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ORIGINAL STUDY

The role of the Berlin Questionnaire in assessing the frequency of obstructive sleep apnea syndrome in patients with risk factors and associated comorbidities

Adriana Neagos[1], Hedi Balogh Szarkozi[2], Cristian Mircea Neagos[3], Gabriela Jimborean[2], Mioara Szatmary[2]

[1]Department of Otorhinolaryngology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Targu Mures, Romania

[2]Department of Pneumophthisiology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Targu Mures, Romania

[3]ENT Clinic, County Emergency Clinical Hospital, Targu Mures, Romania

ABSTRACT

BACKGORUND. Sleep is a complex biological process and represents a reversible state of unconsciousness in which metabolism and motor activity are reduced. Sleep disorders are a group of conditions that disrupt a person's normal sleep patterns. Sleep disorders are one of the most common clinical problems encountered. Inadequate or non-restorative sleep can interfere with normal physical, mental, social and emotional functioning. Sleep pathology is a frequent condition, but often underdiagnosed.

MATERIAL AND METHODS. In this retrospective study, we aimed to investigate patients with suspected obstructive sleep apnea syndrome based on the response to the Berlin Questionnaire, which suggests the presence of an increased or decreased risk of sleep disorders. We conducted a study in patients with cardiovascular, metabolic, pulmonary antecedents, which were associated with risk factors, such as: age, body mass index, neck circumference, abdominal circumference, history of snoring.

RESULTS AND CONCLUSIONS. The Berlin Questionnaire is a useful tool for detecting mild, moderate and severe apnea syndrome, being used for its early diagnosis, especially in cases where polysomnography is more difficult to perform, in order to select patients for the continuation of the examination protocols. This questionnaire is a reliable tool for the exclusion of obstructive sleep apnea and can be a particularly important tool in the allocation of diagnostic resources in patients suspected of having a breathing disorder during sleep.

KEYWORDS: sleep breathing disorders, apnea, Berlin Questionnaire, cardiovascular diseases.

INTRODUCTION

Sleep is a complex biological process and represents a reversible state of unconsciousness in which metabolism and motor activity are reduced. There are two different types of sleep: rapid eye movement (REM) sleep and non-REM (NREM) sleep. NREM (dreamless sleep) sleep is further divided into four stages (N1, N2, N3, N4). The first stage, N1, is the most superficial stage, being characterized by a transition from wakefulness to sleep. Benzodiazepines work by increasing sleep in the N2 sleep stage. The adult enters the deep stages of sleep N3 and N4. After about 70 to 80 minutes of deep sleep, sleep becomes superficial and a period of REM follows, which is usually associated with active dreaming and body movements. This cycle repeats at approximately 90-minute intervals. Towards morning, REM sleep is more dominant compared to stage 3 and 4 sleep.

Sleep disorders are a group of conditions that disrupt a person's normal sleep patterns. Sleep disorders are one of the most common clinical problems encountered. Inadequate or non-restorative sleep can interfere with normal physical, mental, social and emotional functioning. Sleep disorders can affect overall health, safety and quality of life and are common in both adults and children. However, children with sleep disorders may have different symptoms than adults. Children with sleep problems may exhibit motor hyperactiv-

Corresponding author: Adriana Neagos, Associate Professor, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, 34 Gh. Marinescu Street, Targu Mures, Romania

ORCID: https://orcid.org/0000-0002-9299-2638

e-mail: neagos.adriana@gmail.com

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ity, inattention, irritability, or oppositional behaviour rather than obvious drowsiness. Sleep disorders are common and can have serious consequences on patients' health and quality of life. While some sleep disorders are more difficult to treat, most can be easily managed with appropriate interventions[1]. There are different forms of sleep disorders, such as parasomnia, hypersomnia, narcolepsy, restless legs syndrome, to which sleep breathing disorders are added[2].

Sleep breathing disorders include a number of respiratory conditions, such as: snoring, obstructive sleep apnea/hypopnea syndrome (OSAHS), central sleep apnea (CSA), hypoventilation syndromes.

The pathophysiology of OSAHS is based on upper airway occlusion during sleep. Airway occlusion is called apnea if it is complete and hypopnea if it is partial. Sleep-related obstructive breathing events are classified as mild (5–15 events per hour of sleep), moderate (15–30 events per hour of sleep), or severe (more than 30 events per hour of sleep). The prognosis of sleep disorders depends, to a large extent, on the cause of the occurrence[2].

Considering the multitude of consequences it has on the body, the patient with sleep apnea syndrome requires a multidisciplinary approach: ENT, pneumology, cardiology, neurology, endocrinology, oral-maxillo-facial surgery, psychiatry.

If a sleep apnea syndrome is suspected, the correct and detailed application of a diagnostic algorithm is necessary, which includes: clinical evaluation, application of sleepiness assessment questionnaires, performance of cardio-respiratory polygraphy, auto-CPAP titration and treatment recommendation upon confirmation of diagnosis or performance of polysomnography in case of inconclusive results.

Obstructive sleep apnea syndrome is more and more frequently diagnosed and treated by raising the awareness of the population and the medical staff about the suggestive symptoms and possible risks of this pathology. Referral of patients to sleep laboratories is required to decrease morbidity and mortality due to the pathology associated with sleep breathing disorders. Patients with undiagnosed sleep apnea syndrome may develop cardiac (treatment-resistant hypertension, heart rhythm disorders), neurocognitive (depression, attention disorders) or metabolic (type 2 diabetes) complications.

The causes and risk factors of insulin resistance remain poorly understood. After accounting for the important roles of adiposity, age, sex and race/ethnicity, up to 50% of individual variability in insulin resistance remains unexplained. In recent years, evidence has accumulated in support of a role of sleep disorders, including insufficient sleep, poor sleep quality and insomnia, as well as obstructive sleep apnea, as independent risk factors for the development and exacerbation of insulin resistance[3,4]. These patients are subject to perioperative risks and have an increased risk of work or road accidents. Numerous studies have demonstrated the existence of a close association between the positive diagnosis of obstructive sleep apnea syndrome (OSAS), and the presence in these patients of some comorbidities, personal antecedents, and common risk factors. The main risk factors considered in the studies, with statistical significance, were: age, weight, height, body mass index (BMI), smoking history, neck circumference, abdominal circumference. Numerous reviews and meta-analyses have been conducted to investigate risk factors for sleep disorders in the general population[5,6].

The diagnosis of obstructive sleep apnea syndrome is confirmed on a polysomnography if there are five or more predominantly obstructive breathing events per hour (AHI of 5 or greater), in a patient who has one or more sleep-related symptoms or conditions that include: drowsiness, fatigue, restless sleep, insomnia, apnea, gasping or choking, mood disorders, diagnosed hypertension, cognitive dysfunction, cerebrovascular accident, coronary artery disease, atrial fibrillation, congestive heart disease, or type II diabetes. Alternatively, the diagnosis of OSAS is also confirmed if there are 15 or more predominantly obstructive respiratory events per hour (AHI of 15 or greater), regardless of associated symptoms or conditions. OSAS is generally classified as mild, moderate, or severe. Mild OSAS refers to an AHI between 5 and 14 on a polysomnography. Moderate OSAS refers to an AHI between 15 and 30. Patients with an AHI greater than 30 on the polysomnography are classified as having severe OSAS.

Effective ways of treatment should not be applied without an accurate diagnosis of OSAS, but the medical history and physical examination are insufficient to establish the diagnosis or its severity. Using the accepted reference standard test – laboratory polysomnography (PSG), which is assisted – can be expensive and involves long waiting times for studies, so various groups have developed portable technologies to classify patients according to the presence or absence of OSAS and, for the first, the level of severity. Such devices are intended for use in sleep laboratories or at home[7]. Although screening tools such as the Berlin Questionnaire (BQ), the STOP-BANG Questionnaire (SBQ), the STOP Questionnaire (STOP), and the Epworth Sleepiness Scale (ESS) are widely used for OSA, the results regarding their diagnostic accuracy are controversial[8].

In this retrospective study, we aimed to investigate patients with suspected obstructive sleep apnea syndrome based on the appropriate response to the Berlin Questionnaire (high/low risk). We also aimed to highlight the presence or absence of the relationship between the positive response to the questionnaire (high risk) and the presence of the main comorbidities and risk factors associated with obstructive sleep apnea syndrome and known to evolve into complications following the lack of diagnosis or treatment of the sleep disorder.

MATERIAL AND METHODS

The target population for the current study was represented by patients hospitalized in the following medical departments: Occupational Medicine, Medical Clinic and ENT Clinic, for one month of 2021, at the Targu Mures County

Emergency Clinical Hospital. The inclusion criteria in the study were represented by patients who had one or more days of hospitalization, presenting in the antecedents one or more comorbidities (cardiovascular, metabolic, pulmonary or others). The presence of one or more risk factors associated with OSAS was also recorded (age, BMI, smoking history, neck circumference, abdominal circumference, snoring history, arterial hypertension).

The Berlin Questionnaire used as a reference in this study presents the patients' personal data, data related to the body mass index, followed by 3 categories of questions: Category 1 – questions related to snoring – intensity, frequency/week, how it bothers the people around, the presence of periods of apnea and their frequency; Category 2 – related to daytime fatigue, falling asleep while driving; Category 3 – refers to blood pressure. The answers to each question in a category are marked with 1 point, only for the high frequencies of the monitored parameters, the maximum score obtained being 9.

Following these diagnostic data, the consent of a number of 84 patients was requested in order to complete the Berlin Questionnaire, of course with their prior education and in the presence of their relatives to ensure the certainty of the answers. Following the compliance of each patient's decision, 7 of the 84 did not give their consent in order to complete the questionnaire, reaching a final of 77 patients included in the study.

The data required for the study, extracted from the patient records, for further processing, were: sex, environment of origin, age, height, weight, BMI, smoker/non-smoker/ex-smoker status, neck circumference, abdominal circumference, presence/absence of snoring, hypertension status, associated metabolic, cardiovascular, pulmonary pathologies and other comorbidities. The total number of patients who met the study inclusion criteria was 77, each of whom completed the Berlin Questionnaire. The group was then divided into two main groups according to the result obtained as follows: Grade I (Low Risk), Grade II (High Risk).

Quantitative data were centralized and analysed by calculating the mean and standard deviation, and the Student's T-Test was applied using the Statistical Package for Social Sciences (SPSS) program.

RESULTS AND DISCUSSIONS

The Berlin Questionnaire is a useful tool for detecting mild, moderate and severe apnea syndrome, being used for its early diagnosis in the clinical environment, especially in cases in cases where polysomnography is more difficult to perform[8].

The total number of patients obtained in the study following the fulfilment of the inclusion criteria was 77. The data collected and processed were structured as 4 criteria: demographic data, OSAS-associated risk factors present in the patients included in the study (height, weight, BMI, neck circumference, abdominal circumference, smoker/non-smoker/ex-smoker, arterial hypertension, snoring yes/no), the presence of comorbidities (cardiovascular, metabolic, pulmonary, others) and the conclusion after completing the Berlin Questionnaire (high risk/low risk). The Berlin Questionnaire has a superior predictive value compared to the Epworth, or the STOP Questionnaire. It should continue to be used in the screening of OSAHS in the general population[9].

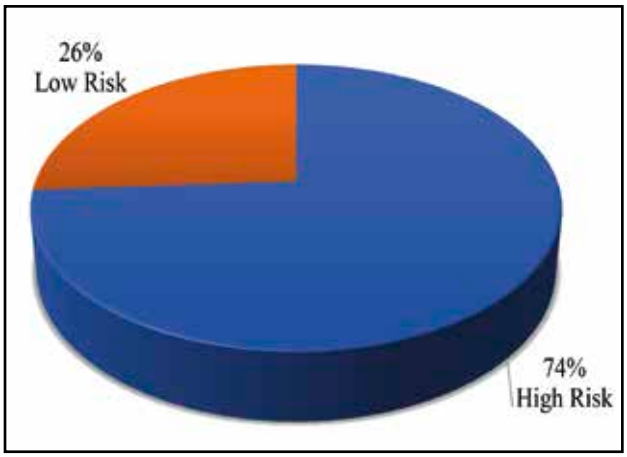

Chart 1. Distribution by risk groups of patients included in the study according to the results of the Berlin Questionnaire.

Evaluating the results obtained after completing the Berlin Questionnaire, the 77 patients were divided into two groups: Group 1 – Grade I (Low Risk) – 26%, Group 2 – Grade II (High Risk) – 74% (Chart 1).

Analysing the demographic data of the study group, it can be observed that the majority representative of this study, according to gender distribution, was male, with a percentage of 71% (Chart 2).

Considering the distribution according to the area of origin, there was a notable difference, with the rural area repre-

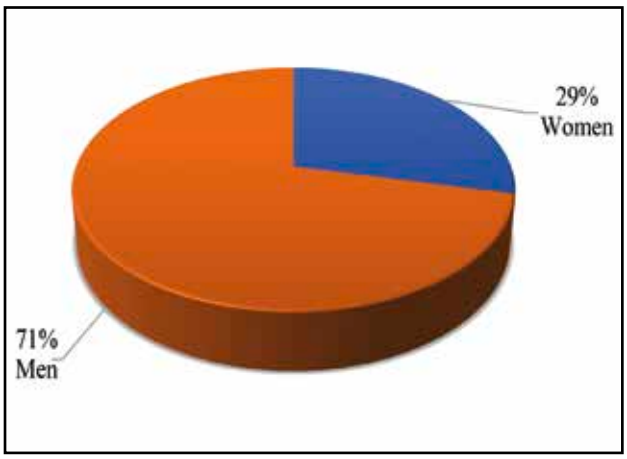

Chart 2. Gender distribution of patients included in the study.

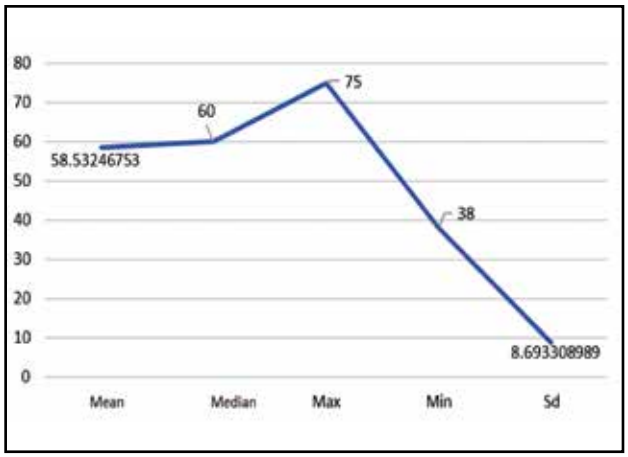

Chart 3. Distribution by age groups of patients who completed the Berlin Questionnaire.

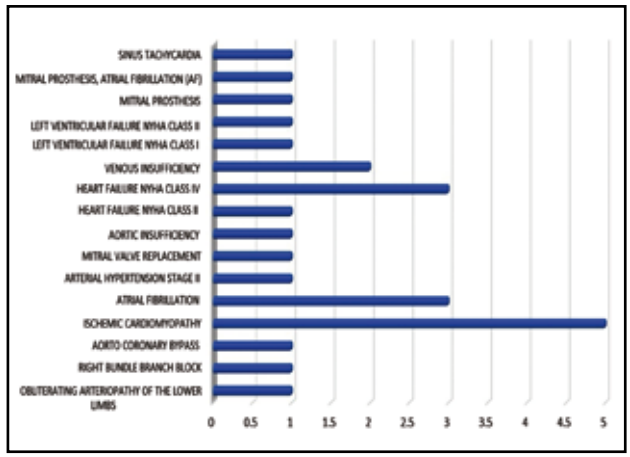

Chart 4. Frequency of cardiovascular pathologies associated with sleep disorders in the evaluated patient group.

senting 69% of the total.

The patients had a mean age of 58.53 years, with a maximum of 75 and a minimum of 38 years. Analysing the group according to the age group with the highest frequency present in the study, we observe the fact that the group between 61-70 years represents the majority, totalling a number of 32 patients, representing 41.56% of the total (Chart 3).

The presence or absence in the antecedents of associated cardiac pathology was also analysed, as being an important risk factor in the occurrence of OSAS (Chart 4).

Equally relevant to our study is the fact that, in addition to OSAS-associated risk factors, associated comorbidities also play an extremely important role. Thus, analysing our group based on the information collected from the medical records, we observe considerable percentages on the presence of metabolic, cardiovascular and pulmonary complications, of great importance also being the fact that they represent important criteria for including patients in the studied group. The assessment of patients using the Berlin Questionnaire can also be performed in patients with associated pulmonary pathology. Four OSA screening questionnaires were used and validated in selected studies, including the Berlin Questionnaire (BQ)[10]. Within the metabolic sphere, a percentage of 35% is represented by patients who have been diagnosed with diabetes. In the cardiovascular and pulmonary spheres, the percentage of patients diagnosed with the mentioned disorders were 32% and 51%, respectively. Apart from the main criteria for inclusion in the study, a significant percentage of 73% of patients presenting multiple other comorbidities was also revealed.

The Berlin Questionnaire is a self-administered questionnaire that was developed to identify subjects with obstructive sleep apnea (OSA) in primary care and is one of 4 approved questionnaires[10,11]. Starting from the idea of using the results of the Berlin Questionnaire to suspect an obstructive sleep apnea syndrome, the group of 77 patients with different comorbidities was divided into two previously mentioned groups: 20 patients Grade I (represented by patients at low risk of OSAS) and 50 patients Grade II (represented by patients at high risk of presenting OSAS). Thus, following a statistical analysis of the two groups, it was observed how there is a statistically significant association between the presence of risk factors, comorbidities and the high risk of presenting OSAS in patients who completed the Berlin Questionnaire. It can be said that the Berlin Questionnaire is useful as a clinical screening test and as an epidemiological tool for the population in the sleep clinic. Despite limited evidence, it may have potential clinical and research utility in other populations. Adopting more consistent methodological definitions and focusing more on the general population and specific clinical populations is recommended to determine its utility as a clinical or epidemiological screening tool[12].

Analysing Table 1, we can see an obvious majority in terms of gender distribution of the two groups, namely the male sex, with a F/M ratio of 35%/65% among patients included in Grade I risk, respectively 26%/74% in the case of those in Grade II risk. The Chi-square test was applied with a value of p=0.65 (>0.05). Referring to the distribution of our group based on the environment of origin, we detect some difference in percentages between the two groups, namely Grade I with an Urban/Rural ratio of 60%/40%, and Grade II with an Urban/Rural ratio of 72 %, respectively 28%. Analysing these data from a statistical point of view, we also applied the Chi-square test here, resulting in a value of p=0.47 (>0.05). So, we can conclude that these variables are not statistically significant in relation to the results of the Berlin Questionnaire. This explains the reduced sensitivity of the questionnaire regarding the assessment of the risk of occurrence of the sleep apnea syndrome in relation to their environment of origin. It is considered that this questionnaire is not always reliable in predicting the sleep apnea syndrome. This questionnaire can be a tool for excluding obstructive sleep apnea and can be a tool in allocating diagnostic resources. It can be used in shift workers, professional drivers, with greater accu-

Table 1. Distribution by gender, environment of origin and age of patients to whom the Berlin Questionnaire was applied with division by risk level.

Demographic data	The Berlin Questionnaire Grade I (Low risk)	The Berlin Questionnaire Grade II (High risk)	p (student's test)	p (Chi-square test)
Gender F/M	35% / 65%	26% / 74%		0.65
Urban/Rural	60% / 40%	72% / 28%		0.47
Age	64.3±5.04	56.5±8.7	0.0000007	

racy in identifying patients at risk of sleep apnea[13].

We followed the same variables in relation to other factors predisposing to the occurrence of OSAS, namely: BMI, history of nicotine consumption, neck circumference, abdominal circumference, history of snoring presented in Table 2.

It can be observed that in Grade I there is an average of BMI=25.49±1.9, and in Grade II a relatively noticeable increase, we could say, with a BMI=27.2±2.51. In our study, after applying the Student t-test, we reached a result of p=0.00171 (<0.05), highlighting the fact that there is a strong association between an increased body mass index (BMI) and the high risk of suspected OSAS based on The Berlin Questionnaire. The mentioned qualitative variables were further processed using the Chi-square test, resulting in a value of p<0.0001, which indicates a strong statistical association described as follows: our study group, which was suspected to be at high risk of presenting OSAS after completing the Berlin Questionnaire, comprised a considerably higher number of smoking patients compared to the low-risk group. Therefore, smoking is considered a major risk factor in the occurrence of OSAS. The Berlin Questionnaire is a self-administered questionnaire that was developed in order to identify subjects with obstructive sleep apnea (OSA) in primary care. This study evaluated the performance of the questionnaire to predict OSA in the general population[14].

It is known that, from an anatomical point of view, a circumference above the normal reference range of these values could produce a relatively significant worsening of a restful sleep through a reduction of the upper airways. The two main groups in our cohort (Grade I and Grade II) have been further divided into two subgroups each, namely patients with neck circumference within normal limits and patients with values of the variable above the limit of normality. Thus, for the neck circumference we obtained a ratio of 21%/79% in the case of patients from the Grade I group and a ratio of 25%/75% in the case of patients included in the Grade II group, the first percentage of the ratio signifying the value within normal limits. The relevance of the variables between the two main groups was statistically calculated by means of the Chi-square test and, surprisingly, it was discovered that, regardless of the fact that patients with neck circumference above normal values were in the majority, the test result was p=0.95 (>0.05). Analysing the information, we can show that an increased neck circumference does not represent a risk factor that is taken into account in a unitary way; it should also be associated with other risk factors. Our observations are also supported by other authors.

Analysing the abdominal circumference in our study group, again, the majority are patients with increased values of this parameter. Using the Chi-square test, we obtain an unfavourable answer with a value of p=0.08. The conclusion can be viewed from the same perspective as neck circumfer-

Table 2. Distribution of patients included in the study according to the presence of risk factors.

Risk factors	Grade I (Low risk)	Grade II (High risk)	p (student's test)	p (Chi-square test)
BMI	25.49±1.9	27.2±2.51	0.001717376	
Smoker/Non-Smoker/Ex-Smoker	25% / 55% / 20%	75% / 7% / 0%		<0.0001
Normal/elevated neck circumference	21% / 79%	25% / 75%		0.95
Normal/increased abdominal circumference	7% / 93%	25% / 75%		0.08
Snoring	5%	98%		<0.0001
Arterial hypertension	5%	84%		<0.0001

Table 3. Distribution of patients included in the study according to the presence of comorbidities.

Pathology	Grade I (Low risk)	Grade II (High risk)	p (Chi-square test)
Metabolic syndrome: Diabetes mellitus (DM)	10%	44%	0.014
Associated heart conditions	10%	40%	0.026
Associated pulmonary conditions	20%	20%	0.003
Other comorbidities	35%	72%	0.002

ence, so statistically insignificant or, in other words, there is no association between the suspicion of a possible obstructive sleep apnea syndrome and increased abdominal circumference, an element that is considered only in a unitary manner.

Another factor of great importance is the presence or absence of snoring during sleep. It is worth noting that this variable is found in a particularly large number of hospitalized patients and yet, at the moment it is not given the necessary attention by the general population. In our study, a strong statistical significance is demonstrated between the two main groups, Grade I and Grade II, with a percentage of only 5% of patients, belonging to Group I, stating that they snore during sleep, and Group II with an impressive percentage of 98% of snoring patients. Applying the Chi-square test, a $p<0.0001$ was obtained, concluding our expectations, namely that snoring during sleep should be classified, especially by medical personnel, as an alarming factor regarding the suspicion of obstructive sleep apnea syndrome and the patient should be educated and referred to qualified personnel in order to diagnose and possibly treat this pathology.

Taking into account the fact that the average age of the patients included in the study is 58.53 years, with a maximum of 75 years, it is not surprising that an impressive percentage of 84% of patients in group II presented arterial hypertension during hospitalization. However, analysing group I on the same criteria, we observe a significant decrease in the number of cases with arterial hypertension, representing only 5%. Statistically, the Chi-square test was applied to the two main groups and a value of $p<0.0001$ was obtained. Deduced from the above, we can confirm a close link between the suspicion of obstructive sleep apnea and patients with a confirmed diagnosis of hypertension. The interpretation made in this sense supports the idea that in patients with arterial hypertension, the risk of association of sleep pathology is much more frequent, and these patients should be included in the next stage of polysomnographic investigations.

Finally, we reached the most important aspect of this study, namely the association of the suspicion of obstructive sleep apnea syndrome and the comorbidities known as factors for the occurrence and progression of the syndrome. As highlighted before, numerous other studies have demonstrated in much larger cohorts and with the help of much more laborious data, a strong association between OSAS and comorbidities[15]. Table 3 shows all the data collected from the medical records of the patients included in the study regarding the pathologies they presented during the hospitalization: cardiovascular, metabolic, pulmonary and other comorbidities.

Thus, analysing the table, we observe the ratios between the two main risk groups as a result of completing the Berlin Questionnaire. Data were processed and statistically calculated using the Chi-square test.

Considering a *p*-value threshold of less than 0.05 associated with a statistically close correlation, it is not at all surprising that in all four variables this association is observed between the suspicion of OSAS based on the questionnaire result and the patients' comorbidities. The correlation with the existence of comorbidities also explains the importance of using this questionnaire in patients who work in shifts and are at risk of sleep apnea. The Berlin Questionnaire appears to be a valid tool to rule out obstructive sleep apnea and may be a useful tool to help allocate diagnostic resources[15].

Our main objective was to focus on the first 3 categories of disorders, but we cannot overlook that also in the case of the "Other comorbidities" category a $p=0.002$ was found. This fact also indicates the possibility of many other conditions, such as ischemic cardiomyopathy, arterial fibrillation, chronic pulmonary block, which could be classified as risk factors and, above all, indicates the importance and attention that must be provided by medical personnel and the general population on OSAS. The questionnaire was not always reliable in predicting OSAS by means of the apnea-hypopnea index associated with polysomnography[16].

CONCLUSIONS

The application of the Berlin Questionnaire is effective in selecting patients with suspected obstructive sleep apnea syndrome, in order to select them for further examination protocols, taking into account snoring the most as well as possible comorbidities.

This questionnaire is a reliable tool for the exclusion of obstructive sleep apnea and can be a particularly important tool in the allocation of diagnostic resources in the case of patients suspected of having a sleep breathing disorder.

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Authors' information:

Adriana Neagos, Associated Professor, Department of Otorhinolaryngology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Targu Mures, Romania. E-mail: neagos.adriana@gmail.com. ORCID: https://orcid.org/0000-0002-9299-2638.

Hedi Balogh Szarkozi, MD, Department of Pneumophthisiology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Targu Mures, Romania. E-mail: baloghedikatalin@yahoo.com.

Cristian Mircea Neagos, ENT Resident Doctor, ENT Clinic, County Emergency Clinical Hospital, Targu Mures, Romania. E-mail: cristian.neagos@gmail.com.

Gabriela Jimborean, Professor of Pneumophthisiology, Department of Pneumophthisiology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Targu Mures, Romania. E-mail: gabriela.jimborean@umfst.ro. ORCID: https://orcid.org/0000-0002-2673-370X.

Mioara Szatmary, Assistant Professor, Department of Pneumophthisiology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Targu Mures, Romania. E-mail: mioara.szathmary@gmail.com.

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