Internal Medicine and Medical Investigation Journal



E-ISSN: 7750-2474

Homepage: www.imminv.com

ORIGINAL ARTICLE Evaluating the Relationship between Daytime Sleepiness and Polysomnographic Indices in Patients with Obstructive Sleep Apnea

Running title: Obstructive Sleep Apnea

Abolhassan Halvani¹, Mohammad Mahdi Malek Sabet², Sareh Rafatmagham^{2*}, Seyed Mohammad Amin Hashemipour², Abdolhosein Alimo-

hammadi², Amir Houshang Mehrparvar³, Mohsen Mirshamsi⁴

¹Internal Medicine Department of Islamic University of Medical Science, Yazd, Iran

²Young Researchers and Elites Club, Faculty of Medicine, Islamic Azad University, Yazd branch, Yazd, Iran

³Department of Occupational Medicine and Industrial Diseases Research center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

⁴Student Research Committee, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

* Corresponding Author: Sareh Rafatmagham, E-mail: r.sareh2012@gmail.com

ARTICLE INFO

Article history Received: Nov 04, 2020 Accepted: Feb 01, 2021 Published: March 16, 2021 Volume: 5 Issue: 4

Key words: *Obstructive Sleep Apnea, Polysom-nography*

ABSTRACT

Introduction: Obstructive sleep apnea (OSA) has been a major subject of interest in medical science for the past 50 years. It is also a major cause of death and disability, and the most common pathologic cause of daytime sleepiness. Currently, the gold standard for the diagnosis of OSA is polysomnography, but researchers have long sought easier and more affordable alternative methods for the diagnosis of this condition. This study aimed to determine whether the results of the Epworth Sleepiness Scale (ESS) and the Berlin Questionnaire (BQ) are accurate enough to be recommended as alternatives to polysomnography. Materials and Methods: This descriptive-analytical study was performed on 90 patients with suspected OSA at Farrokhi hospital, Yazd, Iran. ESS and BQ were filled by the patients, and data was analyzed by ANOVA, chi-square test, and Fisher's exact test SPSS ver.17. Results: Of the 90 patients being studied, 69 (76.6%) were male and 21 (23.3%) female. The mean age of patients was 48±12.4 years, mean BMI 31.5±5.6 kg/m2, mean neck circumference 40.8±5.1 cm, mean abdominal circumference 107.2±12.7 cm, mean night spo2 (peripheral oxygen saturation) 89.6±5.5, mean desaturation index 33.1±23.7, and mean total snoring duration 34.3±22.3. Also, the mean ESS score and AHI of the patients were 10.6 ± 5.6 and 30.3 ± 23.5 , respectively. Conclusion: The results suggested that if used appropriately, and in combination with clinical evidence, ESS and BQ can serve as effective instruments for screening patients who need further examination with polysomnography.

INTRODUCTION

Sleep Disordered Breathing (SDB) refers to a group of disorders characterized by recurrent apnea and gas exchange defects during sleep, which cross-sectional studies have shown to be very common in many populations. Approximately 2% of the general population are eligible to receive conventional SDB treatments for reasons such as excessive daytime sleepiness, cardiac disorders, and cognitive impairments (1,2). The most common form of SDB is Obstructive Sleep Apnea (OSA). For the past 50 years, OSA has been a major subject of interest in medical science and has been recognized as a strong predictor of cardiovascular diseases (3). The prevalence of OSA in Iran is reported to be 27.3%. Apnea is defined as a complete cessation of airflow for a minimum of 10 seconds. The prevalence of this disorder is 24% in men and 9% in women, with higher rates in elderly population and smokers (4). Sleep is not a monotonous phenomenon, and consists of two major states: non-rapid eve movement (NREM) sleep also known as quiescent sleep, and rapid eye movement (REM) sleep also known as active sleep. NREM sleep itself consists of four stages, with higher stages representing deeper sleep; the deepest stage is called Slow Wave Sleep (SWS). During REM sleep, dreaming begins and the cerebral metabolic activity and CNS-induced movements intensify. However, this is accompanied by the inhibition of sensory signals sent from these centers to the muscles. In normal sleep, the person undergoes multiple repeating cycles of NREM and REM stages. In a typical 90-120 minute NREM-REM cycle, the person experiences 10 to 20 minutes of stable REM sleep. In NREM sleep, the elimination of the arousal/ awakening effect on respiratory action and the reduced sensitivity of chemoreceptors lead to reduced respiratory drive. As a result, during the early phases of sleep, fluctuations between wakefulness and sleep in the CNS make a person susceptible to periodic breathing. Such breathing may involve short periods of apnea (Cheyne-Stokes respiration) (5). Normally, during NREM sleep, the body goes into a state of decreased sympathetic tone and increased parasympathetic tone, which results in a decreased heart rate, blood pressure, cardiac output, and autonomic nerve activity. This also reduces the burden on the heart muscle and the oxygen demand of the body. During temporary or spontaneous awakening, the body experiences a sudden increase in sympathetic tone, pulse rate, and blood pressure, and a decrease in parasympathetic tone (the opposite of what occurs when going into sleep). In contrast, complete awakening is accompanied by a gradual increase in sympathetic tone without parasympathetic inhibition (6).

People may experience central or obstructive apnea at the onset or during REM stages without having any clinical problem. These episodes of apnea usually last less than 15 seconds and do not recur. Sometimes they can even go on for 30 seconds or more without causing a major problem. However, they are not accompanied by noticeable changes during sleep or after waking up. Although normal in childhood, SDB is more common in older people after the age of 60. The difference between sleep apnea in normal people and those with SDB is that the latter group has an Apnea-Hypopnea Index (AHI) more than five. Although AHI=5 serves as a general threshold for distinguishing between normal and abnormal sleep apnea, many people with higher AHIs may have no symptoms or complaints. Nevertheless, the definition of SDB is based on this index. An individual with an AHI>5 is more likely to experience cardiovascular complications such as hypertension and daytime sleepiness. These people are also more likely to have accidents and develop more severe disabilities than others (7). The current gold standard for the diagnosis of OSA is polysomnography. Polysomnography is a supervised test involving the monitoring of EEG, ECG, EOG (to determine the sleep stage), breathing (by nasal pressure transducer or thermistor), abdominal and chest wall movements, body posture, tibialis anterior EMG, oxygen saturation (by an oximeter), and snoring. Overnight polysomnography is routinely used to diagnose OSA in patients suspected to be suffering from this condition. It is not recommended to use oximetry alone for the diagnosis of OSA. It is also preferable to monitor nasal pressure changes during inhalation and exhalation than using a thermistor to detect changes in the airflow (8).

Irregular breathing during sleep without daytime sleepiness is very common and occurs in one out of every four middle-aged men. But since this condition has no clinical symptoms, it does not qualify as OSA, and there is currently no evidence indicating its negative effects on a person's health. The difficulty of the differential diagnosis of OSA highlights the importance of proper diagnosis and treatment of this condition. Currently, the standard method for the diagnosis of OSA is polysomnography, but since this method is both expensive and time-consuming and also requires hospitalization, many researchers have attempted to find easier and less expensive alternatives. So far, these efforts have resulted in the development of two instruments known as the Epworth Sleepiness Scale (ESS) and the Berlin Questionnaire (BQ) (9). Both instruments facilitate the diagnosis through a detailed analysis of the patient's medical history, but there have been contradictory reports regarding their accuracy (10). Given the importance of access to affordable and easy OSA diagnostic methods in developing countries like Iran, the present study investigated the results of ESS and BQ in Iranian OSA patients to determine whether they are accurate enough to be recommended as alternatives to polysomnography.

MATERIALS AND METHODS

This research is a cross-sectional descriptive-analytical study, and 90 patients were selected to participate. The study was performed on the population of patients who had recently been referred to the occupational medicine clinic of Farrokhi hospital in Yazd, Iran, for sleep disturbances or daytime sleepiness.

The patients were selected by a simple random sampling from among the population of patients who had been referred to the occupational medicine clinic of Farrokhi hospital for sleep tests from February 2013 to August 2014. All patients were willing and able to participate in the study and signed a written consent form. The patients who were not cooperative in the completion of the questionnaires were excluded.

Demographic Characteristics of Participants

Demographic characteristics and medical information of the participants including the diagnostic information, history of disease and treatment, and history of medication and smoking were obtained from their medical files. Anthropometric data including height, weight, neck circumference and BMI were measured by a tape measure and a medical scale. The neck circumference was measured from the middle of the neck and over the thyroid cartilage.

Epworth Sleepiness Scale (ESS) and Berlin Questionnaire (BQ)

Epworth Sleepiness Scale (ESS) and Berlin Questionnaire (BQ) were completed through interviews with patients with the assistance of an internal medicine specialist. The ESS questionnaire, which is self-administered, has eight items that rate a person's likelihood of dozing off in daily situations. An ESS score of more than 10 indicates daytime sleepiness and higher values represent increased severity of sleepiness. This validated questionnaire has a high level of internal consistency (α Cronbach, 0.88) (11). The Berlin Questionnaire was filled based on a conference on sleep in primary care, consisting of one introductory question, 4 questions about snoring, 3 questions on daytime sleepiness, one sub-question about sleepiness behind the wheel (i.e., while driving a motor vehicle), and a question on history of high blood pressure (12).

Data Analysis

The data collected by the questionnaires was analyzed by SPSS software ver.17 with the assistance of a statistic expert. This analysis involved tabulating the results and conducting ANOVA, chi-square test, and Fisher's exact test with P-value<0.05 (considered statistically significant).

RESULTS

A total of 90 patients who were referred to the occupational medicine clinic of Farrokhi hospital were studied. The mean age of these patients was 48 ± 12.4 years with an age range of 24-82 years. Of the 90 patients under study, 69 were male (76.6%) and 21 were female (23.3%). The mean BMI, neck circumference, and abdominal circumference of the patients were 31.5 ± 5.6 kg/m2 with a range of 21.7-49.1 kg/m2, 40.8 ± 5.8 cm with a range of 27-69 cm, and 107.2 ± 12.7 cm with a range of 80-146 cm, respectively. Also, the mean ESS score and the AHI of the patients was 10.5 ± 5.6 with a range of 0-24, and 30.3+23.5 with a range of 0.06-91.1, respectively.

As shown in Table 1, out of 90 patients, 48 patients, including 36 men (40%) and 12 women (13.3%) had no daytime sleepiness, 20 patients including 17 men (18.8%) and 3 women (13.3%) had mild to moderate daytime sleepiness, and 22 patients including 16 men (17.7%) and 6 women (6.6%) had severe daytime sleepiness based on their ESS scores. The chi-square test showed a statistically significant relationship between the severity of daytime sleepiness based on ESS and the severity of OSA (P=0.279).

The chi-square test also showed a statistically significant relationship between the severity of OSA and the risk class (determined based on the Berlin questionnaire) (P=0.042), meaning that people who were categorized as high risk were more likely to be suffering from more severe forms of OSA. Using the Berlin questionnaire, out of 90 patients, 24 patients (26.7%) including 19 men (79%) and 5 women (21%) were categorized as low-risk and 66 patients including 51 men (77.2%) and 15 women (22.7%) were categorized as high-risk. The chi-square test showed no significant relationship between the sleep condition based on ESS and the risk of having OSA based on the Berlin questionnaire (P=0.219). As shown in Table 2, ANOVA demonstrated a statistically significant relationship between the sleepiness condition based on ESS and the mean night spo2 (P=0.04).Using ANOVA, a statistically significant relationship was also found between the sleepiness condition based on ESS and the desaturation index (P=0.01). However, ANOVA showed no significant relationship between the sleep condition based on ESS and the total duration of snoring (P=0.063).

As the results in Table 3 depict, from ANOVA, a statistically significant relationship was found between the risk of OSA (based on BQ) and the mean night spo2 (P=0.03). This means that the probability of having OSA (based on BQ) is statistically related to the mean nocturnal SpO2. ANOVA also showed a significant relationship between the risk of OSA (based on BQ) and the desaturation index (P=0.04). Using the same ANOVA, no significant relationship was found between the risk of OSA and the total snoring duration (P=0.3) and no significant relationship between the mean snoring duration and the severity of daytime sleepiness (according to ESS) was found as well (P=0.013). The relationship between the mean desaturation index of the samples and the severity of sleepiness (according to ESS) was also assessed by ANOVA, which indicated a statistically significant relationship (P=0.033).

As demonstrated in Table 4, ANOVA showed a statistically significant relationship between the mean night SpO2 of the samples and the severity of sleepiness according to ESS (P=0.016).

As can be seen in Table 5, using ANOVA, a significant relationship was found between the mean neck circumference of the samples and the severity of OSA (P=0.027). This means that people with a thicker neck were more likely to have OSA and may have more severe episodes than people with a thinner neck. With ANOVA, no significant relationship was found between the mean BMI in the samples and the severity of OSA (P=0.217), meaning that higher BMI did not increase the risk of having OSA or developing more severe forms of this condition.

The relationship between the severity of sleepiness (based on ESS) and the person's OSA risk (according to BQ) was assessed by the chi-square test, which showed no significant relationship between these two variables (P=0.26). In other words, there was no statistically significant relationship between the ESS's evaluation of daytime sleepiness and the BQ's evaluation of the risk of OSA.

ANOVA showed no significant relationship between the mean abdominal circumference of the samples and the severity of OSA (P=0.066). This suggests that abdominal obesity does not increase the risk of having OSA or developing more severe forms of this condition.

DISCUSSION

In a study carried out by Chikka Bellandur et al. (2011) on 122 OSA patients in India, BQ score was correlated with AHI, O2 saturation, and O2 desaturation, but there was no correlation between this score and the duration of snoring. In this study, the BQ score was significantly related to AHI in all patients, and its ability to predict AHI was similar to PSG. Therefore, it was concluded that BQ is an effective tool for diagnosing patients who are likely to have OSA, and screening patients who are to be referred to PSG. Another finding in this study was that OSA is strongly influenced not only by weight gain but also by pattern of fat distribution in the body (11). The findings of the present study confirm these results. In a study conducted by Edward et al. (2005) on 31 obese middle-aged American patients, of whom 97% were male, there was a weak relationship between PSG parameters, especially AHI, and the ESS scores (12). The present study also observed a weak relationship between the aforementioned parameters.

A study by LUXP et al. (2011) on 90 OSA patients in China reported that BQ is of little value for screening patients with OSA. Also, BQ scores were not correlated with the severity of OSA in Chinese patients (13). These findings are inconsistent with the results of the present study, which showed that BQ scores are accurate enough to be used in screening patients.

In a study by Sean Hesselbacher et al. (2012) on 2121 OSA patients in the United States, they concluded that ESS is of some value for diagnosing sleep apnea but its results can be influenced by various factors such as age, gender, body shape and race, and cannot serve as the sole measure for the diagnosis and screening of OSA in the absence of other clinical evidence (14). The present study also reached a similar conclusion.

A study carried out by Hamdy Ali Mahmoud et al. (2013) on 180 asthmatic patients with COPD and CAD in Egypt reported that BQ was completely reliable in determining the patients that needed further examinations following the completion of ESS (15). These findings are in coherence with the results of the present study.

In a study performed by Sevinc Sarin et al. (2013) on 1375 patients referred for PSG in Turkey, it was concluded that BQ is a poor predictor of OSA (16), which is inconsistent with the conclusion of the present study.

In the study conducted by G.J. Gibson et al. (2005) on 120 OSA patients in the UK, a clear association was observed between ESS score and AHI. The ESS score was not consistent with sleepiness in several patients. To explain this finding, it was argued that some patients may deny being sleepy, be untruthful in their responses, or misunderstand the meaning of sleepiness. They recommended that the questionnaire should be completed in the presence of the patient's spouse to reduce such errors (17). The second part of these findings is consistent with the results obtained in the present study.

Khosrow Sadeghniat et al. (2011) carried out a study on 126 OSA patients in Iran and observed that the patients with daytime sleepiness had higher AHI and lower nocturnal oxygen saturation than patients without sleepiness. They also found a significant relationship between excessive sleepiness, and BMI and neck circumference (18). In the present study, no significant relationship was noted between AHI and the severity of daytime sleepiness, but a significant relationship was observed between nocturnal oxygen saturation and AHI.

CONCLUSION

Despite the fact that no significant relationship was found between the ESS score and AHI, this score showed a significant relationship with other indices such as mean night SpO2 and desaturation index. All of these indices also had a significant relationship with the BQ score. While previous studies on the accuracy of ESS and BQ have reported conflicting results, the findings of this study suggest that if used properly and in combination with clinical evidence, these questionnaires can serve as effective instruments for screening in order to identify patients who need further examination with PSG.

ACNOWLEDGMENTS

The authors would like to thank all those who patiently contributed to this study.

AUTHOR CONTRIBUTION

All authors contributed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL STANDARDS

Verbal consent was taken from patients to participate in the study. Due to the descriptive design of the study, no special ethical consideration was needed.

Table 1. Frequency distribution of the severity of daytime sleepiness (based on ESS) versus the severity of OSA

Severity of daytime sleepiness based on ESS	Normal			Mild to Sev oderate		ere T		otal
Severity of OSA	F	Р	F	Р	F	Р	F	Р
Normal	6	60	0	0	4	40	10	100
Mild	13	68.4	4	21.1	2	10.5	19	100
Moderate	13	52	5	20	7	28	25	100
Severe	16	44.4	11	30.6	9	25	36	100
Total	48	53.3	20	22.2	22	24.4	90	100

(abbreviations; ESS: epworth sleepiness scale, OSA: obstructive sleep apnea, F: frequency, P: percentage)

Table 2. Relationship b	between the sleep	piness condition accord	ing to ESS and th	ne mean night spo2

Sleepiness condition based on	Sample	mean night SpO2	SD	Min	Max
ESS	Frequency	(%)			
Normal	48	91.1	3.8	74	95
Abnormal	42	87.8	6.6	70	96
Total	90	89.6	5.5	70	96
					P=0.04

(abbreviation; ESS: epworth sleepiness scale, SD: standard deviation, SpO2: peripheral oxygen saturation)

Risk of OSA based on the	Sample	mean night	SD	Min	Max
Berlin questionnaire	Frequency	SpO2 (%)			
Low risk	24	91.5	3.7	80	95
High risk	66	88.9	5.9	70	96
Total	90	89.6	5.6	70	96
					<i>P</i> =%0.03

Table 3. Relationship between the risk of OSA according to BQ and the mean night spo2

(abbreviation; OSA: obstructive sleep apnea, SpO2: peripheral oxygen saturation, SD: standard

deviation)

Table 4. Frequency distribution of the mean night SpO2 of the samples versus the severity of sleepiness according to ESS

Severity of sleepiness according to	Frequency	mean night SpO2	SD	Min	Max
ESS		(%)			
Normal	48	91.1	3.8	74	95
Mild to moderate	20	88.2	6.5	73	94
Sever	22	87.5	6.8	70	96
total	90	89.6	5.5	70	96

(abbreviation; OSA: obstructive sleep apnea, SpO2: peripheral oxygen saturation, SD: standard deviation)

Table 5. Frequency distribution of the mean neck circumference of the samples versus the severity of OSA

Severity of OSA	Frequency	Mean neck	SD	Min	Max
		circumference (cm)			
Normal	10	39.1	3.5	35	45
Mild	19	38.7	3.9	31	43
Moderate	25	40.4	4.8	27	49
Severe	36	42.7	5.8	33	69
total	90	40.8	5.1	27	69

(abbreviation; OSA: obstructive sleep apnea, SD: standard deviation)

REFERENCES

1. S.B.Badr and K.p.strohl. pathophysiology of sleep – disorders breathing. In Baum's text of pulmonary diseases. P1405-1421,2004.

2. R.J. looney and al oecvpational air way disease in Bavm's Temt of Pulmunary disease.2004.

3. Gonzales JF, Marshall S, Russian CJ. The Relationship Between the Mallampati Scoring System, the Berlin Questionnaire, and Epworth Sleepiness Scale. The Internet Journal of Allied Health Sciences & Practice. 2011;9:9.

4. Kurihara Y, Kurihara H, Suzuki H, et al: Elevated blood pressure and craniodacial abnormalities in mice deficient in endothelin-1. Nature 1994;368:703-710.

5. R.M. Schwartz stein. physiology of dyspnea. In upto date 2006.

6. M.L. stanchina. A Malhotra and B. P. white. Diagnosis and treatment of respiratory disorders of sleep in bautm's text of pulmonary disease. P1425-1445.2004.

7. Lindberg E, Gislason T.Epidemiology of sleep related obstructive breathing. Sleep med new.2006;4:411-33.

8. Whitelaw wa et al. clinical usefullness of home oxiometry compared with ploy somnography for assessment of sleep apnea. Am j respire crit care med171:188,2005.

9. Kump K, Whalen C, Tishler PV. Browner I, Ferrette V, Strohl KP, Rosenburg C, Redine S.Assessment of the validity and Utility of a sleep symptom questionnaire. Am J Respir Crit Care Med. 1994; 150:735-41.

10. Gould GA. Whyte KF. Rhind GB, et al: The sleep hypopnea symdrome. Am Rev Repir Dis 1988;137:895-898.

11. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep. 1992;15(4):376–381.

12. Redline S, Strohl KP. Recognition and consequences of obstructive sleep apnea hypopnea syndrome. Clin Chest Med. 1998:19:1-19.

13. Chikka Belladar, Carmelaram post,Bangalore. identification of risk factor for obstructive sleep apnea by Berlin questionnaire. 560035,karrnataka India.

14. Weaver EM, Kapur V, Yueh B. Polysomnography vs Self-reported Measures in Patients With Sleep Apnea. Archives of Otolaryngology–Head & Neck Surgery. 2004;130(4):453-8.

15. Lü XP, Zhang C, Ma J, Su L, Jia P, Luo YP, et al. [Application of Berlin questionnaire in the screening of obstructive sleep apnea hypopnea syndrome]. Zhonghua Jie He He Hu Xi Za Zhi. 2011;34(7):515-9.

16. Sean Hesselbacher, jerry Allen sara surani and et al. Body mass index, Gender and Ethnic varhations Alther the clinical implication of the Epworth sleepness scale in in patient with suspected obstructive sleep apnea the open respiratory medicine journal 2012, 6, 20-27.

17. Hamdy Ali,Mahmoud Mahmud, SUZAN Sallama and et al. validation of the Epworth sleepness scale Berlin STO-PANGE,questionnaires and American society of anesthesiologist checklist as screening tools for obstructive sleep apnea in patients with choronic obstructive pulmonary disease asthema and cardiovascular disease.304-10;45-12;45.2013.

18. Sarinc Ulasli S, Gunay E, Koyuncu T, Akar O, Halici B, Unlu M. Validity of Berlin questionnaire for obstructive sleep apnea in a sleep clinic population. European Respira-

tory Journal. 2013;42(Suppl 57):P2033.

19. G. j. Gibson Martin, Walsh jk. Epworth sleepness scale in obstructive sleep apnea an underestimated subjective scale.18;267-710.Nov. 2006.

20. Sadeghniiat-Haghighi K, Yazdi Z, Zohal M. Polysomnographic Findings in Patients With Obstructive Sleep Apnea With and Without Excessive Daytime Sleepiness %J The Journal of Shahid Sadoughi University of Medical Sciences. 2011;19(4):445-53.

JM, Carlsten C, Davis BE, Deschesnes F, Duong M, Durn BL, Howie KJ, Hui L. Effects of interleukin-13 blockade on allergen-induced airway responses in mild atopic asthma. American journal of respiratory and critical care medicine. 2011 Apr 15;183(8):1007-14.

9. Camargo CA, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. Archives of Internal Medicine. 1999 Nov 22;159(21):2582-8.

10. Henderson Jr WR. Role of leukotrienes in asthma. Annals of allergy. 1994 Mar;72(3):272

11. Kotwani A, Chhabra SK, Tayal V, Vijayan VK. Quality of asthma management in an urban community in Delhi, India. The Indian journal of medical research. 2012 Feb 1;135(2):184.

12. Arif AA, Rohrer JE, Delclos GL. A population-based study of asthma, quality of life, and occupation among elderly Hispanic and non-Hispanic whites: a cross-sectional investigation. BMC public health. 2005 Sep 21;5(1):1.

13. Afrite A, Allonier C, Com-Ruelle L, Le Guen N, Annesi-Maesano I, Delmas MC, Furhman C, Leynaert B. Asthma in France in 2006: prevalence and control of symptoms. Issues Health Econ. 2008;138:1-8.

14. Olaguibel JM, Quirce S, Juliá B, Fernández C, Fortuna AM, Molina J, Plaza V. Measurement of asthma control according to global initiative for asthma guidelines: a comparison with the asthma control questionnaire. Respiratory research. 2012 Jun 22;13(1):1

15. Waibel V, Ulmer H, Horak E. Assessing asthma control: symptom scores, GINA levels of asthma control, lung function, and exhaled nitric oxide. Pediatric pulmonology. 2012 Feb 1;47(2):113-8.

16. Kämpe M, Lisspers K, Ställberg B, Sundh J, Montgomery S, Janson C. Determinants of uncontrolled asthma in a Swedish asthma population: cross-sectional observational study. European Clinical Respiratory Journal. 2014;1.

17. Price D, Fletcher M, Van Der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. NPJ primary care respiratory medicine. 2014 Jun 1;24:14009

18. Gold LS, Montealegre F, Allen-Ramey FC, Jardim J, Sansores R, Sullivan SD. Asthma control and cost in Latin America. Value in Health Regional Issues. 2014 Dec 31;5:25-8.

19. Hoy HM, O'Keefe LC. Practical guidance on the recognition of uncontrolled asthma and its management. J Am Assoc Nurse Pract. 2015;27(8):466-75. Hoy HM, O'Keefe LC. Practical guidance on the recognition of uncontrolled asthma and its management. Journal of the American Association of Nurse Practitioners. 2015 Aug 1;27(8):466-75. 20. Nathan RA, Thompson PJ, Price D, Fabbri LM, Salvi S, González-Díaz S, et al. Taking Aim at Asthma Around the World: Global Results of the Asthma Insight and Management Survey in the Asia-Pacific Region, Latin America, Europe, Canada, and the United States. J Allergy Clin Immunol Pract. 2015;3(5):734-42.e5.