„OVIDIUS" UNIVERISTY OF CONSTANTA
DOCTORAL SCHOOL
MEDICAL FIELD

Doctoral Thesis

OBSTRUCTIVE SLEEP APNEA SYNDROME FROM SIMPLE TO COMPLEX

THE IMPACT OF SMOKING AND COMORBIDITIES

- ABSTRACT -

PhD Coordinator

Prof. Univ. Dr. Oana CrSItina Arghir

PhD Student

Mihaela Petrof (Trenchea)

CONSTANŢA

2018

Abbreviations used in the text

AAMS	*American Academy of Sleep Medicine,* Academia Americană de Medicină s Somnului
AF	atrial fibrillation
AHI	Apnea- hypoapnea index
BMI	body mass index
CCF	congestive cardiac failure
CO	carbon monoxide
COPD	chronic obstructive lung disease
CSAS	central sleep apnea syndrome
CVA	cerebrovascular accident
DM	diabetes mellitus
DS	daytime sleepiness
EDS	excessive daytime sleepiness
ENT	ENT - diseases
FC	cardiac frequency
HbA_{1C}	glycosylated hemoglobin
HbCO	carboxyhemglobin
ICDS-2	*International Classification of Sleep Disorders*, version 2
ICDS-3	*International Classification of Sleep Disorders*, version 3
IL-6	interleukina 6
IS	insignificant statistically
MS	metabolic syndrome
NC	neck circumference
ODI	oxygen desaturation index
OSAS	obstructive sleep apnea syndrome
OSH	obesity syndrome-hypoventilation
PCR	protein C reactive
PG	cardiorespiratory poligraphy
ppm	parts per million
PSG	polysomnography
PY	index packs per year
RDI	respiratory disturbance index
RDS	respiratory disorder during sleep
SAH	systemic arterial hypertesion
SAS	sleep apnea syndrome
SD	standard deviation
SI	snoring index
SpO_2	oxygen saturation in arterial blood
$TSSpO_290\%$	time spent sleeping SpO_2 under 90%
UARS	upper airway resistance syndrome
WC	waist circumference

CONTENTS

INTRODUCTION 15
CURRENT STAGE OF KNOWLEDGE 19
1. Scientific fundamentals of Sleep Medicine 21
1.1. History 21
1.2. Sleep architecture 22
1.3. Sleep mechanisms 22
1.3.1. Sleep neurophysiological mechanisms 22
1.3.2. Sleep biochemical mechanisms 23
1.4. Sleep physiopathological involvement 24
1.4.1. Alterations of the respiratory system 24
1.4.2. Alterations of the cardiovascular system 25
1.4.3. Alterations of the endocrine system 25
1.5. Sleep pathology classification 25
1.6. Sleep disorders classifications 27
1.6.1. Obstructive sleep apnea syndrome (OSAS) 28
1.6.2. Central sleep apnea syndrome (CSAS) 28
1.6.3. Hypoventilation during sleep syndrome 29
1.6.4. Hypoxemia during sleep sindrome 30
2.Obstructive Sleep Apnea Syndrome 31
2.1. OSAS place in the sleep pathology 31
2.2. Epidemiology and prevalence 31
2.3. Physiopathology 32
2.4. Risk factors 34
2.4.1. Socio-demographic risk factors 34
2.4.2. Risk factors sustained by scientific proof 35
2.4.3. Potential risk factors 36
2.5. OSAS diagnosis 38
2.5.1. Anamnesis, clinical frame and paraclinical investigations 38
2.5.2. Diagnosis and severity criteria 41
2.6. OSAS treatment 43
2.7. Natural evolution and mortality 44
3. Smoking effects on sleep disorders 47
3.1. The physio-chemical components of tobacco and tobacco smoke 47
3.2. Smoking effects on sleep 49
3.3. Smoking effects on OSAS 50
3.4. Smoke exposure in the world and in Romania 55
4. Aggravated comorbidities of the Obstructive Sleep Apnea Syndrome 59
4.1. Hypertension and OSAS 59
4.2. Cardiovascular disorders and OSAS 60
4.3. Cerebrovascular disorders and OSAS 64
4.4. Chronic obstructive pulmonary disorders and OSAS 64
4.5. Diabetes mellitus and OSAS 67
4.6. Metabolic syndrome and OSAS 67
4.7. ENT disorders and OSAS 68
4.8. Endocrine disorders and OSAS 70
4.9. Mental disorders and OSAS 72

PERSONAL CONTRIBUTION 75
1. Research premises. Smoking-potential risk factor of OSAS 77
1.1. Smoking – OSAS interrelation 77
1.2. Smoking influence on OSAS comorbidities 77
2. The aims of the research 81
3. General methodology 83
4. Study 1. Defining the demographic, clinical, anthropometric and polygraphic characteristics in patients screened and susceptible of RDS 87
4.1. Resources and method 87
4.2. Results 89
4.2.1. Demographic characteristics 89
4.2.2. Clinical characteristics 91
4.2.3. Anthropometric characteristics 93
4.2.4. Polygraphic characteristics 96
4.3. Discussions 102
5. Studiul 2 - Establishing the RDS spectrum and the assessment of RDS patients depending on the smoke exposure and comorbidities 105

5.1. Resources and method 105
5.2. Results 107
5.2.1. RDS diagnosis 107
5.2.2. Characteristics of RDS patients 109
5.2.3. Characteristics of RDS patients exposed to smoking 119
5.2.4. Comorbidities spectrum of RDS patients 125
5.3. Discussions 131
6. Study 3 - Determining the prevalence of OSAS among the patients who have been polygraphic screened for RDS, defining the demographic,clinical, anthropometric and polygraphic characteristics of OSAS patients, identifying the comorbidities spectrum and deifining smoking as a potential risk factor in determining the emergence of OSAS 135
6.1.Resources and method 135
6.2. Results 136
6.2.1. OSAS prevalence 136
6.2.2. Demographic characteristics of OSAS patients 136
6.2.3. Clinical, anthropometric and polygraphic aspects in OSAS patients 138
6.2.4 Comorbidities spectrum in OSAS patients 152
6.2.5. Smoking- potential risk factor in OSAS 165
6.3. Discussions 166
7. Study 4. The assessment of individual smoking impact and associated with comorbidities in determining the emergence and severity of OSAS 171
7.1. Resources and methods 171
7.2. Results 172
7.2.1 Characteristics of OSAS patients exposed to smoking 172
7.2.2. Assessing the impact of smoking and the magnitude of smoke exposure on OSAS and comorbidities 180
7.2.3. Characteristics of OSAS patients exposed to smoking with or without comorbidities depending on the severity 183
7.2.4. Assessing the impact of smoking associated with comorbidites on OSAS 188
7.3. Discussions 193
8. Study 5. Assessing biomarkers with potential role in the OSAS pathogeny and severity, linked to smoking and comorbidities 199
8.1. Resources and methods 199
8.2. Results 201
8.2.1. Characteristics of potential biomarkers from the point of view of smoking-OSAS-comorbidities 201
8.2.2. Glycosylated hemoglobin-potential metabolic marker for OSAS 206
8.2.3. Potential inflamatory OSAS biomarkers– Interleukina 6, protein C reactive and fibrinogen 212
8.2.4. The interrelation between the metabolic and inflamatory biomarker in determining the emergence of OSAS 215
8.3. Discussions 217
9. Conclusions 223
10. The originality of the thesis 227
BIBLIOGRAPHY 229
ANNEXES 243

Key words: respiratory disorders during sleep, obstructive sleep apnea syndrome,smoking, prevalmece, comorbidities, potential biomarkers

Note: The tables and figures introduced in the abstract of the PhD thesis keep the original counting within the thesis. The contents in the abstract is found in the thesis.

INTRODUCTION

The interest for obstructive sleep pathology has increased in the last few years in Romania, by means of building over 70 fully functional sleep laboratories in the main pneumology centers, in which Romanian research is able to have a multidisciplinary clinical partnership; we could also state that at the beginning of the 3rd millenium the Sleep apnea syndrome (SAS) remains an almost known, underdiagnosed or lately diagnosed disease.

The risk factors and comorbidities in obstructive sleep apnea syndrome (OSAS) have yet to be completely identified, but cardiovascular diseases (arterial hypertension, specifically a treatment-resistant type, coroniary disease, arrhytmias, myocardial infarction, sudden death), metabolic diseases (metabolic syndrome and diabetes mellitus), obstructive respiratory diseases, endocrine diseases, neurologic and psychic diseases can be considered pathological consequences of OSAS.

The obesity „pandemics" has risen the risk of OSAS and the ongoing rise of obesity contributes to the exponential growth of morbidity and mortality of all causes, especially cardiovascular[1]. The patogenesis of cardiovascular diseases of patients with OSAS is not fully understood, being characterized by a unique pattern of intermitent nocturnal hypoxemia, different from the nocturnal hypoxemia of chronic pulmonary diseases, which activate the pro-inflamatory cascade, accelerate arteriosclerosis[2,3] and amplifies the severity of OSAS[4]. As a result, multicenter studies regarding the assessment of different inflamatory markers associated with OSAS and the potential treatment methods become mandatory.

Smoking and OSAS are interdependent, Smoking being a major risk factor of OSAS through the specific modification of the sleep pattern, thourgh prolonged hypoxia and sustained systemic inflamatory response and can grow the OSAS severity risk. Both Smoking and OSAS have a prevalence in the general population growth, being associated with significant morbidity and mortality. In spite of this, although the association between Smoking and OSAS is plausible, there are not enough studies regarding the impact of Smoking over OSAS, and the evidence is not concludent.

The choice of this theme is sustained both by the high prevalence of respiratory disorders during sleep in the general population of our country, and by the risen prevalence of Smoking, with severe consequences over mortality and general morbidity.

The doctoral thesis is structured following a classical model and it contains a general part made up of four chapter summing 50 pages, and a special, personal research part, made up of nine chapters summing 150 pages, 415 references, 141 figures, 27 tables and 71 detailed annexes.

GENERALITIES

1. Classification of the respiratory disorders during sleep (RDS)

The International Classification of Sleep Disorders ICDS-3[5] used from 2014 up to the present, divides the respiratory disorders during sleep into four different categories: ***OSAS (Obstructive Sleep Apnea Syndrome), Central Sleep Apnea Syndromes (CSAS), Syndromes related to hypoventilation during sleep and Syndromes related to hypoxemia during sleep.***

Obstructive Sleep Apnea Syndromes (OSAS) are characterized by the obstruction of the upper airwaves, frequently being the consequence of anatomic modification and/or abnormal control of the muscles involved in maintaining local permeability and determines the growth of the respiratory effort and inadequate ventilation.

The ***OSAS diagnosis in adults*** requires signs and/or symptoms (daytime sleepiness associated, fatigue, insomnia, snoring, subjective nocturnal respiratory disorders or apnea noticed by peers) or associated medical conditions (arterial hypertension, coronary diseases, atrial fibrilation, congestive cardiac failure, stroke, diabetes mellitus, cognitive disfunctions or mental disorders) accompanied by 5 or more obstructive respiratory events (obstructive or mixt apneas, hypopneas or micro wakings related to respiratory effort) on the sleep time highlighted during PSG. Alternatively, an obstructive respiratory events frequency ≥15 on the sleep time meets the diagnosis criteria, even if the the associated symptoms and disorders are absent. The emphasis is made on the nocturnal respiratory events index in relation to the effective time spent sleeping and not on the entire time of the recorded sleep[5].

The individual term of **Upper airwaves resistance syndrome** (UARS) characterized by the presence of RERA ≥10 per hour of sleep, apnea-hypopnea index (AHI) < 5 per hour of sleep and the minimun nocturnal saturation of oxyen in the arterial blood(SpO_2minimum) ≥ 92% represents a type of OSAS and not a separate diagnosis with a distinct nomenclature[5].

2. OSAS epidemiology and prevalence

In 1993, the first cohort population study was made, the Wisconsin reference study[7] on the middle aged population(30-60 years), which reported an OSAS prevalence of 4% in men and 2% in women.

Between 1995-2014 we identified, on a global scale, 13 population studies[8-20] which prove the permanent interest in the sleep pathology and highlights a constant increase in the prevalence of OSAS[21,22]. The OSAS prevalence does not differ substantially between continents, which suggest that this disease is common both in developed countries, as well as in developing countries. On a global level, studies notice the statistical differences between the population groups on gender categories

which sustain the prevalence of OSAS in men from 4%[7] to 17,6%[19] and in women from 2%[7] to 17%[19].The results can also be influenced in time by the magnitute of the obesity and smoking epidemics.

On the background of the global interest in OSAS pathogeny, the Romanian pneumology experience from the last decade is remarked on an European level. In Romania, the only retrospective study was made between 1997-2007 at the National Pneumology Institute "Marius Nasta" Bucharest, and the results published in 2008 have highlighted an OSAS prevalence of 62,4%, a value much appreciated compared to the reference studies because it has been reported to a strictly selected population[23].

3. Risk factors

Despite all the clinical and scientific progress of the last two decades regarding OSAS, a great majority of these patients (70-80%) remain undiagnosed by individual underestimation of the symptoms[24].

Based on the scientific proof available globally, frequently applied in the Occident, a researcher's group from India,Sharma et al.[25] put forward the first OSAS multidisciplinary guide with applicability in developing countries. According to the new approach, depending on the quality of the scientific proofs, the well-known risk factors can be grouped into three categories: social-demographic factors (age, sex, and race), scientific factors (obesity, adiposity general tendency, neck circumference, craniofacial anomalies) and potential risk factors (genetic predisposition and family history, **smoking**, alcohol consumption, pregnancy, menopause, hormonal imbalance).

Smoking, a well-known and proven factor for the respiratory and cardiovascular disorders, becomes the object of numerous studies[26-33], being assesed mainly from the point of view of the association with snoring and under evaluated as an independent factor of the respiratory pathology during sleep. Smoking influences the severity degree of OSAS, a fact expressed statistically ever since the Wisconsin study in 1993, smokers presenting a high risk of moderate OSAS and severe compared to non-smokers (OR estimated=4,44)[34].

4. Diagnosis criteria and OSAS severity

OSAS diagnosis is complex, involving team work, a partnership between patient and his life partner on one side, and the medical team made up of pneumology specialists, cardiologosts, neurologists,endocrinologists, otorhinolaryngologists, psychiatrists, gastroenterologist and general practitioners on the other side. Anamnesis, the clinical exam and complementary paraclinical investigations have to be sustained by the nocturnal investigation of sleep through cardiorespiratory

poligraphy (PG) at the house of the patient possibly having OSAS and/or polisomnography (PSG) in the sleep study laboratory.

The standardized criteria of respiratory events during sleep have suffered changes in time, depending on the clinical experience and scientific proofs, the last version of the AAMS[35] manual published in 2014. Depending on the abnormal respiratory events frequency during sleep, the ***OSAS severity*** is evaluated as being: ***low*** (5-15 events/h), ***moderate*** (15-30 events/h) and ***severe*** (over 30 events/h).

6. The effects of smoking on sleep disorders, particularly on OSAS

Current smokers have a higher difficulty in initiating and maintaining sleep, being dissatisfied with the quality of their sleep[34] and the prolonging of the latent interval of falling asleep but without comparable modifications to the sleep's architecture between smokers and non-smokers[36].

Smoking can influence the nocturnal architecture of sleep by means of the nicotine action coming from the cigarette smoke, which stimulates the release of multiple important neurotransmitters which collectively participate in the sleep-wake cycle regulation[37], the lowering of the nicotine intake during sleep for current smokers causing frequent wake ups and sleep fragmentation[37], and, in the presence of obstructive secondary pulmonary diseases, smoking can disturb the continuity of sleep and have a bad impact on it[38].

The prevalence of RDS is higher among active smokers compared to ex smokers or non smokers[36],, smoking contributing to developing and progressing OSAS, by **direct** independent mechanisms (the nicotine's effects of directly stimulating neuronal excitability[39] and indirect of enhancement neuromuscular upper airwaves stimulation[40], and **indirect** mechanisms,dependent on the damage extended at a cardio-vascular-cerebral level (hemodynamic, endothelial, thrombogenic, inflamatory, lipid), respiratory, metabolic (changes in the glucose and lipids metabolism with the lowering of sensibility and the growth of insulin resistance), endocrine (by activating the hypothalamus-pituitary-adrenal axis , hypothalamus-pituitary-gonadal, hypothalamus-pituitary-thyroid, mainly the anterior and posterior pituitary gland) and psychic.

7. Smoke exposure around the world and in Romania

Smoking is about to become the main cause of morbidity and mortality in the world[41].

In 2004, in Romania the first health self-assessment study made at the National Center for Health Statistics and Medical Documentation[42] shows a growth in the percentage of Smokers from 25,9% in 1989 to 28% in 1994, the global percentage of smokers being three times bigger for men as compared to women, even though a growth in the frequency of female smokers has been noticed from 11.3% in 1989 to 15.2% in 1994.

8. Aggravated comorbidities in OSAS

Hypertension is the most frequent OSAS comorbidity, and OSAS is an independent risk factor for SAH[43]. SAH frequency in OSAS patients depends on the OSAS severity, with a risk three times higher in patients with hypertension with AHI over 15 respiratory events per hour of sleep, increase of a single respiratory apnea event per hour of sleep accompanying the rise of SAH risk by 1%[44]..

Coronary disease associated with OSAS is representative for atherosclerotic disorder, the rate of atherosclerotic progression, not only does it predict the rate of future cardiovascular events but it also contributes to the risc of CVA[45].

Myocardial infarction has a higher manifestation probability in patients with OSAS than in those without OSAS.

Nocturnal arrhythmias have been evaluated though the Holter method, arterial fibrilation (AF) being the most frequent and important sinusal arrhythmia associated with the respiratory disorders during sleep[46]. **Secondary OSAS brady-arrhythmias**, the consequences of hypoxemia of prolonged apneas have an extremely high prevalence of up to 59% of OSAS patients with pacemakers rising up to 68% in patients with OSAS who associate BAV.[47]

Symptomatic congestive cardiac failure (CCF) is associated with RDS in 40-505 of the cases, OSAS being thought to be the cause of CCF emergence, while CSAS is considered the effect of CCF perhaps even compensated.[48].

Cerebrovascular disorders of the ischemic CVA type have a higher risk of emergence to patients with OSAS secondary to variations of TA, lowering of the cerebral blood flow, the alteration of cerebral self-regulation, the effect on endothelial function, the acceleration of atherogenesis and of the protrombotic and proinflamatory status[49]. The prevalence of leukoaraiosis in patients with concomitent CVA and OSAS, suggest the role of OSAS in CVA aparition.

Chronic obstructive pulmonary disorders bidirectionally associated with OSAS have been given the name of overlap syndrome with COPD, namely ***„overlap syndrome alternative”*** with bronchial asthma, starting from the description of Flenley 30 years ago, as a combination between COPD and OSAS[51]. Dating back from the last century,Flenley recommended a sleep study to all his obese patients with COPD, to those who snored and had persistent headaches after oxygen therapy. Flenley also noticed that patients with COPD-OSAS overlap have an unfavorable evolution as compared to those with individual disorders, COPD and OSAS, matters which are also available in the present times[52].

Due to the fact that in our current practice we meet both combinations, COPD-OSAS as well as asthma-OSAS, the triangle Asthma-COPD-OSAS has been called ***OLDOSA- the syndrome of the combination between obstructive lung disease-obstructive sleep apnea***[51].

Diabetes mellitus associates OSAS through resistance to insuline and glucose intolerance, conditions independent from obesity association. OSAS induces a severe state of resistance to insuline, considered a risk factor for cardiovascular diseases, even in the absence of DM type 2, with the compensatory appearance of hyperinsuline and the growth of exogenous insuline request.

The metabolic syndrome, a term used usually for describing obesity, resistance to insuline, HTA and dyslipedimia, which affects millions of people worldwide and associated with the risk of cardiovascular diseases and DM type 2, is scientifically proven as secondary OSAS, encouraging the systemic evaluation of the co-existence of metabolic anomalies along with OSAS, their association receiving, at the end of the 1990s, the name of „**Z syndrome."**

ENT disorders contribute to the development of OSAS, being mentioned as craniofacial anomalies, without clearly defining their interrelation, although in the current clinical practice we often see the association of RDS with nasal obstruction.

Endocrine disorders which are associated with a rising prevalence of OSAS are hypothyroidism, the groth hormone excess, polycystic ovary disease or testosterone substitution.

Mental disorders are often comorbid with OSAS but also frequently undiagnosed at this category of patients, fact which contributes to the risk of cardivascular diseases, the aggravation of cognitive functions, the accentuation of psychic diseases'symptoms and negatively influencing the therapeutic response to some psychiatric medicine by raising the severity of OSAS.

PERSONAL CONTRIBUTION

1. The aims of the research

Although the interest for obstructive sleep pathology has known a progress in the last years in Romania as well, the number of research studies regarding respiratory pathology during sleep in general and especially for obstructive sleep apnea syndrome is reduced.

In the context of the actual alignment of Romania to the global obesity „pandemia," along with the rising prevalence of smoking , **an evaluation of OSAS from the point of view of the impact of smoking associated with different comorbidities** is imposed with the aim of recognising early diagnosis of OSAS, creating programs for fighting OSAS risk factors, with the decrease of morbidity and mortality.

The aims of the research regarding the obstructive sleep pathology from this perspective of the exposure to smoking and/or smoke-comorbidities, to patients susceptible to RDS, screened by nocturnal cardiorespiratory polygraphy method in two somnology laboratories in Constanta, during a period of 42 months, between 1st October 2011 and 8th April 2015 were:

1. The definition of demographic, anthropometric, clinical and polygraphic characteristics in subjects susceptible to RDS-statistical transverse study
2. The establishment of RDS spectrum depending on the smoke exposure and comorbidities-descriptive transverse statistical study
3. The identification of the OSAS prevalence among the subjects sceened polygraphic for RDS, the definition of the demographic, clinical, anthropometric and polygraphic characteristics of patients diagnosed with OSAS, with the identification of the spectrum of the associated comorbidities and the deifinition of smoking as a risk factor in the OSAS emergence- statistical transversal desriptive study
4. The assessment of the individual smoking impact and associated with comorbidities in identifying the emergence and severity of OSAS
5. The assessment of biomarkers with potential role in the pathogeny and severity of OSAS, in relation to smoking and comorbidities-statistical analitical observational study case-witness type 1:1.

2. Resources and methods

The clinical studies included a lot of 326 adult subjects (237 men and 89 women), with ages between 20-83 years, who addressed themselves to the somnlogy laboratory, personally or at the doctor's recommendations (penumologist, cardiologist, endocrinologist, ENT doctor, diabetologist,

neurologist or general practitioner) susceptible of RDS have confirmed polygraphic according to the manual AAMS 2014.[35]

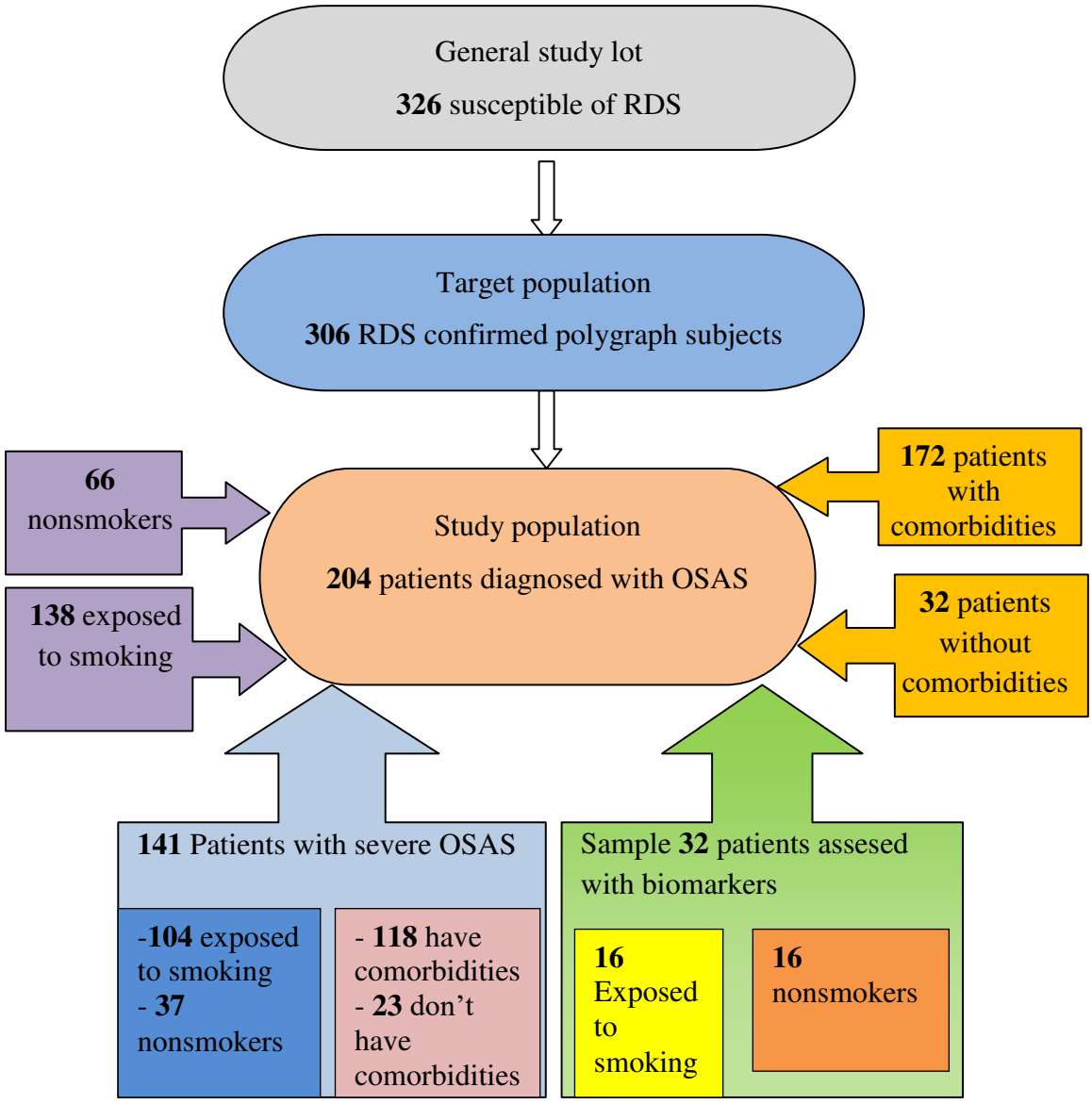

Figure 2. The studies'organigram (RDS=respiratory disorders during sleep; OSAS= obstructive sleep apnea syndrome; AS=active smokers, FS=former smokers)

All the participants have willingly expressed their consent regarding the participation to the study through an informed consent dated and signed at the somnology laboratory.

Based on the anamestic, clinical and paraclinical evaluation, I have made the **Stastistical Study Sheet** which contained socio-demographic data (sex,age, address, social status), clinical (daytime and nighttime symptoms), anthropometric (NC, WC, BMI, Mallampati score), exposure and addiction to smoking, personal comorbidities history and grouped according to specific categories and data: AHI, ODI, SpO_2minimum, SpO_2medium, TSS$pO_2$90%, SI and FC

A separate analysis has been done to the subgroup of 138 patients diagnosed with OSAS and exposed to smoking (actual or beforehand) and with or without morbidities, the status of active smoker being confirmed thourough the values of carbon monoxide (CO) in the exhaled air and in the concentration of carboxyhemoglobin (HbCO) blood equivalent determined by means of a mathematical algorhithm of coleration with the CO values of the exhaled air[53].

32 patients diagnosed with OSAS have given their consent in participating to ***additional biological tests*** (glycosylated hemoglobin, interleukin 6, C-reactive protein, fibrinogen, blood sugar,total cholesterol, HDL-cholesterol, LDL-cholesterol, Gamma-glutamyltransferase, alanine aminotransferase, aspartate aminotransferase) and we have tested potential biomarkers with roles in pathogeny and severity of OSAS, in relation to smoking and comorbidities.

The data has been analysed statistically using the IBM SPSS (version 20.0) program, and I expressed the medium continuous variables±standard and medial deviation (SD) and the quality variable thorough percentage. The statistical procedures have been: descriptive tests, parametric testes (the t test, One-Way Anova test) and non-parametric(Mann-Whitney U test, testul Kruskal-Wallis test), corelation analysis though Pearson (r) or Spearman coefficients and liniar regression analysis with the determination of the independent contribution of each variable which I considered a risk factor at the apparition of the dependent variable effectively appreciated.

Taking into consideration the null hypothesis according to which the difference between the studied groups are not due to chance, we consider statistically significat the value of $p<0,05$ (95% sure that there is a link between factors) and $p<0,01$(99% sure there is a link between factors). The values of $p>0,05$ are insignificant statistically (IS), the assurance under 95% to consider there is a link between factors, and the null hypothesis cannot be rejected. Depending on the numerical value of the correlation coefficient (r). I assessed statistically the variables interrelation as such: lack of link between variables (r=0), low correlation (r=0,2-0,4), medium correlation (r=0,4-0,6), high correlation (r=0,6-0,8), very high correlation (r=0,8-1) and perfect correlation (r=1).

The statistical analysis of the risk factors has been done with the program Epi info version 7.2 and it expressed: the proportion and prevalence of the exposed and non exposed to risk factors, the relative risk (RR), (RR>1 means the link between casualty and risk factor and the emergence of the disease; RR<1 expresses the protective role of the risk factor) and ***odd ratio (OR)*** or the chance report(OR>1 has a statistical significance and it expresses the link between the risk factor and the emergence of the disease; OR close to 1 expresses the lack of influence of the risk factor over the disease).

3. Results

Study 1. Defining the demographic, clinical, anthropometric and polygrsaphic characteristics in patients screened and susceptible of RDS

The study lot included 326 adult subjects presentic a risk of developing RDS, 237 men and 89 women. The average age of the screened subjects was of 53,15+/-11,47 years. Over 50% of theinvestigated cases were adults ≥50 years (n=219/326; 67,17%), mostly men (n=145/219; 66,21%), with the average age statistically significantly(p=0,001) lower than women (51,82+/-11,42 years vs 56,70+/-10,76years).

The sex distribution highlighted a male predominance (73% vs 27%), with statistically significant differences depending on the screened subjects's sex (p=0,010).

The symptoms of the patients were polymorphic (100%) as well as frequently associated with daytime (57,1%). The daytime symptoms, daytime sleepiness (DS) and morning headaches were 2 times more frequent in men than in women (52,74% vs 61/89; p<0,01), with the maximum values in the age group 50-59 years (38,17%; p<0,05). The DS risk to the value ≥10 points on the Epworth score is influenced by the age decade (p=0,001) but does not differ according to sex (p=0,221). The nocturnal symptoms were reported by all investigated subjects, over ½ of them (60,12%) simultaneously having ≥4 symptoms, regardless of sex (p=0,196) but with differences in the age decades(p=0,013). The most frequent nocturnal symptoms were: snoring (99,1%), nocturnal wake (81,3%) and nocturnal apnea noticed by the others (79,1%), men presenting a high relative risk(RR) of nocturnal apnea (RR=1,27; p<0,0002). (Table III)

Table III. Statistical representation of the nocturnal symptoms depending on the sex of the subjects

Sex	Snoring		Nocturnal apnea		Nocturnal awakenings		Nocturia		Sleep suffocation	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Men	235	2	201	34	184	53	139	98	105	132
Women	88	1	57	28	81	8	58	31	56	33
Cases total	323/326		258/326		265/326		197/326		161/326	
OR	**1,3352** (0,1196-14,9105)		**2,9040** (1,6255-5,1880)		0,3429 (0,1559-0,7540)		0,7581 (0,4566-1,2586)		0,4688 (0,2841-0,7734)	
RR	**1,0028** (0,9780-1,0283)		**1,2755** (1,0891-1,4938)		0,8530 (0,7761-0,9376)		0,9000 (0,7474-1,0837)		0,7041 (0,5684-0,8722)	
χ^2	**0,054**		13,5939		7,5853		1,1463		8,9445	
P	0,814		**0,0002**		**0,0058**		0,284		**0,0027**	

The medium neck circumference (NC) was 43,15±3,51cm, significantly higher in men (44,15±3,08cm vs 40,48±3,20, p=0,000) and in patients with the age between 40-49 years (44,22±3,08 ani; p=0,024), associated with a growing number of daily symptoms (p=0,007) as well as nocturnal (p=0,041).

The medium waist circumference (WC) was 108,56±10,36 cm, statistically significantly risen in men(109,89±9,8cm vs 105,03±11,01 cm; p=0,000) and associated with nocturnal apnea (p=0,000), nocturia (p=0,001), DS (p=0,000) and Epworth score ≥18 points,both in men (p=0,000) and in women (p=0,007).

The body mass index (BMI) had an average value 33,73±6,51 kg/m^2, slightly risen in women (34,34±7,14kg/m^2 vs 33,51±6,26kg/m^2; p=0,304), with statistical difference on age decades (p=0,001), superior in men with ages 50-59 years old (35,04±6,36 kg/m2; p=0,017) and women 30-39 years old (37,88±9,88 kg/m^2; p=0,013).

Apnea/hipopnea index (AHI) had an average value of 33,01±27,08/h, with medial values significantly risen in men (32,00 vs 15,00; p=0,037), especially those from the decade 50-59 years (40,99±26,21/h; p=0,028). AHI is correlated to snoring (p=0,030), nocturnal apnea (p=0,000), nocturia (p=0,004) and DS (p=0,000) and the Man-Whitney statistical analysis shows median AHI values 4 times higher in people who snore (26,00 vs 4,00; p=0,031) and 3 times higher in obese people (40,00 vs 13,00; p=0,000). (Figura 19)

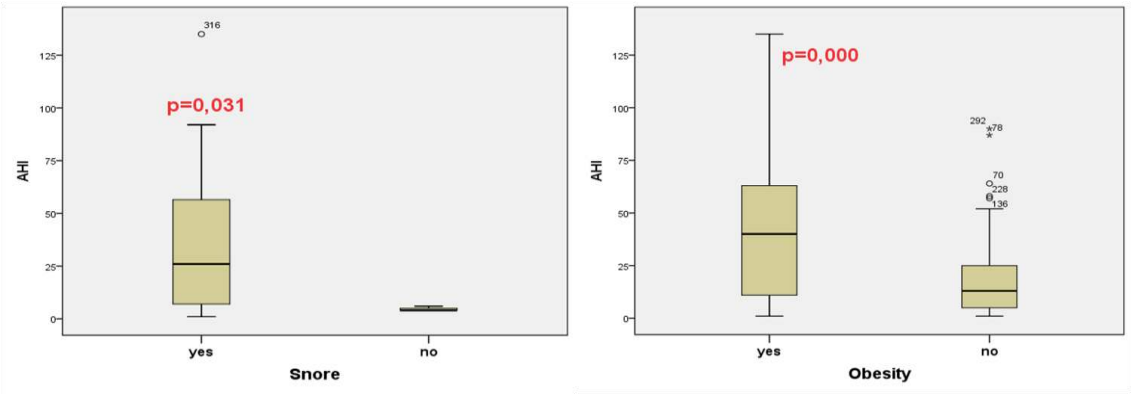

Figura 19. Distribution of median values linked to snoring and obesity

Oxygen dessaturation index (ODI) had an average value 34,61±29,27/h, with statistical differences among sexes (p=0,029) higher in men (36,78±29,41/h vs 28,82±28,27/h), maximum for those in the decade 50-59 years (43,52±31,01/h; p=0,025), with median values risen 4 times for people who snore (25,30 vs 25,20; p=0,035) and 3 times for the obese (38,60 vs 13,00; p=0,000).

Nocturnal oxygenation indexes had average values of 78,31±10,52% **SpO_2minimum**, 92,18±3,91% **SpO_2medium** și 11,15±12,85% **TS$SpO_2$90%**, with statistical differences only for SpO_2 minimum in women (80,31±10,82% vs 77,56±10,32%; p=0,035) and on the age decade (p=0,036).

Nocturnal Desaturation, established in the presence of SpO_2minimum ≤80%, SpO_2medium≤88% și TS$SpO_2$90% ≥5%, was present only in 13,5% of the subjects, insignificant

statistically(IS) among sexes (p=0,470), age groups (p=0,320) and compared to the severity of snoring (p=0,088).

The Snoring Index (SI) had the medium value 64,18±101,44/h, over 2/3 of the subjects are light snorers(78,5%), with a sex ratio 2,6B:1F, 32,03% of them being in the age group 50-59 years, both men (29,73%) and women (38,03%). SI median values were high in nocturnal desaturator (43,30 vs 19,70; p=0,023) cu SpO_2 medium≤88% (63,60 vs 19,00; p=0,008) și $TSSpO_2$90%≥5% (33,70 vs 13,30; p=0,000) but IS to those withSpO_2 minimum≤80% (p=0,077). The severity of snoring has been significantly associated with NC (p=0,044), AHI (p=0,033), ODI (p=0,036), $TSSpO_2$90% (p=0,001) the status of nocturnal desaturator(p=0,029).

Study 2. Establishing the RDS spectrum and the assessment of RDS patients depending on the smoke exposure and comorbidities

93,86% of the subjects assessed in the sleep laboratory have confirmed RDS (n=306) according to the classification ICDS-3 din 2014[5], depending on the polygraphic profile, patients being categorized as OSAS (n=204/306; 66,67%), CSAS (n=10/306; 3,27%), OHS (n=14/306; 4,57%) and UARS (78/306; 25,5%). (Figure 24). Although according to the classification AAM UARS is considered a subgroup of OSAS and not an individual entity, I excluded these cases from the OSAS group in the absence of confirmed PSG. RDS polygraph unconfirmed subjects have also been excluded.

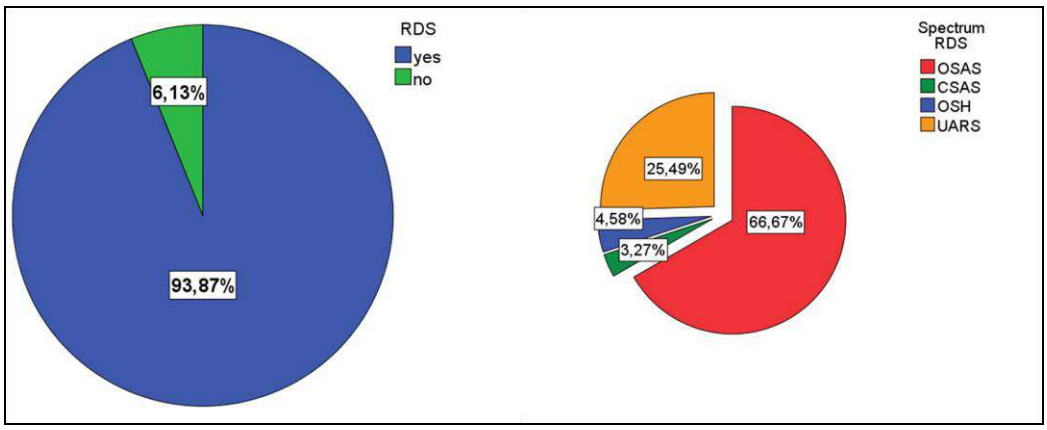

Figura 24. RDS prevalence and disorder spectrum

Confirmed RDS patients have mainly been men (72,5%), with the average age higher than that if the non-RDS subjects (53,35±11,2 ani vs 52,73±13,7 ani), RDS patients from the age 50-70 years(65%) being twice as more than those from the group 30-49 years (29,7%), statistically significant men(p=0,001). (Table VII)

Table VII. Demographic characteristics of RDS patients vs. Non-RDS patients

Characteristics	***RDS target population* (n=306)**	***Non- RDS population* (n=20)**
Sex: Male/female	222B : 84F	15B : 5F
Average age	53,35±11,243	50,15±14,057
Average age men	51,76±11,280	52,73±13,724
Average age women	57,55±10,057	42,40±13,390
Location : Urban Rural	222 (215B : 7F) 84 (77B : 7F)	19 (15B : 4F) 1 (0B : 1F)
Ocupation: Employed Retired Unemployed	146 (126B :20F) 127 (79B : 48F) 33 (17B :16F)	9 (5B : 4F) 7 (6B :1F) 4 (4B : 0F)

The most frequent symptom, with relevance for RDS in patients investigated with the polygraph was snoring(99,3%; p=0,049), followed by morning headaches in men(p<0,05).

WC average values (108,96±10,45 cm) și BMI (34,01±6,52 kg/m^2) in patients with RDS was significantly higher compared to non-RDS patients(p=0,008, respectively p=0,003), the majority(70,58%) were obese (p=0,005), 50,7% had moderate RDS and severe with AHI≥15/h. WC appears as a predictive sign of OSAS in the analyzed population (p=0,000) and not NC as study show[54], NC predicting OHS along BMI (p=0,000).

AHI and ODI indexes are higher in men (p=0,045 AHI; p=0,019 ODI), with a discrepant distribution for the age group 50-59 years for AHI(p=0,044) and 20-29 years for ODI(p=0,037).

The average values of nighttime oxygenation in RDS patients have been lower for SpO_2minimum(77,92±10,65%) and SpO_2medium (91,99±3,94%) and risen in TS$SpO_2$90% (11,76±13,02%), the noctrnal desaturator beingobvious only in 14,4% of these, with a sex ratio of 2,14B:1F, without statistical significance among sexes (p=0,483) and age groups (p=0,327).

SI average values (66,69±103,66/h) were lower compared to international studies (247±271/h)[338], the majority of RDS cases being light snorers with SI<100 events/h (77,8%), severe snorers having high values of TS$SpO_2$90% (p=0,007).

Smoking prevalence in RDS patients was **66,67%**, the structure of the target population being made up of 115 active smokers (37,6%), 89 ex smokers (29,1%) and 102 non smokers (33,33%) with a significant statistical sex ratio in favour of men, both active smokers(4B:1F; p=0,000), as well as ex smokers(7B:1F; p=0,000).(Figure 45).

Active smokers develop RDS a decade earlier than ex-smokers (48,89±10,56 years vs 57,92±8,31 years; p=0,000) but comparable to non smokers(54,39±12,43 ani). The average exposure period was 27,11±9,34 years and the average tobacco consumption 21,93±10,85PY,with the highest values in subjects of 50-59 years old (23,61±11,03PY; p=0,044), 62,6% of smokers having a tobacco consumption of over 20PY, with an average higher consumption in men (p=0,002) versus women.

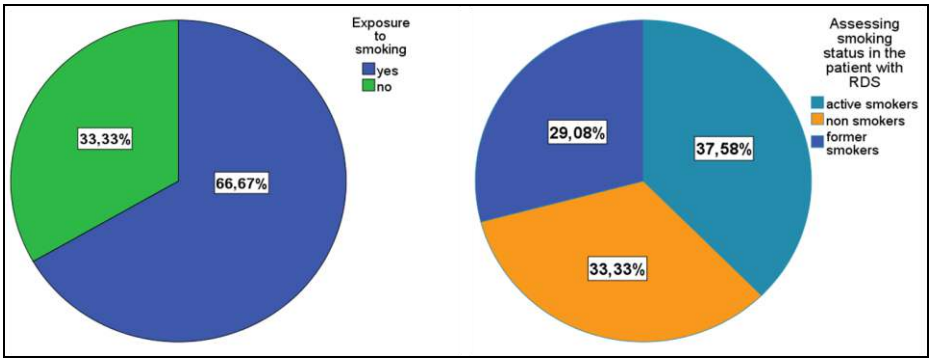

Figure 45. RDS patients smoke exposure

RDS active smokers had a higher medium ***Fagerström score*** in men (6,63±2,27 points vs 5,48±2,11 points; p=0,029) and to subjects of the group age 40-49 years (6,93±2,05 points; p=0,040), 60% of these haveing a ***severe addiction to nicotine*** in the group age 50-59 years (p=0,020).

Smoking exposure of the patients with RDS has correlated positively with nocturnal apneas (r=0,13; p=0,022), but not with anthropometric indexes NC (r=0,007; p=0,926), WC (r=-0,050; p=0,474), BMI (r=-0,070; p=0,317) and Mallampati score (r=-0,010; p=0,888), suggestive medium BMI values for obesity have not been different in active smokers (34,73±7,03 kg/m^2; p=0,292) as compared to ex-smokers (33,81±5,69 kg/m^2) and non smokers (33,37±6,57 kg/m^2).

RDS patients exposed to smoking had medium high values of AHI și ODI, statistically significant for AHI in active smokers(39,24±27,39/h; p=0,045) versus non smokers and for ODI fo active smokers(41,72±31,39/h; p=0,037) versus ex-smokers (35,74±27,61/h) and non-smokers (31,67±26,88/h).

There is a significant statistic link between tobbaco consumption and SI (p=0,024) in patients with RDS exposed to smoking, the biggest tobacco consumption being registered by moderate snorers (23,61±12,27 PY; p=0,441).

83,33% of RDS patients have comorbidities, 62,74% have twice as many associated diseases, especially in men (68,23%; p=0,000) and in those of the group age 50-59 years (36,47%; p=0,000).

The spectrum of RDS comorbidities is dominated by cardiovascular diseases (78,43%) of which SAH (73,72%), coronary disease (35,68%), CCF (16,47%) and arrhythmias (8,62%); followed by lung diseases (40%), of which COPD (70,58%) and bronchial asthma (40%), ENT diseases (33,72%), DM (20,39%), MS (18,43%), endocrine diseases (7,05%), cerebrovascular diseases(5,88%) and mental disorders(3,13%). (Figura 56)

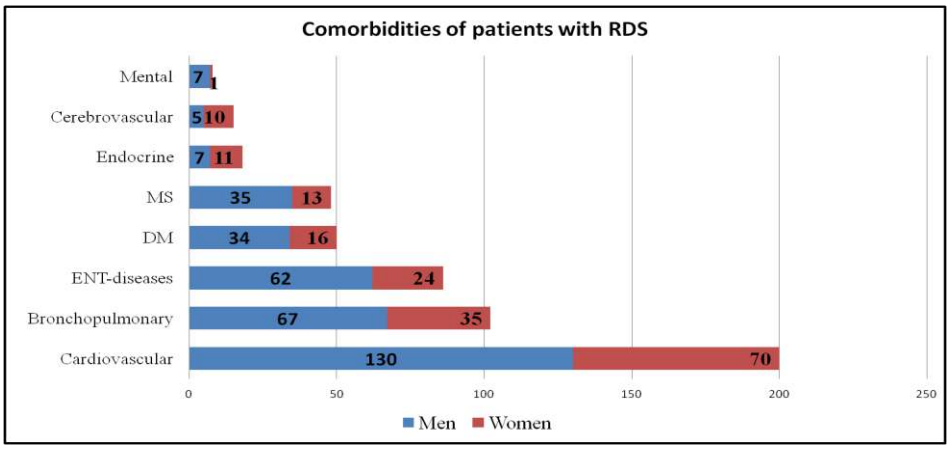

Figure 56. RDS patients comorbidities spectrum according to sex

The link between cardiovascular diseases with nocturnal awakenings(r=0,167; p=0,008) and nocturia ș (r=0,321; p=0,000), of lung diseases (r=0,173; p=0,006) and cerebrovascular (r=0,159; p=0,011) with sleep suffocation, of MS (r=0,154; p=0,014), DM (r=0,142; p=0,023) and ENT disorders(r=-0,163; p=0,009) with nocturia are a red flag for RDS.

NC și WC are significantly risen (p=0,000) in patients with MS (44,74±3,41 cm NC; namely 114,43±11,11 cm WC) and the BMI in patients with DM (38,33±6,44 kg/m^2; p=0,000). NC becomes predictive in men with RDSand ***cardiovascular comorbidities*** (p=0,000), ***bronhopulmonary*** (p=0,000), ***ENT*** (p=0,000), ***endocrine*** (p=0,000), ***DM*** (p=0,000) and ***MS*** (p=0,000), WC being high only for those with ***cardiovascular disorders*** (p=0,003).

The highest relative risk of mergence of RDS is present in c***ardiovascular disorders*** (RR=1,2180; p=0,0000), both in men (RR=1,1818; p<0,0007) and in women (RR=1,3444; p<0,0002), dominated by ***SAH*** in both sexes (RR=1,1415, p<0,005 men; RR=1,2668, p<0,0008 women) and followed by ***coronary disease*** (R=1,1210, p<0,02 men, RR=1,1250, p<0,03 women). Lung disorders come right after cardiovascular ones (RR=1,1133; p<0,002), being encountered mostly in men (RR=1,1142; p<0,02), the risk of RDS rising in the presence of COPD (RR=1,6110; p=0,0000), especially in men (RR=1,1044; p<0,03), as well as bronchial asthma (RR=1,2857; p<0,004).

Study 3 – Determining the prevalence of OSAS among the patients who have been polygraphic screened for RDS, defining the demographic,clinical, anthropometric and polygraphic characteristics of OSAS patients, identifying the comorbidities spectrum and deifining smoking as a potential risk factor in determining the emergence of OSAS

OSAS diagnosis was confirmed in **62,58%** of the confirmed RDS subjects (n=204/306), (Figure 61) excluding those susceptible of UARS who were not diagnosed through PSG. OSAS was defined

by the values AHI≥5/hour of sleep and the ratio AHI in supine position/AHI in non-supine position ≥2 in over 50% of the OSAS patients[55] and the risk factors of OSAS have been analysed according to the new multidisciplinary approach proposed by Sharma et al in 2014[25].

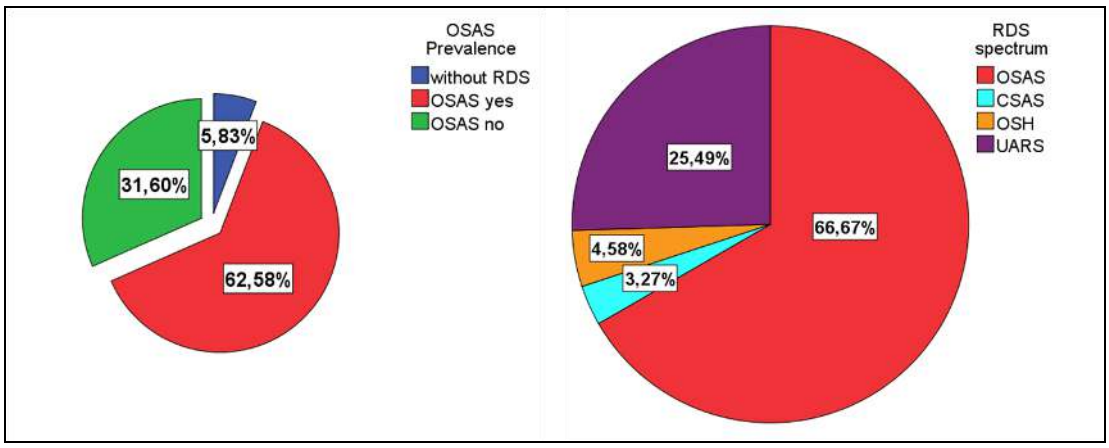

Figura 61. The OSAS prevalence in general population and target RDS population

OSAS was diagnosed in middle aged adults with an average of 52,84±10,61 years, mainly men (78,43%), with a sex ratio 3,63B:1F and a risen in the group age frequency of 50-59 years(35,8%).

The predominant OSAS symptoms were snoring (100%), nocturnal apneas (87,7%) and nocturnal awakenings (80,9%), snoring being considered the main symptom of OSAS, as it was present in all study patients, with the frequency peak of men belonging to the group age 50-59 years. (Figure 63)

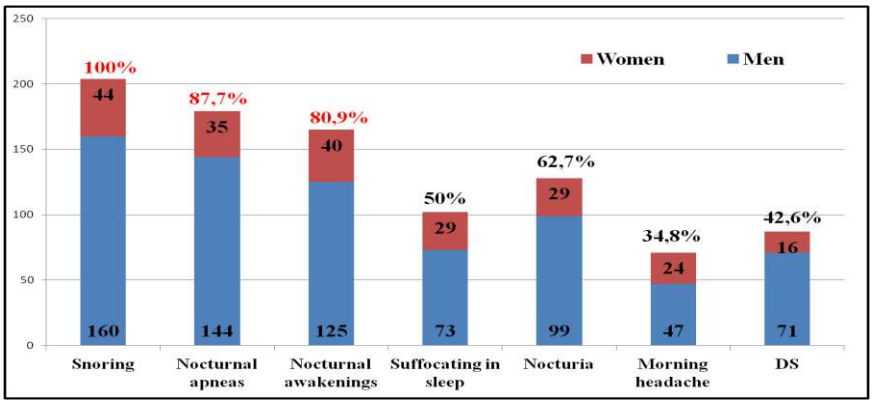

Figure 63. OSAS patients sex distribution

The symptoms associated with a high risk of OSAS emergence were nocturnal apneas in both sexes (R=1,5158 in men and RR=1,2727 in women; p<0,004) and DS in men (RR=1,2880, p<0,002).

Epworth score (9,15±5,38 points) was negatively correlated to the average age of the patient with OSAS (r=-0,142; p=0,043) and reached maximum values in severe cases of OSAS(p=0,000), the DS risk being influenced by the age group 50-59 years in values ≥10 points (p=0,017).

OSAS patients had higher medium values of the statistically significant anthropometric indexes (p=0,000) as opposed to non-OSAS ones (44,8±3,45cm NC, 112,46±9,9cm WC, 36,74±7,15kg/m^2 BMI). Men have higher NC values (44,84±3,13cm; p=0,000) and WC (112,46±9,9cm; p=0,046) compared to women with BMI high values (36,74±7,15kg/m^2; p=0,083). NC and WC threshold values associated with high risk of OSAS emergence were for women NC≥40cm (RR=2,1606; p<0,003) and WC≥100cm (RR=2,200; p<0,002) and for men NC≥43cm (RR=1,4525; p<0,00009) and WC≥102 cm (RR=1,8760; p<0,00002).

Of the RDS spectrum, OSAS patients had the highest AHI average values (45,91±23,91/h), uninfluenced by sex, maximal in the decade 50-59 years (50,62±20,88/h; p=0,028) but the criteria for positional OSAS have not been met, only 24% of them manifesting AHI supine/AHI nonsupine≥2.

The majority of OSAS patients developed severe forms (69,11%), correlated with nocturia (p=0,001) and of DS (p=0,000) and accompanied by medium high values of anthropometric indexes, WC in both sexes (115,65±9,425cm; p=0,000 men și 111,89±10,379; p=0,006 women), NC and BMI only in men (45,84±3,28cm; p=0,000 NC, 36,17±6,49kg/m^2; p=0,000 BMI).

Nocturnal desaturation of OSAS patients has highlighted low SpO_2minimum (72,96±7,69%) with a prolonged desaturation time(13,46±10,44% TSS$pO_2$90%), the nocturnal desaturation status having a frequency of 17,65%, statistically significant in obsese men (p=0,013).

The prevalence of OSAS comorbidities was of **84,3%**, mostly in men (p=0,006) and in those with the group age 50-59 years (38,37%; p=0,000), with a high frequency in severe OSAS types (68,6%).

The OSAS patients comorbidities spectrum was dominated by cardiovascular diseases (79,7%) led by SAH (74,41%), followed by coronary disease (34,88%), CCF (13,95%) and atrial fibrillation (7,55%),lung diseases (39%) represented by COPD (30,23%) and bronchic ashtma (8,13%), ENT diseases (34,9%), DM (18%), MS (16,9%), endocrine diseases (4,31%) and mental disorders (1,7%). (Figure 86)

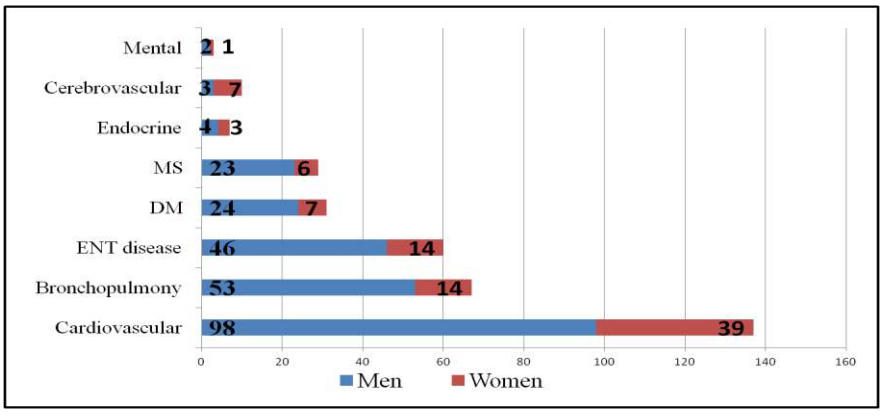

Figure 86. OSAS patients comorbidities spectrum

Hypertensive OSAS patients who mostly belong to the 60-69 years decade (42,18%; p=0,000), have high NC values in men (45,25±2,80cm; p=0,000) and mainly haves evere OSAS (68,75%; p=0,679). OSAS patients who associate with nictoria have a relatively higher SAH risk (OR=3,1127; RR=1,5777; p<0,0002), this SAH risk rising in severe OSAS sever associated with DSE in Epworth score≥18points (OR=2,91 vs 1,23 la non sleepy).

Men with OSAS developed a coronary disease 5 years earlier (57,97±8,35 years) compared to patients evaluated during the study ***Sleep Heart Health Study***[56] (63,5±10,7years), without our study proving the rising of the severe OSAS risk in the presence of coronary disease (OR=0,9779; p>0,9), fact highlighted in the above mentioned study (OR=1,68)[56].

In patients with IC the OSAS prevalence has been 57,14%,the majority being moderate forms of OSAS (29,16%) and severe (66,66%).

Our study patients with atrial fibrillation and OSAS are approximately two decades younger than the patients from the study conducted by Gami [57] (56,92±9,18 years vs 71±12years) and have NC statistical values signficantly higher (43,38±3,6cm; p=0,007).

OSAS-COPD patients have a higher average overlap (57,11±7,173ani; p=0,001) versus those without COPD, are mainly men (88,46%), 75% of them in moderate COPD stages (p=0,010). Men with OSAS-COPD overlap syndrome have NC and WC risen significantly (45,52±2,913cm; p=0,031 namely 113,59±8,627cm; p=0,004) but without threshold predictive values and relatively high risk for obese individuals (RR=3,5833; p<0,002) versus women.

Patients with bronchial asthma and nocturnal apnea do not show relatively high risk of OSAS (RR=0,2458; p<0,004), asthmatic women (53,3%) developing OSAS approximately 6 years before men (49,88±13,2 years vs 55,43±11,02 years; p=0,397) and presenting higher NC values as opposed to women with OSAS without bronchial asthma NC (43,50±3,66cm vs 40,39±2,31cm; p=0,004), WC (120,75±6,69cm vs 106,36±10,04cm; p=0,000) and BMI (41,75±7,62kg/m^2 vs 35,63±6,64 kg/m^2; p=0,027).

OSAS-DM prevalence according to sex has risen in women as compared to Lam at al study's data[58] (15,9% vs 7,3%), in these patients the OSAS presence led to the NC growth (45,42±3,38cm; p=0,013), WC (118,13±10,48cm; p=0,000) and BMI (39,78±6,86kg/m^2; p=0,000) versus non-OSAS patients. The majority of diabetic patients have developed moderate OSAS(17,2%) and severe (75%), without significant growth in AHI, ODI and nocturnal oxygen indexes versus patients without associated DM.

OSAS patients did not opresent high risk for MS (OR=0,8142; p>0,5), only 14,7% of them associating MS, men with OSAS versus non-OSAS seem more prone to MS, most of them being obese (p=0,038) and hypertensive (p=0,000) as compared to women.

ENT comorbidities have been present at 29,4% of the patients diagnosed with OSAS, with a high frequency of nasal polyps (45%) and deviated septum (38,33%) manifested individually or by association, more frequent in men (76,67%) who presented high values of NC (44,39±3,11cm; p=0,001) compared to women. In the presence of ENT disorders, the Mallampati positive score gains predicitve values for OSAS, corelates to AHI (r=0,358; p=0,005), AHI values grow in the presence of the Mallampati score class IV (59,78±27,3/h; p=0,042).

According to the risk factors classification proposed by Sharma et al.[25], a relatively high risk of OSAS emergence in obese men with NC≥43cm, with or without ENT predisposed modifications (RR=1,4873; p<0,003 vs RR=1,3662; p<0,0002).

Active or past exposure to smoking in obese men with thick neck ≥43cm, raises the risk of OSAS (RR=1,3953, p<0,003 in active smokers; respectively RR=1,3149, p<0,003 for those with a smoker past),maintained high risk and in the presence of ENT predisposed modifications (RR=1,4295; p<0,03). (Table XVIII and Table IX)

Table XVIII. *OSAS Risk Factor scientifically proven and linked to smoke exposure*

Risk factor strongly sustained by scientific proof-smoke exposure history	**OSAS yes (204)**	**OSAS no (102)**	RR	χ^2	p
1 Risk factor+smoke exposure	9	12	0,6264 (0,3799-1,0329)	5,7331	0,01664
2 Risk factor+smoke exposure	38	25	0,8830 (0,7101-1,0979)	1,4345	0,231
3 Risk factor+smoke exposure	74	24	**1,2082** (1,0355-1,4097)	5,0574	**0,0245**
- male+obesity+NC≥43cm+smoke exposure	58	13	**1,3149** (1,1333-1,5256)	9,3593	**0,0022**
- male+ENT modifications+NC≥43cm+smoke exposure	3	2	0,8985 (0,4373-1,8461)	0,1013	0,750
- obesity+ENT modifications+NC≥38cm in women+smoke exposure	8	2	1,2082 (0,8769-1,6645)	0,8243	0,3639
4 Risk factors+smoke exposure	17	4	1,2338 (0,9862-1,5433)	2,0639	0,15082
- male+obesity+NC≥43cm+ENT modifications + smoke exposure	14	1	**1,4295** (1,2192-1,6720)	5,0309	**0,0248**
- male+age≥65ani+NC≥43cm+obesity+smoke exposure	3	3	0,7463 (0,3339-1,6677)	0,7625	0,3825

Tabel XIX. OSAS risk factors scientifically associated to active smoking

Risk factor strongly sustained by scientific proof+active smoking	**OSAS yes (204)**	**OSAS no (102)**	RR	χ^2	p
1 Risk factors+active smoking	4	6	0,5920 (0,2760-1,2699)	3,2973	0,06939
2 Risk factors+active smoking	25	14	0,9562 (0,7451-1,2271)	0,1318	0,7165
3 Risk factors+active smoking	41	9	**1,2879** (1,0980-1,5105)	6,3025	**0,0120**
- male+obesity+NC≥43cm+active smoking	32	4	**1,3953** (1,2053-1,6154)	9,0370	**0,0026**
- male+ENT modifications+NC≥43cm+active smoking	1	1	0,7488 (0,1868-3,008)	0,2508	0,6164
- obesity+ENT modifications+NC≥38cm in women+active smoking	5	1	1,2563 (0,8705-1,8130)	0,7625	0,3825
4 Risk factors+active smoking	11	1	1,3964 (1,1552-1,6875)	3,5013	0,0613
- male+obesity+NC≥43cm+ENT modifications+active smoking	10	1	1,3824 (1,1270-1,6956)	3,0077	0,0828

The data of our study come to sustain the international proofs[59,60,61], contributing to highlighting smoking as a potential risk factor sustained by strong scientific proofs in diagnosing OSAS.

Study 4. The assessment of individual smoking impact and associated with comorbidities in determining the emergence and severity of OSAS

The prevalence of smoking history among the patients diagnosed with **OSAS 67,65%**, depending on the smoke exposure, the structure of the OSAS population consisting of 39,7% active smokers, 27,9% ex-smokers and 32,4% non-smokers.

OSAS patients with a smoking history are mainly males (84%, p=0,005), belonging to the age group 50-59 years (41,3%; p=0,049), active smokers being younger than non smokers or ex-smokers (50,1±9,2 years vs 52,26±12,47 years și respectiv 57,47±8,52 years; p=0,000),

Medium exposure to smoking of OSAS patients was of 27,76±9,12 years, higher than in severe forms of OSAS in active smokers versus ex-smokers (28,43±8,47 years vs 25,03±8,96 years; p=0,055) and the medium tobacco consumptioniar was higher in active smokers versus ex-smokers (29,19±9,1 PY, p=0,028 vs 24,15±10,6 PY, p=0,073).

The average values of **CO** in **exhaled air** were higher in **active smokers** (18,22±9,12ppm; p=0,000) as opposed to non-smokers (1,55±0,96ppm), the presence of OSAS in active smokers being accompanied by the growth of CO in the exhaled air, namely of HbCO blood equivalents as compared to non-OSAS patients (19,94±9,32ppm vs 15,35±8,1ppm; p=0,014 CO, namely 3,82±1,5% vs 3,09±1,3%; p=0,016 HbCO), especially men versus women(21,09±9,26 ppm vs 13,92±7,35ppm; p=0,010 CO, namely 4,004±1,42% vs 2,88%±1,17%; p=0,010 HbCO).

OSAS patients who are active smokers versus non-OSAS patients have threshold values CO≥6ppm in the exhaled air and HbCO≥1,5%, with a specificity of 100% and the highest sensibility (96,3% pentru CO, 93,83% pentru HbCO), statistically significant in males belonging to the age group 50-59 years (p=0,000 CO≥6ppm, p=0,004 HbCO≥1,5%) compared to women. (Figure 97)

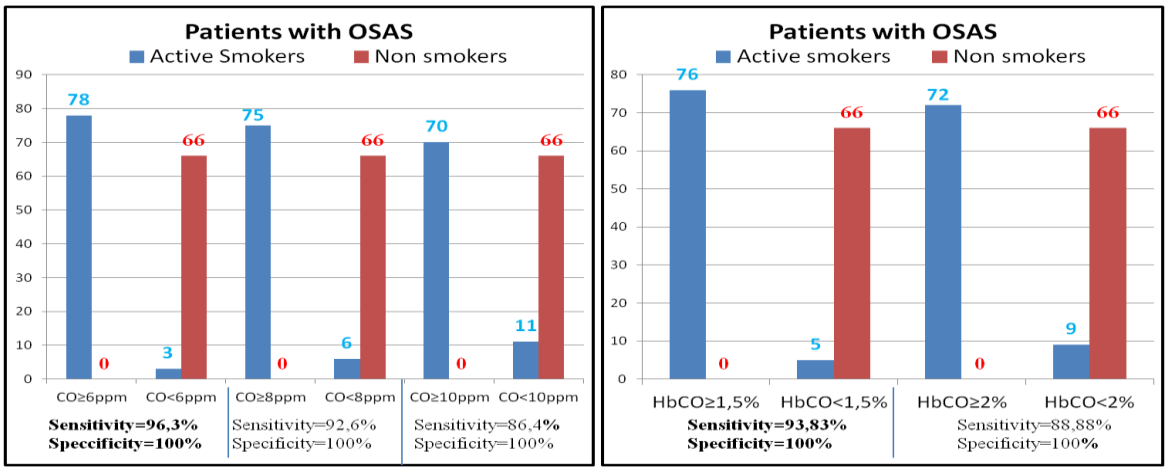

Figure 97. Specificity and sensibility of active smoking reported to CO values in the exhaled air and the HbCo blood equivalent concentration in patients with OSAS

In OSAS patients smoke exposure has been correlated to DS (r=0,151; p=0,031), with high values of Epworth score in active smokers versus ex-smokers and non smokers (9,75±5,1 points; p=0,236 vs 9,33±5,5 points și 8,26±5,57 points).

Smoke exposure in patients with OSAS has contributed to a raise in the values of NC, WC and BMI compared to non smokers (44,36±3,24 cm vs 43,26±3,78 cm, p=0,033 NC; 112,75±9,8cm vs 109,53±10,9 cm, p=0,036 WC; 35,62±6,63 kg/m^2 vs 34,28±6,78 kg/m^2 , p=0,182 BMI), registering superior values of NC(44,44±3,4cm; p=0,047) and WC (113,33±10,6cm; p=0,035) in active smokers versus non smokers, maximum for active smokers≥20PY (45,04±3,2cm, p=0,008 NC; 114,23±10,4cm, p=0,019 WC), only NC being correlated to the CO in the exhaled air and HbCO blood equivalent (r=0,222; p=0,046).

OSAS patients with a smoking history versus nonsmokers have high values of AHI (48,02±21,9/h vs 41,48±27,2/h; p=0,068), ODI (51,1±26,7/h vs 41,9±26,5/h; p=0,017) and TSSpO$_2$90% (14,5±10,4% vs 11,25±10,1%; p=0,036), statistically significant in active smokers with tobacco consumption ≥25PY as opposed to non smokers for AHI (52,6±20,33/h; p=0,029) and in tobacco consumption ≥20PY for ODI (51,5±24,4/h; p=0,032) and TSSpO$_2$90% (15,2±10,8%; p=0,039).

The values SpO$_2$minimum and SpO$_2$medium obtained were low as opposed to non smokers, both in OSAS patients and in those with a smoking history [(72,79±7,7% vs 73,32±7,7%; p=0,647), namely

(91,07±3,6% vs 91,52±4,7%; p=0,462)], as well as for active smokers with tobacco consumption ≥20PY [(73,30±8,6%; p=0,989) namely (91,52±4,7%; p=0,541)].

Patients with OSAS, comobbidities and smoking history were mainly **men**(81,82%, p=0,001), mostly active smokers (55,37%, p=0,034) and belonging to the age group 50-59 years (46,26%; p=0,005). Active smokers with OSAS from our study have lung diseases more often than non smokers (41,97% vs 19,69%; p=0,004) compared to cardiovascular diseases which frequently appear in nonsmokers (55,5% active smokers vs 66,66% nonsmokers; p=0,170).

Active smokers with OSAS-COPD overlap show smoking exposure, tobacco consumption and CO values in the exhaled air higher compared to patients without COPD (34,20±8,8years vs 26,56±8,4years, p=0,002; 29,57±10,9 PY vs 20,22±10,1PY, p=0,003; namely 23,61±10,8ppm vs 17,66±7,5ppm, p=0,005) and out of the cardiovascular disorders, the OSAS active smokers patients, only the IC association accompanied the higher tobacco consumption versus those without IC (32,57±8,5PY vs 23,5±11,3PY; p=0,044).

Active smokers patients with OSAS have shown, as opposed to non smokers, high values of AHI and ODI in the presence of SAH (p=0,048, namely p=0,022), coronary disease (p=0,005; namely p=0,003) and ENT disorders (p=0,034, respectively p=0,008) and low values of SpO_2medium in those with MS (p=0,019) and DM (p=0,024).

The percentage of severe OSAS has been higher to those exposed to smoking versus non smokers (75,36% vs 56,06%; p=0,015), especially in active smokers (80,25%; p=0,016), supporting the OSAS dependence on smoke exposure to a tobacco consumption ≥20PY (p=0,045), with a risk 1,65 times higher of OSAS than in those with a tobacco consumption <10PY (p<0,008).

The risk of developing severe OSAS grows in the presence of comorbidities 3,24 times in patients exposed to smoking (p<0,01) and 3,38 times in patients with a tobacco consumption ≥20PY (p<0,01) compared to nonsmokers, the highest risk being met in men, with a smoke exposure history (OR=4,6444; p<0,001) as well as active smokers (OR=3,00; p<0,03).

Evaluation OSAS patients who do not associate COPD has shown severe OSAS risk 10,93 times higher in the presence of smoke exposure(p<0,0001), 11,66 times higher in active smokers (p<0,0001) and 9,8 times higher in ex-smokers(p<0,001) as opposed to nonsmokers, the highest severe OSAS risk being in males exposed to smoking (OR=18,1373; p<0,0003), both active smokers (OR=18,75; p<0,0003) and ex-smokers (OR=17,1053; p<0,001) compared to nonsmokers.

Depending on the tobacco consumption, compared to patients with OSAS-COPD overlap, the highest severe OSAS risk, in the absence of COPD, goes to active smokers with ≥20PY (OR=14,70; p<0,00005), followed by those with tobacco consumption 10-19PY (OR=6,3636; p<0,03); the risk of

severe OSAS is maximum in men without COPD but big active smokers ≥20PY (OR=21,7391; p<0,0002), followed by moderate smokers with 10-19PY (OR=10,7143; p<0,02).

The impact of smoking on the severity of OSAS objectified in the subgroup of patients (n=78) grouped in ratio 1:1, only men, belonging to the same age group, active smokers-non smokers have proven significant raised values in active smokers compared to non smokers regarding AHI (57,92±20,58/h vs 40,79±24,31/h; p=0,001), ODI (61,87±28,59/h vs 40,49±24,63/h; p=0,001), $TSSpO_2$90% (16,87±11,02% vs 10,18±9,97%; p=0,006), SI (94,4±125,9/h vs 40,52±47,73/h; p=0,015), BMI (37,19±7,75kg/m^2 vs 33,43±5,8kg/m^2; p=0,018) and WC (117,00±11,27cm vs 109,26±9,6cm; p=0,002); men active smokers had severe OSAS mainly (89,74%; p=0,004), associated with comorbidities (79,93%; p=0,002), with statistical significance for severe OSAS-COPD, namely SAH (84,21; p=0,003 namely 42,86%; p=0,030) versus nonsmokers.

Study 5. Assessing biomarkers with potential role in the OSAS pathogeny and severity, linked to smoking and comorbidities

Assessing the group of OSAS patients who gave their consent regarding the participation in the supplementary biological tests(n=32), grouped in ratio 1:1, exposed to smoking (n=16) with non smokers (n=16), according to sex, group age, ratio and the severity degree of OSAS have not highlighted differences to the OSAS study population (n=204) to which regards age, sex distribution and age groups, smoker status, symptoms and anthropometric indexes, potential seric, inflamatory and metabolical biomarkers were analysed from the perspective of smoking-OSAS-comorbidities: protein C reactive (PCR), fibrinogen, interleukina 6 (IL6) and glycosylated hemoglobin (HbA_{1C}).

PCR in the OSAS patients'subgroup has registered average values of 1,24±3,5 mg/dl, medial values 6,1 higher in OSAS patients with bronchial asthma compared to those with associated asthma (1,291 mg/dl vs 0,211mg/dl; p=0,017), uninfluenced by smoke exposure (p=0,451) and by the severity of OSAS (p=0,067), unassociated with anthropometric and polygraphic indexes.

When it comes to PCS seric values >1mg/dl OSAS patients present a PYcienții SpO_2minimum lower in significant statistic to $TSSpO_2$ 90% raised (R^2=0,902; p=0,013) and OSAS patients exposed to smoking, the values of PCR>1mg/dl are associated to a high tobacco consumption, contributing to the rise of $TSSpO_2$90% (R^2=0,848; p=0,026).

Medium values of fibrinogen in OSAS patients (3,624±1,026 g/dl), were not influenced by BMI (3,77±1,03 g/dl in obese vs 2,95±0,72 g/dl in overweight people; p=0,074), did not present difference in the degrees of OSAS severity (p=0,074) but they had high values in patients exposed to smoking

with severe OSAS (3,88±0,585 mg/dl; p=0,016), (Figure 121) correlated to the lowering of SpO_2minimum (R^2=0,310; p=0,048) versus nonsmokers.

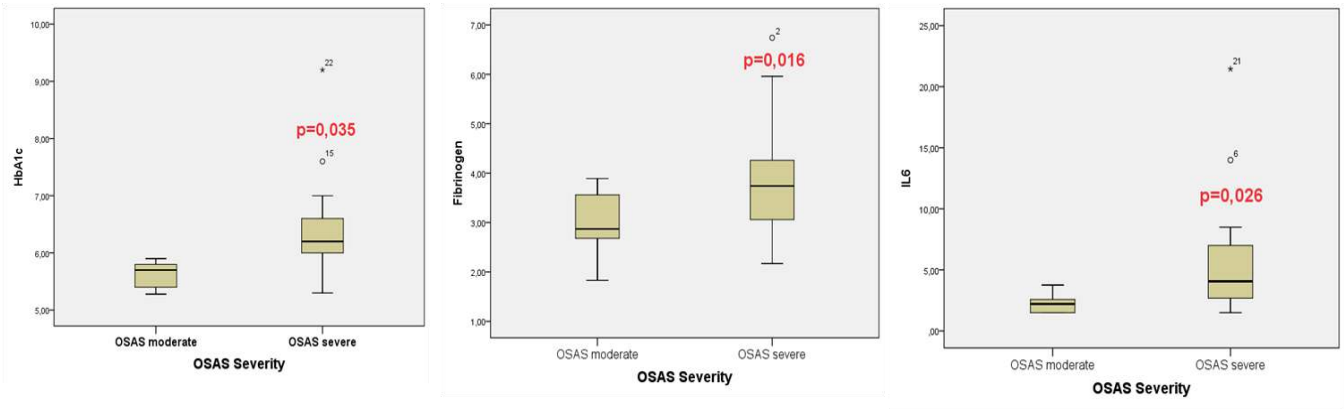

Figura 121. The distribution on median values of HbA_{1C}, IL6 and Fibrinogen in the study sample in connection to OSAS severity and smoke exposure

IL6 in OSAS patients from the study subgrup had average values ofl 4,79±4,07 pg/ml. Median values were 1,8 times higher in obese people as opposed to oveweight people (4,06 pg/ml vs 2,21 pg/ml; p=0,012), the majority of obese people having IL6>3,8 pg/dl (61,53%; p=0,012) and associated anthropometric indexes WC (p=0,007) and BMI (p=0,008), as well as polygraphic indexes AHI (p=0,024), ODI (p=0,029), SpO_2medium (p=0,031) and $TSSpO_2$90% (p=0,015).

IL6 was associated with OSAS severity, severe forms having median values IL6 twice as big than moderate forms (4,065 pg/ml vs 2,21 pg/ml; p=0,012), the majority of severe OSAS patients from the study sample presenting IL6>3,8 pg/ml (61,53%; p=0,007), 37,5% of them having AHI between 30-50/h and 62,5% AHI≥50/h. Smoke exposure of severe OSAS patients raises the median values of IL6 versus moderate OSAS (5 pg/ml vs 1,98 pg/ml; p=0,026) compared to non smokers (4 pg/ml vs 2,58 pg/ml; p=0,226). (Figure 135)

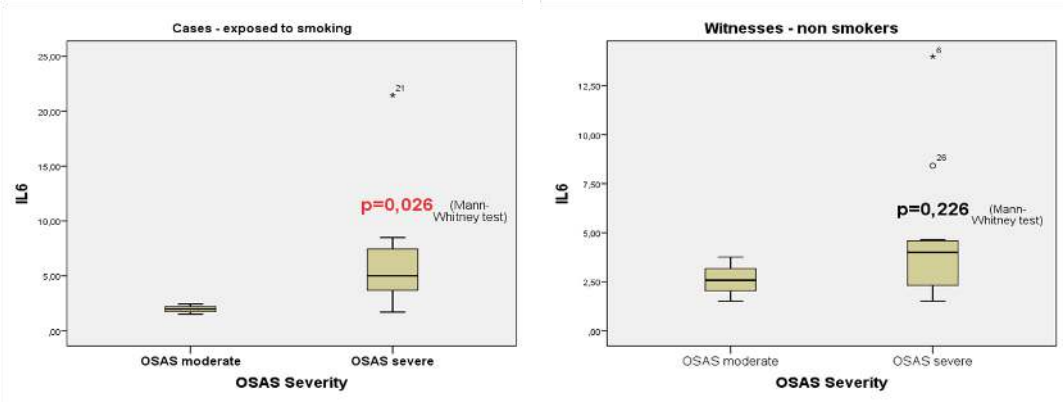

Figure 135. The distribution of median values IL6 in the study group depending on the OSAS severity

HbA_{1C} in the study sample diagnosed with OSAS has recorded average values of 6,202±0,75%, correlated to AHI (p=0,007), ODI (p=0,013) and $TSSpO_2$90% (p=0,015) and associated to severity, being high in severe OSAS versus moderate OSAS (6,33±0,76% vs 5,63±0,29%; p=0,036).

Seric levels of HbA_{1C} were higher in patients with OSAS associated to DM (7,12±1,17%; p=0,000) and MS (7,34±1,15%; p=0,000), also associated to OSAS severity (p=0,002 DM, namely p=0,000 MS), the risk of DM emergence being 9,44 times bigger in OSAS patients and HbA_{1C}≥6,2% (p<0,03) and of MS is 14 times bigger in patients with OSAS HbA_{1C}≥6,3% (p<0,01).

In OSAS patients without known DM, HbA_{1C} was correlated to AHI (p=0,008) and ODI (p=0,017), HbA_{1C} reaching to values up to AHI>50/h versus 15-30/h (6,17±0,22% vs 5,63±0,24%; p=0,028), 9 out of 10 patients with AHI>50/h having HbA_{1C}≥6% (p=0,002), without highlinghting the correlation with SpO_2minimum (p=0,100), SpO_2medium (p=0,325) or $TSSpO_2$90% (p=0,078). In values HbA_{1C}≥6% correltion between AHI and ODI is significant statistically (R^2=0,913; p=0,000), while the values of HbA_{1C}≥6,2% ensure a moderate asociation between AHI and SpO_2minimum (R^2=0,589; p=0,016) compared to the association at the border of statistical significance between AHI and SpO2medium (R^2=0,414; p=0,061), namely TSSpO290% (R^2=0,430; p=0,055).

Smoke exposure contributes to the develpoment of DM at 85,7% among patients with severe OSAS (AHI≥50/h) when the values of HbA_{1C} surpass the limit of 6,0% versus nonsmokers (p=0,010).

In OSAS patients without known MS, HbA_{1C} was correlated to the severity of OSAS (p=0,027), with high values directly proportional with AHI (p=0,005) and ODI (p=0,011), the values of HbA_{1C}≥6% strongly influencing the link between AHI and ODI (R^2=0,956; p=0,000), as well as AHI and SpO_2minimum (R^2=0,329; p=0,041), at the threshold of statistical significance cu SpO_2medium (R^2=0,414; p=0,061) and $TSSpO_2$90% (R^2=0,430; p=0,055).

Smoke exposure in severe OSAS patients may lead to the development of MS, 23% of the patients with AHI between 30-50/h and 77% of those with AHI ≥50/h versus non smokers have the values of HbA_{1C}≥6,0% (p=0,010), at this threshold value of HbA_{1C} highlighting the high correlation between AHI and ODI (R^2=0,953; p=0,000) and moderate between ODI and SpO_2minimum (R^2=0,451; p=0,012), respectively between SpO_2minimum and $TSSpO_2$90% (R^2=0,537; p=0,004).

The interaction between metabolic and inflamatory biomarkers HbA_{1C} and PCR contribute both to the develoment of OSAS, the highest impact being obvious especially in patients with MS (R^2=0,808; p=0,038), DM (R^2=0,769; p=0,022) and cardiovascular diseases (R^2=0,531; p=0,000),as well as the progression towards severe forms of OSAS(R^2=0,548; p=0,000).

Associating inflamatory biomarkers becomes eminent in the presence of smoke exposure of OSAS patients, the highest importance representing the association between IL6 and PCR (R^2=0,587; p=0,001), both in the presence of obesity (R^2=0,527; p=0,005), as well as of cardivascular comorbidities (R^2=0,319; p=0,044), with an impact on OSAS severity (R^2=0,527; p=0,005), followed by the association between IL6 and fibrinogen in patients with OSAS with or without associated cardiovascular diseases (R^2=0,407, p=0,019; respectiv R^2=0,255, p=0,046).

The individual action of the biomarkers enhancers with a role in OSAS development is reflected in the data from the studies in literature [62-68] but the effects are cummulated with the synergic association between them, both in the development, as well as in the progress of OSAS, is less approached in international studies, Hall et al[62] being one of the researchers who proved the synergic association between PCR and HbA_{1C} in the development of OSAS(p=0,033).

4. Conclusions

1. The research aimed at analysing the impact of smoking an/or comorbidities among patients with RDS, namely OSAS, in a carefully selected population and thoroughly guided for the nocturnal polygraphic investigation of sleep in a sleep laboratory.

2. The prevalence of RDS is high (93,86%) among adults screened by polygraph with ages over 53, their debut being deferred by 4 years in favour of men, with a ratio among the sexes of 2,64B:1F.

3. Snoring is the main symptom which contributes to RDS diagnosis (p=0,049) and also a main factor of nocturnal desaturation expressed by SpO_2 minimum ≤88% (p<0,009) and $TSSpO_2$90% ≥5% (p=0,000), the severity of snoring being associated with the prolonging of the nocturnal desaturation time(p=0,007).

4. Over half the patients with moderate and RDS are obese(p=0,005).

5. The prevalence of smoking in patients diagnosed with RDS is high (66,67%), especially men, with a sex ratio greater than one (4B:1F in active smokers and 7B:1F in ex smokers; p=0,000). Over ½ the active smokers with RDS have an average of tobacco consumption of over 20PY, with significant statistical differences between men and women (p=0,002), and a severe nicotine addiction, evaluated by Fagerström score(p=0,020).

6. Smoke exposure of RDS patients was positively correlated to nocturnal apneas (p=0,022) and the tobacco consumption with the snoring index(p=0,024).

7. The RDS comorbidities spectrum is polymorphic, dominated by cardiovascular diseases (78,43%),with a high SAH prevalence (73,72%), lung diseases (40%), ENT disorders(33,72%), diabetes mellitus (20,39%) and metabolic syndrome (18,43%).

8. Cardiovascular diseases (p=0,000), diabetes mellitus (p=0,023) and metabolic syndrome (p=0,014) are frequently associated with nocturia, which can be considered a red flag for RDS.

9. The OSAS prevalence in patients susceptible of RDS, 100% snorers, grew (62,58%), especially in men between the ages of 50-59 years, with a sex ratio of 3,6B:1F, snoring being considered a cardinal symptom of OSAS.

10. Among the anthropometric indexes with a high risk of OSAS, at the threshold values NC≥ 40cm in women (p<0,003) and ≥43cm in men (p<0,00009), of WC≥100cm in women(p<0,002) and ≥102 cm in men (p<0,00002), WC stands out as a predictive indicator of OSAS among the patients diagnosed with RDS (p=0,000).

11. The symptoms associated with high risk of OSAS have been nocturnal apneas in both sexes (p<0,004), and daytime sleepiness in men(p<0,002), associated with high values of Epworth score in patients with severe OSAS (p=0,000), especially in the age group 50-59 years (p=0,017).Nocturia (p=0,001) and daytime sleepiness (p=0,000), associated with high average values of the WC anthropometric values, in both sexes (p=0,000 men; p=0,006 women), NC (p=0,000) and BMI (p=0,000) in men there are defining markers for the evaluation of the OSAS severity.

12. OSAS comorbidities are frequent (84,3%), mainly with cardiovascular pattern (79,7%) and a high prevalence of SAH (74,41%), OSAS hypertensive patients making up the majority of the age group 60-69 years (p=0,000). OSAS-COPD overlap frequently appears in men (p=0,000), with a ratio 7,6B:1F, especially between 50-59 years (p=0,014), and it is associated with high anthropometric indexes like NC (p=0,031), WC (p=0,004) and BMI (p<0,002).

13. The high risk OSAS patient's profile is the smoker man of past smoker, with obesity and thick neck ≥43cm (p<0,003).

14. The prevalence of smoking in patients with OSAS was 67,65%, with an average exposure time of 27,76 years and a medium tobacco consumption higher in active smokers (p=0,028) versus ex smokers (p=0,073), is superior to the data from international and national studies, being twice as frequent in smokers(p<0,000) versus non smokers..

15. In OSAS patients, smoking increases the value of indexes like NC (p=0,033) and WC (p=0,036) and of the indexes of nocturnal dessaturation like ODI (p=0,017) and TSS$pO_2$90% (p=0,036), versus non smokers, especially in active smokers with a tobacco consumption ≥20PY (p=0,008 NC; p=0,019 WC; p=0,032ODI; p=0,039 TSS$pO_2$90%), AHI values increasing to a superior tobacco consumption ≥25PY (p=0,029). This way, the OSAS patient becomes addicted to smoking from a tobacco consumption of minumum 20PY (p=0,045) and the magnitude of the smoke exposure plays a major role in the OSAS diagnosis, with a high risk of tobacco consumption ≥20PY (p<0,008) versus <10PY.

16. Active OSAS smokers have average raised values of CO in the exhaled air (p=0,014) and HbCO blood equivalent (p=0,016) versus non-OSAS cases, especially in men (p=0,010), in the age group 50-59 years, with threshold values for the CO over 6ppm (p=0,000) and HbCO over1,4% (p=0,004), the only correlation established with the anthropometric indexes being between NC and CO in the exhaled air (p=0,046), respectively the concentration of HbCO blood equivalent (p=0,046).

17. The risk of OSAS emergence increases three times in the presence of comorbidities, and the patients exposed to smoking (p<0,01) versus nonsmokers, the highest risk belonging to men, active smokers (p<0,03) or ex-smokers (p<0,001).

18. Lung diseases associated with active smoking and OSAS (p=0,004) and OSAS-COPD overlap are obviously influenced by the tobacco consumption (p=0,003), the duration of the smoke exposure (p=0,002) and the values of CO in the exhaled air (p=0,005) versus OSAS patients without COPD. The risk of OSAS severity is high for the patients without COPD, but exposed to smoking (p<0,0001), both in active smokers (p<0,0001) as well as in ex-smokers (p<0,001), with a tobacco consumption ≥20PY (p<0,00005).

19. The severe OSAS patient's profile is the active smoker man with comorbidities (p=0,002), especially COPD (p=0,003) and SAH (p=0,030).

20. Of the seric biomarkers investigated, IL6 (p=0,012) and HbA_{1C} (p=0,027)have high statistically significant values in association to OSAS degrees of severity, the presence of smoking in severe OSAS causing the rise of the plasma firinogen's level (p=0,016). Althoug PCR was not associated with OSAS severity (p=0,067), the seric values PCR>1mg/dl negatively influence nocturnal dessaturation (p=0,013) by lowering SpO_2minimum, along with prolonging $TSSpO_2$90%, and the overlap of smoking, with a high tobacco consumption, significantly prolongs the dessaturation time of $TSSpO_2$90% (p=0,026).

21. Obese OSAS patients have significantly high values of IL6 (p=0,012), over half of them registering values of IL6>3,8pg/dl (p=0,012), smoking contributing negatively to the growth of the values of IL6 (p=0,026).

22. The values HbA_{1C} were high in OSAS patients and DM (p=0,000), OSAS and MS (p=0,000), the risk of DM emergence growing up to HbA_{1C} over 6,2% (p<0,03) and of MS over 6,3% (p<0,01). Smoke exposure of severe OSAS patients contribute to the development of diabetes mellitus (p=0,010) and to metabolic syndrome(p=0,010) when the values of HbA_{1C} surpass the threshold value of 6%, with an impact on nocturnal hypoxia proven by strong association between AHI and ODI (p=0,000 in DM; p=0,000 in MS), as well as between AHI-SpO_2minimum in diabetics (p=0,041) and ODI-SpO_2minimum (p=0,012), respectively SpO_2minimum-$TSSpO_2$90% (p=0,004) in those with MS.

23. The synergic action of the inflamatory biomarkers IL6-PCR (p=0,005) and IL6-fibrinogen (p=0,019) over the severity of OSAS becomes obvious in smokers, especially in the presence of cardivascular comorbidities (p=0,044 IL6-PCR; p=0,046 IL6-fibrinogen). The interaction between metabolic and inflamatory biomarkers, expressed through HbA_{1C}-PCR, induces OSAS in patients with cardiovascular diseases (p=0,000), metabolic syndrome (p=0,038) and diabetes mellitus(p=0,022), contributing to the progression of the OSAS severity (p=0,000).

5. The originality of the thesis

This is the **first thesis** which approaches, **in Romania,** the pathology of sleep respiratory disorders, especially OSAS, correlated with smoking and associated diseases, intricate morbid conditions, with rising prevalence and dual interaction, which enclose a vicious circle with an impact over the global mortality and morbidity growth.

This is **the first literature study**, which assessed smoking from the point of view of CO concentration in the exhaled air and of the equivalent carboxyhemoglobin, proving the independent role of smoking over OSAS and the impact of the fatal combination OSAS-smoking, often underestimated and ignored, over the cardiovascular and metabolic risk.

This is the **first** analytical observational **study in Romania**, which analysed the impact of potential serum, inflamatory and metabolic biomarkers involved in the emergence and progress of OSAS, represented by C reactive protein, fibrinogen, IL6 and HbA_{1C} and their synergic action associated with smoking over the OSAS comorbidities (cardiovascular, diabetes mellitus, metabolic syndrome).

The research had clinical aplicability by implementing the personalised study sheet in the smoking screening associated with OSAS among the patients susceptible of respiratory disorders during sleep, which are addressed to the somnology laboratory of the Pneumology Constanta Hospital.

Bibliography

[1] Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ et al. Sleep disordered breathing and mortality: Eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 2008;31:1071–8.
[2] Garvey JF, Taylor CT, McNicholas WT. Cardiovascular disease in obstructive sleep apnoea syndrome: The role of intermittent hypoxia and inflammation. Eur Respir J.2009; 33:1195-1205.
[3] Ryan S,Taylor CT, McNicholas WT. Systemic inflammation:A key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome?Thorax 2009;64:631–6.
[4] Schulz R, Hummel C, Heinemann S, Seeger W, Grimminger F.Serum levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea and severe nighttime hypoxia.Am J Respir Crit Care Med.2002;165:67–70.
[5] American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed. Darien IL: American Academy of Sleep Medicine, 2014.
[6] Guilleminault C, Kirisoglu C, Poyares D, Palombini L, Leger D at al. Upper airway resistance syndrome: A long-term outcome study. Journal of Psychiatric Research 2006; 40:273–279.
[7] Young T, Palta M, Dempsey J, Weber S, Badr S. The occurrence of sleep disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:230-5.
[8] Bearpark H, Elliott L, Grunstein R, Cullen S et al. Snoring and sleep apnea: a population study in Australian men. Am J Respir Crit Care Med 1995; 151:1459–1465.
[9] Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med 1998;157:144-148.
[10] Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J at al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 2001;163:608-613.
[11] Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 years. Am J Respir Crit Care Med 2001;163:685-689.
[12] Ip MS, Lam B, Lauder IJ, Tsang KW, Chung KF et al. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. Chest 2001;119-62-69.
[13] Ip MS, Lam B, Tang LC, Lauder IJ, Ip TY, Lam WK. A community study of sleep-disordered breathing in middle-aged Chinese women in Hong Kong: prevalence and gender differences. Chest 2004;125:127-134.
[14] Udwadia AF, Doshi AV, Lonkar SG, Singh CI. Prevalence of sleep-disordered breathing and sleep apnea in middle-aged urban Indian men. Am J Respir Crit Care Med 2004;169:168-173.
[15] Kim JK, In KH, Kim JH, You SH, Kang KH, Shim JJ et al. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am J Respir. Crit Care Med 2004;170:1108-1113.
[16] Sharma SK, Kumpawat S, Banga A, Goel A. Prevalence and risk factors of obstructive sleep apnea syndrome in a population of Delhi, India. Chest 2006;130:149-156.
[17] Nakayama-Ashida Y, Takegami M, Chin K et al. Sleep disordered breathing in the usual lifestyle setting as detected with home monitoring in a population of working men in Japan.Sleep 2008;31:419-25.
[18] Neruntarat C, Chantapant S. Prevalence of sleep apnea in HRH Princess Maha Chakri Srinthorn Medical Center, Thailand.Sleep Breath 2011 Dec;15(4):641-8.
[19] Franklin KA, Sahlin C, Stenlund H et al.Sleep apnoea is a common occurrence in females.Eur Respir J 2013;41:610-5.
[20] Kang K, Seo JG, Seo SH, Park KS, Lee HW. Prevalence and related factors for high-risk of obstructive sleep apnea in a large korean population: results of a questionnaire-based study. J Clin Neurol. 2014 Jan;10(1):42-9.
[21] Lam JCM. "Obstructive Sleep Apnea and Cardiometabolic Complications", for the degree of Doctor of Medicine at The University of Hong Kong in May 2009.
[22] Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population - a review on the epidemiology of sleep apnea. Journal of Thoracic Disease 2015;7(8):1311-1322.
[23] Munteanu I, Bădescu C, **Trenchea M**, Mihălțan F. Prevalența sindromului de apnee în somn – experiența Institutului de Pneumologie "Marius Nasta" București. Pneumologia vol.57, nr.4/2008: 222-226.
[24] Kapur V, Strohl KP, Redline S, Iber C, O'Connor G, Nieto J. Underdiagnosis of sleep apnea syndrome in US communities. Sleep Breath 2002;6:49–54.
[25] Sharma SK, Katoch VM, Mohan A, Kadhiravan T, Elavarasi A, Ragesh R et al.Consensus and evidence-based Indian initiative on obstructive sleep apnea guidelines 2014 (first edition). Lung India 2015 Jul-Aug; 32(4): 422–434.
[26] Bloom JW, Kaltenborn WT, Quan SF. Risk Factors in a General Population for Snoring. Importance of Cigarette Smoking and Obesity. Chest 1988 Apr; 93(4):678-83.
[27] Schmidt-Nowara WW, Coultas DB, Wiggins C, Skipper BE, Samet JM. Snoring in a Hispanic-American population. Risk factors and association with hypertension and other morbidity. Arch Intern Med. 1990 Mar;150(3):597-601.
[28] Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men.Thorax 1991 Feb;46(2):85-90.

[29] Sohn CH, Jeong DU, Sung JH, Chang SH at al. Obstructive Sleep Apnea Symptoms Prevalence and Sleep Apnea-Associated Factors in Korean Adult Population: A Cross-sectional Survey of Three Rural Communities. Sleep Med Psychophysiol. 1998 Jun;5(1):88-102.
[30] Khoo SM, Tan WC, Ng TP, Ho CH. Risk factors associated with habitual snoring and sleep-disordered breathing in a multi-ethnic Asian population: a population-based study. Respir Med 2004; 98:557–566.
[31] Franklin KA, Gislason T, Omenaas E, Jogi R, Jensen EJ, Lindberg E et al. The influence of active and passive smoking on habitual snoring. Am J Respir Crit Care Med 2004;170:799–803.
[32] Ohida T, Kaneita Y, Osaki Y, Harano S, Tanihata T, Takemura S et al. Is passive smoking associated with sleep disturbance among pregnant women? Sleep. 2007 Sep;30(9):1155-61.
[33] Nagayoshi M,Yamagishi K,Tanigawa T,Sakurai S, Kitamura A, Kiyama M et al. CIRCS Investigators. Risk factors for snoring among Japanese men and women: a community-based cross-sectional study.Sleep Breath 2011 Jan;15(1):63-9.
[34] Wetter DW, Young TB, Bidwell TR, Badr MS, Palta M. Smoking as a risk factor for sleep-disordered breathing. Arch Intern Med 1994; 154 : 2219-24.
[35] Berry RB, Gamaldo CE, Harding SM, Lloyd RM, Marcus CL, Vaughn BV; for the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules,Terminology and Technical Specifi cations, Version 2.0.3. Darien,IL:American Academy of Sleep Medicine 2014.
[36] Soldatos CR, Kales JD, Scharf MB et al.Cigarette smoking associated with sleep difficulty.Science 1980; 207:551–3.
[37] Saint-Mleux B, Eggermann E, Bisetti A et al. Nicotinic enhancement of the noradrenergic inhibition of sleep-promoting neurons in the ventrolateral preoptic area. J Neurosci 2004; 24:63–7.
[38] Kutty K. Sleep and chronic obstructive pulmonary disease. Curr Opin Pulm Med 2004; 10:104–12.
[39] Mitchell RA, Loeschcke HH, Massion WH, Severinghaus JW. Respiratory responses mediated through superficial chemosensitive areas on the medulla. J Appl Physiol. 1963; 18:523-533.
[40] Strohl KP, Gottfried SB, Van de Graaff W, Wood RE, Fouke JM. Effects of sodium cyanide and nicotine on upper airway resistance in anesthetized dogs. Respir Physiol 1986;63:161-75.
[41] World Health Organization. WHO Report on the Global Tobacco Epidemic, 2013. Geneva, Switzerland: World Health Organization; 2013.
[42] Fumatul și sănătatea publică în România. Cunoștințe, atitudini și practici legate de consumul de tutun în rândul populației generale din România. CPSS, 2004.
[43] Dart RA, Gregoire JR, Gutterman DD, Woolf SH. The association of hypertension and secondary cardiovascular disease with sleep-disordered breathing.Chest 2003;123:244-60.
[44] Montesi SB, Edwards BA, Malhotra A, Bakker JP. The effect of continuous positive airway pressure treatment on blood pressure: A systematic review and meta-analysis of randomized controlled trials. J Clin Sleep Med. 2012;8:587–96.
[45] Drager LF, Bortolotto LA, Krieger EM, Lorenzi-Filho. Additive effects of obstructive sleep apnea and hypertension on early markers of carotid atherosclerosis. Hypertension 2009;53:64-69.
[46] Dimitri H, Ng M, Brooks AG et al. Atrial remodeling in obstructive sleep apnea: Implications for atrial fibrillation. Heart rhythm 2012;9(3):321–327.
[47] Maeder MT, Schoch OD, Rickli H. A clinical approach to obstructive sleep apnea as a risk factor for cardiovascular disease.Vasc Health Risk Manag. 2016 Mar 21;12:85-103.
[48] Brooks D, Horner RL, Kozar LF et al. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest 1997;99:106-9.
[49] Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A et al.; American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology; American Heart Association Stroke Council; American Heart Association Council on Cardiovascular Nursing; American College of Cardiology Foundation. Sleep apnea and cardiovascular disease: an American Heart Association /american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing.Circulation 2008 Sep 2;118(10):1080-111.
[50] Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Oda N, Tanaka A et al. Silent brain infarction and platelet activation in obstructive sleep apnea. Am J Respir Crit Care Med.2007;175:612– 617.
[51] Ioachimescu OC, Teodorescu M. Integrating the overlap of obstructive lung disease and obstructive sleep apnoea: OLDOSA syndrome. Respirology 2013; 18:421–431.
[52] Rezaeetalab F, Rezaeitalab F, Ahmadhosseini SH, Akbarirad M, Akbarirad F, Azami G. Sleep Overlap Syndrome: A Narrative Review**.** J Cardiothorac Med. 2016; 4(4): 497-504.
[53] Deveci SE, Deveci F, Açik Y & Ozan AT. The measurement of exhaled carbon monoxide in healthy smokers and non-smokers. *Respiratory Medicine*, 2004; *98*(6), 551-556.
[54] Davies RJO, Ali NJ and Stradling JR. Neck circumference and other clinical features in the diagnosis of the obstructive sleep apnoea syndrome. Thorax 1992; vol. 47, no.2,pp.101–105.
[55] Chen WC, Lee LA, Chen NH, Fang TJ, Huang CG et al.Treatment of snoring with positional therapy in patients with positional obstructive sleep apnea syndrome. Scientific Reports. 2015.Dec 11;5:18188.

[56] Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ et al. Predictors of sleep disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med 2002;162:893–900.
[57] Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE et al. Association of atrial fibrillation and obstructive sleep apnea. *Circulation*,2004; *110*(4), 364-367.
[58] Lam DC, Lui MM, Lam JC, Ong LH, Lam KS & Ip MS. Prevalence and recognition of obstructive sleep apnea in Chinese patients with type 2 diabetes mellitus. *Chest*, 2010; *138*(5), 1101-1107.
[59] Kashyap R, Hock LM, Bowman TJ. Higher prevalence of smoking in patients diagnosed as having obstructive sleep apnea.Sleep Breath 2001 Dec;5(4):167-72.
[60] Moreno CR, Carvalho FA, Lorenzi C, Matuzaki LS, Prezotti S et al. High risk for obstructive sleep apnea in truck drivers estimated by the Berlin questionnaire: prevalence and associated factors. Chronobiol Int. 2004;21(6):871-9.
[61] Boussoffara L, Boudawara N, Sakka M, Knani J. Tabagisme et sévérité du syndrome d'apnées hypopnées obstructives du sommeil. Rev Mal Respir. 2013 Jan;30(1):38-43.
[62] Hall TS, Herrscher TE, Jarolim P, Fagerland MW, Jensen T, Agewall S et al. Myeloid-related protein-8/14 and C-reactive protein in individuals evaluated for obstructive sleep apnea. *Sleep medicine*, 2014; *15*(7), 762-768.
[63] Wessendorf TE, Thilmann AF, Wang YM, Schreiber A, Konietzko N & Teschler H. Fibrinogen levels and obstructive sleep apnea in ischemic stroke. *American Journal of Respiratory and Critical Care Medicine*, 2000; *162*(6), 2039-2042.
[64] Shamsuzzaman A, Amin RS, Calvin AD, Davison D & Somers VK. Severity of obstructive sleep apnea is associated with elevated plasma fibrinogen in otherwise healthy patients. *Sleep and Breathing*, 2014; *18*(4), 761-766.
[65] Huiguo L, Jin L, Shengdao X, Guanxin S, Zhenxiang Z & Yongjian X.The change of interleukin-6 and tumor necrosis factor in patients with obstructive sleep apnea syndrome. *Journal of Tongji Medical University*, 2000; *20*(3), 200-202.
[66] Papanas N, Steiropoulos P, Nena E et al. HbA1c is associated with severity of obstructive sleep apnea hypopnea syndrome in nondiabetic men. *Vascular health and risk management*, 2009; *5*, 751.
[67] Kurosawa H, Saisho Y, Fukunaga K, Haraguchi M, Yamasawa W, Kurihara I et al. Association between severity of obstructive sleep apnea and glycated hemoglobin level in Japanese individuals with and without diabetes. *Endocrine journal*, 2017; *65*(1), 121-127.
[68] Archontogeorgis K, Nena E, Papanas N & Steiropoulos P. Biomarkers to improve diagnosis and monitoring of obstructive sleep apnea syndrome: current status and future perspectives. *Pulmonary medicine*, *2014*.