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ORIGINAL: Diagnostic Value of Oxygen Desaturation Index in Sarcoidosis Patients Suspected to Have Obstructive Sleep Apnea

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ABSTRACT

Introduction: sarcoidosis patients are at increased risk for obstructive sleep apnea syndrome (OSAS) probably due to factors such as steroid use, obesity, sarcoid neuropathy and etc. Therefore, we aimed to define the diagnostic value of the oxygen desaturation index (ODI) in predicting OSAS in patients with sarcoidosis.

Material and Methods: This cross-sectional study was performed in 81 sarcoidosis patients suspected to have OSAS admitted to the pulmonary clinics of the Masih Daneshvari Hospital, affiliated with Shahid Beheshti University of Medical Sciences (SBUMS), Tehran, Iran. Patients were examined using the Epworth Sleepiness Scale (ESS) and the Fatigue Assessment Scale (FAS), and those with FAS score≥ 22 and ESS score > 10 were included. All patients underwent a portable polysomnography (PSG) and a high-resolution pulse oximeter wristwatch simultaneously.

Results: Of 81 patients, 57 (70.4%) were female and 24 (29.6%) were male, and the mean age was 48.9±10.4 years (range, 28 to 75). The AHI score was positively correlated with ESS and ODI scores ($r=0.51$, $p<0.001$; $r= 0.85$, $p<0.001$, respectively). A positive correlation was found between ODI and ESS ($r=0.57$, $p<0.001$). A kappa coefficient value of 0.26 indicated a fair agreement between AHI and ODI scores. The cutoff based on maximal accuracy for ODI to predict AHI ≥15 was ODI ≥15. ODI ≥15 has been indicated to have sensitivity of 100%, and hence NPV of 100%, specificity of 96.4%, PPV of 36.6%, and 99.9 of accuracy for predicting moderate and severe OSAS.

Conclusion: ODI from a high-resolution pulse oximeter wristwatch is a sensitive and specific tool to predict moderate and severe OSAS in sarcoidosis patients.

Introduction

Sarcoidosis, as a chronic multisystemic disorder, is characterized by granulomatous inflammation. Its etiology and pathogenesis is still unclear; though, magnified immune response to unknown antigens is supposed to be a key pathogenic mechanism (1). Sarcoidosis mostly occurs among middle-age women. Nonspecific systemic symptoms, like weight loss, malaise, and fatigue, are attributed to the

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sarcoidosis (2). Also, pulmonary involvement is very common features (2, 3).

Obstructive sleep apnea syndrome (OSAS) is a disorder of repetitive upper airways collapse which leading to sleep fragmentation, hypercapnia, hypoxemia, variation in intrathoracic pressure, and increased sympathetic activity (4). OSAS has been found to occur in 2%–4% of the adult population (5, 6). Patients with sarcoidosis are at increased risk for OSAS probably due to factors such as steroid use, obesity (caused by steroids), sarcoid neuropathy or upper airway resistance secondary to airway disease.

Polysomnography (PSG) is the gold standard procedure for diagnosing OSAS. Although, PSG is a time-consuming and costly method (7). Also, most portable sleep monitoring tools need intensive patient training or help from well-trained experts, and manual scoring of reports by PSG specialists. Lack of suitable and economical diagnostic tools is a significant barrier for diagnosing OSAS. A high-resolution pulse oximeter wrist watch can diagnosis the variation in oxygen saturation caused by episodes of apnea and hypopnea, which need little education to install appropriately. Although oximetry has been assessed as a screening device in patients with suspected OSAS (8, 9), few studies have investigated the diagnostic performance of oximetry for OSAS in the sarcoidosis patients.

On the other hand, the studies that clearly show the OSAS frequency in sarcoidosis patients are not high. Therefore, we aimed to design a cross-sectional study to determine the OSAS frequency in patients with sarcoidosis. In addition, we aimed to define the diagnostic value of the oxygen desaturation index (ODI) in predicting OSAS in patients with sarcoidosis.

Methods

Setting

This cross-sectional study was conducted on sarcoidosis patients who referred to the pulmonary clinics of the Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences (SBUMS), Tehran, Iran. This multidisciplinary respiratory hospital, with 466 active beds, provides advanced services in the pulmonary and respiratory field.

Study design and sampling

A total of 81 sarcoidosis patients with convenience sampling were selected to participate in this study. We computed the sample size according to 4% prevalence of OSAS in adults, using a confidence level of 95% and a marginal error of 5%, and based on the sample size formula, the estimated sample size was 50. However, a sample size of 81 was obtained.

Inclusion and exclusion criteria

Inclusion criteria were a definite diagnosis of sarcoidosis, the Fatigue Assessment Scale (FAS) score ≥ 22, Epworth Sleepiness Scale (ESS) score > 10, patients who were willing to participate and complete the study, patients formally consent to participate and were able to communicate with the research team.

In this study, patients with unstable physical status, patients with neurological and mental disorders, patients took sleeping drugs, and those with incomplete information, were excluded.

Survey instrument

The Fatigue Assessment Scale (FAS)

The fatigue status were assessed by completing the FAS. FAS consisted of 10 items for assessing the fatigue in patients affected by sarcoidosis. This tool score from 10 to 50 points. Fatigue was approved if FAS ≥ 22 points and extreme fatigue was determinted if FAS ≥ 35 points.

The Epworth Sleepiness Scale (ESS)

The ESS was used to assess daytime sleepiness. The ESS determines the likelihood of falling asleep during different scenarios. This tool consists of 8 items, which are scored according to a 0-3 point. This tool rang from 0 to 24 points. The daytime sleepiness was approved if ESS ≥ 11 points. The sleepiness severity was determined by

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the ESS as follow: 0 to 10 (normal range of sleepiness), 11 to 14 (mild sleepiness), 15 to 17 (moderate sleepiness), and 18 to 24 (severe sleepiness).

Demographic questionnaire

This questionnaire includes demographic information such as (age, sex, marital status, body mass index (BMI), diabetes mellitus, hypothyroidism, reflux, smoking, hypertension, and etc.).

Data collection

First, patients with pulmonary sarcoidosis have been categorized into 5 stages according to American Thoracic Society/European Respiratory Society (ATS/ERS) guideline as follow; stage 0: normal chest radiograph, stage 1: bilateral hilar adenopathy (BHA), stage 2: BHA plus pulmonary infiltrates, stage 3: pulmonary infiltrates (without BHA), and stage 4: pulmonary fibrosis.

Both FAS and ESS questionnaires were completed via face-to-face interviews. Regardless of the result of the screening questionnaires, all eligible patients referred to the sleep clinic, and to diagnose the OSAS were examined.

Oximeter

SaO2 monitoring using a high-resolution pulse oximeter wristwatch was simultaneously done along with portable PSG. Each oxygen probe of the oximeter and PSG were connected to various fingers of the non dominant hand. Then, we extracted the oxygen desaturation index (ODI), cumulative time percentage with SpO2 <90% (CT90), lowest and average SpO2 from the oximetry data. Typically, ODI is the average number of desaturation episodes per hour, which are calculated as at least 4% drop in saturation from the average saturation in the immediately preceding 120 seconds, and lasting more than10 seconds. To decrease the bias of oximetry data, only oximetry reports collected between 00:00 hours and 6:00 hours were evaluated, even it was not clear patients were sleep during this time or not. A technician who were blinded to PSG results performed data processing. Oxygen disturbance was detected when ODI was more than five. Oxygen disturbance severity was defined by the ODI as follow: mild ($5 \leq$ ODI <15), moderate ($15 \leq$ ODI < 30), severe (ODI ≥ 30).

Polysomnography

The portable PSG reports were scored by a trained PSG technologist and interpreted by a physician specialized in sleep medicine. Obstructive apnea was determinated as a reduction of airflow ≥90% which lasted at least 10 seconds and there was evidence of continuous respiratory effort. Hypopnea was known as a reduction of airflow ≥30% for ≥10 seconds that was related with an oxygen desaturation of ≥3% or with arousal. OSAS was recognized when apnea/hypopnea index (AHI) was more than five events per hour during the night sleep. OSAS severity was defined by the AHI as follow: mild ($5 \leq$ AHI < 15), moderate ($15 \leq$ AHI < 30), severe (AHI ≥ 30).

Statistical analysis

Data were analyzed using descriptive statistics including mean ± standard deviation (SD), median, frequencies and percentages wherever applicable. The Shapiro-Wilk test was used to calculate the normality of all continuous variables. The Spearman correlation coefficient was used to examine the relationship between AHI, FAS, ODI, and ESS score. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of the ODI was used to describe predictive properties. To assess the agreement between ODI with AHI, the kappa statistic was applied. Kappa coefficient is used for the assessment of agreement or reliability between two or more measurements. Kappa coefficient can be interpreted as follows: values ≤0 as indicating no agreement and 0.01-0.20 as none to slight, 0.21-0.40 as fair, 0.41-0.60 as moderate to good, 0.61-0.80 as substantial, and 0.81-1.00 as almost perfect agreement. A test was considered statistically significant if the probability value (P-value) was less than

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0.05. All analyses were carried out using Stata software (version 14.1) (Stata Corp, College Station, TX, USA).

Ethical approval

The Research Ethics Committee at SBUMS approved the study protocol (Ethics No. IR.SBUMS.NRITLD.REC.1398.022). Also, patients were informed about participating in the study and signed the consent form. Patient data were kept confidential with the access limited to two of researchers and the quality control physician.

Results

Table 1 shows baseline characteristics of patients. Of 81 patients, 57 (70.4%) were female and 24 (29.6%) were male, and the mean age was 48.9±10.4 years (range, 28 to 75). Ten (12.3%) patients were diabetics, 10 (12.3%) were hypertensive, 10 (12.3%) were smoker, and 8 (9.9%) had hypothyroidism. Out of the 81 patients, 23 (28.4%) had 20≤BMI<24.9, 35 (43.2%) had 25≤BMI<30, and 23 (28.4%) had BMI≥30. The mean of FAS score was (30.4±6.3, range 21–46), and the mean of ESS score was (12.9±9.3, range 1–23). Of 81 patients, 29 (35.8%) had mild/moderate sleepiness and 7 (8.6%) had severe sleepiness. Based on PSG findings, 3 patients (3.7%) had 5 ≤ AHI < 15, 20 patients (24.7%) had 15 ≤ AHI < 30, and 6 patients (7.4%) had AHI ≥ 30. Based on oximetry findings, 42 patients (51.9%) had 5 ≤ ODI < 15, 20 patients (24.7%) had 15 ≤ ODI < 30, and 9 patients (11.1%) had ODI ≥ 30.

The AHI score was positively correlated with ESS and ODI scores (r=0.51, p<0.001; r= 0.85, p<0.001, respectively). AHI score was not significantly correlated with FAC score (r=0.10, p=0.373). A positive correlation was found between ODI and ESS (r=0.57, p<0.001). There was no relation between ODI and FAC (r=0.21, p=0.168). The AHI score was positively correlated with BMI (r=0.40, p<0.001). In addition, there was a relationship between ODI score and BMI (r=0.39, p<0.001). The relationship between the ODI and AHI is further indicated in **Figure 1**.

Table 1. Baseline characteristics of participants.

Characteristic	Subgroup	N (%)/Mean±SD
Age	-	48.9±10.4
Gender	Male	24 (29.6)
	Female	57(70.4)
BMI (kg/m²)	-	28.2±4.5
Marital status	Single	4 (4.9)
	Married	77(95.1)
Diabetes mellitus	No	71 (87.7)
	Yes	10 (12.3)
Hypertension	No	71 (87.7)
	Yes	10 (12.3)
Hypothyroidism	No	73 (90.1)
	Yes	8 (9.9)
Current smoker	No	71 (87.7)
	Yes	10 (12.3)
Reflux	No	31(38.3)
	Yes	50 (61.7)
AHI	Below 5	52 (64.2)
	5 – 14	3 (3.7)
	15 – 29	20 (24.7)
	30.0 and Above	6 (7.4)
ODI	Below 5	10 (12.3)
	5 – 14	42 (51.9)
	15 – 29	20 (24.7)
	30.0 and Above	9 (11.1)
FAS	-	30.4±6.3
ESS	-	12.9±9.3

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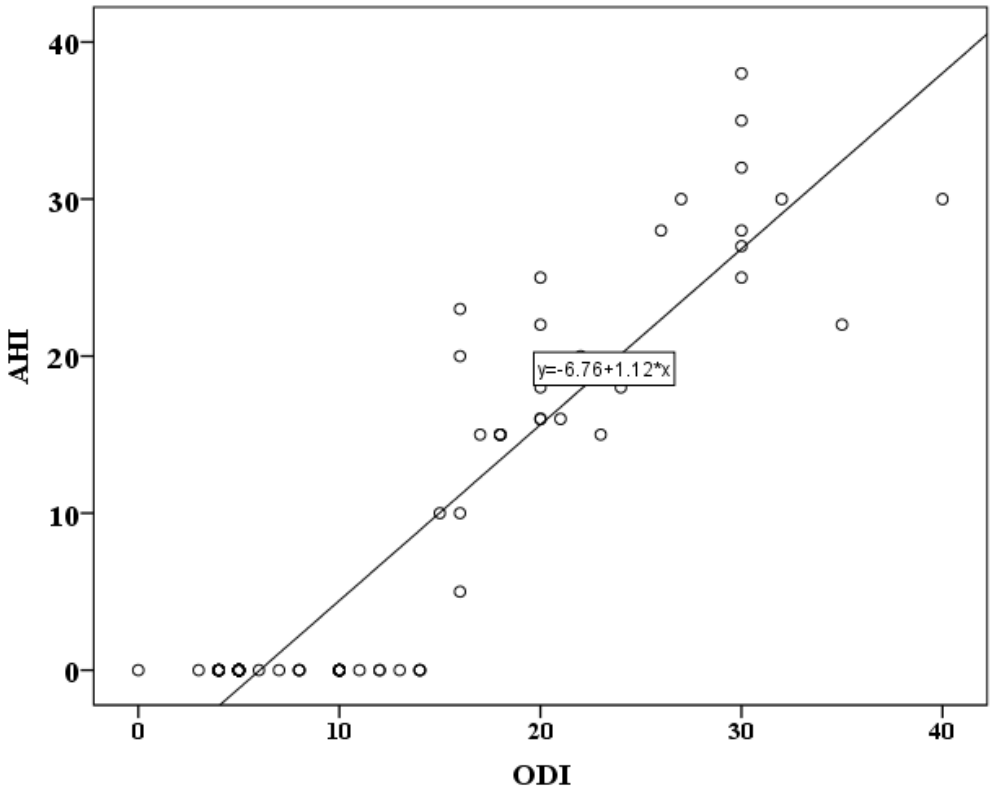

Figure 1. AHI from portable PSG versus ODI from simultaneous oximetry. R2 = 0.85, AHI = 1.12 × ODI − 6.76.

Table 2. Relationship between AHI and ODI.

Characteristic		AHI				Kappa coefficient	*P*-value
		AHI <5	5 ≤ AHI <15	15 ≤ AHI < 30	AHI ≥ 30		
ODI	ODI <5	10 (19.2)	0 (0)	0 (0)	0 (0)	0.26	0.001
	5 ≤ ODI <15	42 (80.8)	0 (0)	0 (0)	0 (0)		
	15 ≤ ODI < 30	0 (0)	3 (100)	16 (80.0)	1 (16.7)		
	ODI ≥ 30	0 (0)	0 (0)	4 (20.0)	5 (83.3)		

Table 3. Predictive Value of ODI for predicting OSAS at AHI≥ 15 Cut-off.

Variable	Sensitivity	Specificity	Accuracy	PPV	NPV
ODI	100	96.4	99.9	36.6	100

NPV=negative predictive value; PPV=positive predictive value.

Based on the chi-square test, there was a significant relationship between AHI and ODI scores (P=0.001). A kappa coefficient value of 0.26 indicated a fair agreement between AHI and ODI scores (**Table 2**).

The cutoff based on maximal accuracy for ODI to predict AHI ≥15 (including moderate and severe OSAS) was ODI ≥15. In fact, ODI ≥15 has been indicated to have sensitivity of 100%, and hence NPV of 100%, specificity of 96.4%, PPV of 36.6%, and 99.9 of accuracy for predicting moderate and severe OSAS (**Table 3**).

Discussion

Few studies have investigated the prevalence of OSAS in patients with sarcoidosis. The present study showed that the OSAS frequency in patients with sarcoidosis was higher than the prevalence of OSAS among general population. Our study illustrated that the OSAS frequency in pateints with sarcoidosis was considrabely high (29/81,

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35.8%). In our study, there was women dominance (approximately 70%) and OSAS severity was mostly moderate (20/29, 69.%). Doğan et al. assessed 46 sarcoidosis patients, showed that 28 (60.9%) were detected with OSAS (10).

AHI is known as the main paramter to assess the severity of OSAS, while ODI and other indexes are considered as secondary paramters. althogh, the ODI may demonstrated to be a useful paramter to detect OSAS because of following reasonable evidences; first, hypopnea with at least a 4% drop in oxyhemoglobin saturation are related to an further risk of cardiovascular disease (CVDs); secondry, hypopnea defined by an oxygen desaturation of ≥3% or with arousal is not associated with a similar outcome (11); third, the recent Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine has proved that most studies have not illustred an relationship between arousal frequency and cardiovascular events (12); forth, an ODI ≥ 5 has been reported to be a predictor of diabetes melitus after baseline adjustment for age, BMI, and hypertension (13); and fifth, hypoxia with oxyhemoglobin saturation ≤ 90% which lasted at least 9 minutes has been shown to be a stronger predictor for cardiovascular complications than AHI (14).

This study showed that ODI had a strong correlation with AHI, and a fair agreement between AHI and ODI was reported. The ODI ≥15 was a good predictor for AHI ≥15 (moderate and severe OSAS) with an accuracy of 99.9%, sensitivity of 100%, *i.e.*, NPV of 100%, specificity of 96.4%, and PPV of 36.6%. Because the sensitivity of ODI ≥15 to diagnose patients with AHI≥15 was 100%, we would be confident to ignore the probability of moderate to severe OSAS if a patient had ODI <15. Actually, the cutoff of ODI ≥15 might be a good option as it could recognize almost all patients with moderate and severe OSAS. Chung et al. reported that ODI had a strong correlation with AHI, and ODI >15 was a useful predictor for AHI >15 with an accuracy of 84%, and ODI >30 for AHI >30 with an accuracy of 93.7%, they also found that the cutoff of ODI >10 had a high sensitivity of 93.3% to recognize moderate and severe OSAS (15). Teramoto et al. conducted a study on elderly habitual snorers, they determined ODI by a decreasement in SpO2 of >4%, illustrated that the sensitivity and specificity for ODI >10 to detect AHI ≥15 were 63% and 95%, respectively (16). A study done by Lin et al. showed that ODI had a high correlation with AHI, and ODI >15 was a useful predictor for AHI >15 with a sensitivity/specificity of 84.0%/84.3%, and ODI >30 for AHI >30 with a sensitivity/specificity of 87.8%/96.6% (17). Their sensitivity and specificity was lower than the results in our study. A systematic review performed by Rashid et al., reporting that ODI ≥ 15 events/hour had the specificity ranged from 75% to 98% and the PPV of 97% for predicting OSAS (18). These variations between the different studies may be due to various statistical analysis methods, different definitions of variables such as hypopnea, oxygen desaturation and etc., and various grading of OSA severity.

The AHI and ODI scores were positively correlated with BMI, per unit increase in BMI, AHI and ODI scores were increased. Obesity is a risk factor for OSAS. More than two third of our subjects were obese. Patterson et al. reported that the OSAS prevalence was 52% in sarcoidosis patients with a mean BMI of 38 kg/m^2 (19). In the study conducted by Chitra et al., the mean of BMI was 37.5 kg/m^2 and OSAS rate was 83% (20). Ling et al. found OSAS is mostly related to oxygen desaturation in obese. they illustrated that BMI influences the accuracy of ODI, and ODI should not be only used for the diagnosis of OSAS in patients with a BMI less than 25kg/m2 (21).

In the present study, the ESS score was correlated with AHI and ODI, but the correlation of ESS with ODI was stronger than that with AHI. However, the mean of ESS score was low (12.9), 44.4% of our subjects had various degrees of sleepiness. Goncalves et al. (22) reported that ESS was correlated with arousal index and AHI, whreas Dixon et al. (23) and Pang et al. (24)

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found contradictory results. Temirbekov et al. found a positive correlation between AHI and ESS, but they reported the correlation between ESS and ODI was higher than that with AHI (25).

Strengths and limitations of the study

Several limitations of this study can be addressed. First, the number of patients who developed sarcoidosis was insufficient. Second, high-resolution pulse oximeter wristwatch is a suitable and economically way to predict OSAS, however, it has some limitations. It can't distinguish OSAS from central sleep apnea because it just measures the oxygen saturation fluctuations and does not monitor nasal flow and respiratory effort. Third, our single-hospital experience may not be generalized to the broader community. This study has some strengths. to the best of our knowledge, this was the first study in Iran which evaluated the diagnostic value of ODI in predicting OSAS in patients with sarcoidosis. Furthermore, patients were evaluated by trained and experienced experts.

Conclusion

In conclusion, ODI from oximetry was significntly correlated with the AHI. Based on maximal accuracy, ODI ≥15 were good predictor for AHI ≥15. The ODI ≥15 indicated an accuracy of 99.9%, sensitivity of 100%, NPV of 100%, specificity of 96.4%, and PPV of 36.6% to detect moderate and severe OSAS. ODI from a high-resolution pulse oximeter wristwatch is a sensitive and specific tool to predict moderate and severe OSAS in sarcoidosis patients.

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Conflicts of interest

Authors have no conflict of interests.

Authors' contributions

All authors were involved in the conception and design, analysis and interpretation of the data, drafting of the manuscript and revising it critically for intellectual content, approved the final version for submission, and agreed to be accountable for all aspects of the work.

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