UNIVERSITY OF MEDICINE AND PHARMACY

"CAROL DAVILA", BUCHAREST

DOCTORAL SCHOOL

MEDICINE FIELD

TOBACCO USE AND THE RESPIRATORY CONSEQUENCES

DOCTORAL THESIS ABSTRACT

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BUCHAREST 2024

Thanks

The completion of this doctoral study marks an important moment in my professional and personal journey and in this way I want to express my deep gratitude to my superiors, whose guidance, support and trust were essential in the realization of my project.

- First of all, I would like to thank **the Academic Professor Dr. Mihălțan Florin Dumitru** for the impeccable coordination of this doctoral thesis and the Manager of the "Marius Nasta" Institute, **Lecturer Dr. Mahler Beatrice** for the given support and advice.

- I thank my fellow phyisicians and medical interns of the Institute who contributed with their unconditional help to the completion of this doctoral thesis.

- My thanks also go to my family, my parents and, last but not least, to **my son** who understood me, as much as he could at the age of 4, during the times when I could not be by his side, his positive energy being a constant source of strength for me throughout this journey.

TABLE OF CONTENTS

LIST OF PUBLISHED SCIENTIFIC PAPERS

1. Andreea Dumitrița Slabu, Maria-Beatrice Catrangiu, **Ana-Luiza Iorga- "**Challenges in the management of long-therm corticotherapy treatment at smoker pacient with severe asthma", Internal Medicine 2023, vol. XX No 2 10.2478/inmed-2023-0252

2. Ancuța Constantin, Maria-Beatrice Catrangiu, **Ana-Luiza Iorga**- "Perspectives in smoking related interstitial lung diseases", Internal Medicine 2024 vol XXI No 2

3. **Ana- Luiza Iorga**, Andreea Dumitrița Slabu, Florin Dumitru Mihălțan- "Tobacco consumption and respiratory consequences", Internal Medicine 2024, vol XXI, No 2

4. Beatrice Mahler, Dragos Baiceanu, Traian Constantin Panciu, Radu Marian Florea, **Ana Luiza Iorga,** Marcin Gnat, Cornelia Florina German, Simona Pîrvu, Dorel Paraschiv, Daniel Manea, Mihaela Mihai, Elmira Ibraim, Bogdan Timar, Florin Dumitru Mihalțan- "Air pollutants and their impact on chronic diseases- a retrospective study in Bucharest, Romania", Atmosphere 2023, 14 (5), 867; https://doi.org/10.3390/atmos14050867

5. Iustina Leonte, Karina Ivanov, Angela Stefania Marghescu, Radu Serban Matache, Florica Valeria Negru, **Ana Luiza Iorga,** Silviu Mihail Dumitru, Beatrice Mahler "Sequence of Rare Diagnoses in a Young Patient: Altitude Barotrauma Hemopneumothorax and Desquamative Interstitial Pneumonia", Diagnostics 2023, 13 (14), 2367, https://doi.org/10.3390/diagnostics13142367

LIST OF ABBREVIATIONS AND SYMBOLS

ACOS - Asthma - Chronic Obstructive Pulmonary Disease Overlap Syndrome

DNA - Deoxyribonucleic acid

AOMI - Obliterating arteriopathy of the lower limbs

AVC - Stroke

AVPP - Potential Years of Life Lost

BCI - Ischemic heart disease

COPD - Chronic Obstructive Pulmonary Disease

CO - Carbon monoxide

COHb- Carboxyhemoglobin

CT - Computed tomography

CV - Vital capacity

DZ - Diabetes mellitus

EGFR – Epidermal growth factor receptor

EVALI – E – Cigarette or Vaping Associated Lung Injury

FDA - Food and Drug Administration

FVC – Forced Vital Capacity

GABA – Gamma-aminobutyric acid

GBD - Global Burden Of Diseases

GINA - Global Initiative For Asthma (Ghid pentru Managementul si Prevenirea Astmului)

GOLD - Global Initiative for Chronic Obstructive Lung Disease

Hb - Hemoglobin

HIV- Human immunodeficiency virus

HTA - Hypertension

HTP - Pulmonary hypertension

CHF- Congestive heart failure

INF Gamma-interferon gamma

IT - Tiffeneau Index

LDH- Lactate dehydrogenase

MAPK – Mitogen-activated protein kinase

MEF50 - Maximum expiratory flow rate at 50% of vital capacity

mMRC - mMRC (Modified Medical Research Council) Dyspnea Severity Scale

MPOWER - Monitor Protect Offer Warn Enforce Raise (Monitorizare Protecție Oferi Avertizare Impunere Ridicare)

NAB - N-nitrozoanabazine

NIH - National Cancer Institute (Institutul Național de Cancer)

NNAL- N-acetylnorloline

NNK - 4-methylnitrosamine-1-3-pyridyl-1-butanone

NNN - N- Nitrozonornicotine

NK - Natural Killer

NLR- Nod Like Receiver

WHO - World Health Organization

PY- Number of pack years

PID- Diffuse Interstitial Lung Disease

PKA - Protein kinase A

PLT- Trays

RB- ILD - Respiratory Bronchiolitis Interstitial Lung Disease

RIG - RIG like receiver

SASO- Sleep Apnea Syndrome

TB- Tuberculosis

PTE- Pulmonary thromboembolism

TGF-beta - Transforming Growth Factor Beta

TLR - Tool like receiver

UIP- Usual Interstitial Pneumonia

VEGF - Vascular Endothelial Growth Factor

FEV1 – Maximum expiratory volume in the first second

ESR - Erythrocyte sedimentation rate

WBC- White blood cells

Introduction

It is well known that smoking is the most common etiological factor associated with respiratory diseases and is a widespread habit in the general population as it is involved in 8 million deaths annually.

Although it is currently widely accepted that smoking is not a safe habit by both the scientific and medical community and most of the general population, this was not the case from the beginning. It took many decades to introduce laws and disseminate correct information to the consumer, in order for him to make an assumed decision regarding the health risk of smoking. To a large extent, the delay in faster adoption of laws and the continued increase in incidence has been due to several factors, including: sponsorship of certain studies to produce confusion about the harmful effects of smoking, the use of images of doctors on cigarette packs, and the promotion of consumption through marketing strategies using both celebrities and the association of consumption with the idea of,, freedom", "emancipation" etc.

In this regard, the World Health Organization (WHO) has developed a series of measures, called MPOWER (Monitor, Protect, Offer, Warn, Enforce, Raise) with the aim of reducing the number of smokers worldwide. In this regard, in 2007 the STOP SMOKING Program was established in Romania, where smokers who want to quit smoking receive psychological guidance and medical examination, which aim to initiate and maintain withdrawal. In Romania, statistical data estimate that although the rate of the female population that smokes has become similar to that of men, there is a downward trend in the prevalence of smoking, although we still have among the highest figures at European level. (9)

The paper "Tobacco consumption and respiratory consequences" aims to highlight the importance of smoking cessation in the clinical-paraclinical evolution of patients, precisely to bring back that adjacent to the indicated chronic therapy, it is necessary to encourage the patient, both by the medical staff and at government level, to turn to a specialized center in tobacco science supported by psychologists in the field in order to increase the success rate.

The idea of the research field started from the desire to improve statistics in this regard, since from personal knowledge at national level there are very few studies that refer to this subject.

This paper is formed by two parts, represented by the current state of knowledge, respectively personal contributions.

The first part was subdivided into two chapters for which multiple studies, databases and large representative papers were used in order to be able to render as concisely and clearly as possible the data we have on the impact of smoking on the respiratory system.

The second part of this paper contains the personal contributions and is structured in such a way as to present in a more objective and succinct form, the results obtained in the study carried out in conjunction with the data available in the literature.

The presented study is a prospective one, which was carried out at the "Marius Nasta" Institute of Pneumophthysiology in Bucharest, between 2022 and 2023 on a batch of 106 smoking patients.

The objectives of the study were represented by:

- Identification of smokers' consumption behaviour: type of consumer (occasional/frequent) and frequency of consumption
- Type of cigarettes used: conventional, other types (electronic cigarettes, heated tobacco)
- Degree of dependency – Fagerstrom test
- Identification and monitoring of chronic respiratory diseases
- Identification of respiratory complications
- Monitoring of the clinical-paraclinical status of patients:
    - ➔ Clinical aspects
    - ➔ Biological aspects
    - ➔ Pulmonary function tests: spirometry
    - ➔ Imaging investigations: chest X-ray
- Identifying smoking cessation behaviour
- Identifying the effectiveness of withdrawal methods

The results of the study highlighted the positive impact of smoking cessation on the evolution of both clinical and paraclinical parameters in a relatively short period of time. Also, the present study has demonstrated the effectiveness of the STOP SMOKING program and can be used as a starting point in the implementation of public health policies that bring back to the fore the awareness of the harmful effects of smoking and the need for smoking cessation.

Despite numerous studies on the harmful effects of smoking on the respiratory system, this doctoral thesis is a fresh topic as a result of maintaining an increased prevalence of smoking in the population. The results of the study highlight the need both to review and establish new lines in the monitoring of the smoking patient with the implementation of screening measures at the population level, as well as the need to refer the patient as early as possible to one of the STOP SMOKING centers for psychological counseling and the initiation of therapeutic measures where necessary.

1. General considerations regarding tobacco and its consumption

Smoking at first glance seems like a modern behavior, but archaeological evidence of tobacco use (*Nicotiana tabacum*) suggests centuries-old roots of this habit. (1)

The Mayan tribes began cultivating the tobacco plant 5000 years BC and was initially used by shamans in rituals, after which the custom was taken over by the other members of the tribe for recreational and medicinal purposes. (1) (2)

Tobacco consumption entered the European space in 1492, on the occasion of the return of the first explorers led by Columbus, and over time the navigators began trading with the natives. (1)

1.1 Epidemiological data

According to the World Health Organization (WHO), smoking causes around 8 million deaths annually, of which 7 million as a result of direct exposure and 1.2 million as a result of secondhand smoke (8). Tobacco consumption increases the risk of cardiovascular, respiratory and neoplastic diseases, currently representing the main preventable risk factor for death.

The WHO's annual reports have shown a downward trend in the prevalence of smoking worldwide as a result of the adoption of MPOWER (Monitor, Protect, Offer, Warn, Enforce, Raise) measures that support the protection of the general population by promoting campaigns on quitting tobacco, increasing excise duties, prohibiting advertising promotion and the consumption of tobacco products in public spaces. (9) As a result of the implemented measures, there has been a decrease in the prevalence of tobacco use worldwide in the general population in recent years from 23,6 % (38,6 % in men, 8,5 % in women) in 2018 to 22,6 % (36,7 % in men and 7,8 % in women) in 2020. There was also a decrease in the consumption of conventional cigarettes from 16.1% (27.5% in men, 4.8% in women) in 2018 to 15.5% (26.4% men, 4.6% women) in 2020. (10) (11)

At a European level, smoking continues to be a public health matter, reflected in the high rates of tobacco use, which add up to around 28% compared to 21% worldwide. (12)

Estimates of tobacco consumption in Romania vary greatly depending on the variables used in the epidemiological survey. Tobacco consumption increased significantly in the first part of the post-communist period, from a rate of 25.9% in 1989 to 28% in 1994, with a worrying rate of increase in consumption among the female population from 11.3% in 1989 to 15.2% in 1994(12). Between 1990 and 2019, an estimate of prevalence showed a decrease in tobacco use in the male population by about 18.9% while increasing the prevalence in women by 8.91%. (13)

2. Personal Contributions

2.1 Study incentive

The motivation to choose this research topic came naturally, from a personal interest in the field of tobacco, as a result of the observation already quantified in the specialized works of the effects of smoking on the respiratory system. However, we wanted to emphasize that the STOP SMOKING program can save lives and that it is never too late for a patient to initiate cessation measures. I found out for the first time about the existence of anti-smoking programs in my time as a medical intern and I wanted to deepen the subject in the field of research, and

shortly after the end of my internship I requested my enrollment in the doctoral school to the doctoral coordinator. Subsequently, the interest was amplified when I became coordinator of the Subprogram for Combating and Preventing Tobacco Consumption (STOP FUMAT) within the "Marius Nasta" Institute of Pneumophthysiology in Bucharest.

The results of our study quantify the importance of all stages in increasing the success rate of the program through psychological counseling services that are of equal importance to treatment measures. Most of the time, adjacent to the main purpose of inducing withdrawal, we add another secondary one, but perhaps equally important, namely the awareness of the true dangers associated with consumption so that the patient can make an assumed decision when he wants to expose himself to tobacco. (28)

3. Working hypothesis and general objectives

3.1 Working hypothesis

The purpose of this paper was to demonstrate the benefits of the STOP SMOKING program by following a group of patients for 6 months in whom withdrawal measures were implemented following psychological counseling and nicotine replacement treatment/nicotine cholinergic receptor antagonists.

The working hypothesis was represented by the clinical improvement affirmed by patients following the sessions of the STOP SMOKING program, implicitly the benefit on long-term health and quality of life. The constructive feedback we received during the project made us wonder if patients have a relatively short-term benefit on paraclinical parameters secondary to smoking cessation. To achieve this goal, follow-up of the clinical-paraclinical parameters was done to observe if there is a quantifiable benefit.

At this moment, the need to decrease the incidence and prevalence of smoking is a goal which is present in all guidelines that have smoking as a risk factor. There is a need to refresh the data available in Romania in order to increase the referral of smoking patients by other specialists in the field to anti-smoking centers and to carry out awareness campaigns on the effects of tobacco consumption on health.

3.2 General objectives

The present study is an original, prospective, non-interventional study that included 106 smoking patients who addressed the STOP SMOKING program at the Institute of Pneumophthysiology "Marius Nasta" Bucharest in 2022-2023 with a follow-up of 6 months. The objectives of this work were represented by:

- Determining the effectiveness of the STOP SMOKING program
- Updating the data available in Romania regarding epidemiological data on the present pathology of the smoking patient
- The impact of smoking on clinical aspects
- Identification of smokers' consumption behavior: type of user (occasional/frequent) and degree of dependence (Fagerstrom test)
- Type of smoked cigarettes: conventional, e-cigarettes/heated tobacco
- Monitoring the clinical-biological status of patients
- Blood tests: blood count, evaluation of inflammatory biomarkers specific to diseases due to smoking
- Simple pulmonary function tests (spirometry)
- Imaging tests (radiography/comparative analysis of X-rays through an AI - artificial intelligence - program)
- Identifying smoking cessation behavior – the approached method.

3.3 Ethical considerations

Patients included in the study signed an informed consent. The investigation algorithm and the period of time in which they will have to return for reassessment were explained to the patients. Patients were also informed about the time and number of appointments they will have to attend within the STOP SMOKING program.

The personal data was confidential and no patients' names or photographs were used without their consent. The study procedures were standard in the evaluation of a >35-year-old

smoking patient, consisting of blood tests, X-rays and spirometry. As these assessments should be routinely performed on a smoking patient, no additional costs were required.

Data collection

The follow-up data collected from each patient are the following:

- identification data, environment of origin
- smoking history: number of pack years, type of cigarettes used
- the motivation behind his decision to initiate withdrawal
- Fagerstrom dependency score
- mMRC dyspnea scale
- collecting medical records: anamnesis, medical documents provided by the patient or issued by other pulmonologists or other specialties
- paraclinical data: biological (blood count and inflammatory markers available), respiratory functional samples (spirometry), imaging (x-rays performed on patients at the "Marius Nasta" Institute of Pneumophthysiology in Bucharest): It should be noted that in the absence of the possibility of performing chest CT scans on all patients, the x-rays were subjected to AI software for more information.
- the patients' progression in terms of infectious events, hospitalizations during the period of the study

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 25 and Microsoft Office Excel/Word 2013. Quantitative variables were tested for normality using the Shapiro-Wilk test and were expressed using means and standard deviations or median with interpercentile ranges.

Independent quantitative variables with normal distribution were tested between groups using the Student T-Test/Welch T-Test (based on the equality of variances between groups observed using the Levene test) while independent quantitative variables with non-parametric distribution were tested between groups using the Mann-Whitney U. test (28)

Qualitative variables were expressed as absolute frequencies and percentages, and differences between groups were tested using the Fisher's Exact/Pearson Chi-Square test.

4. General research methodology

The study is a prospective one, carried out on 106 patients who addressed the STOP SMOKING program at the "Marius Nasta" Institute of Pulmonology in Bucharest within a 12 months timeframe, between 2022 and 2023.

4.1 Study protocol

For the elaboration of this paper we have used the following resources as tools as part of the study protocol:

- Analysis of the literature using representative works to which original studies, international guides, meta-analyses from databases such as PubMed, Elsevier, Springer, Google scholar, etc. were added
- Including people who applied to the STOP SMOKING service in the 2022-2023 duration in the study
- Selection of the group of patients according to the inclusion criteria
- Obtaining written consent from the patient to participate in the study by signing the informed consent
- Obtaining the agreement regarding the initiation of the study from the Ethics Commission of the "Marius Nasta" Institute of Pulmonology
- Application of the Fagerstrom questionnaire as well as motivations regarding smoking habits
- Patients were reassessed every 2 weeks for 3 months, then every 6 months
- Carrying out the clinical-paraclinical examination protocol at T0 and T6 respectively
- Data entry in an electronic format and further processing by means of statistical programs
- Interpreting data in the context of similar studies and drawing conclusions
- Publication of preliminary data in peer-reviewed journals to increase the visibility of results and application/use in other peer-reviewed studies

4.2 Characteristics of the subjects

The patients were all smokers at the beginning of the study when they addressed the STOP SMOKING center on their own initiative or following the recommendations received from the pulmonologist (either from the Marius Nasta Institute of Pulmonology or from other medical centers). All patients underwent psychological counseling and were evaluated by the pulmonologist based on a standard form that lead to the following data being analyzed: smoking habits (pack years number, type of cigarettes consumed, addiction score), after which a thorough anamnesis was performed, insisting on symptoms and the presence of possible comorbidities that associate smoking as a risk factor. At the initial visit, the following values were determined: blood count (noting the values of leukocytes, platelets) and inflammatory markers (ESR). Spirometry was also initially performed with the notation FEV1, FVC, IT, MEF50.

The selection of patients for this study was carried out according to the following **Inclusion criteria:**

- active smokers
- patients aged >35 years
- patients who have addressed the STOP SMOKING program
- patients who signed informed consent after having previously been explained the study protocol

Exclusion criteria

- patients aged <35 years
- pregnant or breastfeeding patients
- patients who did not sign the consent or had difficulties in understanding the study modality.

4.3 Parameters followed:

<u>Patient data</u>

The following were recorded: age (years), gender, background of origin, social category, income (minimum, medium, high), possible exposures to occupational pollutants.

Smoking

Information related to the pack-year index calculated by means of the calculation formula was noted: number of cigarettes smoked per day x number of years of consumption. The type of cigarettes smoked (conventional/electronic/heated tobacco), withdrawal motivation (health concerns, economic, peer pressure, religious, etc.), previous attempts to induce withdrawal, Fagerstrom score (Appendix 1) were also recorded. The interpretation of the Fagerstrom dependency score was performed as follows:

1 - 2 = low dependence

3 - 4 = addiction – low to moderate

5 - 7 = moderate dependence

>8 = increased dependence

The symptomatology was evaluated, anamnestic emphasis was placed on the general and respiratory symptomatology, if they existed.

- Dyspnea
- Cough
- Unintentional weight loss
- Asthenia

To classify the degree of dyspnea we used the mMRC scale - modified Medical Research Council Dyspnea Scale (annex 2) with grades from 0 to 4, on 5 steps with the following explanation:

0- dyspnea at high exertion

1- dyspnea when walking briskly or climbing a gentle slope

2- dyspnea that causes the patient to stop after a variable period of walking or that causes the patient to walk more slowly compared to a person of the same age

3- dyspnea that causes the patient to stop several times during exercise or after 100 meters

4- dyspnea on low exertion

Biological

Patients included in the study were biologically assessed by performing a set of available baseline tests that consisted of blood count and inflammatory marker collection. The determination was made at the time of the initial assessment, respectively at six months. For the present study, the following parameters were followed:

- Leukocytes
- Hemoglobin
- Platelets
- ESR

Simple Pulmonary Function Tests

Patients underwent spirometry at baseline by means of a spirograph, stopping the administration of short-acting bronchodilators 6 hours before determination, respectively 12 hours in the case of long-acting bronchodilators (where there was chronic administration). For the study, the spirometer available at the "Marius Nasta" Institute of Pulmonology in Bucharest was used, according to the criteria found in the ATS/ERS 2022 guideline, respecting the necessary parameters (acceptability, respectively repeatability) in order to be valid.

Following the spirometry, the following parameters were used in follow-up:

- Forced vital capacity (FVC) which designates the volume of air that the patient exhales forcibly after achieving a maximum inhalation. The correct value was the highest expressed in liters and percentage.

- The maximum expiring volume in the first second (FEVs) which designates the volume of air that the subject exhales in the first second, value expressed in liters and percentage. We also used the highest value we could get from the patient
- The Tiffneau Index (IT) which designates the ratio between FEVs and FVC. In the present study, the IT that was the one determined from the highest values of FEVs and FVCs.
- Maximum expiratory flow rate at 50% of vital capacity (**MEF50**). The value expressed in liters and percentage. In this study, the highest value was used.

Chest X-ray

As part of the protocol, patients underwent standard chest X-rays at baseline and after 6 months. The female patients were questioned about a possible pregnancy, and those who were pregnant were excluded from the study. The radiographies were interpreted by the physician and the results were divided into 7 categories of lesions for easier comparison of the data. The types of lesions that were described are:

- Hilums with increased projection area
- Accentuated interstitial lung pattern
- Possible bronchieectatic territories
- Hyperinflation
- Existing lung nodules/tumor formations
- Opacities as post-TB sequelae
- Pleurisy

In order to have an additional accuracy of the X-rays performed and for more information, the X-rays were comparatively subjected to the AI software Rayscape CXR, software that analyzes chest X-rays, detects 147 lung pathologies and generates auxiliary visualizations.

5. Acquired results

The increased prevalence of smoking and the increasing incidence of the consumption of conventional/electronic cigarettes among adolescents continue to arouse the interest of the scientific community in several directions: on the one hand, the impact of short- and long-term exposure to the compounds found in these products and their consequences on health, and on the other hand, finding the most effective ways to prevent consumption and to initiate withdrawal. Although the MPOWER measures adopted in 2007 in Romania have demonstrated a benefit in protecting the non-smoking population from passive smoking in public places as well as an awareness of the harmful effects of tobacco on health, the prevalence of smoking in our country remains high compared to the European Union average. Although official data indicate a worldwide decrease in the smoking rate, we cannot fail to note that in 2023, chronic obstructive pulmonary disease, a condition with a close etiological connection to smoking, became the third worldwide leading cause of death. (9) (14)

In this context, the relevance of the STOP SMOKING program remains high, and this paper wants to demonstrate the positive impact of withdrawal both from a clinical point of view but also, more importantly, considering the quality of life in patients with a long exposure time. Starting from this premise, we included patients aged >35 years in the study. It is known that lung function reaches functional maturity around the age of 25 and then begins a physiological functional decline, which is accelerated in smoking patients (>30 cigarettes/day) almost 14 times. (16)

If in the twentieth century, smoking was a habit associated with the male population, along with the emancipation of women, gradually, the incidence increased women, in our study the female prevalence of smoking being 45.3%. Women presented a more frequent association with lung diseases compared to the male population (89.6% vs. 70.7%), men having this association in a lower percentage (29.3% vs. 10.4%). The results are closely related to studies that have shown that women develop more severe COPD, with onset at a shorter time of exposure to smoking compared to men (26). However, women were more compliant in the STOP SMOKING program and had a higher withdrawal rate compared to men, At the end of the study, 58.3% were ex-smokers vs. 35.4% smokers, and the quit rate

was 6.28%. Comparatively, within the male population, 41.37% remained smokers at the end of the study, while 44.82% initiated withdrawal and 13.79% dropped out of the program.

In our group, the average age was 53.51 ± 9.72 years with a median of 53 years, most patients (59.43%) being in the 44 - 63 years age group. It was observed that the highest withdrawal rate was in the 64-73 age group, but without any significant difference between groups.

As for the environment of origin, there is a preponderance of the urban environment 86% vs 16% represented by the rural one. We found a higher dropout rate of the STOP SMOKING program in the case of the rural population, 20% vs 8.8% in the urban area, which can be explained by the difficulty of traveling long distances with a relatively high frequency to reach the maximum potential of the therapy. It is observed that the withdrawal rates versus smokers at 6 months in the case of the rural population are relatively equal compared to the urban area where the percentage of ex-smokers was higher (53.3%). These data support the need to facilitate the accessibility of the STOP SMOKING program in rural areas by implementing public health policies aimed at creating new centers in disadvantaged areas.

Despite the fact that smoking was introduced in Europe as a habit of the wealthy, gradually, along with the industrialization process, smoking became accessible to the lower social classes. In recent years we have witnessed a decrease in the prevalence of smoking in developed countries and an increase in consumption in developing and underdeveloped countries. (15) Smoking patients who applied to the STOP SMOKING program declared that they were employed (74%) vs retired (26%). In the study group, most patients declared that they had a minimum income (59.7%), which was considered a risk factor in initiating and maintaining smoking. Correlating social and psychological factors, we understand the importance of counseling sessions for the program's success. In the medical literature, it is well documented that low social status is a risk factor for continuing to smoke. Also, the low level of education, psychiatric disorders, belonging to disadvantaged categories are risk factors for initiating and maintaining smoking. (17) Although at first glance an optimal solution for initiating withdrawal would be to provide financial incentives to low-income people, a study in Denmark found that high-income people had a higher benefit. (19)

It was found that the Fagerstrom dependency score was in the spectrum of increased values with a mean value of 6.82 ± 1.84 points, the median being 7 points. Also, 64.15% of the patients had scores higher than 6, which places the studied group in the category of medium to high dependence. We can establish a correlation between the Fagerstrom dependency score and the number of pack-years, with 75% of patients reporting a number >20 PY. Data obtained from the study group demonstrated that patients with a high addiction score had a statistically significant increased number of PYs ($p<0.001$, $R= 0.785$). These results, together with the fact that patients with a high addiction score had lower adherence rates, are arguments for the implementation of higher therapies within the STOP SMOKING program for those with a high Fagerstrom score. The Fagerstrom score is a more accurate indicator of the onset of COPD compared to the PY number, and there are studies that demonstrate that the dependency score together with age could establish the probability of lung decline and COPD occurrence. (26)

It is worth noting that in our study only 14.2% of patients were diagnosed or reported the presence of a diagnosis in the respiratory sphere prior to the STOP SMOKING program. Most patients were diagnosed with lung diseases within the anti-smoking program (52.8%) or the time of presentation coincided with a hospitalization for a respiratory pathology. These figures demonstrate the importance of addressing smoking patients, aged >35 years, within pulmonology services, especially immediately after the onset of symptoms. The premise from which we started is represented by the fact that patients with respiratory pathology: broncho-pulmonary neoplasm and COPD are asymptomatic in the early stages of the disease, which prevents the initiation of specialized treatment and delays the need for withdrawal. Despite the fact that excluding a lung disease from screening can create a false sense of security in the patient, which can interfere with the initiation and continuation of withdrawal, studies say that patients are more likely to quit smoking following an unfortunate diagnosis of lung disease. Therefore, the pulmonologist has a very important role in the patient's decision to initiate withdrawal, and discussions about the need for the impact of smoking on health can also be made outside of a tobacco program. (26)

E-cigarettes have become popular in the last decade as a result of intense campaigns to promote consumption as a modern, less harmful variant of conventional cigarettes. Of the

patients who were included in the study, 93.4% said they smoke conventional cigarettes, while 6.6% use electronic devices. The data from our study are similar to those in the literature for the age group studied, observing that the incidence of consumption decreases as age progresses. The prevalence of increased use of electronic devices in the young adult and adolescent population reflects several directions. On the one hand, the desire of the younger generation to break away from a habit associated with the last century that is considered harmful, and on the other hand, the use of a variant that is considered safe by a large part of consumers. Although some of the patients said that they tried to switch from the conventional cigarette to the electronic version, they reported the failure as a result of not obtaining the sensation experienced with the cigarette. This reality is reflected by the fact that young adults and adolescents, most of whom were previously nicotine-naïve, are predominantly attracted to the flavors that make up these electronic cigarettes, and the lower amount of nicotine released at a low pH is not an impediment, while heavy smokers are "accustomed" to denser smoke and a higher amount of nicotine released. (18) .

Nicotine acting on learning and reward centers has a very strong addictive effect, which makes it a particularly potent drug. In the withdrawal process, the motivation to quit smoking has a special role because it represents the foundation on which both the psychological counseling process and the pulmonary examinations are built. In the study group, patients expressed concern about the harmful effects of smoking on health (93.4%), which correlates with the abundance of symptoms experienced (79.2%). Starting from this foundation, we can guess the role of the pulmonologist in explaining as clearly as possible the way in which smoking influences the appearance and maintenance of these symptoms. Patients diagnosed with a respiratory condition often have uncertainties and it is vital that a large part of the examination focuses on the certainty that the patient has a clear understanding of how smoking influences the onset and potential progress of the disease, as well as the benefits of withdrawal in the long term.

It is worth noting in our study that although 59.7% of patients declared that they have a minimum income, only 33% mentioned financial reasons as one of the aspects for which they want to initiate withdrawal.

Regarding the type of intervention during smoking cessation, all patients benefited from psychological counseling and pulmonary examination, following which they received the indication of specific withdrawal medication, either with varenicline (if the dependence score was high) 0.5mg/day for the first 3 days, then 0.5mg twice/day for another 4 days, then increasing the dose to 1mg twice/day for another 1 week, or with nicotine substitutes in the form of 25mg/16 hour patches (in those with a lower degree of dependence) with the possibility of increasing the dose by 1/2 patch during the night in those with a higher degree of dependence and who did not want drug therapy. The conclusion was that at the 6-month evaluation, the withdrawal abandonment rate was higher in the case of those who started drug therapy and we could not continue them due to their lack caused by the withdrawal of the product from commerce.

Every 2 weeks, patients were evaluated and the evaluation form of possible side effects was completed, up to a maximum of 3 months of treatment when patients were either considered ex-smokers or abandoned the fight against withdrawal.

In order to evaluate the effectiveness of the STOP SMOKING program, we reassessed the patients' smoking status after more than 6 months. We concluded that at the end of the study, 35.80% of patients said they were former smokers, while 12.3% had relapsed. Although the purpose of the study was not specifically to document the reasons why patients decided to resume smoking, we noticed that patients reported experiences that are almost overlapping with other studies that stated entourage pressure or the inability to manage stressful situations. The results of our study are similar to those in the literature that documented that if the patient maintains withdrawal for more than 6 months, the chance of success on the long-term increases by 70%. (35)

In our group, patients with respiratory diseases accounted for 79.2% of the total group. The most common diagnosed pathology was COPD (35.8%), which can be explained by the age of inclusion of >35 years, the increased exposure time (75% of patients >20 PY) and the moderate-high Fagerstrom dependence score. The importance of smoking cessation in this category of patients is reinforced both by the GOLD guideline and by other studies that have demonstrated a lower mortality rate at 14.5 years in patients with mild COPD for whom early cessation measures have been initiated. Quitting smoking becomes the most important step in

reducing mortality and decreasing the progression of lung function impairment. As a result of the fact that a smoker is up to 22% prone to developing COPD, it becomes imperative to identify if there are signs of pre-COPD in smoking patients. Currently, the notion of pre-COPD defines the presence of specific symptoms (chronic cough with mucoid expectoration) associated with the main risk factor represented by smoking, without a visible obstructive spirometric limitation. (26). In the study group, 6.6% of patients were diagnosed with chronic bronchitis without a spirometrically documented impairment of the FEV1/CV ratio.

During the study, a significant part of the patients developed infectious respiratory symptoms (31.1%), 22.6% requiring antibiotic treatment. Smoking is a risk factor developing respiratory infections as a result of inducing a phenomenon of local immunodeficiency, respectively structural and functional alterations of the respiratory defense barriers. The COVID-19 pandemic was a time when the importance of respiratory health and the influence of smoking on evolution and mortality became globally aware. Meta-analyses concluded that smoking increases the risk of mortality, doubles the cases of community-acquired pneumonia and, as mentioned in the previous chapter, is involved in the process of reactivation of the *Mycobacterium Tuberculosis* (7.5% cases in our study).

Although until recently the evidence on the link between smoking and bronchiectasis was relatively limited, the occurrence of OCD (overlap syndrome COPD – bronchiectasis) was the first link that was established with smoking. Typically, bronchiectasis is not described as having smoking as a causative agent, but a 2022 study that observed a significant group of patients for over 7.4 years showed a stronger association between smoking and the occurrence of bronchiectasis in women vs men, in the young vs. elderly population, overweight vs. underweight population, the risk increasing at an exposure >10 PY. (36) Our study highlighted the presence of bronchiectasias in 22.6% of patients in the group.

As for the presence of comorbidities related to smoking, the rate in our group was 28.3%. Hypertension was by far the most common cardiovascular comorbidity (22.6%). High blood pressure along with smoking are major cardiovascular risk factors for acute coronary syndrome. It should be noted that 6.6% of patients had a history of ischemic heart disease, and some of them were referred to the STOP SMOKING program by their cardiologists. Smoking

cessation is an important stage in patients with cardiovascular risk factors because smoking increases the risk of ischemic phenomena by inducing a local prooxidant effect that will lead to endothelial dysfunction, as well as to a decrease in nitric oxide levels. Smoking also stimulates the formation of atheroma plaque and accelerates the thrombotic phenomenon. (37)

A study by Tomioka in 2020, which followed a batch of 876 smokers included in a withdrawal program, showed similar results to our study regarding the prevalence of comorbidities: 23.9% of patients were diagnosed with COPD, 15.3% with asthma, 11.6% with neoplasm, while 22.2% had hypertension, and 19.8% had heart disease. (39)

In the studied group, a chest X-ray was performed at T0 for each patient to quantify any present changes. It was observed that 66.7% of the patients had radiological changes, 28.3% of them being referred to a CT scan. The most frequently found change was represented by the interstitial pattern accentuated in a proportion of 36.3%, a result that we frequently correlate with smoking status. Approximately 18.6% of the patients had changes that were compatible with the diagnosis of bronchiectasis, a hypothesis that was confirmed after the continuation of the diagnostic algorithm with a chest CT scan. Since it was not possible to perform the CT scan on all patients for financial reasons, we resorted to comparative X-ray analysis through an artificial intelligence software, Rayscape CXR, a software that analyzes chest X-rays, detects 147 lung pathologies and generates auxiliary visualizations. From this comparative analysis, it resulted that the lesions were approximately similar to the mention that in some interstitial changes, the lesion score was high, which could raise the suspicion of interstitial involvement of the diffuse interstitial lung disease, which brings more information and an earlier diagnosis.

The use of artificial intelligence techniques has the ability to improve the effectiveness of chest X-ray in the context of screening smoking patients for the detection of conditions such as bronchopulmonary neoplasm, tuberculosis or diffuse interstitial lung diseases. This is achieved by using AI algorithms that analyze CRX images to detect abnormalities that could suggest the existence of lung damage, which also happened for some of the patients in our study. AI products generate an abnormality score which can be used to indicate the possible existence of lesions and require additional diagnostic tests, when compared to a certain threshold. (33) (34)

Regarding the frequency of hospitalizations, in the studied group it was demonstrated that the presence of signs of hyperinflation on chest X-ray was a predictive factor for hospitalization with a rate of 18.6% vs. 5.1%. Hospitalizations within the Institute were in the context of infectious exacerbations that negatively impact both the patient's quality of life and increase the rate of progression of the decline of lung function and implicitly the death rate.

In our group of patients, the value of leukocytes was observed at the time of the initial evaluation and at 6 months. The determination of the leukocyte value in the study started from the premise that decreases in their values following smoking cessation are described in the literature. During the initial evaluation, the values of the 2 lots were not very different and implicitly they were statistically significant. At the 6-month evaluation, although there was no statistically significant difference, there is a slight downward trend in the values in the case of the ex-smoker population. A study conducted in 2019 showed a 19% change in leukocyte value between the smoking and former smoking population, with the largest decreases during the withdrawal period being at less than 1 year. (204) The study observed that the mean leukocyte value in the non-smoking population at 6 months was 8,090/uL vs 7,250/uL at the 6-month assessment, although there was a downward trend in the smoking population as well.

Platelet values were also considered at baseline and at 6 months. The involvement of smoking in the thrombotic phenomenon by increasing aggregation is well documented in the literature, with significantly more small platelet aggregates being found in smokers' plasma compared to the population without exposure. (205) At the time of the initial assessment, platelet values were relatively equal between batch I and II, which demonstrated the homogeneity of the included batch. There were no significant changes between the two batches at the 6-month assessment.

Erythrocyte sedimentation rate (ESR) was a parameter that was included in our study, being determined at baseline and at T6. The hypothesis from which we started was represented by a study that showed that the value of the ESR was higher in smokers vs non-smokers and we wanted to observe if there is a change between the values from the initial assessment and the ones after 6 months. Although no statistically significant values were obtained, it is observed that the patients in the study group have a mean ESR value higher than 17.19 ±

18.78, with a median of 12 (7-22) compared to the value obtained by the cited study of 11.74 mm/h (38)

Smoking has a modifying effect on the production of the erythrocyte series by increasing the COHb fraction and implicitly obtaining a hypoxic effect. Although Tiel hypothesized that in order to return to normal, all blood cell values must pass about 5 years of withdrawal, we still followed up to see if the withdrawal impacted hemoglobin values. The evaluation carried out at the time of inclusion did not demonstrate significant differences between the groups studied: 13.48 mg/dL in batch II versus 13.87 mg/dL in batch I. However, at 6 months, a statistically significant trend towards a decrease was observed in the group of ex-smokers, which demonstrates an improvement in the hypoxic state induced by tobacco consumption.

By performing spirometry in the patients included in the group, we aimed to quantify lung function at the time of the initial evaluation and at 6 months. Over the course of the study, however, we noticed that patients became interested in whether withdrawal improved their lung function. Spirometry is not currently included in the protocol of the national STOP SMOKING program as a stage in the withdrawal algorithm. We believe that there would be advantages of introducing spirometry as a stage in the STOP SMOKING program. One of the advantages would be the fact that we could carry out a screening campaign for the smoking population at risk of developing obstructive pulmonary diseases, especially in patients >35 years old who, in the absence of persistent symptoms or symptoms that affect their quality of life, would not address a pulmonology service. Thus, patients diagnosed early could benefit from treatment, from measures to prevent exacerbations by carrying out the vaccination schedule and perhaps the moment of diagnosis would be in itself an impulse for withdrawal. Also, the improved spirometric values at the evaluation in the end of the STOP SMOKING program would be an objective proof of the positive impact on lung function as a result of smoking cessation for both the doctor and especially the patient. The downside of performing spirometry within the STOP SMOKING program is that obtaining normal values could create a false sense of security related to tobacco consumption that could decrease the chance of maintaining smoking cessation, especially in the case of the young population, without comorbidities. A review of the literature by Westerdahl concluded that performing spirometry

as part of the withdrawal program provided a benefit in maintaining withdrawal compared to the population that received only treatment and counseling. (39) We believe that further pilot studies would be needed to implement spirometry as part of the STOP SMOKING algorithm in order to directly quantify whether there is a benefit.

All participants underwent spirometry at the beginning of the study, in which the mainly quantified values were FEV1, CV, FEV1/CV, MEF 50. At the initial evaluation, we observed that the population was homogeneous without statistically significant changes between the studied groups. The slightly higher values of functional parameters within the non-smoking population at the time of inclusion were explained by the lower Fagerstrom addiction score in the non-smoking group.

Smoking impacts lung function by reducing FEV1 as a result of the installed obstructive syndrome. The decline of FEV1 is an aspect that the pulmonologist monitors in smoking patients due to its importance in the diagnosis of COPD and the fact that it represents an independent predictor in morbidity and mortality due to ischemic cardiovascular events (208). The FEV1 values at the time of inclusion were not significantly different between the two lots, with an average value in Batch I of 79.87 ± 24.56, respectively 82.81 ± 23.2 in Batch II, with an average value of 81.29 ± 23.85%. At the 6-month evaluation, however, we noticed an improvement in FEV1 values in batch II with a value of 85 ± 20.18%, while in batch I the progression was negative 76.2 ± 23.98. Although there is only a tendency towards statistical significance towards lower FEV1 values in smoking patients, we consider it to be a sufficient argument to demonstrate the benefit of withdrawal. Following the results obtained, we consulted the literature to compare its data with the data obtained from the study. According to Tracas, the statistically significant benefits of improving lung function obtained after smoking cessation are in the age groups of <40 years, 41-50, and 51-60 years, while continuing smoking accelerates the sharp decline in the age groups of 41-50, 51-60, and > 60 years. (42)

The vital capacity (VC) analysis at the time of the initial assessment did not reveal differences in the values between the two lots at the time of inclusion. During the 6-month evaluation, it was observed that the CV values in the smoking population were significantly lower compared to the non-smoking group 87.2 ± 19.79 % vs 94.67 ± 15.21%, with an improvement in the vital capacity in the second group. Smoking influences vital capacity by

impacting the expansion capacity of the chest by affecting muscle function as a result of increased levels of local free radicals. Studies describe CV impairment in the smoking vs non-smoking population in the absence of significant changes in FEV1 from adolescence onwards. (209) Improvements in FVC have been reported in the literature at 1 month after withdrawal with an increase from 94% (89-108%) to 98% (92-110%) $p<0.08$. (210)

Regarding the values of the Tiffeneau index (FEV1/CV), both at the time of inclusion and at the evaluation performed at 6 months there were no statistically significant differences between the lots. We mention that it was observed that the average values of the index were close to 70% in both batches, with a negative trend in the smoking population.

MEF 50 values were monitored in patients included in the study with no significant differences observed between the study groups at the time of initial evaluation. At the subsequent evaluation, significant differences were observed between the two batches with a negative correlation in the case of patients who continued consumption. Although MEF 50 values are not specific in relation to smoking status, it has been shown that the values are significantly decreased in patients with tobacco exposure.

Regarding the influence of the number of pack-years on the parameters determined during spirometry, a negative correlation was found between the high degree of exposure (>20 pack-years) and lung function. Regarding the Tiffeneau index (FEV1/CV), we note that the mean value in those with exposure >20PA was significantly lower (71.77 ± 8.38%) versus (77.39 ± 8.17%). Although in the literature the decline in lung function is considered to be influenced more by age and less by the degree of exposure, in our study we obtained significantly lower values regardless of age. The FEV1 values between the two groups (<20 PA) and (>20 PA) were very different with a predominance in the normal spectrum in those with exposure <20 PA (96.33 ± 21.93% with a median of 100.95%). Also, the smoking status for >20 PY influenced the vital capacity, determining a significant decrease in the values in case of prolonged exposure and/or in high quantities, with an average of 88.81 ± 18.67% versus 101.01 ± 17.88%. Based on these data, we can conclude that smoking significantly influences the vital capacity, causing the restriction of lung function over time and implicitly a negative evolution of the case as a result of the limited possibilities of therapeutic intervention on this component.

Although in the studied group both FEV1 and CV were low in smoking patients with an exposure >20 PY, we observe that the values of the Tiffeneau index (FEV1/CV) are also low in the group with a higher degree of exposure, reaching a mean value (71.77 ± 8.38) almost compatible with the diagnosis of COPD according to the GOLD guideline versus patients with lower exposure (<20 BP) who obtained mean values of 77.39 ± 8.17%.

MEF50 is a parameter that designates the flow rate that the patient still has to expire from the moment the CV is at its half. The usefulness in the diagnosis of distal obstructive syndrome, in the absence of a diagnosis of COPD, is currently under research. However, one study showed that patients with MEF50 with pathological spectrum values had higher tobacco exposures, more frequent symptoms, used bronchodilator medication more frequently, had a 2 times higher risk of cardiac decompensation, and had more frequent hospitalizations for respiratory complications. (40) In the study group, patients with high smoking exposure had an average of MEF50 values in the pathological sphere with a mean of 62.41 ± 23.97% and a median of 66.05 (46.1-78.25) which is statistically significantly lower compared to the control group 84.09 ± 19.08%.

We observed that in the study group, patients frequently reported respiratory symptoms, with 71.7% reporting one or multiple symptoms. We note the correlation that is established between the increased reporting of symptoms and the main motivation for initiating withdrawal declared by patients, represented by health concerns. The increased frequency of symptoms can be explained by the >35 years age of inclusion in the group in conjunction with the time and degree of exposure, which together determine changes in the pulmonary architecture compatible with the development of respiratory symptoms.

Dyspnea was a frequently described symptom, greatly impacting the quality of life of patients. In our study, 50.9% of patients reported the presence of dyspnea, which we quantified using the mMRC scale, obtaining a mean batch score of 1.68 ± 1.35. From a paraclinical point of view, we studied whether the presence of dyspnea impacted the mean hemoglobin value, but without obtaining significant differences between batches. Interestingly, at the 6-month evaluation, there was a statistically significant difference between the hemoglobin values of patients who complained of dyspnea and those without dyspnea. The explanations for this phenomenon could represent: the smoking cessation that patients initiated, the decrease in

consumption for some patients declared smokers and the finding of improvement in the mMRC score in patients who declared the persistence of dyspnea. The basis of these statements can be supported both on the clinical criterion, our study demonstrating a 6% reduction in those who reported dyspnea at baseline with a prevalence of low mMRC scores in the non-smoking population, and paraclinically through the values obtained in the spirometry. Although the statistical significance was maintained in the case of patients who presented dyspnea versus the control group in terms of spirometric values at the time of the initial evaluation versus at 6 months, we observe an improvement at T6 in the values of all the parameters studied. A study that followed the impact of smoking cessation on respiratory symptoms showed a persistence of dyspnea prevalence in the study group regardless of smoking status. (41)

Cough was the most common symptom reported by patients (51.9%), being described in different forms (irritative/mucoid/mucopurulent). It is worth noting that at the beginning of the study, if 63% of the patients who reported the presence of cough were from group II, at the evaluation at T6 the ratio changes with a reporting of severe cough in group I. The data obtained are consistent with specialized studies that reported an improvement in the reporting of cough in the group of those who underwent withdrawal compared to dyspnea, whose reporting rate remained approximately identical. (213) Another observation to be taken into account in the management of a patient with cough is the fact that this category of patients had significantly more severe pulmonary function (FEV1, FEV1/CV/MEF50) compared to the group without symptoms.

6. Conclusions and personal contributions

1. The smoking patients who attended the smoking cessation initiation sessions within the STOP SMOKING program of the "Marius Nasta" Institute of Pneumophthysiology in Bucharest were mainly represented by men, but at the 6-month evaluation, the abstinence rates were higher in the female group.

2. Patients in the study group were more frequently diagnosed with acute and/or chronic lung diseases compared to the male population.

3. Most of the patients included in the study came from urban areas and declared a minimum income; However, we have observed a comparatively higher dropout rate in rural areas and a lower withdrawal rate among those from vulnerable social categories, this aspect contributing to the need to facilitate the accessibility of tobacco prevention and control programs in rural areas and by implementing new public health strategies aimed at creating new such centers in disadvantaged areas.

4. The average Fagerstrom dependence score of the studied group was moderate, which could be positively correlated with the high number of pack-years (>20), negatively with the number of previous withdrawal induction attempts and the number of presentations within the STOP SMOKING program.

5. Beneficiaries of the STOP SMOKING program were diagnosed with lung conditions more frequently during the study compared to the rate of those who were diagnosed before the program.

6. The motivation for quitting smoking was mainly represented by concern about the impact of tobacco on health, which was positively correlated with the high rate of lung diseases and respiratory symptoms.

7. At the 6-month evaluation, the rate of weaned patients was higher compared to those who remained smokers after going through the STOP SMOKING program; However, at the 6>month evaluation, the proportions between smokers and non-smokers were relatively equal, with some ex-smokers reporting relapses, this aspect also being due to the withdrawal from commerce of adjuvant drugs. I mention that this lead to the modification of the study compared to the initial plan, as we could no longer prove the effectiveness of nicotine withdrawal therapies, making a comparison between patients who received medication with pills (varenicline) and those who received patches, by this mention reminding us of the strong need for currently available medication in the anti-smoking centers at a national level.

8. The patients included in the program were most frequently diagnosed with COPD, respectively respiratory infectious diseases, with a positive correlation between both all respiratory diseases and the intercurrent processes with the need to administer antibiotic treatment.

9. In the study group, one third of the patients had comorbidities with proven links to smoking in the literature, hypertension being the most common one.

10.There was no statistically significant difference between the two groups regarding the biological parameters studied both at the time of inclusion in the study and at the evaluation performed at 6 months, other than the statistically significantly higher values of hemoglobin at T6 in the case of the smokers group.

11. At the time of inclusion, the parameters observed in the spirometry tests were not statistically significantly different between the groups that were studied. At the 6 month evaluation, a statistically significant improvement in FEV1, CV and MEF50 values was observed in the group of former smokers compared to the control group.

12. Most of the patients in the study group reported the presence of respiratory symptoms on a routine basis, with a predominance in terms of the frequency of cough and dyspnea. We note that the prevalence of dyspnea in the study group remained relatively constant throughout the study, however with an improvement in the mMRC scale in the case of ex-smokers. Also, patients who described dyspnea had impaired lung function compared to the control group.

13. Cough was the most common symptom described in the study, which was negatively correlated with altered lung function, with patients being more frequently diagnosed with obstructive syndrome compared to the control group.

14. Most patients had radiological changes, especially pronounced interstitial pattern and bronchiectic territories, however, radiological changes of hyperinflation predicted the increased rate of hospitalization during the study period. From the comparative analysis with the AI software, it resulted that the lesions were approximately similar to the mention that in some interstitial type changes, the lesion score was high, which could raise the suspicion of interstitial involvement such as diffuse interstitial lung diseases, this bringing more information and an earlier diagnosis.

In conclusion, the use of artificial intelligence techniques has the ability to improve the effectiveness of chest X-ray in the context of screening smoking patients for the detection of

conditions such as bronchopulmonary neoplasm, tuberculosis or diffuse interstitial lung diseases. This is achieved by using AI algorithms that analyze CRX images to detect abnormalities that could suggest the existence of lung injury, which also happened for some of the patients in our study.

7.Limitations of the study

- The lack of possibility to administer oral medication to all patients who needed it, this leading to the modification of the study as opposed to the initial plan, since we could no longer prove the effectiveness of nicotine withdrawal therapies, making a comparison between patients who received medication with pills (varenicline) and those who received patches, by this mention reminding us of the strong need for currently available medication in the anti-smoking centers at a national level and at the same time by appealing to the higher competent authorities capable of changing these shortcomings of the anti-smoking programs.
- The lack of a minimum investigations package during the initial examination available for patients who address the anti-smoking center, since directing them to a hospital examination according to an appointment results in the abandonment of the smoking patient of further investigations.
- The emergence of the COVID-19 Pandemic and implicitly the impossibility of scheduling patients and creating working groups for them, meant a decrease in the program's patients addressability.

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ANNEXES

Faberstrom Nicotine Dependence Scale

1. How soon after you wake up do you smoke your first cigarette?
   - Within 5 minutes (3 points)
   - 5 to 30 minutes (2 points)
   - 31 to 60 minutes (1 point)
   - After 60 minutes (0 points)
2. Do you find it difficult not to smoke in places where you shouldn't, such as in church or school, in a movie, at the library, on a bus, in court or in a hospital?
   - Yes (1 point)
   - No (0 points)
3. Which cigarette would you most hate to give up; which cigarette do you treasure the most?
   - The first one in the morning (1 point)
   - Any other one (0 points)
4. 4. How many cigarettes do you smoke each day?
   - 10 or fewer (0 points)
   - 11 to 20 (1 point)
   - 21 to 30 (2 points)
   - 31 or more (3 points)
5. 5. Do you smoke more during the first few hours after waking up than during the rest of the day?
   - Yes (1 point)
   - No (0 points)
6. 6. Do you still smoke if you are so sick that you are in bed most of the day or if you have a cold or the flu and have trouble breathing?
   - Yes (1 point)
   - No (0 points)

Scoring: 7–10 points = highly dependent; 4–6 points = moderately dependent; less than 4 points = minimally dependent.

mMRC Scale

Grade 0	I have dyspnea only with intense exertion
Grade 1	I have dyspnea when walking at a steady pace or when climbing a slope
Grade 2	Dyspnea prevents walking at the same pace as an individual of the same age or imposes stops on flat ground
Grade 3	I have severe shortness of breath and have to stop after less than 100 meters or a few minutes of walking on flat ground
Grade 4	I have dyspnea when dressing and that prevents me from leaving the house