies have demonstrated the prevalence of SRBD to vary from 0.3–5.1%, these prevalence estimates, however, are based on data from predominantly western studies.[2-9]

A ventilatory function is physiologically reduced during sleep in adults. Sleep hypoventilation, especially during the vulnerable rapid eye movement (REM) period, well tolerated by healthy individuals, may represent a potentially hazardous occurrence in patients with other cardinal symptoms of cardiorespiratory diseases. Therefore, some of the respiratory disorders are exacerbated and may progress in severity in the presence of co-existing sleep disorders.

Prevalence of both respiratory diseases and sleep disorders is high among the general population in developing countries like Nepal because of specific risk characterization. Hence, such overlaps are associated with significant morbidity.

It is therefore imperative for clinicians to consider the coexistence of SRBD among patients presenting with respiratory symptom complexes as part of a routine evaluation to prevent worsening of disease and quality of life.[10-14]

The myriad of health problems associated with the co-existence of sleep disorders and respiratory disease mandates a new emphasis on the management of these patients, shifting importance towards recognition of these entities in patients with respiratory disorders such as Chronic Obstructive Pulmonary Disease, Bronchial Asthma and Interstitial Lung Diseases. Untreated severe SRBD has been found to have a statistically significant increased risk of all-cause mortality thus treatment is warranted, especially in patients with cardiorespiratory diseases.[15-16]

A review of the literature and critical appraisal of the available research from similar settings supports the need for diagnosis and treatment of sleep-disordered breathing in patients presenting with respiratory symptom complex in Nepal.

The study aimed to measure the prevalence of Overlap Syndrome (SRBD among patients presenting with Respiratory Symptom Complexes) in Nepal by routine use of Polysomnography in the usual clinical care setting and to identify factors that may predict the presence and severity of SRBD in patients with respiratory disorders.

MATERIALS AND METHODS

This hospital-based cross-sectional study was conducted at B. P. Koirala Institute of Health Sciences, in the Department of Internal Medicine from May 1, 2014, to September 30, 2015, after approval by the Institute's Ethical Review Board.

Case Definitions:

Overlap Syndrome: An entity comprising the coexistence of sleep-related breathing disorder in chronic respiratory disease.

Respiratory Symptom Complex: Any chronic respiratory disease pertaining to clinician-diagnosed Chronic Obstructive Pulmonary Disease (COPD), Bronchial Asthma, Interstitial Lung Disease (ILD) or Bronchiectasis, with background history of cardinal manifestations of respiratory disease of a chronic duration, specifically cough with or without expectoration, dyspnea, chest pain, and/or hemoptysis of 3 or more weeks.

Sleep-Related Breathing Disorder (SRBD): For the purpose of the study, SRBD was defined as an Apnea-Hypopnea Index (AHI) of at least 5 events per hour of sleep, as documented by portable ApneaLinkTM polysomnogram and descriptively defined based on the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events (version 2.0.2).[17] Mild SRBD was defined as an AHI of 5 to <15 events/hour of sleep, moderate SRBD as 15 to <30 events/hour of sleep and severe SRBD as 30 or more events/hour of sleep. With moderate and severe SRBD patients usually requiring different treatment modalities, in this study, moderate to severe SRBD was grouped as one entity for ease of comparison with mild SRBD.

Apnea: Cessation of airflow for 10 seconds or longer during sleep as documented by polysomnography.

Hypopnea: Decrements in airflow during sleep, and if desaturation occurred, as a document by polysomnography.

Desaturation: A fall of 4% or more O_2 saturation from baseline.

Apnea-hypopnea Index (AHI): is a measure of sleep apnea severity and is the number of apneas and hypopneas per hour of sleep, with ≥5 events/hour of sleep being diagnostic of an SRBD.

Respiratory effort-related arousal (RERA): A sequence of breaths characterized by increasing effort leading to an arousal from sleep that does not fulfill criteria for apnea or hypopnea, as documented by polysomnography.

Respiratory Disturbance Index (RDI): The total of apneas, hypopneas, and RERAs per hour of sleep

Metabolic Syndrome: Metabolic syndrome was defined based on the IDF Criteria for Central Obesity[18] as outlined below:

Waist circumference		
Men	**Women**	**Ethnicity**
≥ 94cm	≥ 80cm	Europid, Subsaharan African, Eastern and Middle Eastern
≥ 90cm	≥ 80cm	South Asian, Chinese, and ethnic South and central American
≥ 85cm	≥ 90cm	Japanese

AND:
Two or more of the following:

Fasting TG >150mg/dL or specific medication: yes/no

HDL cholesterol <40mg/dL and <50mg/dL for men and women, respectively, or specific medication: yes/no

BP >130mmHg systolic or >85mmHg diastolic or previous diagnosis or specific medication: yes/no

Fasting plasma glucose ≥100mg/dL or previously diagnosed Type 2 diabetes: yes/no

The calculated sample size was 67 subjects, and addition of 10% to the calculated size in order to avoid bias a sample size of 75 was estimated. For reason of logistics, practicality and time constraints 50 subjects were enrolled. Fifty consecutive patients, 18 years or above, meeting the case definition of the respiratory symptom complex, after informed verbal and written consent were recruited. Subjects who were in respiratory failure or adjudged critically ill were excluded from the study. A structured proforma detailing sleep history and socio-demographic information of every subject were recorded. The data included age, gender, data on medical complaints, sleep-related questions such as excess daytime somnolence, snoring, headache, fatigue, pertinent physical examination findings, weight, height, BMI, and anthropometric measurements on neck, waist and hip circumferences. Laboratory data on acid-base gas analysis; pulmonary function test, chest X-ray and electrocardiogram as deemed necessary and when available, as well as the presence of metabolic syndrome were recorded.

The subjects underwent an overnight in-hospital polysomnogram, which was conducted at the sleep laboratory using the ResMed ApneaLinkTM polysomnogram (portable). The ResMedApneaLink® software was used to analyze and record the Apnea-Hypopnea Index (AHI). The polysomnography study recorded nasal airflow by a nasal pressure transducer, respiratory efforts, and pulse oximetry. Trained hospital personnel monitored the procedure. During the study period, the diagnostic and therapeutic modalities prescribed for each patient were not disturbed.

Data and Statistical Analysis:

Microsoft Excel 2007 worksheet was utilized for data collection and statistically analyzed using the SPSS software version 11.5. Descriptive statistical data were presented as Mean, Standard Deviation, and percentage and proportions. For inferential statistics, the chi-square test with risk ratio was calculated with a confidence interval of 95%, and a p-value of <0.05 inferring statistical significance. Logistic regression analysis of data was performed and correlation of anthropometric measurements and presence of Overlap Syndrome was evaluated using the Pearson Correlation Matrix Analysis.

RESULTS

The study observed that 56 % were male and 44% female, 46% of patients were in the age group of > 60 years with a mean age of 56.88 years (±14.894).

The risk characterization of patients presenting with symptom complex of respiratory diseases in the study population is illustrated in figure 1.

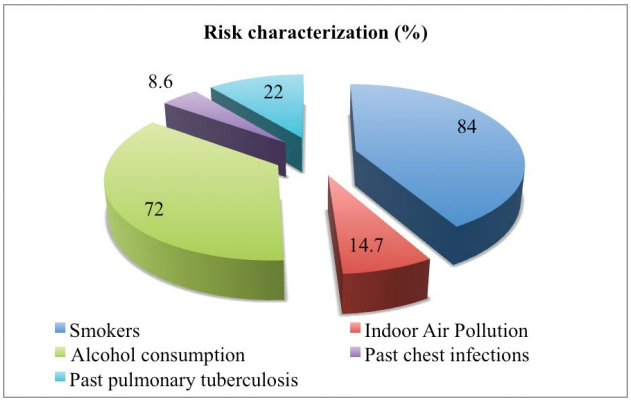

Figure 1: Risk characterization of patients presenting with symptom complex of respiratory diseases

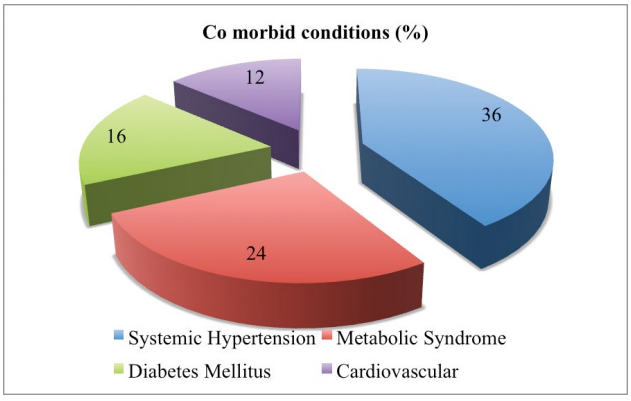

Figure 2: Comorbidities associated with patients presenting with Respiratory Symptom Complex

Figure 2 depicts the comorbidities present. Diabetes Mellitus was seen in 16% of the patients while 36% had Systemic Hypertension. Interestingly, Metabolic Syndrome was seen in 24% of the patients. 12% of the patients had cardiovascular comorbidity in the form of congestive heart failure (6%) and Ischemic Heart Disease (6%).

There were 24 patients (48%) with COPD and 36% (n=18) had Bronchial Asthma. 12% (n=6) of patients were diagnosed with Bronchiectasis, with tuberculosis as the predominant cause. There were 4% of cases of ILD. 30 (60%) patients had SRBD, of which, 14 patients (46.67%) had mild SRBD and 16 (53.33%) patients had moderate to severe SRBD. Cheyne Stokes's respiratory pattern was seen in two patients. Figure 3 depicts the severity of SRBD in relation to gender among the patients reported having sleep-related disturbances and Respiratory Symptoms Complexes.

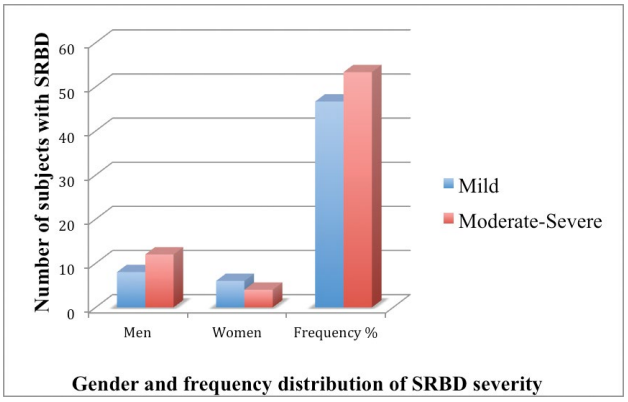

Figure 3: The severity of SRBD in relationship to gender among patients with Overlap Syndrome

62.5% (15/24) of patients with COPD, 55.55% (10/18) patients with Bronchial Asthma, 50% (1/2) patients with ILD and 50% (3/6) patients with Post-TB Bronchiectasis had evidence of SRBD. Of these patients, 10 patients (66.67%) with COPD had moderate to severe SRBD while Bronchial Asthma patients had approximately equal numbers of mild and moderate to severe SRBD. The majority of ILD and Bronchiectasis patients had mild SRBD.

The average duration of the polysomnography evaluation was approximately 7 hours and 8 minutes. Men had a higher mean Apnea-Hypopnea Index (AHI) of 8.50 (IQR 4.00 to 26.00) compared to that with women 3.50 (IQR 2.00 – 11.50) (p-value = 0.018), as well as a higher Respiratory Disturbance Index (RDI) (p-value = 0.003). There was a difference in Obstructive Apnea Events among men and women, with mean events of 10.50 (IQR 2.25 to 99.50) in men as compared to 2.00 events (IQR 0.00 to 11.50) in women (p-value = 0.012). The majority of the subjects (76.67%) with SRBD had nocturnal desaturation of lower than 80%. It was observed that the room air saturation was <90% among 5 subjects, of which three had mild SRBD and the remaining two had normal AHI. In all subjects with moderate to severe SRBD, room air daytime saturation was ≥90%. The results of the polysomnogram are depicted in table 1.

Table 1: Results of the Polysomnogram in Respiratory Symptom Complex patients with SRBD

Measures of Polysomnogram	Total Events	Men	Women	p-value
AHI	6.00 (3.00 – 21.25)	8.50 (4.00 – 26.00)	3.50 (2.00 – 11.50)	0.018
RDI	8.00 (5.00 – 22.50)	10.00 (6.25 – 27.75)	5.00 (4.00 – 13.25)	0.003
Baseline Saturation	93.06 (5.301)	93.61 (5.965)	92.36 (4.348)	0.416
Lowest Saturation	78.42 (11.136)	79.04 (11.164)	77.64 (11.312)	0.664
Obstructive Apnea	5.00 (1.00 – 33.50)	10.50 (2.25 – 99.50)	2.00 (0.00 – 11.50)	0.012
Central Apnea	1.00 (0.00 – 3.00	2.00 (0.00 – 5.00)	0.00 (0.00 – 1.25)	0.010
Hypopnea	17.50 (7.00 – 52.57)	24.50 (7.50 – 49.50)	13.50 (6.00 – 59.50)	0.519

BMI of ≥24.99 kg/m2 (p-value <0.05) was associated with severe SRBD. A neck circumference of ≥40cm was associated with moderate to severe SRBD (p-value <0.001). Similarly, a waist circumference of ≥90cms for men or ≥80cm for women was associated with moderate to severe SRBD (p-value < 0.05). The presence of metabolic syndrome was associated with moderate to severe SRBD (p-value< 0.05).

Multivariate and logistic regression analyses in patients with respiratory symptom complex and SRBD showed that loud snoring increased the odds of a mild to severe SRBD by 8.582 (p-value < 0.05, 95% CI 1.842 – 39.989), the results of which are published elsewhere.[18] The presence of metabolic syndrome in such patients increased the odds of a severe SRBD by 6.488 (p-value > 0.05, 95% CI 0.746 – 56.398). Anthropometric and clinical predictors of SRBD among the patients presenting with Respiratory Symptom Complex based on analyses by multivariate and logistic regression are depicted in table 2.

Table 2: Clinical and Anthropometric Predictors of SRBD in patients with Respiratory Symptom Complex

Parameter	Category	Mild-Severe SRBD		P-value	Moderate-Severe SRBD		P-value
		Present	Absent		Present	Absent	
Loud Snoring	Present	25	6	<0.001	14	17	0.011
	Absent	5	14		2	17	
Metabolic Syndrome	Present	9	3	0.224	8	4	0.003
	Absent	21	17		8	30	
BMI (≥24.99kg/m2)	Present	19	7	0.049	10	16	0.308
	Absent	11	13		6	18	
Neck Circumference (≥40cm)	Present	11	3	0.095	10	4	<0.001
	Absent	19	17		6	30	
Waist Circumference (≥90/≥80cm)	Present	14	7	0.413	10	11	0.044
	Absent	16	13		6	23	

Pearson correlation matrix analysis observed that there was positive correlation between presence of Overlap Syndrome and neck circumference (0.499, p-value <0.001), waist circumference (0.293, p-value < 0.05) and hip circumference (0.371, p-value <0.05).

DISCUSSION

The study has described the clinical presentation and demographics of patients with respiratory symptom complex who have undergone polysomnograms for the presence of SRBD, and the factors associated with the severity of SRBD in such patients.

One of the unique aspects of the study design was introducing the concept of clinically defined symptom complexes or symptom clusters that patients bring into their experience of a wide variety of symptoms.

The study by Heinzer R et al (the HypnoLaus study)[20] demonstrated prevalence of moderate to severe sleep-disordered breathing of 23.4% and 49.7% in women and men respectively in the general population. Interestingly the present study revealed 60% of patients with Respiratory Symptom Complex had SRBD, and of the patients having SRBD, 46.67% had mild SRBD while 53.33% had moderate to severe SRBD. Mild SRBD was the most common type, men more affected than women, and they were more likely to be younger, whereas in women, the older age group was more affected.

Most hospital-based studies have reported that SRBD is more common in men than in women. There is a possibility that this gender difference in prevalence is due to several factors, including failure of women to attend sleep clinics and circumstances related to sociocultural factors.[21-23] The patients with SRBD in this study had known co-morbid conditions, which are known risk factors for the development of sleep disorders such as systemic hypertension, diabetes mellitus, stroke, cardiovascular disorders and metabolic syndrome. An independent association between severities of SRBD and hypertension, diabetes, metabolic syndrome and depression has been reported by The HypnoLaus study.

In the present study, BMI ≥24.99kg/m2 was associated with mild to severe SRBD (p-value < 0.05), as well as neck circumference ≥40cm, and waist circumference for moderate to severe SRBD (p-value = <0.001 and 0.05, respectively).

Polysomnography, in the study, revealed interesting information related to SRBD. Men had a higher AHI of more than twofold as compared to women (p-value < 0.05), and the RDI was twice higher in men as compared to women (p-value < 0.05), findings that are similar to that in the HypnoLaus study. Interestingly, median central apnea events in women were negligible (IQR 0.0 – 1.25), similar to the observation in the study by Bixler E et al wherein there was a general absence of central apneic events noted among women.[24] Another interesting finding in our study was that there were subjects with normal AHI and yet had nocturnal hypoxemia of <90%, implying the possibility of a lower baseline daytime saturation. Episodes of desaturation during sleep in patients with obstructive airway disease, who otherwise had hypoxemia during wake states had been reported by Flenley in a study.[25] Wynne and colleagues have also reported Sleep-Related Breathing Disorders with nocturnal hypoxemia.[26] The study observed markedly low nocturnal oxygen saturation (<80%) in patients of SRBD. Interestingly, more cases of nocturnal desaturation were observed in mild SRBD. A study by Guilleminault had concluded that both the sleep stage and abnormal respiratory event during sleep could affect the level of oxygen saturation.[27] When oxygen saturation was analyzed against the severity of SRBD, there was no difference in the level of drop in the saturation across the severity classes of SRBD (p-value > 0.05). This finding is consistent with the analysis of mean nocturnal saturation with regard to the presence of obstructive sleep apnea in the study by Turcani P et al where it was observed that there was no difference between mean night saturation in subjects with normal or abnormal AHI.[28]

There was also a positive correlation between neck, waist and hip circumferences (r=0.499, p-value <0.001, r=0.293, p-value <0.05, and r=0.371, p-value < 0.05 respectively) and risk of developing Sleep-Related Breathing Disorders in patients with respiratory symptom complexes.

Most studies on sleep-disordered breathing and respiratory diseases are noted among patients with Chronic Obstructive Pulmonary Disease and Bronchial Asthma in the form of overlap syndrome. The high prevalence of Overlap Syndrome with the etiological diagnosis of COPD in the present study is consistent with many of the reported studies in the literature. Lopez-Acevedo et al in 2009 had also reported the presence of overlap syndrome in COPD patients.[29] Turcani et al also described a high prevalence (51.4%) of obstructive sleep apnea in COPD cases.

The burden of sleep-related breathing disorder in Asthma remains high. Many studies have reported a positive correlation between asthma, loud snoring, and obstructive airway disease.[30,31] Correlations are found between SRBD and asthma. Difficulties inducing sleep, sleep fragmentation on polysomnography, early morning awakenings and daytime sleepiness are common in asthmatics. Reasons are multiple: besides specific physiological changes, sleep deprivation-induced by poor disease control, abnormal bedtime behaviors and drug-induced insomnia is considered as the contributing factors. Concurrent obesity is an underlying cause of SRBD in asthmatic patients.

One of the remarkable finding in present study was higher prevalence of sleep-related breathing disorders among women of age 60 years or above as compared to men of the same group which is similar to the study conducted by Klink M et al where they reported that there was an association between sleep disturbances in Asthma,[32] and that the burden was higher among women, and those of advanced age.

An important strength of this study includes the collection of standardized, objective measures of SRBD in a specific sample of patients with respiratory symptoms representing population subgroups at increased risk of having SRBD in a developing country. Additionally, waist circumference, which provides better clinical information to explain obesity-related health risk to a greater extent than BMI in cardio-metabolic and cardiorespiratory diseases, was utilized.

CONCLUSIONS

The study concludes that the prevalence of Overlap Syndrome is high in developing countries like Nepal because of specific risk

characterization. Polysomnography in patients with Respiratory Symptom Complex who have characteristics of high neck, waist and hip circumferences can detect SRBD. The highest prevalence of Overlap Syndrome was observed in COPD and Bronchial Asthma patients.

Thus, this study depicts a complex intertwined relationship between the Respiratory Symptom Complexes and Sleep Disorders in Nepal indicating that there is a high prevalence of SRBD among the patients presenting with symptom complex of respiratory diseases.

Recommendations

Recognition of overlap of SRBD and Respiratory Symptom Complex (Overlap Syndrome) has high impact implications in the management of such patients besides the standard respiratory care. Hence it is recommended that all patients presenting with respiratory symptoms of chronic duration undergo a routine sleep study.

Limitations of the Study

The study has important limitations. Owing to logistics and time constraints, the study had a small sample size. Temporal associations could not be determined due to the cross-sectional nature of this study. It was conducted in a cross-sectional setting, aiming to detect persons with underlying chronic respiratory diseases with already existing, but undiagnosed SRBD. Also, control for or elimination of all potential confounders was not ensured. Certain factors such as variability in the positioning of the thermistor, alterations in breathing patterns between nasal and oral breathing, changes in body posturing during sleep and lack of manual analysis of the portable polysomnography results may have altered results of Hypopneas, apnea events and other polysomnography parameters. The results were not interpreted by standard board-certified personnel. Nevertheless, it provides information on contemporary clinical presentation and demographics of patients with Respiratory Symptom Complex who have SRBD, and it examines the possibility of identifying an Overlap Syndrome in these patients.

REFERENCES

1. Bosquet J, Khaltaev N. Global surveillance, prevention and control of Chronic Respiratory Diseases: A comprehensive approach. Global Alliance against Chronic Respiratory Diseases. Geneva, Switzerland: World Health Organization, 2007. Crossref
2. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328(17):1230-5. Crossref
3. Lavie P. Incidence of sleep apnea in a presumably healthy working population. Sleep 1983;6:312-8. Crossref
4. Berry DT, Webb WB, Block AJ, Switzer DA. Sleep-disordered breathing and its concomitants in a subclinical population. Sleep 1986;9:478-83. Crossref
5. Gislason T, Almqvist M, Eriksson G, Taube A, BomanG. Prevalence of sleep apnea syndrome among Swedish men: an epidemiological study. J Clin Epidemiol 1988;41:571-6. Crossref
6. Cirignotta F, D'Alessandro R, Partinen M, Zucconi M, Cristina E, Gerardi R, et al. Prevalence of every night snoring and obstructive sleep apneas among 30-69-year-old men in Bologna, Italy. Acta Psychiatr Scand 1989;79:366-72. Crossref
7. Bearpark H, Elliot L, Grunstein R, Cullen S, Schneider H, Althaus W, Sullivan C. Snoring and sleep apnea: a population study in Australian men. Am J Respir Crit Care Med 1995;151:1459-65. Crossref
8. Oslon LG, King MT, Hensley MJ, Saunders NA. A community study of snoring and sleep-disordered breathing: prevalence. Am J Respir Crit Care Med 1995;152:717-20. Crossref
9. Ohayon M, Guillemenault C, Priest RG, Caulet M. Snoring and breathing pauses during sleep: telephone interview survey of a UK population sample. BMJ 1997;314:860-3. Crossref
10. Pack AI, Maishin G. Who should get treated for sleep apnea? Ann Intern Med 2001;134:1065-7. Crossref
11. Anandam A, Patil M, Akinnusi M, Jaoude P, El-Solh AA. Cardiovascular mortality in obstructive sleep apnoea treated with continuous positive airway pressure or oral appliance: an onservational study. Respirology 2013;18(8):1184-90. Crossref
12. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley TD. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 2003;348(13):1233-41. Crossref
13. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomized parallel trial. Lancet 2002;359(9302):204-10. Crossref
14. Fletcher EC, Brown DL. Nocturnal oxyhemoglobin desaturation following tracheostomy for obstructive sleep apnea. Am J Med 1985;79(1):35-42. Crossref
15. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, Stubbs R, Hla KM. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 2008 Aug 1;31(8):1071-8. Crossref
16. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med 2009;6(8):e1000132. Crossref
17. Berry RB, Brooks R, Gamaldo CE, Harding SM Lloyd RM, Marcus CL, Vaughn BV. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.0.2. www.aasmnet.org, Darien, Illinois: American Academy of Sleep Medicine, 2013. Crossref
18. Alberti KZMM, Zimmet P, Shaw J. Metabolic Syndrome- a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006;23:469-80. Crossref
19. Koirala P, Ghimire RH, Mishra DR, Bista B, Shah B. Utility of Epworth Sleepiness Scale (ESS) in predicting the presence of Sleep Related Breathing Disorders (SRBD) in patients in Routine

Respiratory Clinical Service. Journal of Nobel Medical College 2017;6(2):9-13. Crossref

20. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3(4):310-18. Crossref

21. Larsson LG, Lindberg A, Franklin KA, Lundbäck B. Gender differences in symptoms related to sleep apnea in a general population and in relation to referral to sleep clinic. Chest 2003;124:204-11. Crossref

22. Jordan AS, McEvoy RD. Gender differences in sleep apnea: Epidemiology, clinical presentation and pathogenic mechanisms. Sleep Med Rev 2003;7:377-89. Crossref

23. Wahner-Roedler DL, Olson EJ, Narayanan S, Sood R, Hanson AC, Loehrer LL, Sood A. Gender-specific differences in a patient population with obstructive sleep apnea hypopnea syndrome. Gend Med 2007;4:329-38. Crossref

24. Bixler EO, Kales A, Soldatos CR, Kales JD, Healey S. Prevalence of sleep disorders in the Los Angeles metropolitan area. Am J Psychiatry 1979;136(10):1257-62. Crossref

25. Flenley DC. Sleep in chronic obstructive lung disease. Clin Chest Med 1985;6(4):651-61. Crossref

26. Wynne JW, Block AJ, Hemenway J, Hunt LA, Flick MR. Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive lung disease (COLD). Am J Med 1979;66:573-79. Crossref

27. Guilleminault C, Cummiskey J, Motta J. Chronic obstructive airflow disease and sleep studies. Am Rev Respir Dis 1980;122(3):397-406. Crossref

28. Turcani P, Skrickova J, Pavlik T, Janousova E, Orban M. The prevalence of obstructive sleep apnea in patients hospitalized for COPD exacerbation. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2014;158:1-7. Crossref

29. Lopez-Acevedo MN, Torres-Palacios A, Elena Ocasio-Tascon M, Campos-Santiago Z, Rodriguez-Cintron W. Overlap syndrome: an indication for sleep studies? : A pilot study. Sleep Breath 2009;13(4):409-13. Crossref

30. Ekici A, Ekici M, Kurtipek E, Keles H, Kara T, Tunckol M, Kocyigit P. Association of Asthma-Related Symptoms With Snoring and Apnea and Effect on Health-Related Quality of Life. Chest 2005;128(5):3358-63. Crossref

31. Lewis DA. Sleep in patients with asthma and chronic obstructive pulmonary disease. Curr Opin Pulm Med 2001;7(2):105-12. Crossref

32. Klink M, Quan SF. Prevalence of reported sleep disturbances in a general adult population and their relationship to obstructive airways diseases. Chest 1987;91(4):540-6. Crossref