"OVIDIUS" UNIVERSITY OF CONSTANTA
MEDICINE DOCTORAL SCHOOL
DOMAIN: MEDICINE

EVALUATION OF PREDICTIVE FACTORS OF OBSTRUCTIVE SLEEP APNEA

ABSTRACT OF DOCTORAL THESIS

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CONTENT

Keywords: obstructive sleep apnea syndrome, predictive factors, comorbidities, predictive models
Note: The content of the abstract is the one contained in the doctoral thesis; the figures and tables keep the numbering within the thesis

INTRODUCTION

Over time, the investigation of sleep has known several stages. If initially sleep represented an entity considered without pathological implications, later, neurophysiological research and polysomnographic studies allowed the identification and documentation of various diseases related to sleep disturbance.

Sleep pathology is increasingly widespread worldwide, affecting a significant proportion of individuals, but with a pathogenesis, still incompletely elucidated. The spectrum of sleep disorders includes a wide range of conditions that are either transient or cause chronic impairment. In addition, these pathologies have a global impact on the quality of life of patients and have implications that disrupt the daily activities of patients and, in evolution, can lead to exacerbation of pre-existing conditions or lead to multisystem damage.

OSA is the most common sleep disorder and is a disabling disease that affects millions of individuals worldwide, characterized by phenotypic diversity, therefore, the purpose of this study was to assess the interrelationship of different clinical features or associated pathologies and OSA, to identify patients at high risk for this syndrome and to increase both the level of awareness and the degree of diagnosis of this respiratory disorder during sleep, thus identifying alternative, easy and cost-effective methods.

The paper is structured in two parts, includes a general part consisting of 3 chapters in which are presented theoretical data regarding sleep, sleep medicine and sleep pathology, respectively, definition, epidemiology, physiology, etiology, diagnosis and treatment of obstructive sleep apnea syndrome . At the same time, in Chapter 3, the relationship of obstructive sleep pathology with various coexisting diseases (cardiovascular, metabolic, respiratory, neurological, oncological or nephrological) is evaluated. The special part, respectively the personal contribution, includes 7 chapters in which the objectives, the working hypothesis and the 3 research studies are included.

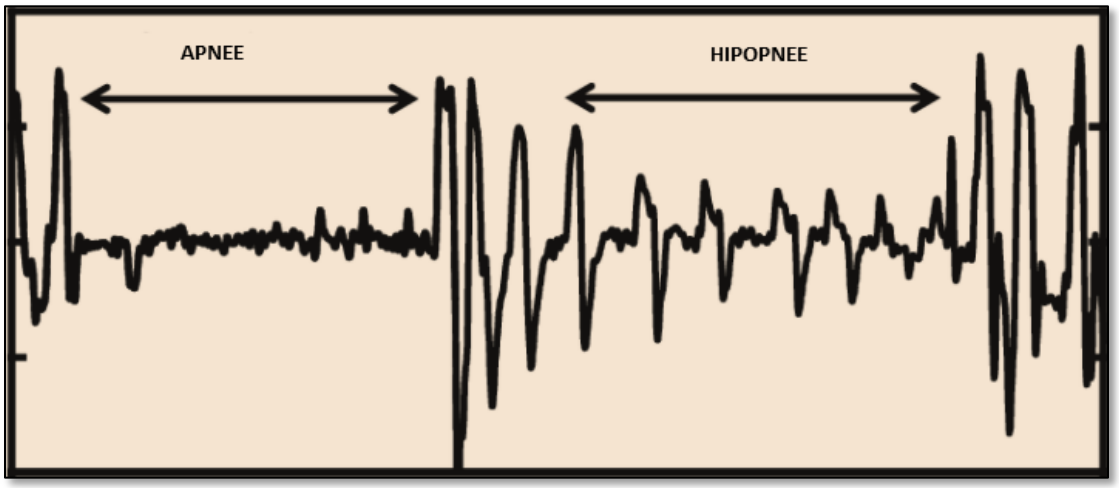
GENERAL PART

1. Obstructive sleep apnea syndrome

2.1. Definition

Obstructive sleep apnea syndrome is a multifactorial, chronic, progressive pathology, representing the most common respiratory disorder during sleep, a heterogeneous condition responsible for a wide range of comorbidities, with a major impact on mortality. Currently, the syndrome is defined by repeated episodes of stopping or reducing airflow in the mouth and nose, a phenomenon caused by partial or complete collapse of the upper airways, changes that occur during sleep as a result of loss of pharyngeal muscle tone. Apnea is a respiratory event lasting 10 seconds or more and consists of a reduction in basal flow by more than 90%, and hypopnea is defined as a reduction in respiratory flow by more than 30% (up to 90%).), for a duration of at least 10 seconds and is accompanied by a desaturation of at least 4% (Figure 5).

Figure 5. Graphic representation of respiratory events



2.1.1. Sleep study

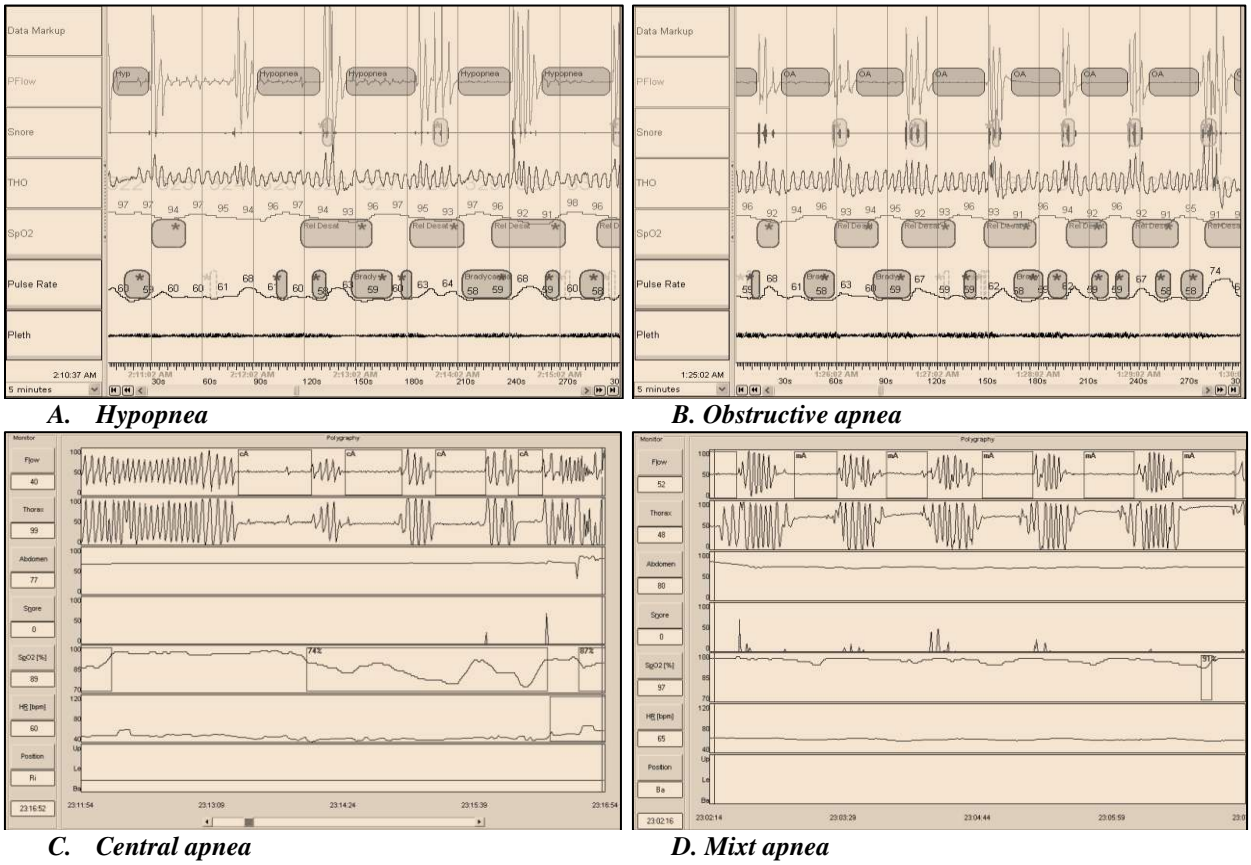
SASO should be suspected in any individual with excessive daytime sleepiness, snoring, suffocation, or sleep apnea, especially when associated with risk factors for the condition, such as obesity, male sex, or age over 50 year old. The identification of OSA cannot be performed exclusively clinically [50], therefore, all patients with this suspicion require an objective assessment performed using diagnostic tools used in sleep medicine and which include multi-parametric tests that study the sleep and are represented by cardio-respiratory polygraphy and polysomnography.

Cardio-respiratory polygraphy (PG) is the investigation that can be used in the study of sleep to assess the diagnosis of sleep apnea syndrome, identifying respiratory events such as hypopnea and central, obstructive or mixed apnea (Figure 9).

Polysomnography (PSG) is the investigation of sleep that quantifies multiple electrophysiological parameters, being considered the "gold standard" examination in the diagnosis of OSA. It is used both to identify the syndrome and to evaluate other sleep pathologies that may coexist [51].

The main objective in identifying OSA and defining the severity of the syndrome is to determine the apnea-hypopnea index. This indicator is represented by the number of respiratory events, respectively apnea and hypopnea, which occur in one hour of sleep. Although various threshold levels of SASO severity are described in the literature, we typically consider OSA to be mild when the value of the apnea-hypopnea index is in the range of 5 - <15 events / hour, moderate OSA when the apnea-hypopnea index parameter has a value between 15 and 30 events / hour and severe OSA when there are more than 30 respiratory events in one hour of sleep.

Figure 9. Respiratory events on a polyhraphy



A. Hypopnea ***B. Obstructive apnea***

C. Central apnea ***D. Mixt apnea***

PERSONAL CONTRIBUTION

1. Hypothesis/ Objectives

Obstructive sleep apnea syndrome is a complex pathology with an increasing prevalence in recent decades that impacts morbidity and mortality, with multisystemic consequences and involving high costs in both diagnosis and therapy. However, it is still a much underdiagnosed and, implicitly, undertreated entity, therefore, this paper aims to identify the predictive factors of obstructive sleep apnea syndrome and their correlation with the severity of the disease.

The secondary objective is to develop predictive models that could identify subjects at high risk of developing OSA, thus helping to prioritize patients to the sleep study and contributing to early diagnosis and treatment.

2. General methodology

In order to meet the proposed objectives, we conducted a research that included three studies conducted in a population sample that included individuals newly diagnosed with obstructive sleep apnea syndrome using cardio-respiratory polygraphy, investigated in the Sleep Laboratory and in the ENT Clinic of the Constanța County Emergency Clinical Hospital.
Patients were enrolled in the study consecutivelly, depending on the time of presentation and investigation in the Sleep Laboratory and taking into account the selection criteria. The research took place over a period of 48 months, between October 2015 and September 2019.
To be included in the research, the subjects of the studied cohort met the following inclusion criteria:
- Age over 18 years
- IAH ≥ 15 events / h
- Newly diagnosed SASO
- The possibility to go through all the parameters followed in the research
- Signing informed consent

Patients who were not enrolled in the research met at least one of the following exclusion criteria from the study:
- Age under 18 years
- IAH <15 events / h
- Diagnosis of another sleep pathology
- known OSA
- CPAP / BiPAP usage history
- Existence of pathologies such as: type 1 diabetes, familial dyslipidemia
- Psychiatric, neurological or other factors that did not allow the application of various tests used in the study
- Pregnancy
- The patient's refusal to sign the informed consent

Statistical data were processed using IBM SPSS Statistics version 27 and Microsoft Excel 2010. We used parametric and nonparametric statistical tests to evaluate the data and test the working hypotheses. Statistical significance was taken into account when the p-value was less than 0.05.

3. Study 1 - Characterization of the study group by defining demographic, clinical, anthropometric and polygraphic parameters

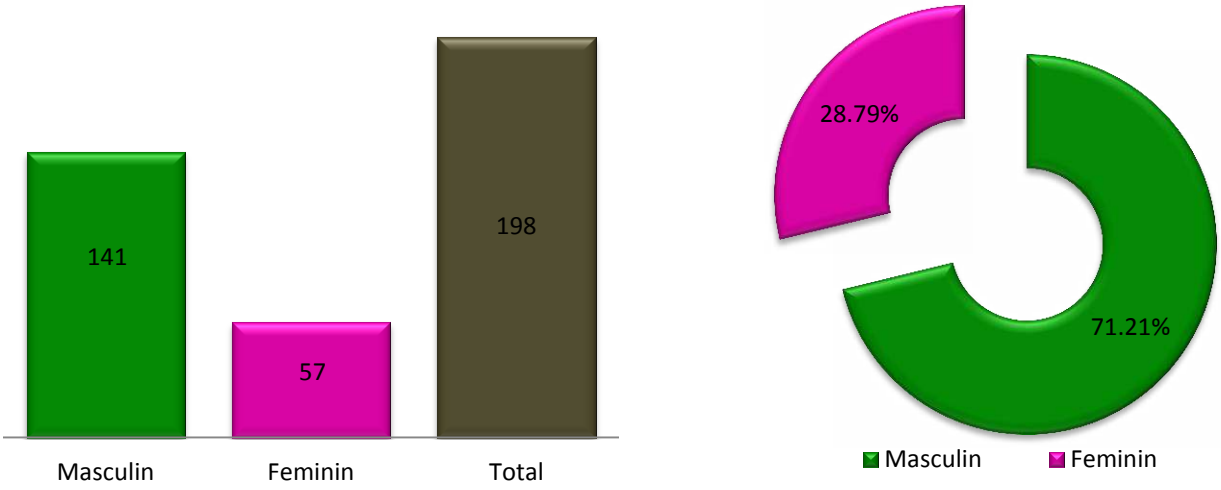
The objective of this study was to define the characteristics of patients with OSA, identifying clinical presentation phenotypes using simple and standardized assessment tools in a cohort of patients newly diagnosed with obstructive sleep apnea syndrome. The characterization of the working cohort population was performed through an observational, analytical, prospective study.

The study group included 198 patients, broken down by gender, as follows (Figure 2):

- 141 male patients (71.21%)

- 57 female patients (28.79%)

Figure 2. Distribution of patients in the study group by gender

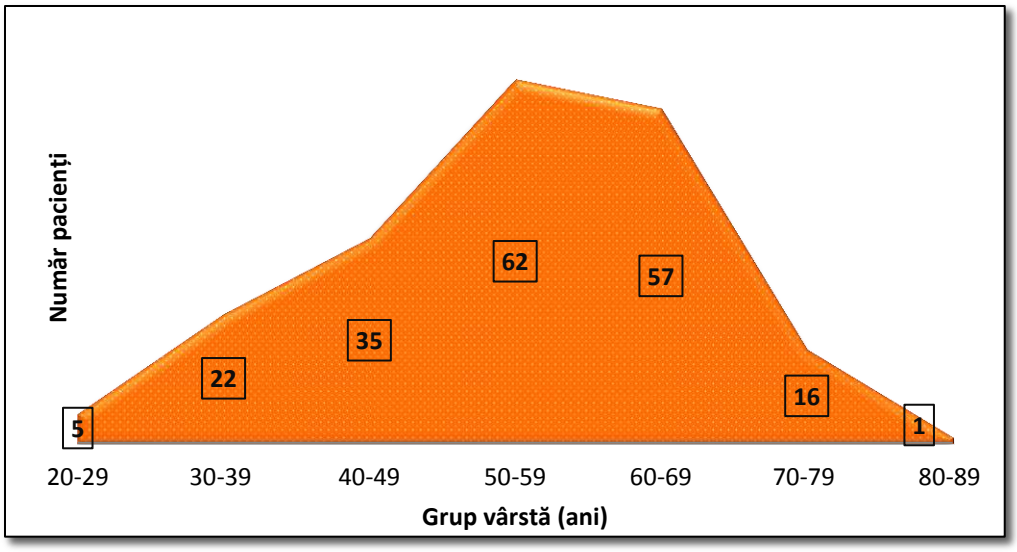


The ages of the patients enrolled in the study were between 25-82 years, the average age of the study group being 53.87 years, respectively, the standard deviation being 11.60 years. (Table 2)

Table 2. Minimum, maximum, average ages and standard deviation for the studied group.

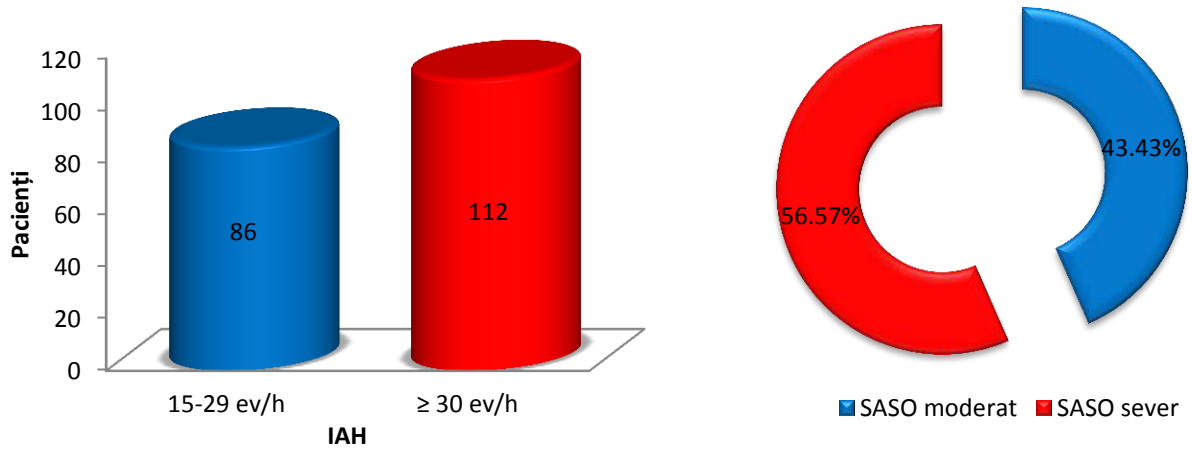
	N	Minimum	Maximum	Mean	Std. Deviation
Age (years)	198	25	82	53.87	11.601

Figure 3 . Distribution of patients in the study group reported by age groups



It is found that, out of the total of 198 patients included in the working group, 86 patients (43.43%) were diagnosed with moderate OSA and 112 patients (56.57%) were diagnosed with severe OSA. (Figure 9).

Figure 9. Distribution of patients in the study group according to the value of AHI



Regarding the AHI at the level of the whole group, it varied in the range 15.2 - 110 events / h and had an average value of 38.55 events / h with a standard deviation of 20.29 events / h. (Table 10)

Tabelul 10. Minimum, average, maximum values and standard deviation of the AHI

	N	Minimum	Maximum	Mean	Std. Deviation
AHI (events/h)	198	15.2	110.0	38.552	20.2962

4. Study 2 - Determining the prevalence of comorbidities in a newly diagnosed population with OSA and evaluating the correlations between OSA and associated diseases

In our study we followed the interrelation OSA - comorbidities, having the following objectives:
- determining the prevalence of cardiovascular pathology in a newly diagnosed population with OSA
- determining the prevalence of metabolic pathology in a newly diagnosed population with OSA
- determining the prevalence of ENT pathology in a population newly diagnosed with OSA
- correlation of the presence of pathologies associated with demographic, anthropometric, polygraphic parameters

4.4.1. Cardiovascular pathology

Regarding the cardiovascular pathology, we analyzed the presence of hypertension and atrial fibrillation in relation to the demographic and polygraphic parameters of the patients enrolled in the research.

Figure 50. Hypertension frequency in the studied group

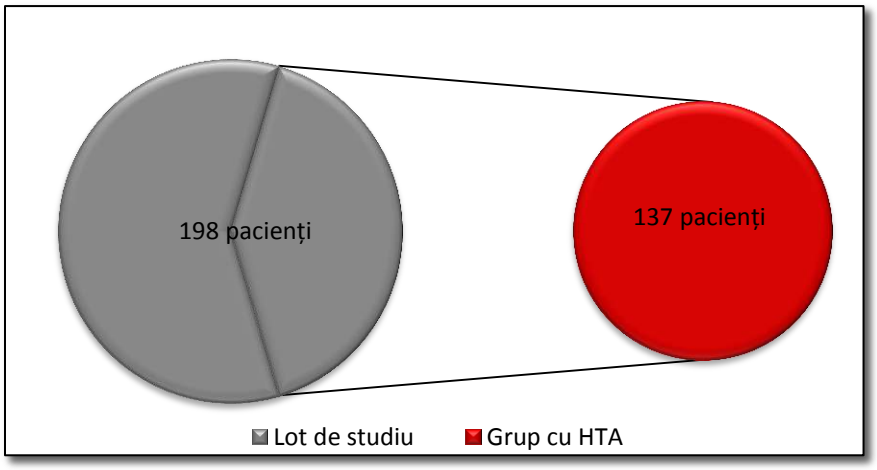
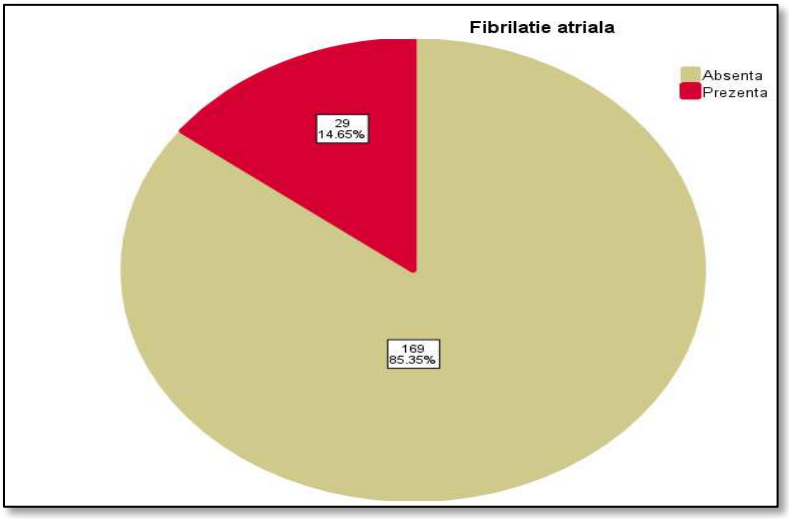


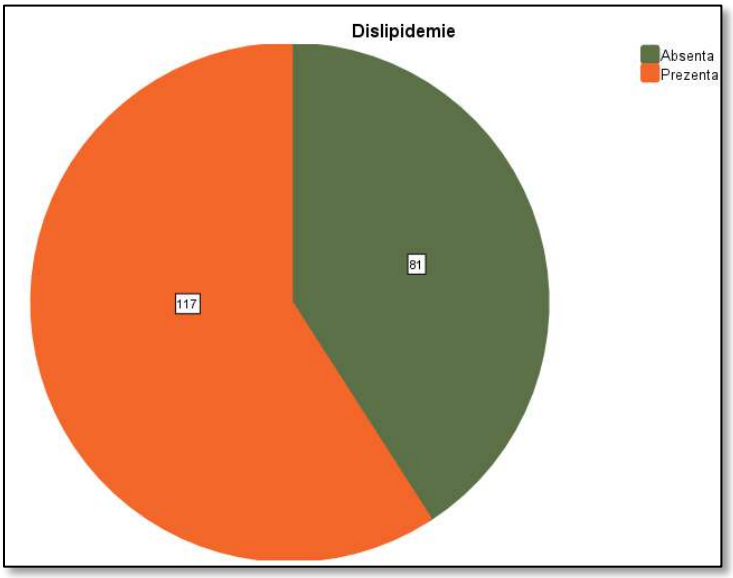
Figure 55. Atrial fibrilation frequency in the studied group



4.4.2. Metabolic diseases

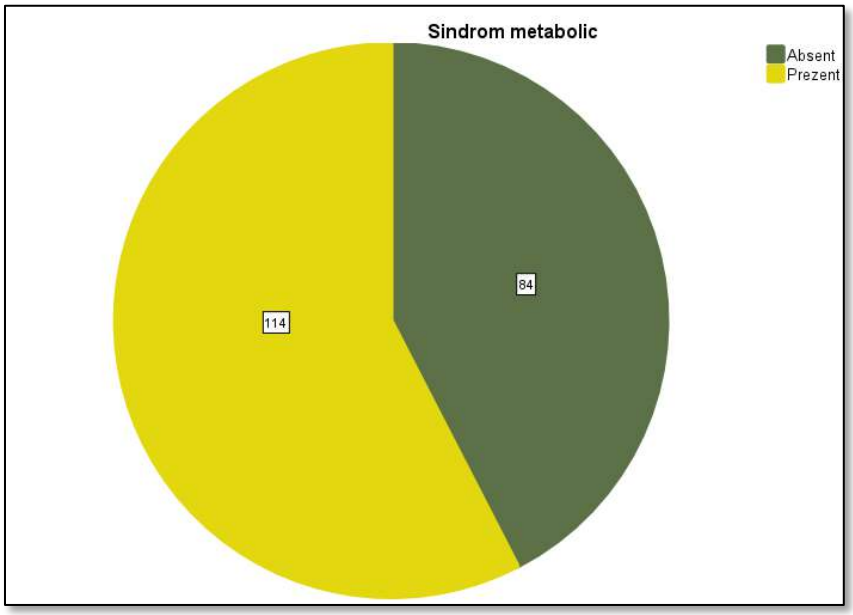
Known or newly diagnosed dyslipidemia, represented by hypercholesterolemia, hypertriglyceridemia or mixed conditions, was identified in 117 patients (59.10%) of the 198 subjects of the study group (Figure 59).

Figure 59. Distribution of patients with dyslipidemia in the study group



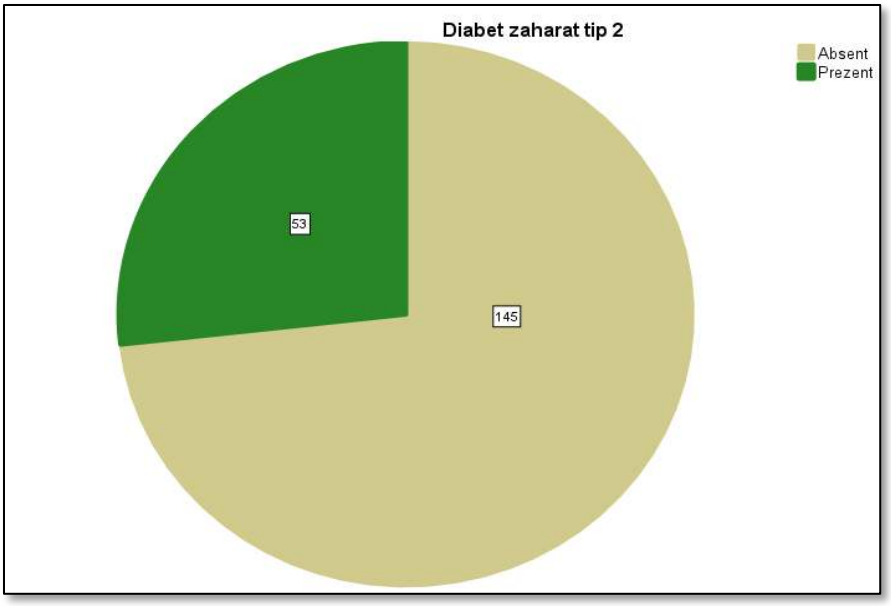
Metabolic syndrome was found in 114 patients (57.6%) out of the 198 subjects within the study cohort.(Figure 62).

Figure. 62 Metabolic syndrome frequency in the study group



The research also looked for the presence of known or newly diagnosed type 2 diabetes in the study group. This condition was identified in 53 patients (26.8%) of the total 198 subjects in the group. (Figure 66)

Figure 66. Frequency of type 2 diabetes in the studied sample



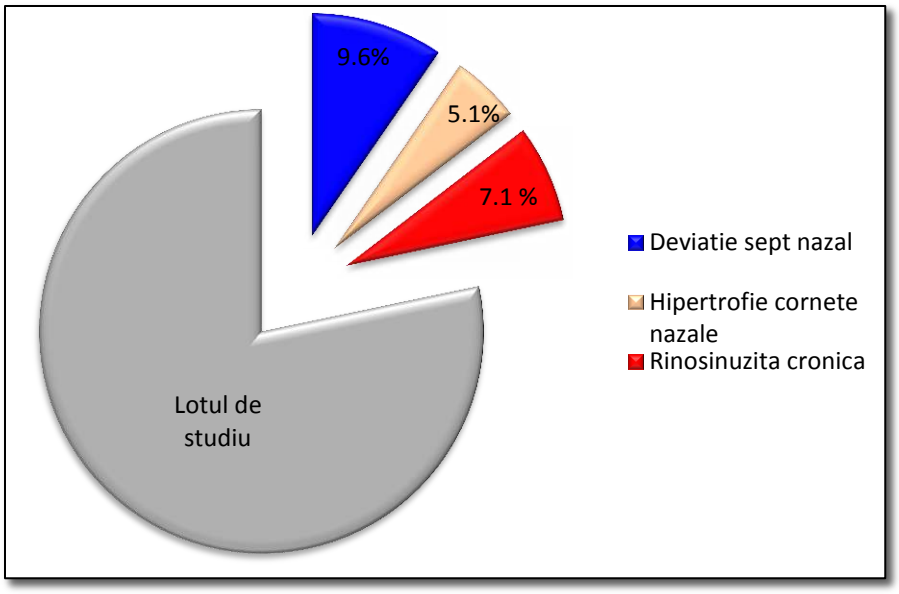
4.4.3. ENT diseases

Regarding the research group, out of the 198 patients enrolled in the study, for 43 patients (21.71%) ENT pathologies were identified (Table 90, Figure 70)

Table 90. Frequency of ENT pathology in the study group

		Frequency	Percent
Valid	Turbinate hypertrophy	10	5.1%
	Chronic rhinosinusitis	14	7.1%
	Nasal septum deviation	19	9.6%
	Absent	155	78.3%
	Total	198	100.0%

Figure 70. ENT disease frequency in the study group



5. Study 3 - Development of predictive models in order to facilitate the OSA diagnosis based on the researched variables

The research followed the correlation of the parameters analyzed in the prospective studies described above, respectively, Study 1 and Study 2, as well as clinical, physical variables, anthropometric measurements and comorbidities with the hypopnea apnea index, using only parameters of statistical significance (Table 98) . At the same time, it should be noted that the variables investigated have important limitations in terms of syndrome predictability when used in isolation, but can be a cost-effective and useful diagnostic method when grouped in a model, this amendment being the premise proposed study.

We applied multivariate statistics to evaluate significant predictors of OSA severity. The values of the coefficients of the multiple linear regression model were used to elaborate a predictive formula of the AHI both at the level of the whole group and differentiated by sex, and the obtained equation was tested retrospectively in the studied sample. Subsequently, we constructed the ROC curves to test the sensitivity and specificity of the resulting models.

Table 98. Correlations : AHI - demographic, anthropometric, clinical variables and comorbidities in the study group and differentiated by sex

Variables	Study grup	Male	Female
	P	**P**	**P**
BMI	0,000	0,000	0,001
NC	0,001	0,000	0,02
WC	0,000	0,000	0,001
WHR	0,01	0,01	0,01
ESS	0,000	0,000	0,000
Mallampati Class	0,000	0,000	0,000
Hypertension	0,000	0,000	0,000
MS	0,000	0,000	0,000

5. Conclusions

- The characteristics of SASO differed depending on the gender of the subjects, being able to outline different clinical phenotypes. Thus, the female population was diagnosed more frequently after the 5th decade, AHI levels were lower and symptoms were more frequently reported. In contrast, the male population showed more severe forms of the disease and had more significant anthropometric indices

- It is necessary to increase awareness of the syndrome, because the onset of symptoms is insidious, most patients either have symptoms a few years before diagnosis, or there are patients in whom the syndrome has clinical expression only when multisystem consequences occur.

- The number of comorbidities increases with the severity of obstructive sleep apnea syndrome, a phenomenon that has bidirectional implications.

- Determining the predictors of obstructive sleep apnea syndrome and developing screening formulas based on basic components (history, medical history, physical examination) that do not involve additional costs, leads to the identification of subjects likely to have OSAS, thus increasing the diagnosis rate of the purpose of improving the quality of life of affected individuals

- The therapeutic sanction is absolutely necessary for all patients regardless of the severity of the obstructive sleep pathology, as the absence of therapy leads to complications

- The increasing prevalence of OSAS raises public health problems with a resounding epidemiological impact, so it is necessary to increase education on this disease outlining the need to identify alternative screening methods for patients at high risk of developing the syndrome.

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