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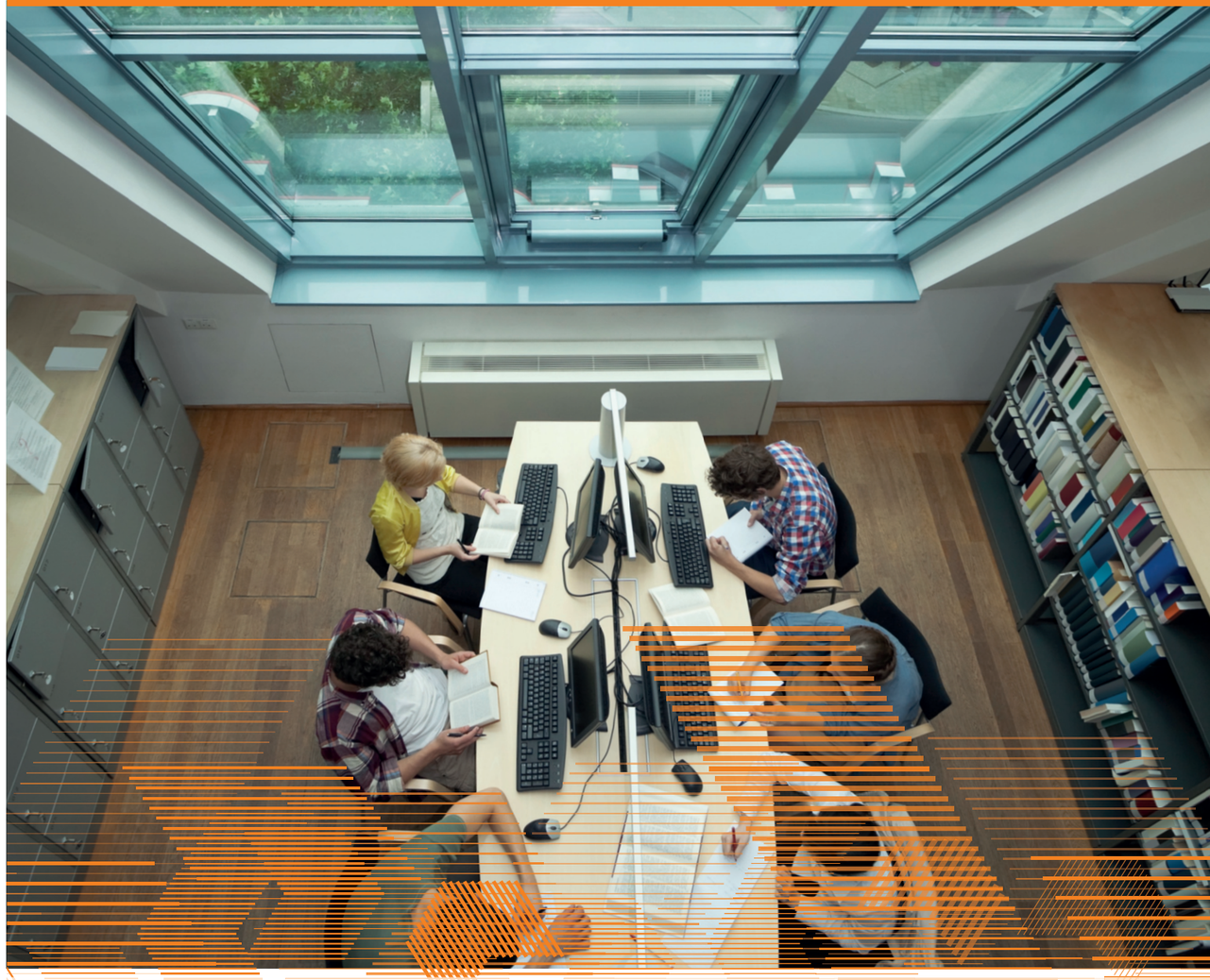

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Indexed in: Science Citation Index Expanded (SCIE), Journal of Citation Reports (JCR), Index Medicus/MEDLINE, Scopus, EMBASE/Excerpt Medica

ISSN 2531-0437 (online)

Register 122.190 of Gabinete para os Meios de Comunicação Social

Printed in Spain

Printed in acid free paper

Legal deposit: B-20.760-2019

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IN MEMORIAM

In memoriam of Jordi Mancebo

It is with a profound feeling of loss that Portuguese Intensivists mourn the loss of Dr. Jordi Mancebo.

Director of the Intensive Care Department at the Hospital of Santa Creu and Sant Pau in Barcelona, Cataluña, he was an associate professor at Universitat Autonoma de Barcelona and visiting professor at the Mayo Clinic, Denver Health Medical Center, Loyola University of Chicago, at the National Institutes of Health Bethesda, Yale University School of Medicine, Mc Gill University in Montreal and the University of Toronto among others. As a result he did multiple research stints at the Service de Réanimation Médicale at the Centre Hospitalier Universitaire Henri Mondor in Créteil and at the Centre Hospitalier Université in Montréal. He was Honorary Member of the European Society of Intensive Care Medicine due to his contributions to the field and to the Society.

A prolific researcher, author, and teacher, he was responsible for teaching many of us in his preferred fields of respiratory failure, mechanical ventilation and ventilator weaning.

Deeply involved with other Scientific Societies, such as the European Society of Intensive Care Medicine and the Pan-American and Iberian Federation of Intensive and Critical Care medicine, Jordi was also a close friend of the Portuguese Society of Intensive Care Medicine, both directly and indirectly, either as a frequent speaker or teacher at our events or in receiving many of us in his department to learn.

From the late 90s he was deeply involved in the Mediterranean meetings on Non-Invasive Ventilation (NIV) which were organized in Italy, Spain, Portugal and France. In this forum both intensivists and pulmonologists from each county joined forces to discuss, on a yearly basis, the state of the art of NIV, of which Jordi was a great enthusiast and pioneer.

Kind, modest, "friend of his friend", highly intelligent, his qualities made him the role-model for many young (and not-so-young) intensivists. A standard too high for many of us.

Now, though he is no longer physically among us, I am sure that he will be always be alive in our memories, and he will often be with us when we are faced with difficult patients.Fins sempre, Jordi.

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Received 8 August 2022; Accepted 9 August 2022
Available online 7 October 2022

https://doi.org/10.1016/j.pulmoe.2022.08.002
2531-0437/

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PULMONOLOGY

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EDITORIAL

Tele-consultation: A new promised land?

KEYWORDS
Chronic respiratory disease;
Tele-medicine;
Tele-consultation;
Position paper

The Covid19 pandemic has been responsible for an unprecedented pause in the out-patient respiratory practice due to the clinical emergency. Therefore, the respiratory community has been forced to find alternative but equally effective ways to continue monitoring individuals with respiratory diseases.[1,2] A focus on tele-medicine was already present before the pandemic.[3] However, the pandemic has given the right incentive to overcome some logistic and practical issues and to rapidly implement the available technology to support this emergent field.[4] Tele-medicine represents the '*Distribution of health services in conditions where distance is a critical factor, by health care providers that use information and communication technologies (ICT) to exchange information useful for diagnosis where doctor is able to perform diagnosis at distance*'.[5]

In this issue of Pulmonology, the position paper of the Portuguese Pulmonology Society on the basis of available literature provides guidance on tele-consultation practices for Pulmonologists.[6] Tele-consultation programs provide consultation from remote distance when a respiratory assessment or support is already in place. Many studies focused on the feasibility of remote monitoring in several respiratory conditions indicating that it is effective, safe, cost efficient, and well tolerated by patients.[7] Indeed, among the several advantages encountered in using tele-consultation, the most important are the facilitated access to specialist consultation, the improved comfort in particular for people with physical disabilities, the reduced infection risks, and travelling expenses.[8]

There are still some legal and organizational issues that need to be clarified and detailed.[9] First, tele-consultation should be provided through hospital software which are set up in place to guarantee security, data privacy and confidentiality of all the information gathered.[9] Second, there are many barriers to teleconsultation such as low education, demographics (e.g., older individuals), modest socioeconomic conditions with no access or confidence with technology, unavailable high speed internet connection, cognitive, motor, visual, phonation and speech abilities, hospital and patient costs to ensure the dedicated personnel and right equipment.[10,11] Lastly, many countries have not yet provided any dedicated rule or law to regulate privacy, data security, legal and economic issues related to telemedicine.[9]

In order to set up an effective respiratory tele-consultation lab, first, hospital dedicated rooms, PC and software for teleconsultation have to be set up to record and monitor all remote consultation provided. Second, all respiratory questionnaires usually used in clinical practice to check disease status and quality of life, as well as adherence to therapy or devices use, need to be available in the tele-consultation environment.[12,13] Third, all sensors used with miniaturised processors, body area networks, and wireless data transmission technologies allowing the assessment of physical, and physiological parameters have to be easily accessible via software connection in dedicated computers so to add these gathered information and to implement the effectiveness of teleconsultation.[4]

In the literature, the use of tele-consultation has been reported as useful in the management of chronic obstructive pulmonary disease, asthma, interstitial lung diseases, chronic respiratory failure, and home mechanical ventilation, among other clinical situations.[14]

In the position paper by Morais et al.,[6] the Portuguese respiratory physicians' college of experts once again highlights the importance of the tele-consultation and provides a checklist based on the specifics of each respiratory disease to better tailor tele-consultation. The authors advise that first there should be some general guidance on providing the best possible experience in not only technical effectiveness but also the correct suitability and patient selection. Before starting, the most important issues are: first, to guarantee the use of a secure platform provided by the hospital which complies with legal data protection requirements, privacy and a suitable physical, acoustic, and visual environment in

https://doi.org/10.1016/j.pulmoe.2022.08.008

dedicated rooms. Second, to ensure that the connection is working correctly to allow a two ways communication without technical problems. Third, to obtain verbal or written consent for the virtual consultation. Following these first steps, it appears clear that the referral needs to be appropriate. All respiratory tele-consultations need to follow a first de visu consultation either by the same or other respiratory units or out-patients' facilities. This is needed to rule out any current clinical exacerbation or clinical instability together with any physical or cognitive impairment. The authors suggest that the only exception to first visit in remote tele-consultations may be considered for smoking cessation and sleep disordered breathing. Once all the general steps are in place, scrutinizing each respiratory condition becomes easy and feasible ensuring an appropriate clinical assessment as if in a face to face clinical out-patient visit. Thus, the authors clearly list all the steps and tools needed during each tele consultation based on a specific respiratory disease. These lists come in handy when setting up a tele-consultation lab from the beginning, allowing an appropriate flow and time schedule for each dedicated respiratory condition.

In conclusion, the Covid19 pandemic brought new opportunities to continue quality of care for individuals with respiratory diseases via remote monitoring and tele-consultation.[15] Potentially, in the future these new aids will continue to be implemented and will become an essential part of the clinical daily practice of care. The manuscript by Morais and colleagues[5] offers practical, easy to follow recommendations to help standardising this setting.

Tele-medicine, artificial intelligence, virtual reality, robotics are increasingly helping (invading?) the medical activities. [1,4,16] However, as physicians we need to be aware that technology has never been able to substitute the empathy of the in-person doctor-patient relationship. Therefore, as health care providers, we will always be asked to balance the advances of present and future available technologies and the direct empathic approach with our most severely affected respiratory patients.

Funding

This manuscript was not funded.

Conflicts of interest

No financial or personal relationship can cause a conflict of interest regarding this article.

References

1. Mazzoleni S, Turchetti G, Ambrosino N. The COVID-19 outbreak: from "black swan" to global challenges and opportunities. Pulmonology. 2020;26(3):117−8.
2. Crimi C, Impellizzeri P, Campisi R, Nolasco S, Spanevello A, Crimi N. Practical considerations for spirometry during the COVID-19 outbreak: literature review and insights. Pulmonology. 2021;27(5):438−47.
3. Ambrosino N, Vitacca M, Dreher M, et al. Tele-monitoring of ventilator-dependent patients: a European Respiratory Society Statement. Eur Respir J. 2016;48(3):648−63.
4. Angelucci A, Aliverti A. Telemonitoring systems for respiratory patients: technological aspects. Pulmonology. 2020;26(4): 221−32.
5. Bashshur R, Shannon G, Krupinski E, Grigsby J. The taxonomy of telemedicine. Telemed J E Health. 2011;17(6):484−94.
6. Morais A, Bugalho A, Drummond M, et al. Teleconsultation in respiratory medicine - a position paper of the Portuguese Pulmonology Society. Pulmonology. 2022 Jun:0437(22)00114-3. https://doi.org/10.1016/j.pulmoe.2022.04.007. Epub ahead of print.
7. Ambrosino N, Pierucci P. Using telemedicine to monitor the patient with chronic respiratory failure. Life. 2021;11(11): 1113.
8. Wong A, Bhyat R, Srivastava S, Boissé Lomax L, Appireddy R. Patient care during the COVID-19 pandemic: use of virtual care. J Med Internet Res. 2021;23(1):e20621.
9. Pierucci P, Santomasi C, Ambrosino N, et al. Patient's treatment burden related to care coordination in the field of respiratory diseases. Breathe. 2021;17(1):210006.
10. Fields BG. Regulatory, legal, and ethical considerations of telemedicine. Sleep Med Clin. 2020;15(3):409−16.
11. Fradgley EA, Paul CL, Bryant J. A systematic review of barriers to optimal outpatient specialist services for individuals with prevalent chronic diseases: what are the unique and common barriers experienced by patients in high income countries? Int J Equity Health. 2015;14:52.
12. Vitacca M, Bazza A, Bianchi L, et al. Tele-assistance in chronic respiratory failure: patients' characterization and staff workload of 5-year activity. Telemed J E Health. 2010;16(3):299−305.
13. Ribeiro C, Conde S, Oliveira P, et al. Portuguese adaptation of the S3-non-invasive ventilation (S3-NIV) questionnaire for home mechanically ventilated patients. Pulmonology. 2022;28(4): 262−7.
14. Carpagnano GE, Pierucci P, Migliore G, et al. Tailored post-acute care coordination for survivors of moderate to severe COVID-19 Infection. J Am Med Dir Assoc. 2022;23(3):447−9.
15. Paneroni M, Vitacca M, Bernocchi P, Bertacchini L, Scalvini S. Feasibility of tele-rehabilitation in survivors of COVID-19 pneumonia. Pulmonology. 2022;28(2):152−4.
16. Colombo V, Aliverti A, Sacco M. Virtual reality for COPD rehabilitation: a technological perspective. Pulmonology. 2022;28(2): 119−33.

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Received 12 August 2022; Accepted 16 August 2022
Available online 29 September 2022

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COMMENT

Human biological monitoring of nanoparticles, a new way to investigate potential causal links between exposure to nanoparticles and lung diseases?

V. Forest*, J. Pourchez

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Received 2 August 2022; accepted 8 August 2022
Available online 15 September 2022

In addition to ultra-fine particles produced naturally or unintentionally released as a consequence of human activities, engineered nanomaterials are produced purposefully to take advantage of their unique physicochemical characteristics associated with their nanostructure. The growing development and applications of nanomaterials lead to an increasing release of these materials into the environment and consequently we are increasingly exposed to them.

Inhaled nanoparticles can deeply affect human health, especially, but not exclusively, in the context of air pollution. An update of the World Health Organization's air quality database was released in April 2022, warning that significant harm can be caused by even low levels of air pollutants.[1] As lungs are directly and constantly exposed to airborne pollutants, the effects of air pollution on the respiratory system has received much attention. Correlations have been reported between air pollution, especially particulate matter (PM), and the incidence and mortality of lung cancers.[2—4] PM was classified as a group I human carcinogen by the International Agency for Research on Cancer (IARC) based on data from human, animal and mechanistic studies.[5,6] But other cancers are also suspected to be related to air pollution such as childhood leukemia, cancers of the gastro-intestinal tract, bladder and kidney cancers or breast cancers.

In any case, inhaled nanoparticles can accumulate within the lungs where they are able to induce tissue damages. It has been especially reported that biopersistent engineered nanoparticles can induce pro-inflammatory reaction and oxidative stress, creating a microenvironment favorable to the development of diseases and especially cancers. In addition, due to their small size, inhaled nanoparticles can also cross the blood-air barrier and be distributed to other organs where they can trigger further damage.

Although epidemiological studies are informative, they are time- and resource- consuming. To get a better understanding of the chain of events from exposure to disease, alternative approaches such as the biological monitoring of biopersistent nanoparticles in patients could be used. Indeed, such biomonitoring would allow for the quantification of the internal dose of inhaled biopersistent particles, which differs from the external dose that can be measured by ambient monitoring (*i.e.*, atmospheric metrology). The assessment of the internal dose is a first step towards the characterization of persistent engineered nanoparticles in tissues and the understanding of this potential source of adverse effects.[7—9]

This approach has led to suggestions about the contribution of silica submicron particles to the development of sarcoidosis,[10] providing new research avenues. Similarly, it could improve understanding of the factors, which if they not actually cause may at least contribute to the development of cancers.

Combining the biomonitoring of nanoparticles in human samples and toxicological studies could improve understanding of the pathways involved in cancer development and also play a part in prevention, by limiting exposure to the incriminated sources of hazard.

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https://doi.org/10.1016/j.pulmoe.2022.08.005

In conclusion, the biological monitoring of nanoparticles in human samples appears as an alternative approach to time- and resource- consuming epidemiological studies to highlight relationships between exposure to nanoparticles and lung diseases development.

Conflicts of interest

none.

CRediT authorship contribution statement

V. Forest: Conceptualization, Writing — original draft. **J. Pourchez:** Writing — review & editing.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. World Health Organization. Billions of people still breathe unhealthy air: new WHO data. 2022; published online April 4. https://www.who.int/news/item/04-04-2022-billions-of-people-still-breathe-unhealthy-air-new-who-data [Accessed 22 April 2022].
2. Mayoralas-Alises S, Diaz-Lobato S. Air pollution and lung cancer. Curr Respir Med Rev. 2012;8:418—29.
3. Raaschou-Nielsen O, Andersen ZJ, Beelen R, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). Lancet Oncol. 2013;14:813—22.
4. Wong GWK. Air pollution and health. Lancet Respir Med. 2014;2:8—9.
5. IARC. Outdoor Air Pollution. Lyon, 2013 https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Outdoor-Air-Pollution-2015 [Accessed 21 April 2022].
6. Loomis D, Grosse Y, Lauby-Secretan B, et al. The carcinogenicity of outdoor air pollution. Lancet Oncol. 2013;14:1262—3.
7. Bergamaschi E, Poland C, Guseva Canu I, Prina-Mello A. The role of biological monitoring in nano-safety. Nano Today. 2015;10:274—7.
8. Groopman JD, Kensler TW. The light at the end of the tunnel for chemical-specific biomarkers: daylight or headlight? Carcinogenesis. 1999;20:1—11.
9. Forest V, Vergnon J-M, Pourchez J. Biological monitoring of inhaled nanoparticles in patients: an appealing approach to study causal link between human respiratory pathology and exposure to nanoparticles. Chem Res Toxicol. 2017;30:1655—60.
10. Forest V, Pourchez J, Guibert C, et al. Nano to micron-sized particle detection in patients' lungs and its pathological significance. *Environ Sci*: Nano. 2019;6:1343—50.

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ORIGINAL ARTICLE

Genetic polymorphisms in *MIR1208* and *MIR5708* are associated with susceptibility to COPD in the Chinese population

Y. Zhou[a,1], F. Bai[b,1], X. Li[c], G. Zhou[d], X. Tian[e], G. Li[c], Y. Zhang[f], X. Zhou[f], D. Xu[g,*], Y. Ding[f,*]

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Received 6 November 2020; accepted 24 July 2021
Available online 15 September 2022

KEYWORDS
MIR5708;
MIR1208;
Chronic obstructive pulmonary disease;
Single nucleotide polymorphism

Abstract
Background: Chronic obstructive pulmonary disease (COPD) is a complex disease characterized by limited airflow and is influenced by genetic and environmental factors. The purpose of this study was to investigate the effects of gene polymorphisms in *MIR5708* and *MIR1208* on COPD risk.
Methods: Four single nucleotide polymorphisms (SNPs) in *MIR5708* (rs6473227 and rs16907751) and *MIR1208* (rs2608029 and rs13280095) were selected and genotyped among 315 COPD patients and 314 healthy controls using the Agena MassARRAY platform. SPSS 18.0 was used for statistical analysis and data processing. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the association between genetic variants of *MIR1208* and *MIR5708* and COPD risk.
Results: The results suggested that rs16907751 variants in *MIR5708* contributed to an increased susceptibility to COPD in the allelic ($P = 0.001$), co-dominant (homozygous) ($P = 0.001$), dominant

Abbreviations: COPD, chronic obstructive pulmonary disease; miRNAs, micro RNAs; SNPs, single nucleotide polymorphisms; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium; BMI, body mass index; RR, respiratory rate; PR, pulse rate.

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https://doi.org/10.1016/j.pulmoe.2021.07.004

(*P* = 0.017), recessive (*P* = 0.002), and additive (*P* = 0.002) models. The effects of *MIR5708* and *MIR1208* gene polymorphisms on the risk of COPD were age-, sex-, smoking status-, and BMI-related. Furthermore, the C-A and G-A haplotypes of rs2608029 and rs13280095 in *MIR1208* were identified as risk factors for COPD in the population over 70 years (*P* = 0.029) and in women (*P* = 0.049), respectively. Finally, significant associations between rs16907751genotypes with pulse rate and forced expiratory volume in 1 s were found among COPD patients.

Conclusion: Genetic polymorphisms in *MIR5708* and *MIR1208* are associated with increased risk of COPD in China.

Introduction

Chronic obstructive pulmonary disease (COPD) is a multifactorial chronic respiratory disease characterized by irreversible pulmonary airflow obstruction.[1,2] Many studies have shown that the development of COPD is influenced by environmental factors and a complex set of genetic traits.[2—4] Recently, genome-wide association and exome sequencing studies have been used to identify the hereditary factors of COPD among different populations, but the effect of genetic variants on COPD is still unclear.[5]

Micro RNAs (miRNAs) are a class of endogenous non-coding RNAs, 22—25 nucleotides in length that can bind to the 3′-UTR region of mRNA transcripts, thereby inhibiting their translation and expression.[6,7] Variants in miRNAs are thought to be involved in post-transcriptional regulation and influence disease susceptibility.[7,8] Zhou et al and Wang et al found that the miR-146a rs2910164 single nucleotide polymorphism (SNP) is associated with improved lung function in smokers with COPD.[7,8] Related studies in the Korean population have suggested that gene polymorphisms in miR-196a2, miR-146a, and miR-499 could be associated with asthma phenotypes.[6] Fawzy et al also found a significant association between the miR-196a2 rs11614913 polymorphism and the bronchodilator response in Egyptians with COPD.[9] Therefore, it is important to explore the effect of miRNA variants on susceptibility to COPD.

MIR5708 and *MIR1208* are miRNAs located on chromosome 8. *MIR5708* has been identified as a risk locus for rheumatoid arthritis through gene-based association testing.[10] *MIR1208* is thought to be involved in the regulation of tumor-related pathways by binding to the upstream gene circMTUS1.[11] Relevant studies have also recognized *MIR1208* as a tumor suppressor gene that can increase sensitivity of renal cancer cells to cisplatin.[12] Moreover, genetic polymorphisms of *MIR1208* rs2648841 have been found to be related to chemotherapy toxicity in children with acute lymphoblastic leukemia.[13] However, to the best of our knowledge, the influence of *MIR5708* and *MIR1208* polymorphisms on the risk of COPD has not been studied.

Therefore, we performed this case-control study to investigate the relationship between *MIR5708* (rs6473227 and rs16907751) and *MIR1208* (rs2608029 and rs13280095) polymorphisms and susceptibility of Chinese to COPD, and to explain the roles of genetic factors in the pathogenesis of COPD through statistical analysis.

Methods

Study population

This study recruited 314 COPD patients (76% men) and 315 healthy controls (75% men). Patients with appropriate symptoms including dyspnea, cough, sputum production, wheezing, and chest tightness were considered as suspected cases of COPD, which were further confirmed by a post-bronchodilator fixed ratio of forced expiratory volume in 1 second/-forced vital capacity (FEV_1/FVC) < 0.70.[14] Meanwhile, patients with other respiratory diseases, autoimmune diseases, cardiovascular diseases, and others were excluded. Healthy controls were recruited from the physical examination center of Hainan General Hospital, matched by age and sex with $FEV_1/FVC > 0.70$, and no disease or family history. Demographic and clinical characteristics of all subjects were surveyed, and informed consent was obtained regarding the purpose and procedure of this study. This study was approved by the Hainan General Hospital and followed the Declaration of Helsinki guidelines.

SNP selection and genotyping

The selection of SNPs was based on haplotype or genotype data. Two SNPs in *MIR1208* (rs2608029 and rs13280095) and two in *MIR5708* (rs6473227 and rs16907751) were selected from the database of the 1000 Genomes Project (https://www.internationalgenome.org/) with the criteria of minor allele frequency (MAF) > 0.05, and $r^2 > 0.80$. The online design of the corresponding primers was performed in AgenaCx Tools (https://agenacx.com/online-tools/), and the primer sequences are listed in Supplementary Table 1. Genomic DNA of all participants was extracted and purified from cryopreserved serum using a GoldMag-Beads Kit (GoldMag, Xi'an, Shaanxi, China), and spectrophotometry (Beckman, Fullerton, CA, USA) was used to determine DNA concentration. SNP genotyping and data collection were conducted using the Agena MessARRAY platform and Agena Bioscience TYPER software (Agena Bioscience, San Diego, CA, USA), respectively.

Statistical analysis

The statistical data of this case-control study were processed using SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA), Microsoft Excel software, and PLINK software (version 1.07) (http://www.cog-genomics.org/plink2/).

Independent-sample t-test and chi-squared test were used to assess differences in clinical indexes between COPD patients and healthy controls, where appropriate. The association between each SNP and the risk of COPD was evaluated by logistic regression analysis under different genetic models, and was represented by odds ratios (ORs) and 95 % confidence intervals (CIs) after adjusting for age and sex. Hardy-Weinberg equilibrium (HWE) for each SNP in the control group was determined using Fisher's exact test. Statistical significance was set at $p < 0.05$.

Results

Clinical indexes of participants and genotypic characteristics of selected SNPs

Demographics and clinical indexes of all 629 participants comprising 315 COPD patients (mean age 71.93 ± 10.11 years) and 314 healthy controls (mean age 71.23 ± 6.83 years old) are displayed in Table 1. Statistically, cases and controls were matched by age (P = 0.306) and sex (P = 0.908).

Table 2 lists the detailed information of the four SNPs in *MIR2708* and *MIR1208*; MAFs > 0.05 and SNPs in the control group conformed to HWE ($P > 0.05$). Moreover, a significant association between the rs16907751 polymorphism and COPD risk was found in the allelic model (P = 0.001).

Association of MIR1208 and MIR5708 polymorphisms and COPD susceptibility

We carried out an association analysis on genetic variants and COPD susceptibility and the relevant data are presented in Table 3. The results suggested that the TT genotype at rs16907751 in *MIR5708* was a risk factor for COPD in the co-dominant (OR = 4.62, 95% CI = 1.84−11.62, P = 0.001), dominant (OR = 1.49, 95% CI = 1.07−2.08, P = 0.017), recessive (OR = 4.27, 95% CI = 1.71−10.66, P = 0.002), and additive (OR = 1.57, 95% CI = 1.19−2.07, P = 0.002) models.

To further explore the association between SNPs and COPD risk, we conducted a stratified analysis according to age, sex, BMI, and smoking status. According to the data listed in Table 4, rs6473227 in *MIR5708* was associated with an increased risk of COPD in the population with a body mass index (BMI, kg/m^2) less than or equal to 24 in the allelic (OR = 1.66, 95% CI = 1.13−2.44, P = 0.010), homozygous co-dominant (OR = 2.97, 95% CI = 1.34−6.62, P = 0.008), recessive (OR = 2.15, 95% CI = 1.06−4.35, P = 0.033), and additive (OR = 1.72, 95% CI = 1.16−2.55, P = 0.007) models. Moreover, rs16907751 in *MIR5708* was found to be significantly associated with an increased risk of COPD in males, non-smokers, patients older than 70 years, and individuals with a BMI ≤ 24. In addition, females heterozygous at rs2608029 (OR = 2.24, 95% CI = 1.09−4.64, P = 0.029) were more susceptible to COPD risk in both dominant (OR = 2.19, 95% CI = 1.07−4.47, P = 0.031) and additive (OR = 1.99, 95% CI = 1.02−3.91, P = 0.045) models.

We continued with a haplotype analysis and found a block (rs2608029 and rs13280095) in *MIR1208* (Table 5). The C-A haplotype of rs2608029 and rs13280095 was found to be related to an increased risk of COPD (OR = 2.59, 95% CI = 1.10−6.06, P = 0.029) in the population over 70 years, whereas $G_{rs2608029}A_{rs13280095}$ was found to be a risk factor for COPD in women.

Association analysis of clinical indexes of COPD and gene polymorphisms

Then, the effects of genetic variants in *MIR5708* and *MIR1208* on COPD were investigated in terms of clinical indices, including respiratory rate (RR), pulse rate (PR), FVC, FEV_1, and FEV_1/FVC (Table 6). The results suggested that rs16907751 in *MIR5708* was significantly associated with PR (P = 0.009) and FEV_1 (P = 0.049) in the genotypic model.

Table 1 Clinical characteristics of cases and controls.

Variables	Case (n = 315)	Control (n = 314)	P
Age (Mean ± SD)	71.93 ± 10.11	71.23 ± 6.83	0.306[a]
≤ 70	127 (40%)	137 (44%)	
> 70	188 (60%)	177 (56%)	
Gender			0.908[b]
Male	239 (76%)	237 (75%)	
Female	76 (24%)	77 (25%)	
BMI (kg/m^2)			
≤ 24	251 (80%)	67 (21%)	
> 24	29 (9%)	78 (25%)	
Tobacco smoking status			
Yes	147 (47%)	52 (17%)	
No	166 (53%)	118 (38%)	
Comorbidity			
Yes	93 (30%)		
No	174 (55%)		

SD, standard deviation; BMI, body mass index.
[a] P was calculated by t test.
[b] P was calculated by Pearson's chi-squared test.

Table 2 Information regarding SNPs in *MIR5708* and *MIR1208*.

Gene	SNP	Chromosome	Position	Allele A/B	MAF		HWE-*P*	OR(95% CI)	*P*
					Case	Control			
MIR5708	rs6473227	8	81285892	A/C	0.448	0.462	0.651	0.94(0.76—1.18)	0.614
MIR5708	rs16907751	8	81375457	T/C	0.238	0.164	0.411	1.59(1.20—2.11)	0.001
MIR1208	rs2608029	8	129170126	C/G	0.167	0.145	0.648	1.18(0.87—1.60)	0.298
MIR1208	rs13280095	8	129179090	C/A	0.116	0.112	1	1.04(0.73—1.48)	0.821

SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; 95% CI, 95% confidence interval.
Bold $P < 0.05$ indicates statistical significance.

Table 3 Association of *MIR5708* and *MIR1208* polymorphisms with COPD risk.

SNP	Model	Allele/Genotype	Case	Control	OR(95% CI)	*P*
rs6473227	Co-dominant (HOM)	AA vs CC	65(20.6%)	69(22.0%)	0.88(0.57—1.38)	0.584
	Co-dominant (HET)	AC vs CC	152(48.3%)	152(48.4%)	0.94(0.65—1.35)	0.724
	Dominant	AA-AC vs CC	217(68.9%)	221(70.4%)	0.92(0.65—1.29)	0.632
	Recessive	AA vs AC-CC	65(20.6%)	69(22.0%)	0.92(0.63—1.35)	0.669
	Additive				0.94(0.75—1.17)	0.579
rs16907751	Co-dominant (HOM)	TT vs CC	23(7.3%)	6(1.9%)	4.62(1.84—11.62)	0.001
	Co-dominant (HET)	TC vs CC	101(32.1%)	91(29.0%)	1.29(0.91—1.82)	0.149
	Dominant	TT-TC vs CC	124(39.4%)	97(30.9%)	1.49(1.07—2.08)	0.017
	Recessive	TT vs TC-CC	23(7.3%)	6(1.9%)	4.27(1.71—10.66)	0.002
	Additive				1.57(1.19—2.07)	0.002
rs2608029	Co-dominant (HOM)	CC vs GG	5(1.6%)	5(1.6%)	1.13(0.32—3.97)	0.852
	Co-dominant (HET)	CG vs GG	95(30.1%)	81(25.8%)	1.26(0.89—1.79)	0.199
	Dominant	CC-CG vs GG	100(31.7%)	86(27.4%)	1.25(0.89—1.77)	0.202
	Recessive	CC vs CG-GG	5(1.6%)	5(1.6%)	1.05(0.30—3.68)	0.940
	Additive				1.21(0.88—1.67)	0.233
rs13280095	Co-dominant (HOM)	CC vs AA	3(1.0%)	4(1.3%)	0.82(0.18—3.71)	0.792
	Co-dominant (HET)	CA vs AA	67(21.3%)	62(19.7%)	1.11(0.75—1.64)	0.608
	Dominant	CC-CA vs AA	70(22.2%)	66(21.0%)	1.09(0.74—1.60)	0.656
	Recessive	CC vs CA-AA	3(1.0%)	4(1.3%)	0.80(0.18—3.61)	0.768
	Additive				1.06(0.75—1.52)	0.731

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; HOM, homozygous; HET, heterozygous
P value was calculated by logistic regression analysis with adjustment for age and sex.
Bold $P < 0.05$ indicates statistical significance.

Furthermore, no association was found between rs6473227, rs2608029, and rs13280095 and the clinical indices of COPD.

Discussion

According to the latest Global Health Observatory data, COPD was ranked as the third leading cause of death worldwide, accounting for approximately 5% of all deaths globally in 2015 (3.17 million deaths). The prevalence and burden of COPD are projected to increase over the coming decades.[15] It has been clearly demonstrated that the interaction between genotype and environment plays an important role in COPD phenotypes.[16,17] Genetic background plays a critical role in the development of COPD, and related studies have proposed significant differences in genetic susceptibility to COPD among different races and ethnicities.[18] Therefore, the effect of genetic polymorphisms of candidate genes on the risk of COPD among Chinese was examined.

As a result, statistical analysis of the genotyping results of 315 COPD patients and 314 healthy controls among Chinese patients identified *MIR5708* rs16907751 as a risk factor of COPD, and significant associations between rs16907751 and clinical indexes including PR and FEV_1 in COPD patients were found. The examined mutation loci have been rarely reported; only rs6473227 showed a close relationship with atopic dermatitis in a related case-control analysis.[19] Our results suggest that rs6473227 may contribute to an increased risk of COPD in individuals with a BMI less than 24. A related study pointed out that neuroimmune interactions are implicated in chronic inflammations such as atopic dermatitis, COPD, and asthma[20]; therefore, we hypothesized that *MIR5708* rs6473227 may increase susceptibility to inflammation-related disorders. In addition, we found that *MIR5708* rs16907751 may increase the risk of COPD in patients with normal BMI. There have been studies supporting our findings and reported that low BMI is a risk factor for accelerated decline in lung function compared to normal

Table 4 Stratification analysis of the associations between *MIR1208* and *MIR5708* polymorphisms and COPD risk.

SNP	Model	Age >70		Male		Female		Non-Smoking		BMI ≤24	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
rs6473227	Allele	0.91(0.68−1.22)	0.546	0.96(0.74−1.24)	0.753	0.90(0.57−1.41)	0.637	0.84(0.60−1.17)	0.300	1.66(1.13−2.44)	0.010
	Co-dominant (HOM)	0.75(0.40−1.39)	0.353	0.93(0.55−1.55)	0.771	0.79(0.33−1.91)	0.596	0.71(0.36−1.37)	0.306	2.97(1.34−6.62)	0.008
	Co-dominant (HET)	1.08(0.66−1.79)	0.756	0.89(0.59−1.36)	0.604	1.09(0.52−2.26)	0.818	0.84(0.48−1.45)	0.527	1.68(0.89−3.18)	0.107
	Dominant	0.97(0.61−1.56)	0.905	0.90(0.61−1.34)	0.618	0.98(0.50−1.94)	0.958	0.79(0.47−1.33)	0.378	1.16(0.66−2.07)	0.603
	Recessive	0.71(0.42−1.20)	0.203	0.99(0.64−1.55)	0.976	0.75(0.35−1.62)	0.462	0.79(0.44−1.40)	0.413	2.15(1.06−4.35)	0.033
	Additive	0.88(0.65−1.20)	0.413	0.96(0.74−1.24)	0.734	0.90(0.58−1.40)	0.651	0.84(0.60−1.17)	0.302	1.72(1.16−2.55)	0.007
rs16907751	Allele	2.00(1.36−2.95)	<0.001	1.63(1.18−2.26)	0.003	1.47(0.84−2.59)	0.179	1.62(1.03−2.56)	0.036	1.67(1.00−2.78)	0.047
	Co-dominant (HOM)	16.14(2.03−128.4)	0.009	4.64(1.68−12.78)	0.003	4.63(0.50−42.97)	0.178	−	−	2.90(0.64−13.16)	0.168
	Co-dominant (HET)	1.45(0.90−2.34)	0.127	1.27(0.85−1.90)	0.238	1.30(0.66−2.57)	0.448	1.10(0.64−1.88)	0.723	1.48(0.79−2.78)	0.225
	Dominant	1.75(1.10−2.77)	0.018	1.51(1.03−2.21)	0.036	1.43(0.74−2.78)	0.286	1.36(0.81−2.29)	0.249	2.03(1.12−3.67)	0.020
	Recessive	14.47(1.83−114.70)	0.011	4.31(1.58−11.79)	0.004	4.22(0.46−38.70)	0.203	−	−	2.59(0.57−11.64)	0.216
	Additive	1.89(0.65−1.20)	0.002	1.58(1.15−2.18)	0.005	1.51(0.84−2.70)	0.171	1.57(0.99−2.47)	0.054	1.57(0.95−2.59)	0.079
rs2608029	Allele	1.05(0.68−1.61)	0.837	1.02(0.72−1.45)	0.924	1.86(0.99−3.50)	0.053	0.94(0.61−1.47)	0.800	1.11(0.66−1.87)	0.688
	Co-dominant (HOM)	1.42(0.08−23.83)	0.810	1.08(0.26−4.42)	0.916	1.30(0.08−21.55)	0.855	0.32(0.06−1.70)	0.180	0.44(0.09−2.11)	0.304
	Co-dominant (HET)	1.03(0.63−1.68)	0.918	1.05(0.70−1.57)	0.827	2.24(1.09−4.64)	0.029	1.22(0.71−2.09)	0.467	1.79(0.92−3.46)	0.085
	Dominant	1.03(0.63−1.69)	0.894	1.05(0.70−1.56)	0.817	2.19(1.07−4.47)	0.031	1.10(0.66−1.85)	0.717	1.27(0.72−2.24)	0.402
	Recessive	1.41(0.08−23.61)	0.813	1.06(0.26−4.34)	0.931	1.01(0.06−16.59)	0.994	0.30(0.06−1.58)	0.155	0.37(0.08−1.75)	0.209
	Additive	1.04(0.65−1.67)	0.867	1.04(0.73−1.50)	0.815	1.99(1.02−3.91)	0.045	0.97(0.61−1.53)	0.896	1.28(0.74−2.22)	0.384
rs13280095	Allele	0.74(0.45−1.23)	0.247	0.89(0.60−1.33)	0.576	1.67(0.82−3.40)	0.156	0.77(0.46−1.28)	0.308	1.08(0.58−2.00)	0.816
	Co-dominant (HOM)	−	−	0.72(0.12−4.39)	0.718	1.15(0.07−18.97)	0.923	0.32(0.06−2.03)	0.247	0.38(0.05−2.85)	0.343
	Co-dominant (HET)	0.69(0.39−1.22)	0.203	0.93(0.59−1.46)	0.760	1.91(0.86−4.26)	0.114	0.91(0.50−1.67)	0.769	1.68(0.78−3.61)	0.182
	Dominant	0.68(0.39−1.19)	0.178	0.92(0.59−1.43)	0.715	1.85(0.85−4.05)	0.122	0.84(0.47−1.49)	0.546	1.56(0.83−2.91)	0.164
	Recessive	−	−	0.73(0.12−4.45)	0.732	1.00(0.06−16.36)	0.998	0.37(0.07−2.06)	0.255	0.33(0.04−2.51)	0.287
	Additive	0.67(0.39−1.17)	0.159	0.92(0.61−1.38)	0.675	1.68(0.82−3.47)	0.158	0.80(0.48−1.32)	0.375	1.24(0.66−2.35)	0.508

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; HOM, homozygous; HET, heterozygous
"-" indicates no results.
P value was calculated by logistic regression analysis with adjustment for age and sex.
Bold $P < 0.05$ indicates statistical significance.

Table 5 Haplotype analysis of the association between *MIR5708* and *MIR1208* polymorphisms and COPD risk.

Gene	SNP	Subgroup	Haplotype	Fre-case	Fre-control	OR(95% CI)	*P*
MIR1208	rs2608029|rs13280095	Overall	CC	0.116	0.111	1.08(0.76−1.54)	0.681
			CA	0.051	0.034	1.55(0.88−2.73)	0.128
			GA	0.167	0.146	1.21(0.88−1.66)	0.242
MIR1208	rs2608029|rs13280095	Age (>70)	CC	0.080	0.105	0.67(0.38−1.16)	0.155
			CA	0.053	0.023	2.59(1.10−6.06)	0.029
			GA	0.133	0.128	1.04(0.65−1.67)	0.867
MIR1208	rs2608029|rs13280095	Female	CC	0.145	0.086	1.82(0.87−3.80)	0.110
			CA	0.053	0.026	2.13(0.61−7.41)	0.237
			GA	0.197	0.118	1.96(1.00−3.86)	0.049

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index
P value was calculated by logistic regression analysis with adjustment for age and sex.
Bold $P < 0.05$ indicates statistical significance

Table 6 Association analysis on the clinical indexes of COPD and gene polymorphisms.

SNP		RR (breaths/min)	PR (beats/min)	FVC (L)	FEV_1 (L)	FEV_1/FVC (%)
rs6473227	AA	22.00 ± 2.44	84.44 ± 9.36	3.30 ± 1.78	1.21 ± 0.55	31.65 ± 30.57
	CA	22.42 ± 2.43	87.28 ± 12.34	1.95 ± 0.74	1.24 ± 0.55	40.08 ± 29.36
	CC	22.33 ± 2.55	86.06 ± 11.96	1.99 ± 0.60	1.19 ± 0.49	46.26 ± 27.17
	P	0.543	0.286	0.164	0.907	0.078
rs16907751	TT	23.35 ± 3.05	93.90 ± 12.96	1.95 ± 0.80	0.99 ± 0.35	36.96 ± 27.96
	TC	22.10 ± 2.42	85.93 ± 13.06	1.90 ± 0.50	1.11 ± 0.40	41.70 ± 27.62
	CC	22.28 ± 2.41	85.54 ± 10.44	2.49 ± 4.70	1.31 ± 0.68	39.79 ± 30.68
	P	0.123	0.009	0.639	0.049	0.866
rs2608029	CC	22.60 ± 3.05	83.60 ± 5.18	2.35 ± 0.78	1.53 ± 0.83	49.21 ± 33.36
	GC	22.43 ± 2.45	88.06 ± 10.13	1.86 ± 0.71	1.19 ± 0.58	44.47 ± 30.47
	GG	22.24 ± 2.47	85.62 ± 12.38	2.45 ± 4.54	1.22 ± 0.60	37.24 ± 28.53
	P	0.812	0.239	0.640	0.558	0.276
rs13280095	AA	22.26 ± 2.53	85.98 ± 12.18	2.39 ± 4.28	1.22 ± 0.60	38.27 ± 28.97
	CA	22.36 ± 2.18	87.64 ± 9.82	1.85 ± 0.69	1.19 ± 0.58	42.96 ± 30.68
	CC	24.67 ± 1.53	86.67 ± 4.16	2.45 ± 0.92	1.70 ± 0.92	65.46 ± 9.31
	P	0.239	0.629	0.740	0.367	0.215

RR, respiratory rate; PR, pulse rate; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s.
Bold $P < 0.05$ indicates statistical significance.

BMI,[21] thereby suggesting a protective role of high BMI in COPD patients.

Tobacco smoking is widely recognized as the most important risk factor for COPD,[22] but it is not the only risk factor for COPD. Qian et al. concluded that both non-smokers and smokers are likely to suffer from COPD, which may be the result of differential miRNA expression between.[23] At present, there has been no report on the association between miR5708 and miR1208 and the risk of disease COPD. However, our study further provided evidence that allele T of *MIR5708* rs16907751 may increase susceptibility of non-smokers to COPD. There have been reports confirming that up to 30% of patients with COPD do not have a smoking history.[18] Therefore, multiple genes and exposure to environmental and occupational factors are thought to jointly affect COPD development.

Furthermore, we also found that the effects of *MIR5708* and *MIR1208* on the risk of COPD were age- and sex-dependent. Related epidemiological studies have shown that the prevalence of COPD increases with age,[24] and Mercado et al. also showed that aging of the lung resulted in loss of lung elasticity and reduced ability to respond to environmental stress and damage.[25] Our findings also indicated *MIR5708* rs16907751 as a risk factor for COPD in patients over 70 years of age. Based on the stratified analysis, our results suggested that *MIR5708* rs16907751 and *MIR1208* rs2608029 are associated with increased COPD risk in men and women, respectively, and further confirmed gender differences in COPD susceptibility conferred by these two SNPs. Aryal et al. stated that the differences in sex were derived mainly by smoking status, hormone levels, and behavioral differences.[26] Current data indicate that in China, the prevalence of COPD in men is higher than that in women, but the difference varies with exposure to risk factors and socioeconomic development in different geographic regions.[27,28] However, in our current study, we did not focus on the effect of environment, occupational differences, and regional constraints. Moreover, the small sample size and incomplete sample information in some cases are also limitations of our study. Subsequent functional experiments are needed to verify the effects of these SNPs on COPD.

Conclusion

In summary, this study is the first to indicate that genetic variants in *MIR5708* and *MIR1208* are associated with an increased risk of COPD in the Chinese population, and the effects of these SNPs are related to age, sex, smoking status, and BMI.

Conflicts of interest

All authors declared no conflict of interests.

Funding

This study was supported by the National Natural Science Foundation of China (No. 81660013 and No. 81860015) and Key Research and Development Plan of Hainan Province (No. ZDYF2018116).

Acknowledgements

We appreciate all participants contributed to this study, especially Alexandra S, who modified the sentences in this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2021.07.004.

References

1. Reséndiz-Hernández JM, Falfán-Valencia R. Genetic polymorphisms and their involvement in the regulation of the inflammatory response in asthma and COPD. Adv Clin Exp Med. 2018;27(1):125—33.
2. Li Y, Cho MH, Zhou X. What do polymorphisms tell us about the mechanisms of COPD? Clin Sci. 2017;131(24):2847—63.
3. Ding Y, Xu H, Yao J, et al. Association between RTEL1 gene polymorphisms and COPD susceptibility in a Chinese Han population. Int J Chron Obstruct Pulmon Dis. 2017;12:931—6.
4. Yuan C, Chang D, Lu G, Deng X. Genetic polymorphism and chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2017;12:1385—93.
5. Ding Y, Li Q, Wu C, et al. TERT gene polymorphisms are associated with chronic obstructive pulmonary disease risk in the Chinese Li population. Mol Genet Genomic Med. 2019;7(8):e773.
6. Trinh HKT, Pham DL, Kim SC, Kim RY, Park HS, Kim SH. Association of the miR-196a2, miR-146a, and miR-499 Polymorphisms with asthma phenotypes in a Korean population. Mol Diagn Ther. 2017;21(5):547—54.
7. Zhou S, Liu Y, Li M, et al. Combined effects of PVT1 and MiR-146a single nucleotide polymorphism on the lung function of smokers with chronic obstructive pulmonary disease. Int J Biol Sci. 2018;14(10):1153—62.
8. Wang R, Li M, Zhou S, et al. Effect of a single nucleotide polymorphism in miR-146a on COX-2 protein expression and lung function in smokers with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015;10:463—73.
9. Fawzy MS, Hussein MH, Abdelaziz EZ, Yamany HA, Ismail HM, Toraih EA. Association of MicroRNA-196a2 variant with response to short-acting β2-agonist in COPD: an egyptian pilot study. PLoS One. 2016;11(4):e0152834.
10. Lenert A, Fardo DW. Detecting novel micro RNAs in rheumatoid arthritis with gene-based association testing. Clin Exp Rheumatol. 2017;35(4):586—92.
11. Shang Q, Li Y, Wang H, Ge S, Jia R. Altered expression profile of circular RNAs in conjunctival melanoma. Epigenomics. 2019;11(7):787—804.
12. Kim EA, Jang JH, Sung EG, Song IH, Kim JY, Lee TJ. MiR-1208 increases the sensitivity to cisplatin by targeting TBCK in renal cancer cells. Int J Mol Sci. 2019;20(14).
13. Gutierrez-Camino A, Umerez M, Santos B, et al. Pharmacoepigenetics in childhood acute lymphoblastic leukemia: involvement of miRNA polymorphisms in hepatotoxicity. Epigenomics. 2018;10(4):409—17.
14. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195(5):557—82.
15. Labaki WW, Rosenberg SR. Chronic obstructive pulmonary disease. Ann Int Med. 2020;173(3):Itc17—32.
16. Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. N Eng J Med. 2019;381(13):1248—56.
17. Corlateanu A, Mendez Y, Wang Y, Garnica RJA, Botnaru V, Siafakas N. Chronic obstructive pulmonary disease and phenotypes: a state-of-the-art. Pulmonology. 2020;26(2):95—100.
18. Ma Y, Tong X, Liu Y, Liu S, Xiong H, Fan H. ACE gene polymorphism is associated with COPD and COPD with pulmonary hypertension: a meta-analysis. Int J Chron Obstruct Pulmon Dis. 2018;13:2435—46.
19. Kim JH, Lee SY, Kang MJ, et al. Association of genetic polymorphisms with atopic dermatitis, clinical severity and total IgE: a replication and extended study. Allergy Asthma Immunol Res. 2018;10(4):397—405.
20. Blake KJ, Jiang XR, Chiu IM. Neuronal regulation of immunity in the skin and lungs. Trends Neurosci. 2019;42(8):537—51.
21. Sun Y, Milne S, Jaw JE, et al. BMI is associated with FEV(1) decline in chronic obstructive pulmonary disease: a meta-analysis of clinical trials. Respir Res. 2019;20(1):236.
22. Wang L, Tang Y, Chen Y. HIF1A gene rs10873142 polymorphism is associated with risk of chronic obstructive pulmonary disease in a Chinese Han population: a case-control study. Biosci Rep. 2018;38(2):BSR20171309.
23. Qian Y, Mao ZD, Shi YJ, Liu ZG, Cao Q, Zhang Q. Comprehensive analysis of miRNA-mRNA-lncRNA networks in non-smoking and smoking patients with chronic obstructive pulmonary disease. Cell Physiol Biochem. 2018;50(3):1140—53.
24. Raherison C, Girodet PO. Epidemiology of COPD. Eur Respir Rev. 2009;18(114):213—21.
25. Mercado N, Ito K, Barnes PJ. Accelerated ageing of the lung in COPD: new concepts. Thorax. 2015;70(5):482—9.
26. Aryal S, Diaz-Guzman E, Mannino DM. COPD and gender differences: an update. Transl Res. 2013;162(4):208—18.
27. Zhu B, Wang Y, Ming J, Chen W, Zhang L. Disease burden of COPD in China: a systematic review. Int J Chron Obstruct Pulmon Dis. 2018;13:1353—64.
28. Ntritsos G, Franek J, Belbasis L, et al. Gender-specific estimates of COPD prevalence: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2018;13:1507—14.

Pulmonology 29 (2023) 13–19

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ORIGINAL ARTICLE

Influence of inhalation device, active substance, and drug formulation on the compliance of patients with obstructive pulmonary diseases. A physicians' perspective

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Received 7 July 2020; accepted 23 November 2020
Available online 30 December 2020

KEYWORDS
Inhalation device;
Compliance;
COPD;
Asthma

Abstract
Aim: To investigate the perspective of physicians treating chronic airway diseases on the importance of device and substance characteristics influencing the compliance of patients with chronic obstructive airways diseases.
Objective: We surveyed physicians' perspective on the impact of device and substance characteristics on patients' compliance.
Methods: This study was carried out by running a structured questionnaire, to a total of 144 physicians, conducting personal interviews and evaluating answers on a scale from 1 for most to 6 for least important influencing parameter.
Results: Overall, the most important parameters influencing patients' compliance according to physicians' perspective were rapid onset of action, type of inhalation device and duration of action. Adverse events were considered as the least important parameter. When COPD and asthma were examined separately, the most important parameters influencing compliance were rapid onset of action, ease of use and duration of action. Rapid onset of action was significantly more important in asthma than COPD.
Conclusion: Onset and duration of action and ease of use were classified higher as important parameters to increase patients' compliance, according to physicians' perspective.

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https://doi.org/10.1016/j.pulmoe.2020.11.008

Introduction

Obstructive airway diseases, Chronic Obstructive Pulmonary Disease (COPD) and Asthma, are increasing in frequency throughout the world, having a significant impact on quality of life. More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally.[1,2]

Similarly, the global prevalence rates of asthma in adults is increasing.[3] Compliance plays a major role in disease outcome, as it has been associated with increased morbidity and mortality.[4,5] A better understanding of the factors associated with adherence, can lead to more appropriate decisions regarding management. It has been shown that treatment success is proportionally linked to patients' compliance, both in COPD and asthma.[6] On the other hand, suboptimal adherence to inhaled medication is linked to increased hospitalizations and economic health costs.[7–10]

The present study surveyed doctors' perspective on the role of active substance, type of inhalation device, onset of action, drug formulation, duration of action and adverse events as parameters influencing patients' compliance.

Methods

Participants

A total of 144 prescribing doctors participated in the study with the majority being pulmonologists. Specifically, there were 104 pulmonologists (72%), 3 intensivists, 7 allergologists, 27 internists & 3 pediatricians) participated in the study. Excluding the 3 pediatricians, all other participants declared that were actively involved in the management of COPD and asthma. Regarding the workplace of respondents, 74% worked in a public hospital, 19% in a private practice and 7% in a private clinic.

Design of the study

During the National Respiratory Congress, physicians were asked to answer a questionnaire regarding the importance of device and substance characteristics influencing the compliance of patients with chronic obstructive airways diseases. The importance of parameters was evaluated on a scale of 1–6, with one representing the most and six representing the least important. Evaluated parameters included rapid onset of action, duration of action, ease of use, low flow resistance, ability of the device to confirm the dose, type of inhalation device, and the formulation of the drug. Participants were asked to determine the importance of the above-mentioned parameters in chronic obstructive lung diseases in general and subsequently in COPD and asthma separately. The average time to complete the questionnaire was 12 min.

Statistical analysis

Descriptive statistics: The continuous (e.g. age) and ordinal study parameters (e.g. the scaled answers to the Study questions) were presented using mean, median, standard deviation (SD), standard error of the mean (SE) and range, while the nominal parameters (e.g. gender) were presented using tables of frequencies.

Inference: The data analysed were subjective rankings (scores) by the physicians, on various parameters (characteristics) of inhalation devices. In the case of Question 1 (overall evaluation of parameters influencing patients' compliance/ 6 parameters) the data were ranked on a six-point scale. In the case of Question 2A (parameters influencing the compliance of patients with Asthma / 7 parameters) and Question 2B (parameters influencing COPD patients' compliance / 7 parameters) the data were ranked on a seven-point scale.

All above parameters were compared between male and female physicians using Mann-Whitney U-test, while they were compared between age groups using Kruskal Wallis test.

For the parameters belonging to Question 1 (overall evaluation of parameters influencing patients' compliance /6 parameters), Friedman's test checked the overall difference between scores, i.e. if at least one of the parameters had a different score from the rest. Afterwards these six parameters were compared with each other using Wilcoxon signed-rank test (15 comparisons). Bonferroni correction was also applied, so the alpha level (two-tailed) for these comparisons was set at $0.05/15 = 0.0033$.

For the (scaled) parameters belonging to Question 2A (parameters influencing the compliance of patients with Asthma / 7 parameters), Friedman's test checked the overall difference between scores, i.e. if at least one of the parameters had a different score from the rest. Afterwards the seven parameters were compared with each other using Wilcoxon signed-rank test (21 comparisons). Again, Bonferroni correction was applied, so the alpha level (two-tailed) for these comparisons was set at $0.05/21 = 0.0024$. The same procedure as above was applied (the alpha level [two-tailed] for these comparisons was set at $0.05/21 = 0.0024$) for the scaled parameters belonging to Question 2B (parameters influencing the compliance of patients with COPD / 7 parameters). Finally, the parameters influencing COPD and Asthmatic patients' compliance were compared between patients with Asthma (Question 2A) and COPD patients (Question 2B) using Wilcoxon signed-rank test (7 comparisons). No Bonferroni adjustment was applied since these comparisons were independent. All analyses were performed using R 4.0.3.

Results

Overall evaluation of parameters influencing patients' compliance

On average ''Rapid onset of action'' was ranked lower (more important- influential) than all the other parameters. It was statistically significantly lower than all other parameters except that of ''Type of inhalation device''. On the contrary, ''Adverse events'' was ranked statistically significantly higher (less important- influential) than all the other parameters. (Fig. 1). Statistical significance among studied parameters is shown in Table 1.

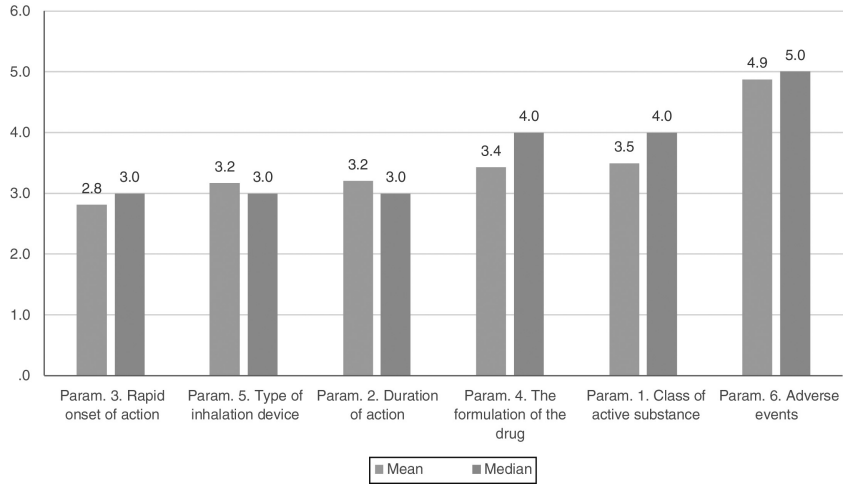

Fig. 1 Overall evaluation of parameters influencing patients' compliance. Mean and Median of the six evaluated parameters: Scale: 1= most important, 6= least important.

Table 1 Descriptive statistics regarding the six Parameters of Question 1: Overall evaluation of parameters influencing patients' compliance. Scale: 1 = 1st most important, 6 = 6th least important. P-values of the 15 applications of Wilcoxon signed-rank test. Base: Observed cases.

	Mean	Median	SD	SE	Range	N
Param. 1. Class of active substance	3.50	4.00	2.15	0.18	5.00	143
Param. 2. Duration of action	3.20	3.00	1.33	0.11	5.00	144
Param. 3. Rapid onset of action	2.81	3.00	1.31	0.11	5.00	143
Param. 4. The formulation of the drug	3.43	4.00	1.59	0.13	5.00	143
Param. 5. Type of inhalation device	3.17	3.00	1.66	0.14	5.00	144
Param. 6. Adverse events	4.87	5.00	1.29	0.11	5.00	143

p-values of the 15 applications of Wilcoxon signed-rank test (alpha=0.0033)	Param. 1	Param. 2	Param. 3	Param. 4	Param. 5	Param. 6
Param. 1. Class of active substance						
Param. 2. Duration of action	0.1970					
Param. 3. Rapid onset of action	0.0037	0.0035				
Param. 4. The formulation of the drug	0.7666	0.3678	0.0035			
Param. 5. Type of inhalation device	0.2710	0.8740	0.0909	0.2583		
Param. 6. Adverse events	<0.001	<0.001	<0.001	<0.001	<0.001	

Note: P-values that were marginally ≥0.0033 are marked with blue colour, while p-values <0.0033 (Statistically significant difference between the two parameters) are marked with yellow colour.

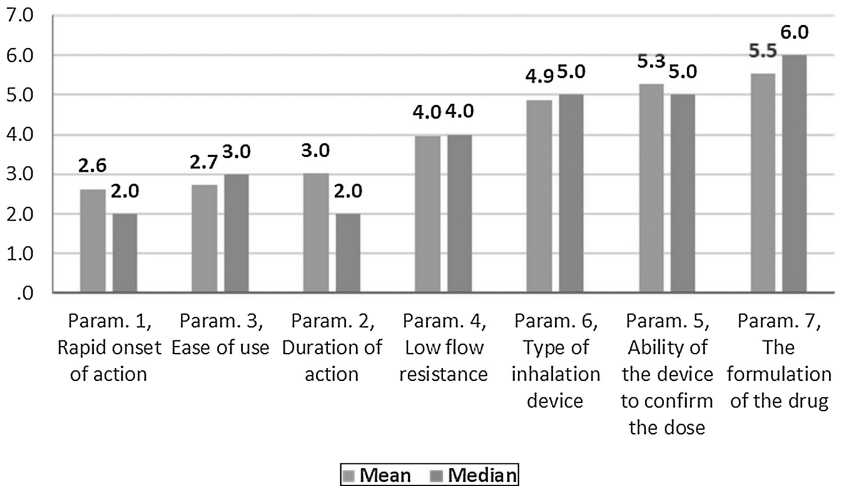

Fig. 2 Evaluation of parameters influencing the compliance of patients with Asthma. Mean and Median of the seven Parameters: Scale: 1= most important, 7= least important.

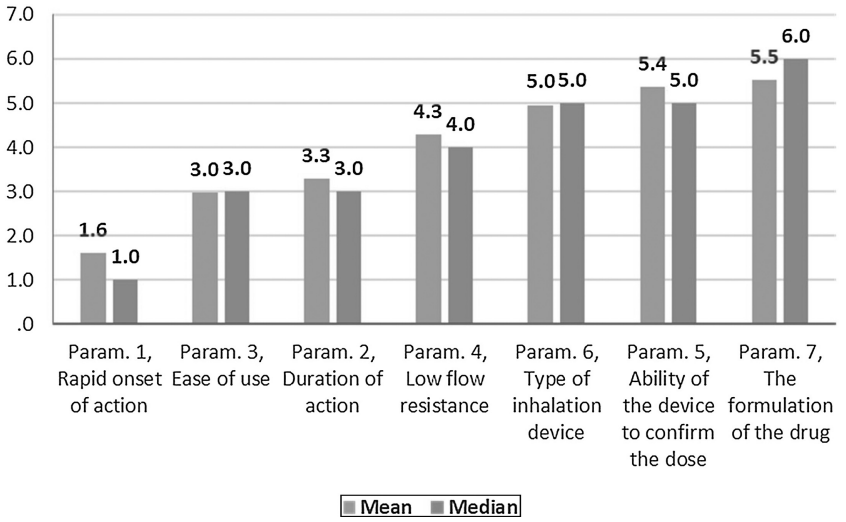

Fig. 3 Evaluation of parameters influencing the compliance of patients with COPD. Mean and Median of the seven Parameters: Scale: 1= most important, 7= least important.

Parameters influencing the compliance of patients with Asthma

On average ''Rapid onset of action'' was ranked statistically significantly lower (more important-influential) than all the other parameters. The next most influential parameters were ''Ease of use'' and ''Duration of action'' that were ranked statistically significantly lower (more important- influential) than the other 4 parameters. On the contrary, ''The formulation of the drug'' was ranked statistically significantly higher (less important) than all other parameters. (Fig. 2). Statistical significance among studied parameters is shown in Table 2.

Parameters influencing the compliance of patients with COPD

On average ''Rapid onset of action'', ''Duration of action'' and ''Ease of use'' were ranked statistically significantly lower (more important-influential) than the other four parameters (''Rapid onset of action'', ''Duration of action'' and ''Ease of use'' were not statistically significantly differentiated between each other). The parameter ''The formulation of the drug'' was ranked statistically significantly higher (less important) than all other parameters, except that of ''Ability of the device to confirm the dose''.

(Fig. 3). Statistical significance among studied parameters is shown in Table 3.

Table 2 Descriptive statistics regarding the seven Parameters influencing the compliance of patients with Asthma. Scale: 1 = 1st most important, 7 = 7th least important. P-values of the 21 applications of Wilcoxon signed-rank test. Base: Observed cases (N = 140).

	Mean	Median	SD	SE	Range	N
Param. 1. Rapid onset of action	1.61	1.00	1.32	0.11	6.00	140
Param. 2. Duration of action	3.29	3.00	1.66	0.14	6.00	140
Param. 3. Ease of use	2.98	3.00	1.42	0.12	6.00	140
Param. 4. Low flow resistance	4.29	4.00	1.61	0.14	6.00	140
Param. 5. Ability of the device to confirm the dose	5.36	5.00	1.38	0.12	5.00	140
Param. 6. Type of inhalation device	4.96	5.00	1.43	0.12	6.00	140
Param. 7. The formulation of the drug	5.52	6.00	1.62	0.14	6.00	140

p-values of the 21 applications of Wilcoxon signed-rank test (alpha=0.0033)	Param. 1	Param. 2	Param. 3	Param. 4	Param. 5	Param. 6	Param. 7
Param. 1, Rapid onset of action							
Param. 2, Duration of action	<0.001						
Param. 3, Ease of use	<0.001	0.0683					
Param. 4, Low flow resistance	<0.001	<0.001	<0.001				
Param. 5, Ability of the device to confirm the dose	<0.001	<0.001	<0.001	0.0005			
Param. 6, Type of inhalation device	<0.001	<0.001	<0.001	0.0004	0,0360		
Param. 7, The formulation of the drug	<0.001	<0.001	<0.001	<0.001	0.3268	<0.001	

Note: P-values<0.0024 (Statistically significant difference between the two parameters) are marked with yellow colour.

Comparison of parameters influencing the compliance between patients with COPD and asthma

The following parameters were differentiated in the comparison between patients with Asthma and COPD patients,: Rapid onset of action was ranked statistically significantly lower (more important-influential) in Asthmatic patients, Low flow resistance was ranked statistically significantly higher (less important-influential) in Asthmatic patients, duration of action and ease of use were marginally statistically significantly higher (less important-influential) in Asthmatic patients (Table 4).

Discussion

In this study surveying the opinion of physicians treating patients with chronic obstructive airways diseases (asthma and COPD), rapid onset of action, ease of use and duration of action were the most important parameters favoring patients' compliance for both diseases.

As expected, rapid onset of action was the most important factor influencing compliance both in COPD and asthma. Interestingly, it was statistically more important in asthma than in COPD. This finding reflects the difference in pathophysiology and clinical behavior between asthma in COPD as perceived by physicians. In general, asthma is considered a disease which is more likely to be complicated with

Table 3 Descriptive statistics regarding the seven parameters influencing the compliance of patients with COPD. Scale: 1 = 1st most important, 7 = 7th least important. P-values of the 21 applications of Wilcoxon signed-rank test. Base: Observed cases (N = 138).

	Mean	Median	SD	SE	Range	N
Param. 1. Rapid onset of action	2.62	2.00	2.05	0.17	6.00	138
Param. 2. Duration of action	3.01	2.00	1.78	0.15	6.00	138
Param. 3. Ease of use	2.72	3.00	1.40	0.12	6.00	138
Param. 4. Low flow resistance	3.97	4.00	1.55	0.13	6.00	138
Param. 5. Ability of the device to confirm the dose	5.26	5.00	1.37	0.12	5.00	138
Param. 6. Type of inhalation device	4.88	5.00	1.52	0.13	6.00	138
Param. 7. The formulation of the drug	5.53	6.00	1.75	0.15	6.00	138

p-values of the 21 applications of Wilcoxon signed-rank test (alpha=0.0024)	Param. 1	Param. 2	Param. 3	Param. 4	Param. 5	Param. 6	Param. 7
Param. 1, Rapid onset of action							
Param. 2, Duration of action	0.0247						
Param. 3, Ease of use	0.5336	0.1928					
Param. 4, Low flow resistance	<0.001	0.0001	<0.001				
Param. 5, Ability of the device to confirm the dose	<0.001	<0.001	<0.001	<0.001			
Param. 6, Type of inhalation device	<0.001	<0.001	<0.001	<0.001	0.0641		
Param. 7, The formulation of the drug	<0.001	<0.001	<0.001	<0.001	0.0817	<0.001	

Note: P-values<0.0024 (Statistically significant difference between the two parameters) are marked with yellow colour.

Table 4 Mean and Median values regarding the seven Parameters influencing the compliance of patients with ASTHMA/ COPD. P-values of the 7 applications of Wilcoxon signed-rank test. Base: Observed cases (N = 138).

Parameters	ASTHMATIC		COPD		P-VALUE
	Mean	Median	Mean	Median	(alpha=0.007)
Param. 1, Rapid onset of action	1.6	1.0	2.6	2.0	<0.001
Param. 2, Duration of action	3.3	3.0	3.0	2.0	0.0437
Param. 3, Ease of use	3.0	3.0	2.7	3.0	0.0482
Param. 4, Low flow resistance	4.3	4.0	4.0	4.0	0.0038
Param. 5, Ability of the device to confirm the dose	5.4	5.0	5.3	5.0	0.2468
Param. 6, Type of inhalation device	5.0	5.0	4.9	5.0	0.4422
Param. 7, The formulation of the drug	5.5	6.0	5.5	6.0	0.4871

Note: P-values marginally <0.05 are marked with blue colour, while p-values <0.005 are marked with yellow colour.

episodes of acute shortness of breath in need of immediate relief. Duration of action was also considered as an important parameter influencing compliance, irrespective of the underlying diagnosis. This parameter was numerically more important in COPD compared to asthma. Duration of action is clinically relevant for bronchodilators as their duration of action has a direct impact on patients' symptoms and therefore compliance. The above physicians views also correlate with patients' perspectives.[11] The fact that adverse events were not considered at all as an important compliance factor, confirms the strong belief of physicians in the safety of inhaled medications. Ease of use was also considered as a key factor for compliance. In asthma ease of use is especially important during an acute event of dyspnea needing immediate relief. In COPD patients, who are usually older with several comorbidities ease of use is also an understandable parameter that can affect compliance.

The increased number of inhaler devices in recent years has resulted in a confusing number of choices for physicians and patients. The prescribing physician must balance the efficacy of inhaled medications with patients' preferences, personality traits and their physical ability to handle devices appropriately. The selection of an inhalation device for patients with asthma and COPD has become a complicated issue as several parameters should be taken into account, such as: device/drug availability, clinical setting, patient age, the ability to use the selected device correctly, device use with multiple medications, cost and reimbursement, drug administration time, convenience in both outpatient and inpatient settings, and physician and patient preference, as stated previously.[12–16] Unfortunately, such studies are scarce in the literature.

Strengths of this study are the detailed questionnaire, and the relatively high number of respondents. However, we acknowledge certain limitations of the study. First, we recognize that we explored a complex issue which is difficult to approach by öne- shot strong and direct answers'' as the answers do not take into account the individualization of the patient path, the level of functional severity, the different phenotypes, the age of the patient and the patient's history. Another limitation is that this study exclusively included specialists and lacks the views of general practitioners. Thus, the results cannot be generalized for non-specialists. Furthermore, the study reflects the beliefs of the physicians of a single country and comparative studies among different countries could provide significant insights. Given the limited number of relevant studies, the present work adds to our understanding of physicians' perspectives on patient compliance.

In conclusion, rapid onset of action, ease of use and duration of action, were classified higher among the parameters examined. Further studies are needed among physicians of different specialties and nationalities to identify more rigorously factors increasing patient compliance. Evidence-based guidelines for the selection of the appropriate inhalation device in specific clinical settings are needed.

Conflict of interest

All authors have no conflicts of interest to disclose.

References

1. Mirza S, Clay RD, Koslow MA, Scanlon PD. COPD Guidelines: A Review of the 2018 GOLD Report. Mayo Clin Proc. 2018;93:1488–502.
2. Barrecheguren M, Gonzalez C, Miravitlles M. What have we learned from observational studies and clinical trials of mild to moderate COPD? Respir Res. 2018;19:177.
3. Dharmage SC, Perret JL, Custovic A. Epidemiology of Asthma in Children and Adults. Front Pediatr. 2019;7:246.
4. Sanduzzi A, Balbo P, Candoli P, et al. COPD: adherence to therapy. Multidisciplinary Respir Med. 2014;9:60.
5. George M. Adherence in Asthma and COPD: New Strategies for an Old Problem. Respir Care. 2018;63:818–31.
6. Baddar S, Jayakrishnan B, Al-Rawas OA. Asthma control: importance of compliance and inhaler technique assessments. J Asthma. 2014;51:429–34.
7. Ngo CQ, Phan DM, Vu GV, et al. Inhaler Technique and Adherence to Inhaled Medications among Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Vietnam. Int J Environ Res Public Health. 2019;16.
8. Koehorst-Ter Huurne K, Groothuis-Oudshoorn CG, vanderValk PD, Movig KL, van der Palen J, Brusse-Keizer M. Association between poor therapy adherence to inhaled corticosteroids and tiotropium and morbidity and mortality in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2018;13:1683–90.
9. Sicras-Mainar A, Huerta A, Sánchez D, Navarro-Artieda R. [Use of resources and costs associated with non-adherence to inhaled corticosteroid treatment in asthma]. Semergen. 2018;44:13–22.
10. Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir Med. 2013;107:1481–90.
11. Ambrosino N, Bertella E. Lifestyle interventions in prevention and comprehensive management of COPD. Breathe (Sheffield, England). 2018;14:186–94.
12. Alismail A, Song CA, Terry MH, Daher N, Almutairi WA, Lo T. Diverse Inhaler Devices: A Big Challenge for Health-Care Professionals. Respir Care. 2016;61:593–9.
13. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest. Chest. 2005;127:335–71.
14. Bouros D, Evangeliou MN. Critical Steps: A Non-Interventional, Multicenter, Prospective, Observational Study on Critical Handling Errors with DPI Use, in Asthma and COPD Patients. J Pulm Respir Med. 2016;6:4.
15. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest. 2005;127:335–71.
16. Melethil S, Yousaf M, Yousaf A. Physicians perspective and preference in the choice of metered dose inhaler with spacer vs nebulizer. Ann Allergy Asthma Immunol. 2018;121:S22–62.

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ORIGINAL ARTICLE

Comparative bench study evaluation of a modified snorkeling mask used during COVID-19 pandemic and standard interfaces for non-invasive ventilation

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Received 26 January 2021; accepted 23 May 2021
Available online 8 June 2021

KEYWORDS
Covid-19;
Non-invasive ventilation;
Mechanical ventilation;
ARDS

Abstract
Purpose: The aim of this bench study is to compare the standard NIV and nCPAP devices (Helmet, H; Full face mask, FFM) with a modified full face snorkeling mask used during COVID-19 pandemic.
Methods: A mannequin was connected to an active lung simulator. The inspiratory and expiratory variations in airways pressure observed with a high simulated effort, were determined relative to the preset CPAP level. NIV was applied in Pressure Support Mode at two simulated respiratory rates and two cycling-off flow thresholds. During the bench study, we measured the variables defining patient-ventilator interaction and performance.
Results: During nCPAP, the tested interfaces did not show significant differences in terms of ΔPawi and ΔPawe.

During NIV, the snorkeling mask demonstrated a better patient-ventilator interaction compared to FFM, as shown by significantly shorter Pressurization Time and Expiratory Trigger Delay ($p < 0.01$), but no significant differences were found in terms of Inspiratory Trigger Delay and Time of Synchrony between the interfaces tested. At RR 20sim, the snorkeling mask presented the lower ΔPtrigger ($p < 0.01$), moreover during all the conditions tested the snorkeling mask showed the longer Pressure Time Product at 200, 300, and 500 ms compared to FFM ($p < 0.01$). A

Abbreviations: ICUs, Intensive care units; nCPAP, Non-invasive continuous positive airway pressure; NIV, Non-invasive ventilation; Pmus, Simulated effort; PSV, Pressure support ventilation; WHO, World Health Organization; ARDS, Acute respiratory distress syndrome; PaO_2/FiO_2, Inspired oxygen fraction ratio; RRsim, Simulated respiratory rate; iPS, Inspiratory pressure support; ΔPawi, Maximum inspiratory deflection; ΔPawe, Expiratory peak; TI, Mechanical inspiratory time; TE, Mechanical expiratory time; VT, Tidal volume; VT_{neu}, Neural tidal volume; Ttot, Total mechanical breath duration; Paw, Airway opening pressure; ΔPtrigger, Trigger pressure drop; PTPt, Inspiratory pressure-time product; PTP, Pressure time product; $Time_{press}$, Pressurization time; $Delaytr_{insp}$, Inspiratory trigger delay; $Delaytr_{exp}$, Expiratory trigger delay; $Time_{sync}$, Time of synchrony.

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https://doi.org/10.1016/j.pulmoe.2021.05.009

major limitation of snorkeling mask is that during NIV with this interface it is possible to reach maximum 18 cmH_2O of peak inspiratory pressure.
Conclusions: The modified snorkeling mask can be used as an acceptable alternative to other interfaces for both nCPAP and NIV in emergencies.

Introduction

In March 2020, the World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak a pandemic, due to the increasing number of cases reported worldwide,[1] with high rates of hospitalization and ICU admission.[2] The high number of SARS-CoV-2 cases initially in Lombardy, and subsequently throughout the whole country, made Italy one of the most affected countries in Europe.[3]

As happened in March 2020, wherein Lombardy in few days a total of 1593 patients, affected by severe respiratory failure due to COVID-19, were admitted to the ICU,[4] out of a total of 1202 ICU beds available,[2] the National health care system is now again under pressure from a growing second wave of patients hospitalized or admitted to ICU for acute respiratory failure.

COVID-19 is characterized by a viral interstitial pneumonia[5] with fever, dry cough, dyspnoea, and bilateral ground-glass opacities,[6] with about 67% of patients evolving to severe pneumonia.[7,8]

Preliminary reports described that COVID-19 patients, compared to conventional Acute Respiratory Distress Syndrome (ARDS), are characterized by moderate to severe hypoxemia despite a relatively high pulmonary compliance.[9,10] Due to the enormous number of COVID-19 patients with acute respiratory failure and to the shortage of ICU beds and ventilators, in many Italian hospital, the management of patients with respiratory failure was entrusted to Non-Invasive Ventilation (NIV) or Non-invasive continuous positive airway pressure (nCPAP).

Several respiratory managements were applied to treat ARDS COVID 19 related. The High flow nasal cannula was used, also as first-line therapy, in Chine, and in USA (although with a high risk of air contamination). The NIV or CPAP were applied in hospitalized patients in China, Italy, and USA with the same proportion (20%, 11% and 19%).[11]

In particular, in a scenario of a discrepancy between facilities and a large number of casualties, as with COVID-19 pandemic, the application of NIV or nCPAP has been useful as a respiratory supportive strategy, especially in patients with mild to moderate ARDS and a PaO_2 to Inspired oxygen fraction ratio (PaO_2/FiO_2) >150. In our country, the Helmet[4,10] has been the most widely used device for non-invasive respiratory support during COVID-19 outbreaks both in general wards and in ICU.[10]

Unfortunately, a major problem of ventilator and device for NIV shortages rapidly emerged because of the further spread of the virus in other regions of Italy. To relieve the pressure on our National Health System, a device converting a full-face snorkeling mask into a mask for CPAP or NIV has been designed and proposed for clinical use, with the help of 3D printers.

Given the large diffusion of this modified full face snorkeling mask in COVID-19 patients, we designed this bench study to evaluate and compare a helmet, a full-face mask, and a modified full face snorkeling mask in delivering nCPAP and NIV in Pressure Support Ventilation mode (PSV).

Methods

The study was performed at the Respiratory Mechanics Lab (Ventilab) of the Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore in Rome, Italy.

Bench study

Non-invasive CPAP and non-invasive positive pressure ventilation delivered in PSV mode were applied to a mannequin (LaerdalMedical AS, Stavanger, Norway) connected to an active test lung system (ASL 5000; Ingmar Medical, Pittsburgh, PA) set using a single-compartment model, an active inspiration simulated by a semi-sinusoidal pressure waveform (Rise Time 15%, Pause 0% and Release Hold 25%) and the following mechanical properties of the respiratory system: resistance 5 $cmH_2O/l/s$ and compliance 40 ml/cmH_2O. nCPAP was applied via Helmet (H) (CPAP-Castar Starmed, Mirandola, Italy), PerforMax Full face mask (Philips Respironics, Murrysville, PA, USA) (FFM), and a modified full face snorkeling mask (SEA VU DRY, Mares Spa, Rapallo, Italy), while non-invasive PSV was delivered through FFM and snorkeling mask. The Helmet used for this bench study is a transparent latex-free polyvinylchloride hood, joined by a rigid plastic ring to a soft collar and secured by two padded armpit braces at four hooks (two in the front and two in the back of the plastic ring). The helmet used was the size Small to attain a good seal and avoid air-leaks.

The snorkeling mask total internal volume is 1350 ml, but the mouth-and-nose pocket internal volume is only 80 ml, while the FFM internal volume is 500 ml and the H internal volume is 15,000 ml (a real pressurized gas reservoir during inspiration).

The snorkeling mask differs from Performax full face mask for shape and design characteristic; it presents a complete separation between inspiratory and expiratory circuits with the following main features: hypoallergenic silicone mouth-and-nose pocket connected to a polycarbonate transparent main body; quick-release buckles for easy doffing and a polycarbonate Charlotte valve with an inspiratory and

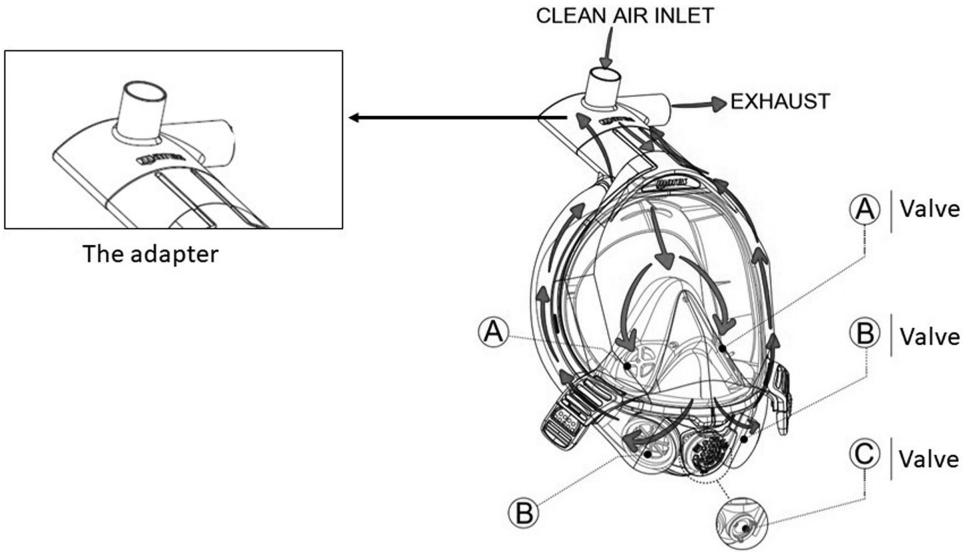

Figure 1 Mares snorkeling mask features: presence of two separate limbs; the inspiratory one is highlighted by blue arrows, the expiratory one by red arrows. The adapter created with 3 d printers features two channels: the central upward-pointing channel is the inspiratory channel, the side channel is the expiratory channel.

an expiratory channel. See Fig. 1 for details. The snorkeling mask presents two parallel connections with a complete separation between inspiratory and expiratory limbs, while Performax Full face mask is characterized by a single limb connected to the Y piece. The measure of masks used was the medium size for FFM and large size for snorkeling mask to attain a good seal and avoid air-leaks. nCPAP (10 cmH_2O) was applied at a simulated respiratory rate (RRsim) of 20 breaths per min (b/min) and a simulated level of inspiratory effort (Pmus) of 12 cmH_2O, using a standard CPAP device delivering a flow rate of 60 l/min with reservoir (Drager CF 800 Continous Flow CPAP System; Dragerwerk AG & Co, Lubeck, Germany). During nCPAP test we applied a PEEP valve in the expiratory limb.

NIV in PSV mode was delivered at 2 RRsim (20 and 30 b/min) and a Pmus of 12 cmH_2O with the mechanical ventilator (Puritan Bennet 840; Covidien Health-Care, Mansfield, MA) set in inspiratory pressure support (iPS) of 10 cmH_2O, Positive End-Expiratory Pressure (PEEP) of 8 cmH_2O, the fastest rate of pressurization, and a cycling-off flow threshold of 25 and 50% of the peak inspiratory flow. We set the inspiratory flow trigger at the lowest value not determining autocycling: this threshold was 5 L/min during all conditions tested. This setting was chosen for comparing the performance of these interfaces under the condition of highest pressurization rate and fast or slow cycling-off criteria.[12]

Measurements

Air flow (V′) was measured with a pneumotachograph (Fleish No.1, Metabo, Epalinges, Switzerland), while airway pressure (Paw) was measured by a pressure transducer with a differential pressure of ±100 cmH2O (Digima Clic-1, ICULab system; KleisTek Engineering, Bari, Italy), placed distally from the pneumotachograph. Airflow (V') and airway pressure (Paw) at the helmet inlet during the inspiratory phase were measured using a pneumotachograph (Fleisch n.2; Metabo, Epalinges, Switzerland) and a pressure transducer with a differential pressure of ±100 cmH_2O (Digima Clic-1; KleisTEK, ICU-Lab System, Italy) sited at the distal end of the inspiratory limb of the circuit. When the mannequin was ventilated through the FFM, the pneumotachograph and the pressure transducer were positioned at the Y-connection of the ventilator circuit, instead, when we tested the snorkeling mask the pneumotachograph and the pressure transducer were positioned on the inspiratory channel. All these signals were acquired, amplified, filtered, digitized at 100 Hz, recorded on a dedicated personal computer, and analyzed with specific software (ICU lab 2.3; KleisTEK Advanced Electronic System, Italy and Analysis Plus).

Each trial lasted 5 min; the breaths of the last minute (20 or 30 depending on the trial) were recorded and averaged for analysis.

The measured variables assessed during nCPAP were the maximum inspiratory deflection (ΔPawi, inspiratory drop) and the expiratory peak (ΔPawe), calculated as differences from the preset CPAP level.

During the NIV test, we evaluated the following variables: Ventilator inspiratory and expiratory time (mechanical TI and mechanical TE, respectively), and ventilator rate of cycling were all determined on the flow tracing. The inspiratory duty cycle (mechanical TI/Ttot) was calculated as the ratio between mechanical TI and the total mechanical breath duration (Ttot). Airflow (V′) and tidal volume (VT) delivered to the simulator, airway opening pressure (Paw), and inspiratory muscles effort were displayed online on the computer screen. The signals obtained with the ASL were transmitted to a PC host via 10/100MBit Ethernet, sampled, and processed in real-time by means of specific software (Lab View, Ingmar Medical). The signals obtained with the ASL were integrated with the signals from the ICULab system by using a specific application of the ICULab (ICULab 2.7, KleisTek). The numerical integration of flow over time determined the mechanical tidal volume (mechanical VT). The amount of tidal volume delivered to the simulator during its

active inspiration (i.e., the neural tidal volume, VT_{neu}) was calculated as the volume generated from the onset of inspiratory muscle effort negative deflection to its nadir.

Interfaces performance was evaluated using the following parameters[12−14]:

1) Trigger pressure drop (ΔPtrigger), defined as the pressure swing generated by the simulator inspiratory effort in the airway during the triggering phase; 2) Inspiratory pressure−time product (PTPtrigger), defined as the area under the Paw curve relative to the time between the onset of inspiratory effort and the start of mechanical assistance; 3) pressure-time product at 200 ms from the onset of the ventilator pressurization (PTP200), as the index of pure pressurization performance[15]; 4)Pressure-time product at 300 ms (PTP300) defined as the integration of Paw over time during the first 300 msec and representing the speediness of the ventilator in reaching the preset level of pressure support; 5) Pressure-time product at 500 ms (PTP500), defined as the integral Paw area over insufflation time from the simulated effort onset, representing the ventilator capability of maintaining the pressurization; 6) PTP500 ideal index, expressed as a percentage of the ideal PTP, which is unattainable because it would imply a trigger pressure drop and an instantaneous pressurization of the ventilator (Fig. 2).

Patient-ventilator interaction was evaluated by determining:

1) Pressurization time ($Time_{press}$), defined as the time necessary to achieve the pre-set level of pressure support from the baseline value; 2) Inspiratory trigger delay ($Delaytr_{insp}$), calculated as the time lag between the onset of inspiratory muscle effort negative swing and the start of the ventilator support (i.e., Paw positive deflection); 3) Expiratory trigger delay ($Delaytr_{exp}$), assessed as the delay between the end of the inspiratory effort and the end of the mechanical insufflations (i.e., flow deflection); 4) Time of synchrony ($Time_{sync}$), defined as the time during which inspiratory muscle effort and Paw are in phase (ideally 100%); 5) SimulatorVT/mechanicalVT, intended as the percentage of VT delivered during inspiratory muscle effort negative deflection; 6) The time during which simulator respiratory effort and ventilator assistance were synchronous, indexed to simulated inspiratory time ($Time_{sync}/Ti_{neu}$) was also computed[16−18]. 7) Wasted efforts, defined as ineffective inspiratory efforts, not assisted by the ventilator; 8) Autotriggering, namely a mechanical insufflation in absence of inspiratory effort.

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD). Categorical data were presented as numbers and percentages in brackets. All variables were compared with each interface used. Comparisons were made by Student's *t*-test and Chi test, as appropriate. The analysis of variance (ANOVA) for repeated measures was used to detect significant differences between the different experimental conditions. When significant differences were detected, a post-hoc analysis was performed using the Bonferroni test; p values < 0.05 were considered statistically significant. Statistical analysis was performed using MEDcalc version 18.6.

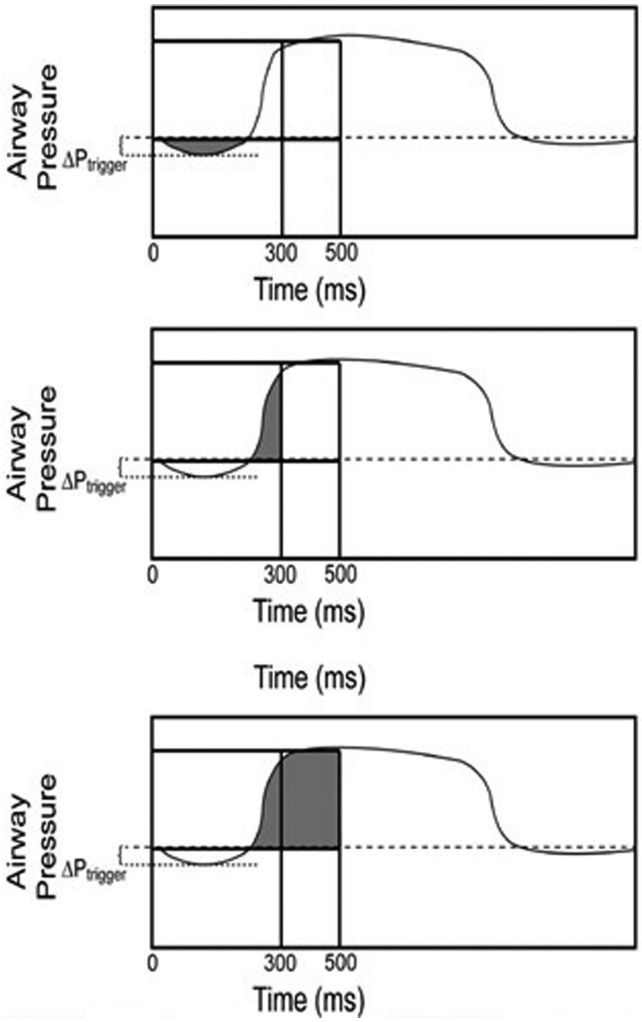

Figure 2 Inspiratory pressure-time product (PTP), PTP at 300 ms, and PTP at 500 ms on the pressure/time trace.

Results

As shown in Fig. 3, during nCPAP, no significant difference in ΔPawi and ΔPawe was observed between the three tested interfaces (ΔPawi $p = 0.67$; ΔPawe $p = 0.10$).

Patient-ventilator interaction described by the measurement of $Delaytr_{insp}$, $Time_{press}$, and $Delaytr_{exp}$ during NIV delivered through the snorkeling mask and FFM are shown in Figs. 4 and 5. At both RRsim tested and both ventilator settings, the snorkeling mask showed a significantly shorter $Time_{press}$ and $Delaytr_{exp}$ compared to FFM ($p < 0.01$). Under all conditions, no significant differences were found in terms of $Delaytr_{insp}$, $Time_{sync}$ (Fig. 6), and $Time_{synch}/Ti_{neu}$ between all the interfaces tested. Under all study conditions, the volume delivered with the snorkeling mask was higher than that delivered with the FFM ($p < 0.01$) (Table 1).

The trigger and pressurization performances of the two masks during NIV are shown in Tables 2 and 3. At RRsim 20,

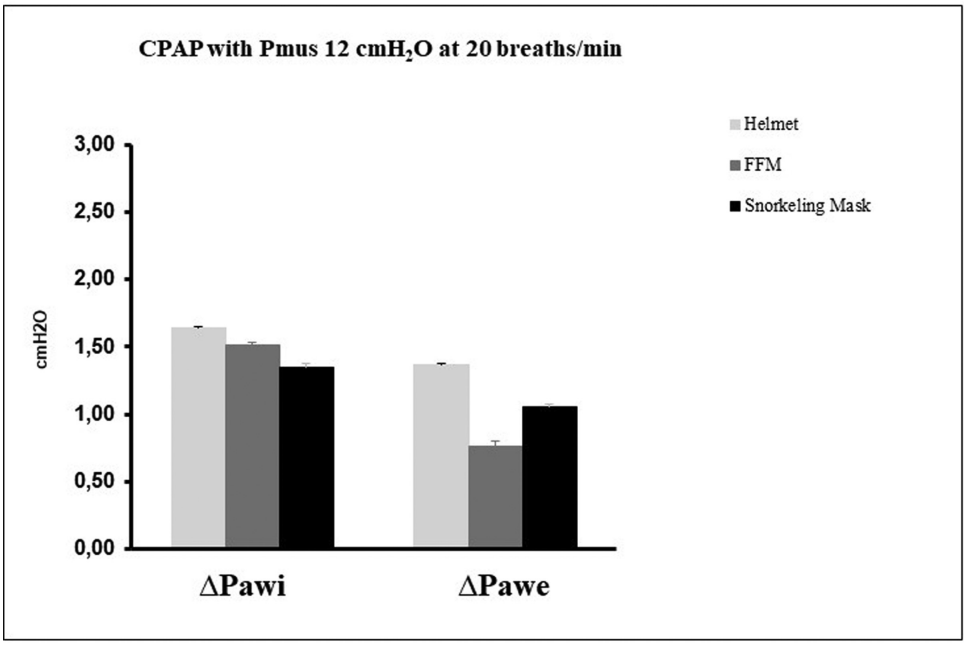

Figure 3 Maximum inspiratory deflection (ΔPawi, inspiratory drop) and the expiratory peak (ΔPawe), during CPAP with Helmet (light gray column), PerforMax Full face mask (FFM, dark gray column) and snorkeling mask (black column) at 20 breaths/min.

the snorkeling mask showed a significantly lower ΔPtrigger than FFM ($p < 0.01$), while no difference was found at RRsim 30. No significant differences were found in terms of PTPtrigger between the interfaces during all tested conditions.

Significant differences in PTP 200, PTP 300, and PTP 500 were found between the snorkeling mask and FFM ($p < 0.01$) in all conditions tested. The snorkeling mask demonstrated a significantly higher capacity to maintain the pressurization at 200, 300, and 500 ms after opening the inspiratory valve.

In all settings, no asynchrony phenomena were detected with both interfaces.

During the NIV test, with the snorkeling mask it was possible to reach a maximum of 18 cmH_2O of peak inspiratory applied pressure. Over this pressure, the presence of air leaks determined important continuous asynchrony phenomena (as continuous auto cycling and double triggering), not modifiable with a change in flow or pressure trigger.

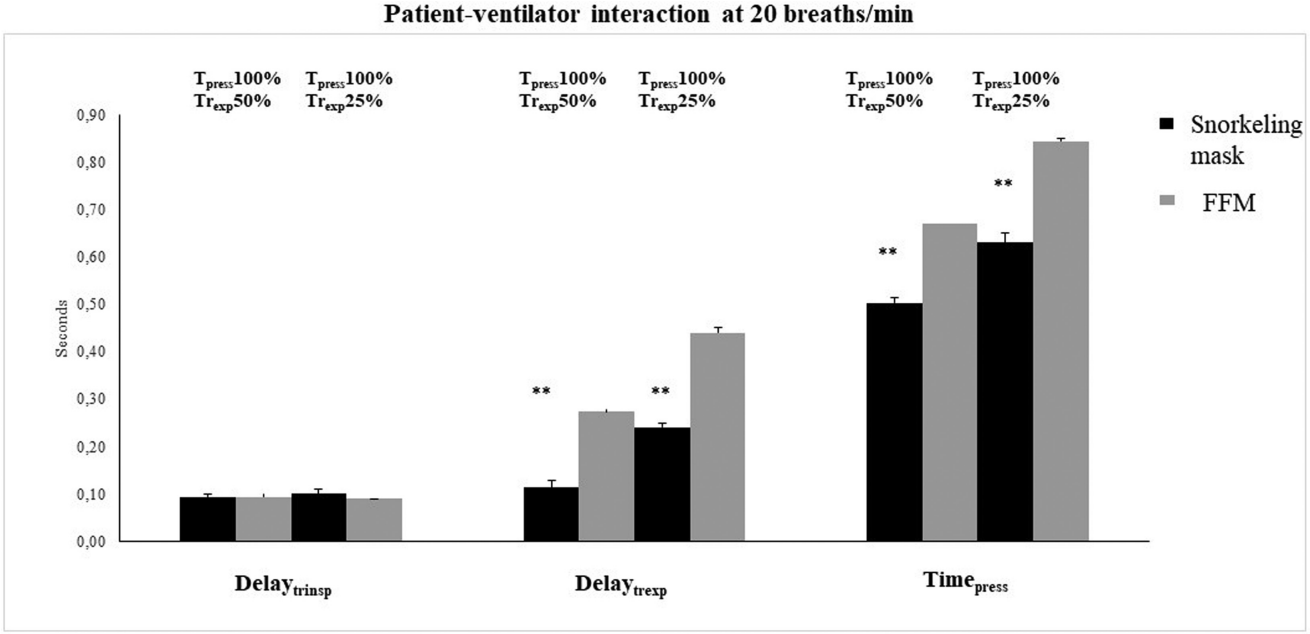

Figure 4 Inspiratory trigger delay ($Delaytr_{insp}$), Expiratory Trigger delay ($Dealytr_{exp}$), and Pressurization Time ($Time_{press}$) with the snorkeling mask (black column) and the PerforMax Full face mask (FFM) (gray column) at 20 breaths/min, with 2 ventilator settings.

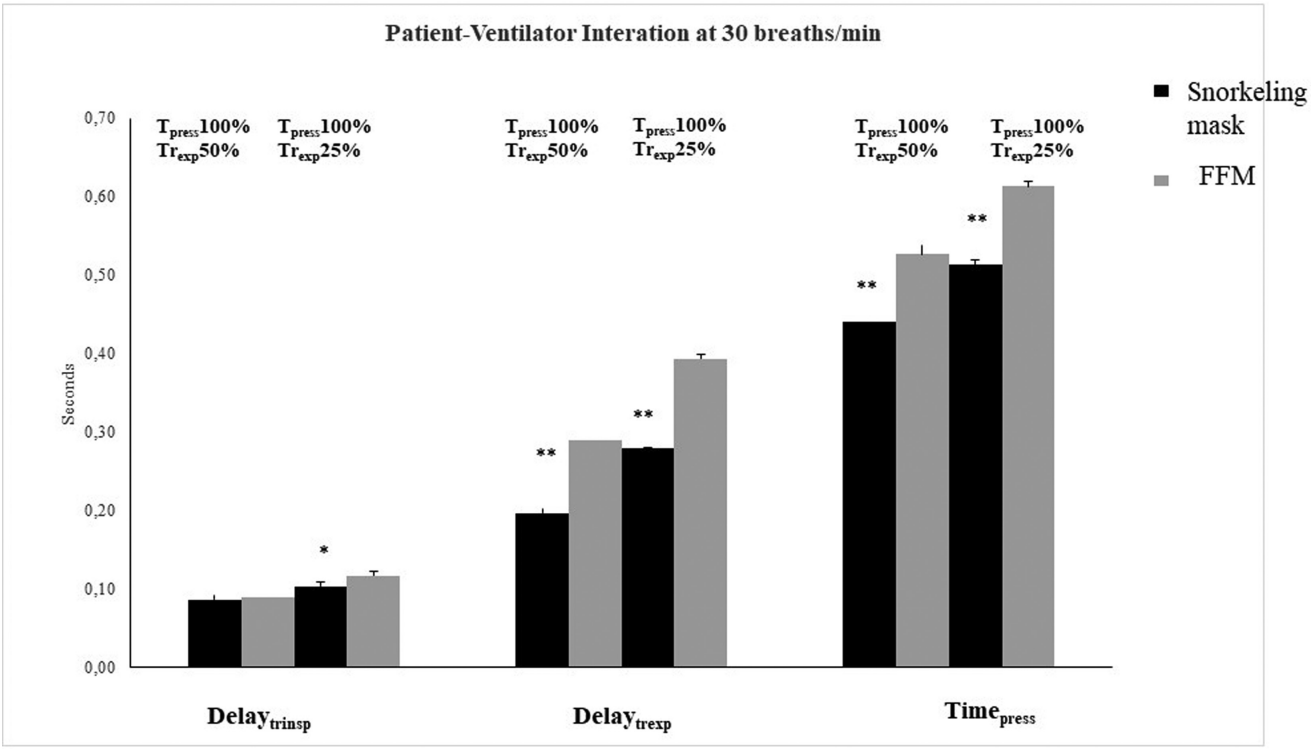

Figure 5 Inspiratory trigger delay ($Delaytr_{insp}$), Expiratory Trigger delay ($Dealytr_{exp}$), and Pressurization Time ($Time_{press}$) with the snorkeling mask (black column) and the PerforMax Full face mask (FFM) (gray column) at 30 breaths/min, with 2 ventilator settings.

Discussion

In this bench study, during nCPAP, the interfaces tested showed a similar performance. Instead, during NIV, the snorkeling mask outperformed the FFM for most of the variables considered and in most of the simulated settings.

During the recent SARS-CoV-2 pandemic, early non-invasive respiratory support allowed for the treatment of a large number of patients with respiratory distress to prevent ICU admission. For several reasons, the CPAP application by Helmet represented the first choice of treatment in patients with mild to moderate COVID-19 related ARDS. The Helmet

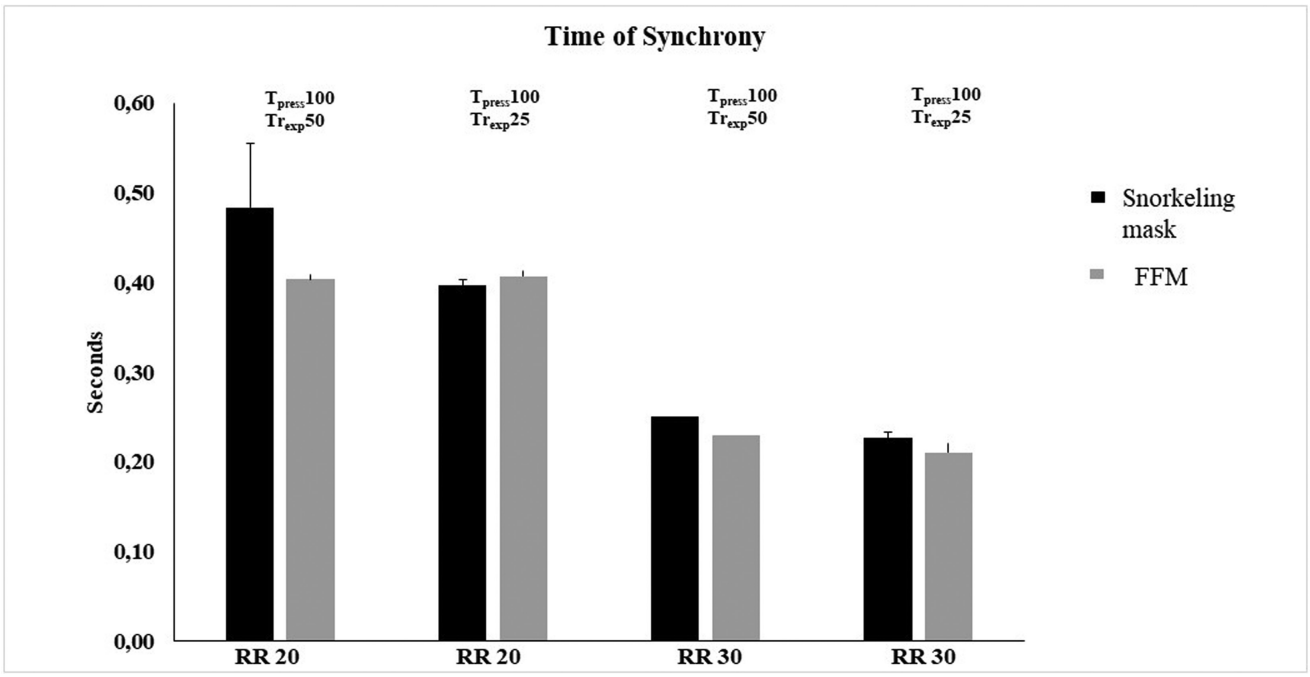

Figure 6 Time of synchrony with the snorkeling mask (black column) and the PerforMax Full face mask (FFM) (gray column) at two respiratory rates (RR 20 and 30 breaths/min), with 2 ventilator settings.

Table 1 Tidal volume delivered with the different interfaces tested.

	Snorkeling mask	*FFM*		*Snorkeling mask*	*FFM*	
	RR 20 Timepress100%/ Trexp50%	*RR20 Timepress100%/ Trexp50%*	*P*	*RR 20 Timepress100%/ Trexp25%*	*RR20 Timepress100%/ Trexp25%*	*P*
VTmech (ml)	754.33±5.77	676±0.00	0.001	814.33±5.77	694±0.00	0.001
VTneu (ml)	606.33± 5.77	459±5.20	0.001	603±0.00	459±5.2	0.001
VTneu/VTmech (%)	80%	68%	0.001	74%	66%	0.001
	Snorkeling mask	*FFM*		*Snorkeling mask*	*FFM*	
	RR 30 Timepress100%/ Trexp50%	*RR30 Timepress100%/ Trexp50%*	*P*	*RR 30 Timepress100%/ Trexp25%*	*RR30Timepress 100%/Trexp25%*	*P*
VTmech (ml)	724.33±5.77	586±5.2	0.001	739.67±6.35	566.33±5.77	0.001
VTneu (ml)	417.33±5.77	304±9.00	0.001	378±0.00	276±0.00	0.001
VTneu/VTmech (%)	58%	52%	0.001	51%	49%	0.02

VT_{mech}, mechanical tidal volume; VT_{neu}, neural tidal volume; VT_{neu}/VT_{mech}, the percentage of tidal volume delivered during inspiratory simulated muscle effort negative deflection; FFM, respironics PerforMax full face mask; RR, respiratory rates.

Table 2 Performance of the interfaces during NIV at 20 RRsim.

	Snorkeling mask	*FFM*		*Snorkeling mask*	*FFM*	
	RR 20 Timepress100%/ Trexp50%	*RR20 Timepress100%/ Trexp50%*	*P*	*RR 20 Timepress100%/ Trexp25%*	*RR20 Timepress100%/ Trexp25%*	*P*
ΔPtrigger (cmH_2O)	1.05±0.01	0.72±0.05	0.004	1.03±0.05	0.78±0.04	0.014
PTPt (cmH_2O/s)	0.04±0.01	0.03±0.01	1	0.05±0.00	0.03±0.00	0.001
PTP200 (cmH_2O/s)	0.88±0.05	0.57±0.09	0.013	0.87±0.12	0.57±0.05	0.04
PTP300 (cmH_2O/s)	2.04±0.08	1.22±0.09	0.004	1.97±0.03	1.21±0.05	0.001
PTP500 (cmH_2O/s)	4.49±0.09	2.66±0.11	0.001	4.35±0.03	2.67±0.03	0.001
PTP500 ideal index (%)	72	56	0.45	71	51	0.5

ΔPtrigger, trigger pressure drop; PTPt, pressure time product during the triggering phase; Paw, airway pressure; PTP200, PTP300 and PTP500, pressure time product during the initial 200, 300 and 500 ms from the onset of the ventilator pressurization expressed as the absolute value; PTP500 ideal index, pressure time product during the initial 500 ms from the onset of the simulated effort, expressed as the percentage of the area of ideal pressurization, with different ventilator settings (see text); FFM, respironics PerforMax full face mask; RR, respiratory rates.

Table 3 Performance of the interfaces during NIV at 30 RRsim.

	Snorkeling mask	*FFM*		*Snorkeling mask*	*FFM*	
	RR 30 Timepress100%/ Trexp50%	*RR30 Timepress100%/ Trexp50%*	*P*	*RR 30 Timepress100%/ Trexp25%*	*RR30 Timepress100%/ Trexp25%*	*P*
ΔPtrigger (cmH_2O)	1.28±0.04	1.75±0.47	0.11	1.94±0.23	2.05±0.11	0.31
PTPt (cmH_2O/s)	0.06±0.01	0.10±0.04	0.12	0.11±0.02	0.13±0.01	0.16
PTP200 (cmH_2O/s)	0.98±0.07	0.56±0.10	0.02	0.63±0.15	0.32±0.03	0.04
PTP300 (cmH_2O/s)	2.26±0.07	1.29±0.10	0.002	1.91±0.08	1.07±0.10	0.006
PTP500 (cmH_2O/s)	5.09±0.03	3.05±0.12	0.007	4.69±0.16	2.77±0.11	0.003
PTP500 ideal index (%)	71	56	0.22	68	48	0.3

ΔPtrigger, trigger pressure drop; PTPt, pressure time product during the triggering phase; Paw, airway pressure, PTP200, PTP300 and PTP500, pressure time product during the initial 200, 300 and 500 ms from the onset of the ventilator pressurization expressed as the absolute value; PTP500 ideal index, pressure time product during the initial 500 ms from the onset of the simulated effort, expressed as the percentage of the area of ideal pressurization, with different ventilator settings (see text); FFM, respironics PerforMax full face mask; RR, respiratory rates.

was demonstrated to be an effective alternative to a face mask in recruiting alveolar units and improve hypoxemia. It can also limit air-leaks and room contamination, increasing the patient's comfort and is better tolerated than the face mask, requiring fewer discontinuations.[10,19,20] The choice of Helmet as privileged interface applied during treatment of ARDS COVID-19 related is affected by the high diffusibility of SARS-CoV-2 infection. This characteristic of the recent pandemic SARS-CoV-2 infection can increase the level of biological hazard to which healthcare workers are exposed thus requiring the use of personal protective equipment (PPE).[21]

Unfortunately, the enormous demand for helmet CPAP resulted in a rapid lack of supply, so many laboratories, to try to fill this gap, started to readjust snorkeling masks into devices for respiratory support.

We, therefore, decided to compare the modified snorkeling mask with the Helmet and one of the most popular full face masks (PerforMax full face mask), during CPAP. We applied CPAP at 10 cmH_2O because this is a value most commonly applied in this clinical setting.[22,23]

In our nCPAP bench study evaluation, the snorkeling mask presented a similar performance in terms of ΔPawi and ΔPawe compared to the other interfaces tested.

The snorkeling mask showed stability in maintaining the PEEP level applied during nCPAP.

The snorkeling mask was initially proposed as an alternative to the helmet for CPAP, but during the emergency, it was often used also for NIV. Therefore, we decided to compare this interface with one of the most popular interfaces used in ICU for NIV (FFM). We limited the comparison only to the FFM because, as previously demonstrated by Chiumello et al.,[24] in pressure support mode, the mask was more efficient than the helmet. In fact, with the helmet, the initial part of the inspiratory pressure applied is dissipated to pressurize its soft wall. Accordingly, Navalesi et al.[25] demonstrated that the helmet significantly worsens patient-ventilator synchrony, when compared to the facemask, as indicated by longer delays between inspiratory muscle effort and support delivery, both at the onset and at the end of inspiration, and by the occurrence of wasted efforts.

Several NIV interfaces, such as Full face mask and Helmet, are characterized by high compliance due to material features that can influence patient-ventilator interaction, and interface performance.

One of the reasons for choosing Respironics mask for this bench study was that this model has relatively low compliance.

For NIV settings, the values of the simulated effort, RRsim, resistance, and compliance, were those already utilized in previous investigations.[26,27] The snorkeling mask demonstrated the better simulated patient-ventilator interaction compared to FFM, as shown by shorter $Time_{press}$ and $Delay_{trexp}$. These results are further validated by interface performance data. Probably the better performance underlined by lower ΔPtrigger, and higher PTP 200, 300, and 500 can be explained by the reduced snorkeling mask inner volumes and its materials (Fig. 1). A prerogative of this mask is the presence of two separate limbs. The fresh air enters through the snorkel's central channel, passing the lens, and keeping it fog-free. It then enters the oral-nasal pocket through non-return valves and flows towards the nose and mouth. The oral-nasal pocket's structure guides exhaled CO2 through 4 no-return valves:

- 2 no-return valves, one each side of the nose, to prevent backward flow,
- 2 no-return valves at the entrance of the exhalation tubes.

Exhaled CO2 is channeled into the soft silicone side tubes through the second pair of no-return valves. This configuration could explain our results in terms of simulated patient-ventilator interaction and performance devices during NIV settings.

A major limitation of the snorkeling mask must be underlined: during NIV with this interface, it is possible to reach a maximum of 18 cmH_2O of peak inspiratory applied pressure. Over this pressure, the presence of air leaks determines continuous asynchronies (as auto cycling and double triggering), not modifiable with a change in flow or pressure trigger. For this reason, our test was limited to single pressure support and PEEP level (PS 10 cmH_2O and PEEP 8 cmH_2O).

Conclusion

The results of this comparative bench study suggest that this modified snorkeling mask can be used as an alternative to other interfaces for both CPAP and NIV in emergencies. The snorkeling mask can be proposed in the event of a new pandemic surge or for countries where the number of COVID-19 patients is such that all user interfaces for non-invasive respiratory support must be used. Particular attention should be paid to the use of this modified snorkeling mask during NIV, related to the maximum pressure limit of 18 cmH_20.

Funding

This study was funded solely by institutional/departmental resources.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are grateful to all ICU doctors, residents, and nurses who fight this COVID 19 pandemic with their efforts and passion.

References

1. WHO Director-General' s opening remarks at the media briefing on COVID-19:11 March 2020. Published March 11, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-themedia-briefing-on-covid-19—11-march-2020. Accessed March 30, 2020.

2. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. JAMA. 2020;323 (16):1545–6. https://doi.org/10.1001/jama.2020.4031.
3. Coronavirus COVID-19 global cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins. Up dated March 30, 2020. Accessed March 30, 2020.
4. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. COVID-19 Lombardy ICU network. baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323 (16):1574–81. https://doi.org/10.1001/jama.2020.5394.
5. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. Covid 19 infection: the perspectives on immune response. Cell Death Differ. 2020;27(5):1451–4. https://doi.org/10.1038/s41418-020-0530-3.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients affected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.
7. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with Sars-CoV2 pneumonia in Whuan, China: a single centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–81. https://doi.org/10.1016/S2213-2600(20)30079-5.
8. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the seattle region-case series. N Eng J Med. 2020;382(21):2012–22. https://doi.org/10.1056/NEJMoa2004500.
9. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 does not lead to "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020;201(10):1299–300. https://doi.org/10.1164/rccm.202003-0817LE.
10. Lucchini A, Giani M, Isgro S, Rona R. The "helmet bundle" in COVID-19 patients undergoing non invasive ventilation. Intensive Crit Care Nurs. 2020;58:102859. https://doi.org/10.1016/j.iccn.2020.102859.
11. Wincka JC, Ambrosino N. COVID-19 pandemic and non invasive respiratory management: every Goliath needs a David. An evidence based evaluation of problems. Pulmonol. 2020;26 (4):213–20. https://doi.org/10.1016/j.pulmoe.2020.04.013.
12. Olivieri C, Costa R, Spinazzola G, Ferrone G, Longhini F, Cammarota G, et al. Bench comparative evaluation of a new generation and standard helmet for delivering non-invasive ventilation. Intensive Care Med. 2013;39:734–8. https://doi.org/10.1007/s00134-012-2765-z.
13. Vignaux L, Vargas F, Roeseler J, Tassaux D, Thille AW, Kossowsky MP, et al. Patient–ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. Intensive Care Med. 2009;35:840.. https://doi.org/10.1007/s00134-009-1416-5. 21.
14. Vignaux L, Piquilloud L, Tourneux P, Jollie P, Rimensberger PC. Neonatal and adult ICU ventilators to provide ventilation in neonates, infants, and children: a bench model study. Respir Care. 2014;59:1463–75. https://doi.org/10.4187/respcare.02540. 22.
15. Olivieri C, Costa R, Conti G, Navalesi P. Bench studies evaluating devices for non-invasive ventilation: critical analysis and future perspectives. Intensive Care Med. 2012;38:160–7. https://doi.org/10.1007/s00134-011-2416-9.
16. Cammarota G, Longhini F, Perucca R, Ronco C, Colombo D, Messina A, et al. New setting of neurally adjusted ventilatory assist during noninvasive ventilation through a helmet. Anesthesiology. 2016;125(6):1181–9. https://doi.org/10.1097/ALN.0000000000001354.
17. Olivieri C, Longhini F, Cena T, Cammarota G, Vaschetto R, Messina A, et al. New versus conventional helmet for delivering noninvasive ventilation: a physiologic, crossover randomized study in critically ill patients. Anesthesiology. 2016;124 (1):101–8. https://doi.org/10.1097/ALN.0000000000000910.
18. Longhini F, Pan C, Xie J, Cammarota G, Bruni A, Garofalo E, et al. New setting of neurally adjusted ventilatory assist for noninvasive ventilation by facial mask: a physiologic study. Crit Care. 2017;21(1):170. https://doi.org/10.1186/s13054-017-1761-7.
19. Antonelli M, Conti G, Pelosi P, Gregoretti C, Pennisi MA, Costa R, et al. New treatment of acute hypoxemic respiratory failure: noninvasive pressure support ventilation delivered by helmet: a pilot controlled trial. Crit Care Med. 2002;30(3):602–8. https://doi.org/10.1097/00003246-200203000-00019.
20. Antonelli M, Pennisi MA, Pelosi P, Gregoretti C, Squadrone V, Rocco M, et al. Noninvasive positive pressure ventilation using a helmet in patients with acute exacerbation of chronic obstructive pulmonary disease: a feasibility study. Anesthesiology. 2004;100(1):16–24. https://doi.org/10.1097/00000542-200401000-00007.
21. Ippolito M, Vitale F, Accurso G, Iozzo P, Gregoretti C, Giarratano A, et al. Medical masks and respirators for the protection of healthcare workers from SARS-CoV-2 and other viruses. Pulmonology. 2020 Jul-Aug;26(4):204–12. https://doi.org/10.1016/j.pulmoe.2020.04.009.
22. Ferrari G, Oliveri F, De Filippi G, Milan A, Aprà F, Boccuzzi A, et al. Non-invasive positive airway pressure and risk of myocardial infarction in acute cardiogenic pulmonary edema: continuous positive airway pressure vs. non-invasive positive pressure ventilation. Chest. 2007;132:1804–9. https://doi.org/10.1378/chest.07-1058. 19.
23. Cammarota G, Vaschetto R, Turucz E, Dellapiazza F, Colombo D, Blando C, et al. Influence of lung collapse distribution on the physiologic response to recruitment maneuvers during noninvasive continuous positive airway pressure. Intensive Care Med. 2011;37:1095–102. https://doi.org/10.1007/s00134-011-2239-8.
24. Chiumello D, Pelosi P, Carlesso E, Severgnini P, Aspesi M, Gamberoni C, et al. Noninvasive positive pressure ventilation delivered by helmet vs standard face mask. Intensive Care Med. 2003;29:1671–9. https://doi.org/10.1007/s00134-003-1825-9.
25. Navalesi P, Costa R, Ceriana P, Carlucci A, Prinianakis G, Antonelli M, et al. Noninvasive ventilation in chronic obstructive pulmonary disease patients: helmet versus facial mask. Intensive Care Med. 2006;33:74–81. https://doi.org/10.1007/s00134-006-0391-3.
26. Costa R, Navalesi P, Spinazzola G, Ferrone G, Pellegrini A, Cavaliere F, et al. Influence of ventilator settings on patient–ventilator synchrony during pressure support ventilation with different interfaces. Intensive Care Med. 2010;36:1363–70. https://doi.org/10.1007/s00134-010-1915-4.
27. Grasselli G, Tonetti T, Protti A, Longer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020. https://doi.org/10.1016/S2213-2600(20)30370-2. Aug 27: S2213-2600(20)30370-2.

Pulmonology 29 (2023) 29–41

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Determinants associated with uncontrolled asthma in Portugal: A national population-based study

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Received 29 November 2019; accepted 28 February 2020
Available online 3 October 2020

KEYWORDS
Asthma;
Control;
Uncontrolled;
Determinants

Abstract
Introduction and objectives: Asthma is a chronic and heterogeneous disease that affects people of all ages and has a high estimated increase in prevalence worldwide. Asthma control represents a main goal in the disease management. International studies revealed low levels of disease control resulting in a significant burden for healthcare systems, not only in terms of quality of life, but also in terms of health costs. Modifiable and non-modifiable factors have been identified as relating to poor asthma control level. In this study we evaluated the distribution of asthma control levels in Portuguese adult population and examine the determinants associated with uncontrolled asthma.
Materials and methods: Using a similar methodology to the one employed in the Asthma Insights and Reality in Europe (AIRE) survey, 327 active asthmatic patients were identified by random phone number and completed a questionnaire during 2011 to 2012. Asthma control was assessed by the evaluation of GINA based symptom control, by Asthma Control Test™ (ACT) and by self-perception of control. To examine the relationship between uncontrolled asthma and its

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https://doi.org/10.1016/j.pulmoe.2020.02.014

determinants, univariate logistic regression analysis, sequential multivariable regression and population attributable risk percentage were determinate.

Results: 35.2% active asthmatic patients had uncontrolled asthma, 64.8% partially controlled and none of the individuals had total control of asthma assessed by ACT test. Factors significantly associated with poor asthma control scores were: age (OR 1.02 per year of age; 95% CI: 1.01–1.03), female sex (OR 1.87; 95% CI: 1.15–3.04), educational level (OR 0.5; 95% CI: 0.28–0.89 at high school level or over), occupation (OR 4.92; 95% CI: 2.12–11.42 if looking for a first job or unemployed) (OR 2.51; 95% CI: 1.35–4.65 if being retired), income (OR 0.23; 95% CI: 0.07–0.72 if >619 euros), BMI (OR 1.09 per BMI unit; 95% CI: 1.03–1.14), having rhinitis symptoms (OR 4.40; 95% CI: 2.56–7.58) and using inhaled corticosteroids (OR 0.44; 95%CI: 0.24–0.82 if used in the past or never used).

Looking for a first job or being unemployed, BMI and having rhinitis symptoms remained significant after multivariate adjustments.

Conclusions: Uncontrolled asthma was associated with several determinants. Their identification can contribute to improve asthma care both from clinical and from public health perspectives.

Introduction

Asthma is a chronic and heterogeneous disease[1] that affects people from all ages and ethnicities worldwide.[2] There is an estimated a global prevalence of 315 million people with asthma,[3] contributing with more than 23 million of Disability-Adjusted Life Years (DALYs).[4] Asthma prevalence has been increasing in many countries, in parallel with the development of urbanization and the adoption of modern lifestyles.[5] It is estimated that by 2025 100 million of people more will have asthma worldwide.[5]

Despite the existence of treatment guidelines, many individuals with asthma remain undertreated and uncontrolled, resulting in a significant burden, not only in terms of quality of life, but also in terms of health costs.[2] Health cost associated with asthma could be direct costs, like treatments and hospitalizations, as well as indirect costs, due to work absences and premature death.[2] In 2010, the yearly cost per asthmatic adult patient in Europe, according to estimates from Accordini et al.,[6] ranged from 509€ for a controlled asthma patient to 2281€ for an uncontrolled asthma patient.

The Global Initiative for Asthma (GINA) was created in 1993 with the objective of disseminating accurate information about asthma and improving the quality of asthma patient care worldwide.[1] At present, according to GINA guidelines, achieving and maintaining asthma control represents one of the main goals for the management of the disease and consists of the evaluation of the control of symptoms and future risk of unfavourable outcomes.[1]

Numerous factors such as age, gender,[7] comorbidities[7,8] psychological aspects[9] and socioeconomic determinants[10] have been studied and reported as associated with asthma control. Behavioural reasons such as smoking habits[7] or therapeutic compliance have also been related to poor asthma control levels.[11]

A multiway and a complex causal relationship between health, education level, work and income has been reported. Having a chronic disease can be considered a risk factor for employment. In Portugal, 66,294 of potential productive life years were lost due to non-communicable diseases (cardiovascular disease, diabetes, cancer and respiratory diseases) in 2013, according Organization for Economic Co-operation and Development (OECD).[12]

The Portuguese National Asthma Survey reported a proportion of 43.1% uncontrolled disease in asthmatic Portuguese population.[13] In a national population study non-modifiable factors such as age and gender were associated with uncontrolled asthma.[14] Self-evaluation of uncontrolled asthma, participation in decisions related to treatment and the presence of comorbidities have also been considered as important contributions to asthma control.[14]

The purpose of this study was to investigate the distribution of asthma control level in Portuguese adult population, using different approaches of control level evaluation, and to examine the determinants associated with uncontrolled asthma.

Methods

Study design

A cross-sectional study at national level (Portugal) was carried out from March 2011 to March 2012, based on the methodology applied in the Asthma Insights and Reality in Europe (AIRE).[15]

A probabilistic sample of individuals diagnosed with ''active asthma'' was identified through telephone numbers and a structured telephone interview was used. In order to select exclusively individuals with active asthma, an adult in each household was asked the following question: ''*Has a physician ever diagnosed any family member in your home*

as having asthma?''. Participants were included as having active asthma if they answered positively at least one of the following questions: ''*Do any of those individuals diagnosed with asthma take any medication for their asthma?*'' and ''*Has any of those individuals diagnosed with asthma had any asthma crises or asthma symptoms in the last year?*''. If more than one household member with asthma was qualified, a respondent was randomly selected for interview.

A total of 557 individuals were identified with active asthma and 327 complete interviews were acquired in adults (≥16 years old).

Control assessment

Asthma control was evaluated in three ways: GINA based symptom control, by Asthma Control Test™ (ACT) and individual self-perception of control assessment.

The asthma symptom control, based on GINA, included four questions, relating to the previous four weeks, about the frequency of daytime symptoms, night waking, relief medication needs and activity limitations due to asthma.

ACT is a quantitative self-assessment tool for asthma control, which consists of 5 simple questions for the interviewee to consider on the impact of asthma on a daily basis over the previous four weeks; relating to shortness of breath, use of rescue medication, nocturnal asthma symptoms and self-evaluation of asthma control.[16] According to Thomas et al.[17] ACT scores equal to or below 19 are considered as identifying patients with poorly controlled asthma, as defined by GINA. ACT is also used for the evaluation of determinants associated with poor asthma control. ACT scores equal to or below 19 points correspond to ''uncontrolled'' asthma and scores of at least 20 points are classified as ''controlled'' (20–24 = ''partially controlled''; 25 = ''totally controlled'').

From the main questionnaire of the study, several determinants for the analysis were selected according to their relevance and the consulted bibliography: age, sex, civil status, region of residence, educational level, occupation, household income, body mass index (BMI), smoking habits, rhinitis symptoms, allergies as a trigger for crises, having family doctor, assistant physician to solve asthma problems, seasonal flu vaccination, Peak Flow Metre use, conducting lung function tests, training to use the inhaler properly, written asthma action plan, forgetting to take medication, inhaled corticosteroid use and number of medications used for asthma. BMI was classified according to the World Health Organization (WHO) criteria for adults,[18] being underweight if BMI <18.5 kg/m^2, pre-obesity if 25.0 $kg/m^2 \geq$ BMI < 30.0 kg/m^2, and obesity if BMI ≥30.0 kg/m^2.

Statistical analysis

Descriptive statistics were described as absolute frequency and proportion for categorical variables and continuous variables were represented as mean (standard deviation) for normally distributed variables and as median (interquartile range) for non-normally distributed variables.

The age differences between sexes was evaluated by the Mann Whitney *U* Test.

For additional analyses two groups of active asthma respondents were considered: controlled (ACT score ≥20) and uncontrolled (ACT score ≤19).

To examine the relationship between uncontrolled asthma and its determinants, an indicator of uncontrolled asthma was used as a dependent variable. The determinants were classified into the following domains, grouping conceptually related variables: demographic, socioeconomic, risk and clinical factors, clinical care and treatment. Univariate logistic regression analysis was done for all determinants. From a public health perspective and in order to measure the contribution of each determinant to the level of asthma control, the population attributable risk percentage (PAR%) was assessed, using the following formula:

$$PAR\% = [Pe \times (OR - 1)/[(1 + Pe \times (OR - 1)]] * 100$$

(Pe = estimate of population exposure)

with OR as the inverse risk (1/OR) in the case of a protective factor (odds ratio lower than 1).

Sequential multivariable regression was performed. Variables with $p < 0.30$ in the univariate analysis were used to build the adjusted models (Forward Likelihood Ratio method). Multivariable adjustments were performed in sequence considering additions to variables for the different domains, where variables from a given domain were adjusted to the multivariable model, as noted in the Table 4. Pseudo *r*-squared (Cox and Nagelkerke) were calculated from the models originated.

For all tests performed, the level of statistical significance was set at 0.05. All analyses were conducted using SPSS version 23 (IBM Corp., Armonk, N.Y., USA).

Results

General characteristics

A total of 327 full interviews were completed with adults who had active asthma. A detailed description of the demo-

Table 1 Respondent characteristics.

Age, median (IQR)	44 (27–58)
Female, n (%)	203 (62.1)
Age at diagnosis of asthma, median (IQR)	15 (5–36)
Duration of asthma in years, median (IQR)	20 (10–30)
Smoking habits (n = 315)	
Non-smoker, *n* (%)	199 (63.2)
Current smoker, *n* (%)	49 (15.6)
Former smokers, *n* (%)	67 (21.3)
Body mass index (n = 310)	
Underweight, *n* (%)	10 (3.2)
Normal weight, *n* (%)	138 (44.5)
Pre-obesity, *n* (%)	115 (37.1)
Obesity, *n* (%)	47 (15.2)

IQR: interquartile range.

Table 2 Asthma control assessment.

GINA based symptom control	
Controlled, *n* (%)	112 (34.3)
Partly controlled, *n* (%)	156 (47.7)
Uncontrolled, *n* (%)	59 (18.0)
ACT score	
Controlled asthma (ACT = 25), *n* (%)	0
Partially controlled (ACT 20–24), *n* (%)	212 (64.8)
Non-controlled asthma (ACT $\leq$19), *n* (%)	115 (35.2)
Patient perceived control	
Completely controlled, *n* (%)	84 (25.7)
Well controlled, *n* (%)	145 (44.3)
Somewhat controlled, *n* (%)	78 (23.9)
Poorly controlled, *n* (%)	18 (5.5)
Not controlled at all, *n* (%)	2 (0.6)

graphic and asthma related variables is summarized in Table 1. Further socioeconomic, risk and clinical factors, as well as clinical care and treatment characteristics are described below.

In the sampled population, 62.1% were female and 37.9% male. In female the median age was 46 (29–58) and in male 37.5 (26–56), without statistic significant differences. A high percentage of the individuals questioned was pre-obese or obese (52.3%) and 36.9% were ever smokers.

Asthma control

Frequency of self-reported symptoms (in the last four weeks) is discriminated in Fig. 1.

In relation to GINA based symptoms control assessment, of the 327 adult individuals interviewed, 18% had uncontrolled asthma, 47.7% partially controlled and 34.3% had totally controlled. Based on ACT test, 35.2% of the subjects had uncontrolled asthma, 64.8% partially controlled and none of the individuals had total control. 93.9% of the individuals perceived their asthma as completely, well or somewhat controlled and only 6.1% perceived their asthma poorly or not controlled at all (Table 2).

Concerning the agreement between ACT asthma control score and the participants' self-perception, about 39.2% of individuals with uncontrolled asthma evaluated by ACT self-reported their asthma as completely or well controlled and only 16.5% had the self-perception that agreed with the objective assessment of asthma control.

Determinants for uncontrolled asthma

We then sought to understand which factors were associated with poor asthma control. In a univariate analysis, the factors significantly associated with poor asthma control scores (ACT score $\leq$19) were: age, female sex, educational level (<high school level), occupation (looking for a first job, being unemployed or being retired), income (<619 euros), higher BMI (obesity), having rhinitis symptoms and using inhaled corticosteroids. In contrast, civil status, region of residence, smoking habits, allergies as a trigger for the crisis, having a family doctor, the assistance of physician used to solve asthma problems, seasonal flu vaccine, peak flow metre use, lung function tests performance, training to use the inhaler properly, written asthma action plan, forgetting to take medication and number of medications used for asthma were not statistically significant determinants in the univariate analysis (Table 3). The PAR% for the significant variables are also in Table 3. In order to understand the relationship of significant variables in the univariate analysis a sequential multivariable adjustment analysis was performed by adding the dimensions of factors sequentially (Table 4). Occupation, BMI and having rhinitis symptoms were the factors that remained statistically significant results besides the sequential adjustments.

Individuals over age of 65 had 2.70 (95% CI: 1.21–5.99) times higher odds for having uncontrolled asthma compared to the youngest group analyzed (16–25 years) and PAR% value of 19.3%. It appears that there is a progressive increase; with each year of age the chance of uncontrolled asthma increases by 2% and female gender increases the odds of uncontrolled asthma by 1.87 (95% CI: 1.15–3.04). However socioeconomic determinants (occupation) seems to attenuate these associations.

Regarding socioeconomic determinants: the increase in education level decreases the odds of having uncontrolled asthma (OR 0.5 high school level or more); higher income decreases the odds of uncontrolled asthma; in relation to occupation, subjects looking for a first job or unemployed had 4.92 higher odds for uncontrolled asthma scores (95% CI: 2.12–11.42) and being retired is associated with 2.51 odds (95% CI: 1.35–4.65) for uncontrolled asthma, when compared with employed asthmatics. The protective role of educational level and income seems to be mediated by risk and clinical factors (BMI and having rhinitis symptoms). Participants looking for a first job or who were unemployed had PAR% value of 26.8% and were much more likely to have uncontrolled asthma regardless of the various adjusted dimensions.

For each kg/m^2 increment of BMI the chance of uncontrolled asthma increased 9%, this association remained significant even when dimensions adjustments were considered. PAR% of uncontrolled asthma associated with obesity was 23.5%.

Nasal symptoms were the symptoms identified as occurring almost every day in the previous four weeks (Fig. 1). Having rhinitis symptoms increases the odds of uncontrolled asthma by 4.4 (95% CI: 2.56–7.58). These associations remained significant regardless of the adjustments considered. The PAR% of uncontrolled asthma associated with rhinitis symptoms was 65.9%.

Clinical factors, such as smoking habits and having allergies as a trigger for asthma crisis, were not significantly associated with uncontrolled asthma. Also, in this analysis, the determinants related to clinical care did not demonstrate significant associations. Of the treatment determinants evaluated (forgetting to take medication, the number of medications used for asthma and the use of inhaled corticosteroids) individuals not using inhaled corticosteroids had significantly lower odds for uncontrolled asthma (OR 0.44 95% CI: 0.24–0.82), but it seems that the effect is mediated by the risk factors and the clinical aspects considered (BMI and having rhinitis symptoms).

Table 3 Univariate analysis for uncontrolled asthma and Population attributable risk %.

Determinants		All participants *n* (%)	Uncontrolled asthma *n* (%)	Risk for uncontrolled asthma (ACT score ≤ 19)		Population attributable risk %
				Crude Odds Ratio (95% CI)	*p* Value	
Demographic						
Age, classes	16–25	67 (20.5%)	17 (14.8%)	**ref**		
	26–45	105 (32.1%)	34 (29.6%)	1.41 (0.71–2.80)	0.327	–
	46–65	109 (33.3%)	42 (36.5%)	1.84 (0.94–3.61)	0.074	–
	> 65	46 (14.1%)	22 (19.1%)	**2.70 (1.21–5.99)**	**0.015**	19.3%
Age, years		44 (27–58)[a]	47.69 (18.7)[b]	**1.02 (1.01–1.03)**	**0.005**	–
Sex	Male	124 (37.9%)	33 (28.7%)	**ref**	**0.012**	
	Female	203 (62.1%)	82 (71.3%)	**1.87 (1.15–3.04)**		35.1%
Civil status	Single	106 (33.0%)	34 (29.8%)	**ref**		
	Married or Cohabited	174 (54.2%)	62 (54.4%)	1.17 (0.70–1.96)	0.543	–
	Divorced, separated or Widow (er)	41 (12.8%)	18 (15.8%)	1.66 (0.79–3.47)	0.181	–
Region of residence	Lisboa e Vale do Tejo	106 (33.3%)	38 (34.5%)	**ref**		
	Alentejo e Algarve	32 (10.1%)	9 (8.2%)	0.70 (0.29–1.67)	0.42	–
	Centro	63 (19.8%)	17 (15.5%)	0.66 (0.33–1.31)	0.236	–
	Açores	12 (3.8%)	4 (3.6%)	0.90 (0.25–3.17)	0.863	–
	Madeira	10 (3.1%)	6 (5.5%)	2.68 (0.71–10.11)	0.144	–
	Norte	95 (29.9%)	36 (32.7%)	1.09 (0.62–1.94)	0.764	–
Socioeconomic						
Educational level	3rd cycle of basic education or less	132 (42.0%)	63 (56.3%)	**ref**		
	High school	80 (25.5%)	25 (22.3%)	**0.50 (0.28–0.89)**	**0.019**	20.3%
	Post-secondary education or more	102 (32.5%)	24 (21.4%)	**0.34 (0.19–0.60)**	**<0.001**	38.7%
Occupation	Employed	158 (51.0%)	44 (40.0%)	**ref**		
	Student	54 (17.4%)	13 (11.8%)	0.82 (0.4–1.68)	0.59	–
	Domestic	10 (3.2%)	5 (4.5%)	2.59 (0.72–9.39)	0.147	–
	Looking for a first job or Unemployed	29 (9.4%)	19 (17.3%)	**4.92 (2.12–11.42)**	**<0.001**	26.8%
	Retired	59 (19.0%)	29 (26.4%)	**2.51 (1.35–4.65)**	**0.004**	22.3%
Income	<340 Euros	16 (7.0%)	11 (12.6%)	**ref**		
	340–618 Euros	46 (20.1%)	26 (29.9%)	0.59 (0.18–1.98)	0.393	–
	619–1531 Euros	92 (40.2%)	31 (35.6%)	**0.23 (0.07–0.72)**	**0.012**	57.4%
	1532–3522 Euros	59 (25.8%)	17 (19.5%)	**0.18 (0.06–0.61)**	**0.006**	54.0%
	>3523 Euros	16 (7.0%)	2 (2.3%)	**0.07 (0.01–0.40)**	**0.003**	48.1%

Table 3 (*Continued*)

Determinants		All participants *n* (%)	Uncontrolled asthma *n* (%)	Risk for uncontrolled asthma (ACT score ≤ 19)		Population attributable risk %
				Crude Odds Ratio (95% CI)	*p* Value	
Risk and clinical factors						
Body mass index (BMI)	Normal weight	138 (44.5%)	40 (37.4%)	**ref**		
	Underweight BMI (kg/m2) <18.50	10 (3.2%)	3 (2.8%)	1.05 (0.26–4.27)	0.946	–
	Pre-obesity BMI (kg/m2) ≥25.0 and <30.0	115 (37.1%)	38 (35.5%)	1.21 (0.71–2.06)	0.487	–
	Obesity BMI (kg/m2) ≥30.0	47 (15.2%)	26 (24.3%)	**3.03 (1.53–6.00)**	**0.001**	23.5%
Body mass index (BMI), kg/m^2		25.2 (22.1–28.3)[a]	26.3 (23.5–29.7)[a]	**1.09 (1.03–1.14)**	**0.001**	–
Smoking habits	Current smoker	49 (15.6%)	18 (15.9%)	**ref**		
	Former smokers	67 (21.3%)	19 (16.8%)	0.68 (0.31–1.50)	0.34	–
	Non-smoker	199 (63.2%)	76 (67.3%)	1.06 (0.56–2.03)	0.851	–
Having rhinitis symptoms	No	118 (43.2%)	25 (22.9%)	**ref**	**<0.001**	
	At least 1 or 2 days a week	155 (56.8%)	84 (77.1%)	**4.40 (2.56–7.58)**		65.9%
Allergies as a trigger for the crisis	No	72 (22.0%)	29 (25.2%)	**ref**		
	Yes	255 (78.0%)	86 (74.8%)	0.76 (0.44–1.29)	0.305	–
Clinical care						
Family doctor	Having	262 (81.6%)	97 (85.1%)	**ref**	0.236	
	Not having	59 (18.4%)	17 (14.9%)	0.69 (0.37–1.28)		–
Assistant physician to solve asthma problems	Family doctor/General clinic	151 (46.5%)	54 (47.8%)	**ref**		
	Pneumologist	48 (14.8%)	18 (15.9%)	1.08 (0.55–2.11)	0.827	–
	Allergologist	78 (24%)	21 (18.6%)	0.66 (0.36–1.21)	0.178	–
	Emergency Care	32 (9.8%)	15 (13.3%)	1.59 (0.73–3.42)	0.241	–
	Other	16 (4.9%)	5 (4.4%)	0.82 (0.27–2.47)	0.72	–
Taking the seasonal flu vaccine	Yes	130 (40.6%)	53 (46.1%)	**ref**	0.137	
	No	190 (59.4%)	62 (53.9%)	0.70 (0.44–1.12)		–

Table 3 (*Continued*)

Determinants		All participants *n* (%)	Uncontrolled asthma *n* (%)	Risk for uncontrolled asthma (ACT score ≤ 19)		Population attributable risk %
				Crude Odds Ratio (95% CI)	*p* Value	
Use the Peak Flow Metre	Never	264 (88.6%)	96 (91.4%)	**ref**	0.259	
	At least once a month or at doctor Appointment/when have symptoms	34 (11.4%)	9 (8.6%)	0.63 (0.28–1.41)		–
Perform lung function tests (past 12 months)	At least every six months or at all Doctor appointment	105 (43.8%)	36 (40.9%)	**ref**		
	Only once	116 (48.3%)	46 (52.3%)	1.26 (0.73–2.18)	0.410	–
	Never	19 (7.9%)	6 (6.8%)	0.89 (0.31–2.52)	0.819	–
Have training to use the inhaler properly	Yes	253 (79.8%)	90 (81.1%)	**ref**	0.679	
	No	64 (20.2%)	21 (18.9%)	0.88 (0.49–1.58)		–
Patients having a written asthma action plan	Yes	77 (24.9%)	23 (21.3%)	**ref**	0.281	
	No	232 (75.1%)	85 (78.7%)	1.36 (0.78–2.37)		–
Treatment						
Forgetting to take medication	Yes	52 (33.3%)	19 (26.8%)	**ref**	0.113	
	No	104 (66.7%)	52 (73.2%)	1.74 (0.88–3.44)		–
Under inhaled corticosteroid	Using	63 (31%)	31 (42.5%)	**ref**	**0.009**	
	Used in the past or never used	140 (69%)	42 (57.5%)	**0.44 (0.24–0.82)**		46.7%
Number of asthma medication	None or one medication	162 (49.5%)	49 (42.6%)	**ref**	0.065	
	Two or more medications	165 (50.5%)	66 (57.4%)	1.54 (0.97–2.43)		–

CI: Confidence Interval; ref: reference.
Data shown in this table exclude missing values and answers ''do not know/do not respond''.
[a] Median (interquartile range).
[b] Mean (standard deviation).

Table 4 Multivariable analysis for uncontrolled asthma with sequential dimensions adjustments.

Determinants		Adjusted to A		Adjusted to A + B		Adjusted to A + B + C	
		Adjusted OR (95% IC)	*P* value	Adjusted OR (95% IC)	*P* value	Adjusted OR (95% IC)	*p* value
Demographic (A)							
Age		**1.02 (1.00–1.03)**	**0.01**	/		/	
Sex	Male	**Ref**		/		/	
	Female	**1.77 (1.08–2.90)**	**0.023**				
Socioeconomic (B)							
Educational level	3rd cycle of basic education or less	**Ref**				/	
	High school	0.61 (0.31–1.22)	0.16	0.67 (0.33–1.34)	0.255		
	Post-secondary education or more	**0.38 (0.21–0.72)**	**0.003**	**0.47 (0.24–0.90)**	**0.023**		
Occupation	Employed	**Ref**		ND			
	Student	0.92 (0.41–2.06)	0.831			0.75 (0.32–1.74)	0.498
	Domestic	1.98 (0.51–7.61)	0.322			5.09 (0.54–47.96)	0.155
	looking for a first job or unemployed	**4.55 (1.95–10.63)**	**<0.001**			**6.05 (2.21–16.57)**	**<0.001**
	Retired	2.11 (0.90–4.93)	0.084			1.71 (0.79–3.69)	0.171
Income	<340 Euros	**Ref**				/	
	340–618 Euros	0.78 (0.23–2.68)	0.692	0.73 (0.19–2.90)	0.66		
	619–1531 Euros	0.35 (0.11–1.15)	0.084	0.36 (0.09–1.40)	0.14		
	1532–3522 Euros	**0.27 (0.08–0.93)**	**0.038**	0.32 (0.08–1.31)	0.112		
	>3523	**0.13 (0.02–0.87)**	**0.035**	**0.12 (0.02–0.88)**	**0.037**		
Risk and clinical factors (C)							
Body mass index (BMI)		**1.07 (1.02–1.13)**	**0.008**	**1.07 (1.01–1.13)**	**0.017**	**1.09 (1.02–1.16)**	**0.012**
Having rhinitis symptoms	No	**Ref**					
	at least 1 or 2 days a week	**4.63 (2.64–8.11)**	**<0.001**	**4.49 (2.49–8.10)**	**<0.001**	**4.71 (2.52–8.81)**	**<0.001**
Treatment (E)							
Under inhaled corticosteroid	Using	**Ref**				/	
	used in the past or never used	**0.48 (0.25–0.89)**	**0.02**	**0.49 (0.26–0.94)**	**0.032**		

CI: Confidence Interval; Ref: Reference.
ND: not determinate because A + B adjustment is occupation.
/: not represented because *p* values >0.05.
A: Age and Sex; R^2 Cox = 0.040 and Nagelkerke = 0.055.
A + B: Occupation; R^2 Cox = 0.074 and Nagelkerke 0.101.
A + B + C: Occupation, IMC and Having rhinitis symptoms; R^2 Cox = 0.201 and Nagelkerke = 0.272.
The following adjusted models A + B + C + D and A + B + C + D + E didn't add any of the determinants considered in Clinical Care or Treatment and are not presented in this table.

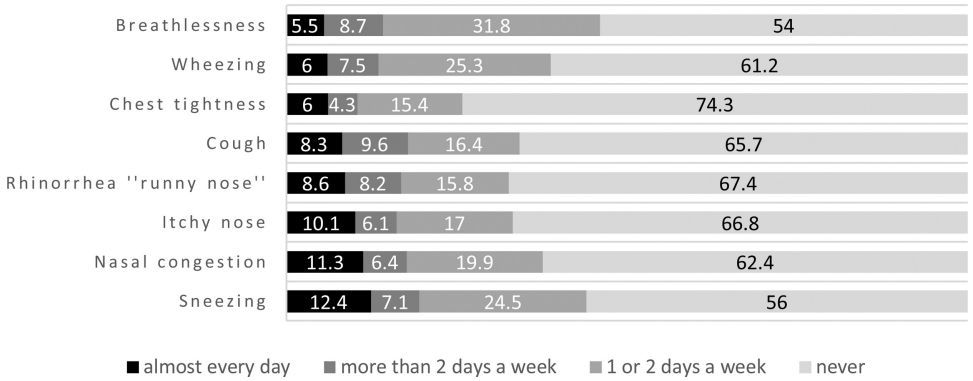

Figure 1 Frequency of self-reported symptoms (in the last four weeks), as cumulative percentages.

Discussion

This study showed that 64.8% subjects had their asthma controlled, and 35.2% of them had uncontrolled asthma, according to the evaluation of a questionnaire for asthma control purpose, the ACT.

Evaluation of asthma control has been assessed in diverse countries worldwide and despite the different measurement tools used, a sub-optimal level of control has been revealed.

Results from a multinational study involving twelve countries of Europe ($n = 3.123$), indicate a similar overall percentage (38.5) for uncontrolled asthma, with the lowest levels of asthma control found in Hungary, The Netherlands and France.[7] Higher levels of uncontrolled asthma (71.3%) were found in surveyed African countries (Algeria, Morocco, and Tunisia),[19] USA (71%),[20] Asia-Pacific countries (92.4%)[21] and Latin America (93%).[22]

From a national perspective, the Portuguese *National Asthma Survey* using Control of Allergic Rhinitis and Asthma Test (CARAT), reported 43.1% of uncontrolled asthma in Portuguese population.[13] In 2007, a study in a central hospital in Lisbon using the ACT questionnaire in the context of allergology consultation found that 23.3% of the respondents presented ACT values ≤ 19[11] and a study carried out in Portuguese pharmacies, with the application of the same questionnaire to evaluate the control, revealed even higher scores for poor asthma control (61.2%).[23]

In this study it was possible to observe that the level of control assessed can differ with the asthma control tool utilized. The different methodologies that can be used in epidemiological studies such as in clinical practice for control assessment [e.g., GINA based symptom control tool[1]; CARAT[24]; Asthma Control Questionnaire (ACQ)[25]; ACT[16]] can make it more difficult to compare results between studies. Additionally, there are different approaches used to gather information (e.g. telephone interview, online questionnaire, face-to-face interview), several methods used to assess asthma control level and different situations in different health systems, literacy and social barriers among the different countries; all of which should be taken into consideration when comparing results from different studies.

Most of the adult patients interviewed overestimated their disease control revealing a discrepancy between patient perception of asthma control and the objective measurement, since 93.9% of the individuals perceived their asthma with some level of control. It has been shown that most of these patients can tolerate their symptoms and lifestyle limitations as inevitable consequences of the disease.[26] The self-perception and expectations about asthma disease may result in misinterpretations of control level.[26]

In terms of demographic factors, our results indicate that uncontrolled asthma was more frequently associated with older age and with female sex.

Asthma disease in the elderly population is of special concern since most of patients are polypathological and polymedicated, which can have a negative impact on disease management.[27] Besides, there are often more difficulties in the execution of proper inhaler techniques.[27,28] Kämpe et al.[29] stated that uncontrolled asthma was more common in older groups ($\geq$65years); Mendes et al.,[23] using a Portuguese population, found that 69% of elderly (>70 years) had uncontrolled asthma.

Our results observing the association between sex and poor asthma control, are in agreement with other studies,[23,29,30] with females associated with poor scores in asthma control. Usually women perceive asthma differently from men, reporting higher levels of symptoms and more limitations in day-to-day life.[31,32] In addition, women have been associated with a higher incidence of later asthma onset and a higher prevalence of non-allergic asthma phenotype, favouring a less effective response to corticosteroid treatments.[1,33,34]

In this study, socioeconomic determinants, especially occupation have a considerable association with poor control score of asthma as well as greater influence on other important determinants. The PAR% for being looking for a first job or being unemployed was 26.8%, suggesting a very significant contribution for poor asthma control. Moreover studies identified that the severity of asthma,[35] the frequency of asthma symptoms and night awakenings because of asthma can contribute to work disability and unemployment.[36]

The inverse association between income[37] and education[29] with poor controlled asthma outcomes has been documented. The PAR% register for having at least post-secondary education was 38.7% suggesting a contribution for preventing worse levels of control in asthma. The same positive contribution was verified for higher levels of income.

Individuals with higher levels of education can have a better understanding of the prescribed therapeutics and may have a greater tendency to adhere to treatment regime.[29] Furthermore, there are work environments associated with trigger agents exposure (e.g., diisocyanates, acrylates or cleaning agents)[38] to which individuals with higher educational levels are less likely to be exposed.[29]

Although only 8.8% of the individuals considered that the price of asthma treatments influenced taking medication according medical indications, asthma expenses related to medical treatments are usually high which can be a significant burden for low-income families,[39,40] and in turn can compromise treatment adherence.

Higher BMI was shown to be associated with uncontrolled levels in asthma, as stated above: Lessard et al.[41] found that regardless of a similar perception of symptoms, obese individuals had poorer asthma control than non-obese asthmatics; Lavoie et al.[42] in a 382 adults study found that patients with higher BMI had poor asthma control (scored higher in ACQuestionnaire) independent of their age, sex and asthma severity; with an odds ratio of 2.99 (95% CI 1.14–7.08) Ferreira et al.[11] reported that obesity is a factor associated with non-control of asthma.

Obesity has a negative impact on overall breathing mechanisms,[43] has been reported as a risk factor for the development of asthma and for increasing exacerbations and hospitalizations.[44] The pro-inflammatory characteristics of obesity can induce more difficulties in asthma control, secondary to a reduction in the response to corticosteroids.[45]

Weight loss has been shown to improve lung function parameters in individuals with obesity and better scores of disease control in asthma patients.[44,46] In this way, nutritional education promoting diet modification and weight loss in obese asthmatic patients must be encouraged.[47] According to our results a considerable number of individuals (PAR% = 23.5%) with uncontrolled asthma could be spared if obesity was not present.

Findings from studies[11,48–50] conclude that rhinitis is an important contributor to a non-optimal asthma control level, as also was supported by our results. Bousquet et al.[51] in a multivariate analysis found that patients with simultaneous asthma and allergic rhinitis are associated with higher levels of acute exacerbations (OR 1.35, 95% CI: 1.03–1.77) with more emergency visits (OR 2.35, 95% CI: 1.12–4.80).

The PAR% register for having rhinitis symptoms in our study (65.9%) suggests that controlling nasal symptoms could contribute positively to preventing worse levels of control in asthma disease. Consequently, it is important to optimize the treatment of both diseases in patients with a concomitant diagnosis.[52]

The presence of smoking habits was not observed to be a determinant associated with poor asthma control in our study, as already stated.[30,53] In this regard, other studies also did not identify smoking as an independent risk factor for uncontrolled asthma[11] or for decline in lung function in asthmatic patients[54] which could be related to a healthy smoker effect,[55] underestimating the effect of tobacco at pulmonary level.

Nor was an association found with determinants of poor asthma control that have been reported in other studies, such as patients having a written asthma action plan[56] and therapeutic compliance. Although a higher number of individuals have reported allergies as a trigger for asthma crises (78%), a significant association with uncontrolled asthma was not detected, which is similar to that reported by other research.[11,53]

Lung function assessment with peak flow metre or lung function tests were not significant determinants for asthma control in our study. However minimizing airflow limitation is one of the main goals for these patients and the importance of these exams in diagnosis and follow-up of asthma has been stressed.[1]

The use of inhaled corticosteroid plays an important role in an asthma treatment plan.[1] Rabe et al.[15] reported that the use of inhaled corticosteroids was low even among patients with severe persistent symptoms. In our study, the use of these medications was associated with lower ACT scores, which represents worse control outcomes. This association with the level of control could be explained by the relation of treatment plan with disease severity. For example, patients with mild asthma degree and well controlled symptoms might only be at step 1 of treatment plan and only using a reliever inhaler as needed, as was defined before 2019 GINA guidelines.[1] However, severe asthma patients may present corticosteroid resistance,[57] of which the molecular pathophysiology is beginning to be understood,[58] leading to the possibility of development of new treatments for these patients.

Strength and limitations

There are some limitations to this study that should be considered: (1) it is a cross-sectional study and cause-effect relationships cannot be established; (2) all the data was reported by respondents and could not be clinically confirmed; (3) only patients with active asthma were questioned, excluding undiagnosed individuals and patients without the presence of symptoms and without medication in the last year; (4) this study did not inquire about comorbidities, such as: other respiratory disease which have been associated to asthma control [e.g. Chronic Obstructive Pulmonary Disease (COPD), obstructive sleep apnoea, gastroesophageal reflux disease (GERD), or psychological aspects][59]; (5) the degree of asthma severity, according to GINA guidelines, was not assessed.

A strength of this study was the identification of active asthmatic patients from the general population without referral bias. It was also important to evaluate different methods of accessing data from the level of asthma control and the analysis of multiple factors and dimensions that could have influenced the level of control of this important chronic disease.

Conclusions

In this study uncontrolled asthma was associated with several factors: age, sex, educational level, occupation, income, BMI, having rhinitis symptoms and use of inhaled corticosteroids as part of a treatment plan. Some of these factors remain associated after full adjustment, notably occupation, BMI and having rhinitis symptoms, which are important modifiable factors.

The values of PAR% for unemployment, obesity and rhinitis symptoms were relatively high (respectively 26.8%, 23.5% and 65.9%). Since these are modifiable factors from the point of view of public health and health planning, intervention strategies more directed to these concerns can promote benefits for asthmatic patients and consequently for other health problems. Similarly, their identification by physicians could contribute to a better clinical approach to asthma disease.

In future research there should longitudinal studies to confirm these associations and other comorbidities, such as COPD or GERD and enquiries made about physiological factors. It is also important to standardize a tool for asthma control evaluation that can be used in epidemiological studies and that can provide reliable comparison between studies.

Funding

This study was supported by a grant from the General Directorate of Health (DGS) of the Portuguese Health Ministry and by a scientific grant from AstraZeneca Foundation. The supporters did not have any role in the design and conduct of the study, nor in the collection, management, analysis, and interpretation of the data, or in the preparation, review or approval of the article.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

We acknowledge the help of Filipe Leão Miranda, Augusto Almeida, Rui Simões, Fernando Martins e Ana Sofia Andrade for valuable inputs, project management, sampling and data collection instruments and algorithms, and previous data analysis. We are also grateful to Fátima Rodrigues for careful review of the manuscript and to all who gave support and participated, making this study possible.

References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention; 2019. Available from: www.ginasthma.org
2. W.H.O. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach; 2007, http://dx.doi.org/10.1177/1479972306070070.
3. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012;12:204, http://dx.doi.org/10.1186/1471-2458-12-204.
4. The global asthma report 2018. Auckland, New Zealand: Global Asthma Network; 2018.
5. Bousquet J, Bousquet PJ, Godard P, Daures J-P. The public health implications of asthma. Bull World Health Organ. 2005;83:548–54.
6. Accordini S, Corsico AG, Braggion M, Gerbase MW, Gislason D, Gulsvik A, et al. The cost of persistent asthma in Europe: an international population-based study in adults. Int Arch Allergy Immunol. 2013;160:93–101, http://dx.doi.org/10.1159/000338998.
7. Braido F, Brusselle G, Guastalla D, Ingrassia E, Nicolini G, Price D, et al. Determinants and impact of suboptimal asthma control in Europe: the international cross-sectional and longitudinal assessment on asthma control (Liaison) study. Respir Res. 2016;17:51, http://dx.doi.org/10.1186/s12931-016-0374-z.
8. Hekking PPW, Amelink M, Wener RR, Bouvy ML, Bel EH. Comorbidities in difficult-to-control asthma. J Allergy Clin Immunol Pract. 2017, http://dx.doi.org/10.1016/j.jaip.2017.06.008.
9. Baiardini I, Sicuro F, Balbi F, Canonica GW, Braido F. Psychological aspects in asthma: do psychological factors affect asthma management? Asthma Res Pract. 2015;1:7, http://dx.doi.org/10.1186/s40733-015-0007-1.
10. Azeez IA, Ladipo MMA, Ige OM. Assessment of socioeconomic status and control of asthma in adults. Ann Ibadan Postgrad Med. 2016;14:85–91.
11. Ferreira MB, Alves RR, Santos AS, Carlos GP, Pedro E, Pregal AL, et al. Controlo da asma em consulta de Imunoalergologia. Rev Port Imunoalergol. 2008;16:29–56.
12. OECD/EU. Health at a glance: Europe 2016 – state of health in the EU cycle; 2016, http://dx.doi.org/10.1787/9789264012639-en.
13. Sá-Sousa A, Amaral R, Morais-Almeida M, Araújo L, Azevedo LF, Bugalho-Almeida A, et al. Asthma control in the Portuguese National Asthma Survey. Rev Port Pneumol. 2015;21:209–13, http://dx.doi.org/10.1016/j.rppnen.2014.08.003.
14. Sousa H. Socioeconomic and clinical determinants of asthma control in the Portuguese Asthma Survey [master's thesis]. Faculdade de Medicina da Universidade do Porto; 2014.
15. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: The Asthma Insights and Reality in Europe (AIRE) study. Eur Respir J. 2000;16:802–7, http://dx.doi.org/10.1183/09031936.00.16580200.
16. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the Asthma Control Test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004;113:59–65, http://dx.doi.org/10.1016/j.jaci.2003.09.008.
17. Thomas M, Kay S, Pike J, Williams A, Carranza Rosenzweig JR, Hillyer EV, et al. The Asthma Control Test (ACT) as a predictor of GINA guideline-defined asthma control: analysis of a multinational cross-sectional survey. Prim Care Respir J. 2009;18:41–9, http://dx.doi.org/10.4104/pcrj.2009.00010.
18. Body mass index-BMI; 2019. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi [accessed 10.11.19].
19. Benkheder A, Bouacha H, Nafti S, Taright S, El Ftouh M, Yassine N, et al. Control of asthma in the Maghreb: results of the AIRMAG study. Respir Med. 2009:103, http://dx.doi.org/10.1016/S0954-6111(09)70023-X.
20. Murphy KR, Meltzer EO, Blaiss MS, Nathan RA, Stoloff SW, Doherty DE. Asthma management and control in the United States: results of the 2009 asthma insight and management survey. Allergy Asthma Proc. 2012, http://dx.doi.org/10.2500/aap.2011.32.3518.
21. Gold LS, Thompson P, Salvi S, Faruqi RA, Sullivan SD. Level of asthma control and health care utilization in Asia-Pacific countries. Respir Med. 2014, http://dx.doi.org/10.1016/j.rmed.2013.12.004.
22. Solé D, Aranda CS, Wandalsen GF. Asthma: epidemiology of disease control in Latin America – short review. Asthma Res Pract. 2017, http://dx.doi.org/10.1186/s40733-017-0032-3.
23. Mendes Z, Madeira A, Costa S, Inácio S, Vaz M, Araújo AT, et al. Avaliação do controlo da asma através do Asthma Control Test TM aplicado em farmácias portuguesas. Rev Port Imunoalergol. 2010;18:313–30.

24. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, Azevedo L, Sa-Sousa A, Branco-Ferreira M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. Allergy Eur J Allergy Clin Immunol. 2010;65:1042–8, http://dx.doi.org/10.1111/j.1398-9995.2009.02310.x.
25. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14:902–7, http://dx.doi.org/10.1034/j.1399-3003.1999.14d29.x.
26. Fletcher M, Hiles D. Continuing discrepancy between patient perception of asthma control and real-world symptoms: a quantitative online survey of 1,083 adults with asthma from the UK. Prim Care Respir J. 2013;22:431–8, http://dx.doi.org/10.4104/pcrj.2013.00091.
27. Melani AS. Management of asthma in the elderly patient. Clin Interv Aging. 2013;8:913–22, http://dx.doi.org/10.2147/CIA.S33609.
28. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med. 2011;105:930–8, http://dx.doi.org/10.1016/j.rmed.2011.01.005.
29. Kämpe M, Lisspers K, Ställberg B, Sundh J, Montgomery S, Janson C. Determinants of uncontrolled asthma in a Swedish asthma population: cross-sectional observational study. Eur Clin Respir J. 2014;1:1–9, http://dx.doi.org/10.3402/ecrj.v1.24109.
30. Laforest L, Van Ganse E, Devouassoux G, Bousquet J, Chretin S, Bauguil G, et al. Influence of patients' characteristics and disease management on asthma control. J Allergy Clin Immunol. 2006;117:1404–10, http://dx.doi.org/10.1016/j.jaci.2006.03.007. S0091-6749(06)00650-6 [pii].
31. Zillmer LR, Gazzotti MR, Nascimento OA, Montealegre F, Fish J, Jardim JR. Gender differences in the perception of asthma and respiratory symptoms in a population sample of asthma patients in four Brazilian cities. J Bras Pneumol. 2014;40:591–8, http://dx.doi.org/10.1590/S1806-37132014000600002.
32. Zein JG, Erzurum SC. Asthma is different in women. Curr Allergy Asthma Rep. 2015:15, http://dx.doi.org/10.1007/s11882-015-0528-y.
33. Van Den Berge M, Heijink HI, Van Oosterhout AJM, Postma DS. The role of female sex hormones in the development and severity of allergic and non-allergic asthma. Clin Exp Allergy. 2009;39:1477–81, http://dx.doi.org/10.1111/j.1365-2222.2009.03354.x.
34. Sundberg R, Torén K, Franklin KA, Gislason T, Omenaas E, Svanes C, et al. Asthma in men and women: treatment adherence, anxiety, and quality of sleep. Respir Med. 2010;104:337–44, http://dx.doi.org/10.1016/j.rmed.2009.10.017.
35. Eisner MD, Yelin EH, Katz PP, Lactao G, Iribarren C, Blanc PD. Risk factors for work disability in severe adult asthma. Am J Med. 2006;119:884–91, http://dx.doi.org/10.1016/j.amjmed.2006.01.016.
36. Taponen S, Lehtimäki L, Karvala K, Luukkonen R, Uitti J. Correlates of employment status in individuals with asthma: a cross-sectional survey. J Occup Med Toxicol. 2017:12, http://dx.doi.org/10.1186/s12995-017-0165-6.
37. Pavord ID, Mathieson N, Scowcroft A, Pedersini R, Isherwood G, Price D. The impact of poor asthma control among asthma patients treated with inhaled corticosteroids plus long-acting β 2-agonists in the United Kingdom: a cross-sectional analysis. NPJ Prim Care Respir Med. 2017:27, http://dx.doi.org/10.1038/s41533-017-0014-1.
38. Lillienberg L, Andersson E, Janson C, Dahlman-Höglund A, Forsberg B, Holm M, et al. Occupational exposure and new-onset asthma in a population-based study in northern Europe (RHINE). Ann Occup Hyg. 2013;57:482–92, http://dx.doi.org/10.1093/annhyg/mes083.
39. Franco R, Nascimento HF, Cruz AA, Santos AC, Souza-Machado C, Ponte EV, et al. The economic impact of severe asthma to low-income families. Allergy Eur J Allergy Clin Immunol. 2009;64:478–83, http://dx.doi.org/10.1111/j.1398-9995.2009.01981.x.
40. Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. Asthma Res Pract. 2017;3:1, http://dx.doi.org/10.1186/s40733-016-0029-3.
41. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? Chest. 2008;134:317–23, http://dx.doi.org/10.1378/chest.07-2959.
42. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. Respir Med. 2006;100:648–57, http://dx.doi.org/10.1016/j.rmed.2005.08.001.
43. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. J Appl Physiol. 2010;108:206–11, http://dx.doi.org/10.1152/japplphysiol.00694.2009.
44. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol. 2018;141:1169–79, http://dx.doi.org/10.1016/j.jaci.2018.02.004.
45. Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DYM. Body mass and glucocorticoid response in asthma. Am J Respir Crit Care Med. 2008;178:682–7, http://dx.doi.org/10.1164/rccm.200801-076OC.
46. Santos LM, Ramos B, Almeida J, Loureiro CC, Cordeiro CR. The impact of weight loss beyond lung function: benefit with respect to asthma outcomes. Pulmonology. 2019;25:313–9, http://dx.doi.org/10.1016/j.pulmoe.2019.07.007.
47. Çelebi Sözener Z, Aydın Ö, Mungan D, Mısırlıgil Z. Obesity-asthma phenotype: effect of weight gain on asthma control in adults. Allergy Asthma Proc. 2016;37:311–7, http://dx.doi.org/10.2500/aap.2016.37.3949.
48. Lin J, Su N, Liu G, Yin K, Zhou X, Shen H, et al. The impact of concomitant allergic rhinitis on asthma control: a cross-sectional nationwide survey in China. J Asthma. 2014;51:34–43, http://dx.doi.org/10.3109/02770903.2013.840789.
49. Vandenplas O, Dramaix M, Joos G, Louis R, Michils A, Verleden G, et al. The impact of concomitant rhinitis on asthma-related quality of life and asthma control. Allergy Eur J Allergy Clin Immunol. 2010;65:1290–7, http://dx.doi.org/10.1111/j.1398-9995.2010.02365.x.
50. Ohta K, Bousquet PJ, Aizawa H, Akiyama K, Adachi M, Ichinose M, et al. Prevalence and impact of rhinitis in asthma, SACRA, a cross-sectional nation-wide study in Japan. Allergy Eur J Allergy Clin Immunol. 2011;66:1287–95, http://dx.doi.org/10.1111/j.1398-9995.2011.02676.x.
51. Bousquet J, Gaugris S, Kocevar VS, Zhang Q, Yin DD, Polos PG, et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the improving asthma control trial. Clin Exp Allergy. 2005:35, http://dx.doi.org/10.1111/j.1365-2222.2005.02251.x.
52. Bergeron C, Hamid Q. Relationship between asthma and rhinitis: epidemiologic, pathophysiologic, and therapeutic aspects. Allergy Asthma Clin Immunol Off J Can Soc Allergy Clin Immunol. 2005;1:81–7, http://dx.doi.org/10.1186/1710-1492-1-2-81.
53. De Vries MP, Van Den Bemt L, Lince S, Muris JWM, Thoonen BPA, Van Schayck CP. Factors associated with asthma control. J Asthma. 2005;42:659–65, http://dx.doi.org/10.1080/02770900500264903.
54. Cerveri I, Cazzoletti L, Corsico AG, Marcon A, Niniano R, Grosso A, et al. The impact of cigarette smoking on asthma: a population-based international cohort study. Int Arch Allergy Immunol. 2012;158:175–83, http://dx.doi.org/10.1159/000330900.

55. Beeklake MR, Lalloo U. The 'healthy smoker': a phenomenon of health selection? Respiration. 1990;57:137–44, http://dx.doi.org/10.1159/000195837.
56. Kaya Z, Erkan F, Ozkan M, Ozkan S, Kocaman N, Ertekin BA, et al. Self-management plans for asthma control and predictors of patient compliance. J Asthma. 2009;46:270–5, http://dx.doi.org/10.1080/02770900802647565.
57. Loke TK, Sousa AR, Corrigan CJ, Lee TH. Glucocorticoid-resistant asthma. Curr Allergy Asthma Rep. 2002, http://dx.doi.org/10.1007/s11882-002-0009-y.
58. Liu JH, Li C, Zhang CH, Zhang ZH. LncRNA-CASC7 enhances corticosteroid sensitivity via inhibiting the PI3K/AKT signaling pathway by targeting miR-21 in severe asthma. Pulmonology. 2020;26:18–26, http://dx.doi.org/10.1016/j.pulmoe.2019.07.001.
59. Boulet LP. Influence of comorbid conditions on asthma. Eur Respir J. 2009;33:897–906, http://dx.doi.org/10.1183/09031936.00121308.

Pulmonology 29 (2023) 42–49

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

A study of the psychometric properties of the Brazilian–Portuguese version of Bronchiectasis Health Questionnaire

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Received 3 October 2020; accepted 30 October 2020
Available online 30 December 2020

KEYWORDS
Bronchiectasis;
Quality of life;
Surveys and Questionnaires;
Dyspnea;
Psychometric properties

Abstract
Introduction and objective: The Bronchiectasis Health Questionnaire (BHQ) is a simple, repeatable, and self-reporting health status questionnaire for bronchiectasis. This study aims to cross-culturally adapt the BHQ into Brazilian Portuguese and evaluate its measurement properties.
Methods: The participants answered the Saint George's Respiratory Questionnaire (SGRQ) and the modified Medical Research Council (mMRC) scale for dyspnea. The Brazilian-Portuguese version of the Bronchiectasis Health Questionnaire (BHQ-Brazil) was used at baseline (test) and after 14 days (retest). The psychometric analyses included internal consistency, test-retest reliability, and construct validity: factorial validity, convergent validity, and discriminative validity, agreement, and ceiling and floor effects.

Abbreviations: QoL-B, Quality of Life Questionnaire-Bronchiectasis; SGRQ, Saint George's Respiratory Questionnaire; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; BHQ, Bronchiectasis Health Questionnaire; SDC, smallest detectable change; COSMIN, consensus-based standards for the selection of health measurement instruments; mMRC, modified Medical Research Council; E-FACED index, exacerbations, forced expiratory volume in the first second, age, chronic colonization by*Pseudomonas aeruginosa*, radiological extension, and dyspnea; EFA, exploratory factorial analysis; PCA, principal component analysis; 95%CI, 95% confidence interval; KMO, Kaiser-Meyer-Olkin; SEM, standard error of the measurement.

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https://doi.org/10.1016/j.pulmoe.2020.10.012

Results: The BHQ-Brazil demonstrated adequate internal consistency (Cronbach's alpha = 0.92) and substantial reliability (intraclass correlation coefficient = 0.86; 95%CI: 0.79–0.90). The exploratory factorial analysis was considered suitable. All items presented a factorial load >0.40. The convergent validity of the BHQ-Brazil with mMRC was moderate ($r = -0.53$, $p < 0.001$), while concurrent validity with the SGRQ was strong (symptoms: $r = -0.72$, activities: $r = -0.60$, impact: $r = -0.60$, total score: $r = -0.75$, all $p < 0.001$). The standard error of measurement was 4.81 points. The discriminative validity demonstrated that individuals with more pulmonary exacerbations, colonization by *Pseudomonas aeruginosa*, worst dyspnea, and a higher number of affected lung lobes presented the lowest quality of life. No floor or ceiling effects were observed.

Conclusion: The BHQ-Brazil presents adequate measurement properties to evaluate the impact of bronchiectasis on health-related quality of life, and can be used in clinical and research settings.

Introduction

Individuals with bronchiectasis present cough, abundant pulmonary secretion, dyspnea, reduced exercise capacity, and frequent pulmonary exacerbations,[1–3] culminating in a worse health-related quality of life.[4–6] Quality of life questionnaires provide valuable information regarding the impact of the disease on health perception.[7]

The Quality of Life Questionnaire-Bronchiectasis (QoL-B) was the first specific questionnaire developed for bronchiectasis.[8–10] This questionnaire has the advantage of quantifying the different quality of life domains. However, it is relatively long and does not present a total score, which makes its use disadvantageous in clinical practice. The Saint George's Respiratory Questionnaire (SGRQ)[11–14] and the Chronic Respiratory Disease questionnaire[14] were developed for individuals with chronic obstructive pulmonary disease and validated for bronchiectasis since both diseases present common clinical symptoms.[11,13–15] These instruments are useful; however, they are extensive and time-consuming. The Chronic Obstructive Pulmonary Disease Assessment Test (CAT) is also a validated questionnaire for bronchiectasis[16–18] but it is not specific for this disease, an important requirement that must be considered during the quality of life assessment.[19]

In this context, the Bronchiectasis Health Questionnaire (BHQ)[20] was developed specifically for bronchiectasis and has the advantage of being short, simple to apply and interpret, and generates a total score. Thus, it can be easily implemented during routine clinical evaluations. It is also the first assessment tool addressing items related to pulmonary exacerbation in bronchiectasis, an important marker of quality of life decline.[6] In the original, Korean, and Danish BHQ versions,[20–22] the exploratory factor analysis (EFA), the standard error of the measurement (SEM), the smallest detectable change (SDC), and the presence of ceiling and floor effects were not investigated. These properties are extremely important when evaluating psychometric properties in quality of life questionnaires. Additionally, the BHQ has been translated into 11 languages but not into Brazilian Portuguese. Therefore, this study aimed to adapt the BHQ to Brazilian Portuguese (BHQ-Brazil) cross-culturally and test its psychometric properties in individuals with bronchiectasis.

Methods

This is a cross-sectional study approved by the Human Research Ethics Committees of the University of Nove de Julho (number: 2.532.903) and the University of São Paulo (number: 2.574.759). All volunteers agreed to participate and signed an informed consent form.

The study was conducted in two phases. In phase I, the original BHQ was cross-culturally adapted to Brazilian Portuguese following previously established guidelines.[23,24] In phase II, the measurement properties of the BHQ-Brazil were tested. In this phase, the consensus-based standards for the selection of health measurement instruments (COSMIN) checklist were used.[25] Also based on recommendations,[25,26] a minimum sample size of 100 individuals was considered for this study. Additionally, based on the recommendation of 10 participants per item,[26] a minimum sample size of 100 individuals was considered sufficient for this study.

The subjects were recruited (convenience sample) by physiotherapists between October 2017 and December 2018 at the Obstructive Diseases Outpatient Clinic of the University of São Paulo Hospital and were sent to the Cardiopulmonary Rehabilitation Center of University of Nove de Julho. Those with a clinical and tomographic diagnosis of bronchiectasis, age $\geq$18 years, and clinically stable (*i.e.*, without coughing, greater volume and/or thicker pulmonary secretion consistency, purulent pulmonary secretions, increased dyspnea, reduced exercise tolerance, greater fatigue, or malaise in the four weeks before the study) were included in the study.[27] The exclusion criteria were smoking or tobacco load >10 pack/years, pulmonary (asthma, chronic obstructive pulmonary disease, interstitial lung disease, or cystic fibrosis) or cardiovascular diseases associated, or the inability to answer the questionnaires.

Phase I — cross-cultural adaptation

The initial translation was done by two independent bilingual translators residing in Brazil, whose native language was Brazilian Portuguese and English as their second language. The two translated versions were compared and combined to produce the first Brazilian version of the BHQ. This version was then back-translated into English by two independent bilingual translators with no prior knowledge and no access to the original version. After this phase, an expert panel composed of two pulmonologists and three physiotherapists compared the original version, translations, and back-translations, and formulated a pre-final version.

The pre-final version was given to a sample of 10 participants to determine whether they understood each item, and the following issue was observed: participants taking long-acting antibiotics demonstrated difficulty in understanding ''Item 10'', which addresses the need for antibiotics due to pulmonary exacerbations in the previous 12 months. The panel then decided to cross-culturally adapt this question as follows: ''*In the last 12 months, I made use of antibiotics to treat an episode of lung infection*.'' This new version was then given to 30 different individuals, who demonstrated no difficulty in understanding the BHQ-Brazil. The translated version was sent to the instrument developer and approved (Supplementary material).

Phase II — evaluation of measurement properties

After meeting the eligibility criteria, the participants answered the SGRQ[10] and the modified Medical Research Council (mMRC) scale for dyspnea,[28] followed by the BHQ-Brazil (test). All questionnaires were administered as an interview form. After 14 days, an evaluation was performed with the same individuals for data collection regarding demographic, anthropometric characteristics, and lung function. During this second visit, the individuals answered again the BHQ-Brazil (retest), which was also administered as an interview form by the same interviewer. The following psychometric analyses were included: reliability (internal consistency and test-retest reproducibility), construct validity (factorial validity and hypothesis-testing), criterion validity (concurrent validity), and agreement.

Testing procedures

Bronchiectasis Health Questionnaire

The BHQ is a specific questionnaire for bronchiectasis and comprises 10 items addressing aspects inherent to the disease. The score ranges from 0 to 100 points, with a higher score indicating a better health status.[20]

Saint George's Respiratory Questionnaire

The SGRQ comprises 50 items and 76 answers, divided into four domains: symptoms, activity, impact, and total. Each item is scored from 0 to 100 points, with higher scores denoting a greater negative impact on the quality of life due to the disease.[11]

Bronchiectasis Severity Scores

The severity of the bronchiectasis was evaluated using the E-FACED index (categorized into mild [0–3 points], moderate [4–6 points] or severe [7–9 points])[27,28] and the Bronchiectasis Severity Index (BSI) (categorized into mild [0 and 4], intermediate [5 and 8], and severe [>9]).[29–31]

Data analysis

Data normality was investigated using the Shapiro-Wilk test, and values were expressed as mean ± standard deviation and 95% confidence interval (95%CI). The paired *t*-test was used to compare BHQ-1 and BHQ-2 scores Effect-sizes were calculated using Cohen's d.[32] The level of significance was set at 5% (2-tailed) for all analyses.

Measurement properties

Reliability

Internal consistency. The Cronbach's alpha was used to calculate the internal consistency for the total BHQ score. Values between 0.75 and 0.95 were considered appropriate.[33,34]

Test-retest reproducibility. The type 1 intraclass correlation coefficients (ICC_{2-1}) and 95%CIs were calculated. The following classification was considered: poor (<0.4), moderate (0.4– 0.75), substantial (0.75–0.90), and excellent (>0.90).[33,34] Concordance was also analyzed using the Bland-Altman plot.

Construct validity

Construct validity was evaluated using the Factorial Validity and Hypothesis-testing.

Factorial validity

The factorial validity was tested using the EFA, and two methods (Kaiser-Meyer-Olkin [KMO] criterion and Bartlett's sphericity test) were applied to analyze whether the data matrix could be submitted to factorization. The KMO indices were interpreted as unacceptable (<0.5), mediocre (between 0.5 and 0.7), good (0.7 and 0.8), very good (>0.8), and excellent (0.9).[33] The principal component analysis (PCA) with varimax orthogonal rotation was used for data extraction. As the factor analysis aims to reduce the number of variables into fewer numbers of factors, only those factors with an eigenvalue >1 were retained for analysis.[35] The factorability of the correlation matrix values were interpreted as minimal (≥0.30), important (≥0.40), and practically significant (≥0.50).[36]

Hypothesis-testing

The convergent validity was tested using Pearson's correlation between the BHQ-Brazil and mMRC scores. The correlation coefficient values were interpreted as weak validity (<0.30), moderate validity (≥0.30 to <0.60), and strong validity (≥0.60).[37]

The discriminant validity (known groups) analyses whether a measure can discriminate groups in which differences are theoretically expected to be found.[37] Then, BHQ-Brazil scores were compared according to the number

of exacerbations (0—2 *versus* 3–6), colonization by *Pseudomonas aeruginosa* (yes or no), mMRC (0—2 *versus* 3—4), and the number of affected lung lobes (1–2 *versus* >2). These dichotomizations were based on E-FACED variables.[30] The discriminant validity was performed using the unpaired *t*-test, as variables exhibited parametric distributions.

Criterion validity

Pearson's correlation coefficients were used to confirm the concurrent validity between the total BHQ-Brazil and SGRQ scores.[37]

Agreement

Agreement was analyzed using the SEM (SEM = SD$\sqrt{}$1-ICC), and interpreted as very good (≤5%), good (5%–10%), questionable (11%–20%), and bad (>20%). The SDC was calculated based on the SEM using the following formula: $SDC = 1.96 \times \sqrt{2} \times SEM$.

Ceiling and floor effects

Ceiling and floor effects were tested by examining the score distribution across participants and considered if 15% achieved the minimum or maximum score on each scale.[34]

Results

Cross-cultural adaptation

The expert panel performed the cross-cultural adaptation of ''Item 10'' of the original questionnaire from ''*In the last 12 months, I needed to take antibiotics for a chest infection*'' to ''*In the last 12 months, I made use of antibiotics to treat an episode of lung infection*.''

Assessment of measurement properties

A total of 103 individuals with bronchiectasis were included; two were excluded due to heart disease. Thus, the final sample consisted of 101 individuals (60 female). None of the patients exacerbated during the study period. Regarding the bronchiectasis etiology, 40% was idiopathic, 24% was due to infection, and other causes 36%. A total of 43% had colonization by *Pseudomonas aeruginosa*, 13% by *Haemophilus influenzae*, and 23% by other bacteria, whereas 21% had no colonization (Table 1).

Reliability: internal consistency and test-retest reproducibility

The BHQ-Brazil exhibited adequate internal consistency. The $ICC_{2,1}$ was considered substantial and demonstrated good test-retest reliability (Table 2). The Bland-Altman plot showed a mean bias of −0.94, with limits of agreement from 9.78 to 7.90 (Fig. 1).

Validity: construct (factorial, convergent, and discriminative validity) and criterion validity

For the EFA adequacy, the correlation matrices showed values between 0.40 and 0.90 in most cases. Bartlett's

Table 1 Characteristics of the participants, n = 101 (60 women).

Characteristics	Value
Age, years old, mean (SD)	49.0 (14.0)
BMI, kg/m^2, mean (SD)	25.0 (4.0)
FVC, L, / % pred, mean (SD)	2.4 (0.8) / 67.0 (17.0)
$FEV_{1,}$ L, / % pred, mean (SD)	1.5 (0.6) /51.0 (18.0)
FEV_1/FVC, mean (SD)	62.0 (15.0)
O_2 dependent, n (%)	11 (10.9)
Number of exacerbations/year, mean (SD)	1 (0.47)
mMRC, mean (SD)	2 (0.93)
n per score 0/1/2/3/4	3/39/35/18/6
Pneumectomy, n (%)	4
E-FACED, mean (SD)	3 (2.0)
n per score mild/moderate/severe	65/29/7
BSI, mean (SD)	7 (4.0)
n per score low/intermediate/severe	27/46/28
BHQ -1 time to answer, min, mean (SD)	3.8 (1.0)
BHQ -2 time to answer, min, mean (SD)	3.6 (0.9)
BHQ -1, mean (SD)	58.8 (8.0)
BHQ -2, mean (SD)	59.0 (9.0)
SGRQ symptom, mean (SD)	55.2 (19.0)
SGRQ activity, mean (SD)	61.0 (20.0)
SGRQ impact, mean (SD)	38.0 (17.0)
SGRQ total, mean (SD)	48.0 (15.0)

SD: standard deviation, BMI: body mass index; kg/m^2: kilograms per square meter; FVC: forced vital capacity; FEV_1: forced expiratory volume in first second; L: liters; %: percentage; pred: predicted value; n: number of patients; mMRC: modified Medical Research Council dyspnea scale; E-FACED: exacerbations, forced expiratory volume in first second, age, chronic colonization by *Pseudomonas aeruginosa*; BSI: Bronchiectasis Severity Index; min: minutes; BHQ: Bronchiectasis Health Questionnaire; SGRQ: Saint George's Questionnaire.

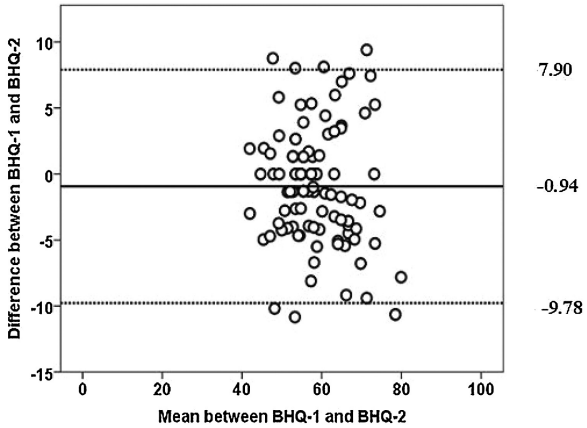

Figure 1 Bland Altman plot (n = 101) for test-retest repeatability. The solid line indicates mean bias, and the dashed lines indicate the upper and lower limits of agreement between the tests.

Table 2 Classification of measurement properties of Bronchiectasis Health Questionnaire in Brazilian Portuguese in participants with bronchiectasis (n = 101).

Properties	Values
Reliability	
Cronbach's alpha	0.92
$ICC_{2.1}$ (95% CI)	0.86 (0.79–0.90) *
Convergent validity	
mMRC	r = −0.53*
Concurrent validity with SGRQ	
Symptoms	r = −0.72*
Activity	r = −0.60*
Impacts	r = −0.60*
Total score	r = −0.75*
Agreement	
Standard error of measurement	4.81 points
Smallest detectable change	6.07 points
Ceiling and floor effects	Absents

ICC: intraclass correlation coefficient; CI: confidence interval; SGRQ: Saint George's Questionnaire; r: Pearson's correlation, mMRC: modified Medical Research Council dyspnea scale, CI: confidence interval.
* $p < 0.001$.

sphericity test rejected the null hypothesis ($p < 0.001$), and the KMO test (0.742) was suitable to proceed to EFA.

Considering the scatter plot graph and using the principal component extraction method with orthogonal varimax rotation, the following three items were identified among the 10 BHQ-Brazil items: (1) tiredness, (2) functionality, and (3) anxiety. Cronbach's alpha coefficients for these items were 0.82, 0.75, and 0.60, respectively. All the items' scores displayed adequate communalities (from 0.60 to 0.79). The initial analysis of the eigenvalues of these three items, after rotation, explained 67.16% of the variance. Thus, as most items presented high factorial loads, the three items extracted could explain the common variance between them (Table 3).

Convergent and discriminative validity

For convergent validity, moderate correlations were found between the BHQ-Brazil score and mMRC scale ($p < 0.001$) (Table 2). The instrument demonstrated good discrimination regarding the number of pulmonary exacerbations, colonization by *Pseudomonas aeruginosa*, the number of affected lung lobes, and the severity of dyspnea (mMRC) (Table 4).

Concurrent validity

Concurrent validity was demonstrated by strong correlations between the SGRQ domains and the total BHQ-Brazil score ($p < 0.001$).

Agreement

The SEM and the SDC of the BHQ-Brazil score were considered very good. No ceiling or floor effects were found (Table 2).

Discussion

The present study addressed the cross-cultural adaptation of the BHQ-Brazil and the evaluation of its psychometric properties, which were not investigated in the original, Korean, and Danish versions.[20–22] The BHQ-Brazil version exhibited adequate internal consistency and substantial reliability when retested after two weeks, presenting values above those recommended for health status questionnaires[34] and similar to those reported by the developers of the original, Korean, and Danish versions.[20–22] It also exhibited greater internal consistency and reliability compared with CAT.[16] The BHQ and CAT are short questionnaires that generate a single final score, which is advantageous for clinical use in bronchiectasis patients.[16–18] However, CAT is not specific for bronchiectasis and does not address any pulmonary exacerbation treatment item.

This study also tested the EFA of the BHQ-Brazil, a psychometric property that was not evaluated in the original, Korean, and Danish studies. Suitability was assessed using the KMO and Bartlett tests. The PCA extracted three factors. The first was related to the presence of pulmonary secretion and blood in the secretion, quality of sleep, and pulmonary exacerbation; the second addressed tiredness, functionality, anxiety, and shortness of breath; while the third factor concerned the presence of pulmonary secretion, embarrassment because of phlegm, and cough. The items of each factor presented high factorial load and good internal consistency between them. The communalities of the items were considered adequate, indicating that the scores of the BHQ-Brazil items share a good level of variance. The total variance explained by the BHQ-Brazil was 67.16%, which led to more than one item for each of the identified factors.

The BHQ-Brazil presented a moderate convergent validity with the mMRC scale, demonstrating that the higher the dyspnea, the lower the BHQ score, determining a worse quality of life. This was probably because the mMRC scale assesses dyspnea during activities of daily living, whereas the BHQ addresses other symptoms related to bronchiectasis. Spinou et al.[20] observed a strong correlation between the BHQ and dyspnea assessed using the visual analog scale; however, this scale evaluates shortness of breath only and does not consider dyspnea during activities of daily living.

The BHQ-Brazil was able to discriminate the impact of the quality of life on those with the highest number of exacerbations, colonization by *Pseudomonas aeruginosa*, worse dyspnea scale scores, and greater number of affected lung lobes. These clinical markers are related to the phenotypes of individuals with an exacerbating profile.[6] The exacerbation and pulmonary colonization by *Pseudomonas aeruginosa* in individuals with bronchiectasis are considered important markers of reduced quality of life.[3,5,6,38] The BHQ-Brazil exhibited strong concurrent validity with the SGRQ with an advantage of a fast application and easy interpretation. The rapid application was confirmed by the shorter time required to complete the questionnaire (3.8 min) compared with both the SGRQ (12 min)[11–14] and QoL-B (10 min).[8–10]

The BHQ-Brazil showed a small SEM and a narrow SDC, indicating a very good agreement with little response variability between test-retest. These psychometric properties had not been evaluated since the publication of the origi-

Table 3 Analysis of the factorial components of each item on the BHQ-Brazil obtained by the varimax rotation method (n = 101).

BHQ items	Factors			h^2
	1	2	3	
4. In the last 2 weeks, my chest has felt clear.	0.76[a]		0.40	0.761
7. In the last 2 weeks, my sleep has been disrupted because of my bronchiectasis.	0.73			0.670
9. In the last 2 weeks, my phlegm (sputum) contained blood.	0.91			0.838
10. In the last one year, I have taken courses of antibiotics for a chest infection.	0.83			0.737
1. In the last 2 weeks, I have been tired.		0.84		0.757
2. In the last 2 weeks, I have been much slower at doing things than other people of my age.		0.82		0.698
3. In the last 2 weeks, I have felt anxious.		0.43		0.604
6. In the last 2 weeks, I have felt short of breath.		0.87		0.792
5. In the last 2 weeks, I have been embarrassed because of my phlegm (sputum).			0.85	0.727
8. In the last 2 weeks, I have had coughing bouts.			0.75	0.623
Numbers of items	4	4	3	
% of explained variance	33.68	19.96	13.52	
% total of explained variance	67.16			
Cronbach's alpha	0.82	0.75	0.60	

Extraction method: Principal component analysis; Rotation method: Varimax with normalization Kaiser; factor 1, 2, 3.
[a] Item 4 contributed more to factor 1. BHQ: Bronchiectasis Health Questionnaire, h^2: commonality.

Table 4 Discriminative validity of Bronchiectasis Health Questionnaire scores according to exacerbation, colonization, number of lobes affected and dyspnea.

Variable	Mean (SD)/CI 95%	Mean (SD)/CI 95%	Difference in mean/CI 95%	ES	p Value
Number of exacerbations in the previous year	**0 – 2 (n = 77)** 60.0 (8.25)/58.0–62.0	**3—6 (n = 24)** 53.0 (6.0)/50.0–55.0	7.0/3.7–10.0	0.87	<0,001
Colonization by *Pseudomonas*	**Not (n = 57)** 60.0 (8.0)/57.0–62.0	**Yes (n = 44)** 56.0 (7.0)/54.0–58.0	4.0/0.75–7.24	0.50	<0.001
Number of lung lobes affected	**1 – 2 (n = 35)** 61.0 (8.3)/58.0–64.0	**> 2(n = 62)** 57.0 (8.0)/54.0–59.0	4.0/0.93–7.8	0.50	=0.01
mMRC	**0—2 (n = 77)** 60.0 (7.8)/59.0–62.0	**3—4 (n = 24)** 52.0 (6.2)/49.0–54.0	8.0/5.0–12.0	1.14	<0.001

SD: standard deviation, CI: confidence interval, mMRC: modified Medical Research Council dyspnea scale, ES: effect size.

nal, Korean, and Danish BHQ versions.[20–22] Also, no ceiling and floor effects were observed, as none of the participants obtained the lowest or highest scores in the BHQ-Brazil. Thus, the BHQ-Brazil can be used to assess the response to interventions such as pulmonary rehabilitation or pharmacological treatments. Besides, BHQ scores may also differ during and after exacerbations. Nevertheless, prospective studies must be conducted to confirm these assumptions.

This study had some limitations. Individuals were recruited from a single referral center for bronchiectasis in São Paulo, which receives patients from all over Brazil. Thus, it is essential to administer the BHQ-Brazil in other states of the country to test its external validity. Moreover, the study included young individuals with less severe bronchiectasis. Thus, future studies focusing on assessing the usefulness of BHQ in an older population and people with different disease severities are suggested.

In conclusion, the Brazilian-Portuguese version of the BHQ presents adequate measurement properties to evaluate the quality of life of individuals with bronchiectasis and can be implemented in clinical practice.

Ethical approval

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration of Helsinki (1964) and its later amendments or comparable ethical standards. Moreover, informed consent was obtained from all individ-

uals included in the study (certification number: 2.532.903 and 2.574.759).

Source of financial support

AL was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, number 1823466). COC was supported by CAPES (number 1803009). SDC is suported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (number 306531/2018-6).

Conflicts of interest

The authors have no conflicts of interest to declare.

Contributions of each author to the paper

AL: Performed the data collection, conceived and designed the study, analyzed the data, read and approved the manuscript.

COC: Performed the data collection, conceived and designed the study, analyzed the data, read and approved the manuscript.

SSB: Conceived and designed the study, read and approved the manuscript.

ACL: Analyzed the data, read and approved the manuscript.

SZR: Conceived and designed the study, read and approved the manuscript.

RAA: Conceived and designed the study, read and approved the manuscript.

RE: Conceived and designed the study, read and approved the manuscript.

SDC: Conceived and designed the study, analyzed the data, read and approved the manuscript and is the guarantor of the study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pulmoe.2020.10.012.

References

1. Qi Q, Wang W, Li T, Zhang Y, Li Y. Aetiology and clinical characteristics of patients with bronchiectasis in a Chinese Han population: a prospective study. Respirology. 2015;20(6):917–24, http://dx.doi.org/10.1111/resp.12574. Epub 2015 Jun 19.
2. Pereira MC, Athanazio RA, Dalcin PTR, Figueiredo MRF, Gomes M, Freitas CG, et al. Consenso brasileiro sobre bronquiectasias de fibrose não cística. J Bras Pneumol. 2019;45(4):1–24, http://dx.doi.org/10.1590/1806-3713/e20190122.
3. Guan WJ, Gao YH, Xu G, Lin ZY, Tang Y, Li H, et al. Inflammatory Responses, Spirometry, and Quality of Life in Subjects With Bronchiectasis Exacerbations. Respir Care. 2015;60:1180–9, http://dx.doi.org/10.4187/respcare.04004. Epub 2015 Jun 9.
4. de Camargo AA, Boldorini JC, Holland AE, de Castro RAS, Lanza FC, Athanazio RA, et al. Determinants of peripheral muscle strength and activity in daily life in people with bronchiectasis. Phys Ther. 2018;98(3):153–61, http://dx.doi.org/10.1093/ptj/pzx123.
5. Yildiz S, Inal-Ince D, Calik-Kutukcu E, Vardar-Yagli N, Saglam M, Arikan H, et al. Clinical determinants of incremental shuttle walk test in adults with bronchiectasis. Lung. 2018;196(3):343–9, http://dx.doi.org/10.1007/s00408-018-0094-x. Epub 2018 Feb 12.
6. Chalmers JD, Aliberti S, Filonenko A, Shteinberg M, Goeminne PC, Hill AT, et al. Characterization of the frequent exacerbator phenotypeïn bronchiectasis. Am J Respir Crit Care Med. 2018;197(11):1410–20, http://dx.doi.org/10.1164/rccm.201711-2202OC.
7. Spinou A, Fragkos KC, Lee KK, Elston C, Siegert RJ, Loebinger MR, et al. The validity of health-related quality of life questionnaires in bronchiectasis: a systematic review and meta-analysis. Thorax. 2016;71(8):683–94, http://dx.doi.org/10.1136/thoraxjnl-2015-207315. Epub 2016 Feb 11.
8. Quittner AL, O'Donnell AE, Salathe MA, Lewis SA, Li X, Montgomery AB, et al. Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. Thorax. 2015;70(1):12–20, http://dx.doi.org/10.1136/thoraxjnl-2014-205918. Epub 2014 Oct 16.
9. Olveira C, Olveira G, Espildora F, Giron RM, Muñoz G, Quittner AL, et al. Validation of a quality of life questionnaire for bronchiectasis: psychometric analyses of the Spanish QOL-B-V3.0. Qual Life Res. 2014;23(4):1279–92, http://dx.doi.org/10.1007/s11136-013-0560-0. Epub 2013 Oct 19.
10. De Camargo C, José A, Luppo A, de Camargo AA, Athanazio R, Rached S, et al. Quality of Life Questionnaire-Bronchiectasis: a study of the psychometric properties of the Brazilian Portuguese version. Clin Rehabil. 2020;34(7):960–70, http://dx.doi.org/10.1177/0269215520925886.
11. Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R. Validation of the St. George's Respiratory Questionnaire in bronchiectasis. Am J Respir Crit Care Med. 1997;156(2Pt1):536–41, http://dx.doi.org/10.1164/ajrccm.156.2.9607083.
12. Martínez García MA, Perpiñá Tordera M, Román Sánchez P, et al. Internal consistency and validity of the Spanish version of the St. George's respiratory questionnaire for use in patients with clinically stable bronchiectasis. Arch Bronconeumol. 2005;41(3):110–7, http://dx.doi.org/10.1016/S1579-2129(06)60410-2.
13. Chan SL, Chan-Yeung MM, Ooi GC, Lam CL, Cheung TF, Lam WK, et al. Validation of the Hong Kong Chinese version of the St. George Respiratory Questionnaire in patients with bronchiectasis. Chest. 2002;122(6):2030–7, http://dx.doi.org/10.1378/baú.122.6.2030.
14. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med. 1991;85 Suppl B:25–31, http://dx.doi.org/10.1016/s0954-6111(06)80166-6.
15. Vodanovich D, Bicknell T, Holland A, Hill CJ, Cecins N, Jenkins S, McDonald CF, et al. Validity and reliability of the chronic respiratory disease Questionnaire in elderly individuals with mild to moderate non-cystic fibrosis bronchiectasis. Respiration. 2015;90(2):89–96, http://dx.doi.org/10.1159/000430992. Epub 2015 Jun 18.
16. Lanza FC, Castro RAS, de Camargo AA, Zanatta DJM, Rached S, Athanazio R, et al. COPD Assessment Test (CAT) is a valid and simple tool to measure the impact of bronchiectasis on affected patients. COPD. 2018;23:1–8, http://dx.doi.org/10.1080/15412555.2018.1540034. Epub 2018 Nov 23.
17. De la Rosa Carrillo D, Olveira C, García-Clemente M, Girón-Moreno RM, Nieto-Royo R, Navarro-Rolon A, et al. COPD Assessment Test in Bronchiectasis: minimum clinically important difference and psychometric vali-

dation: a prospective study. Chest. 2020;157(4):824–33, http://dx.doi.org/10.1016/j.chest.2019.08.1916. Epub 2019 Aug 22.
18. Finch Simon, Laska Irena F, Abo-Leyah Hani, Fardon Thomas C, Chalmers James D. Validation of the COPD Assessment Test (CAT) as an outcome measure in bronchiectasis. Chest. 2020;157(4):815–23, http://dx.doi.org/10.1016/j.chest.2019.10.030. Epub 2019 Nov 12.
19. Bowling A. Disease measurement: a review of disease-specific quality of life measurement scales (second edition). Which Life Res. 1996;12:1147–8.
20. Spinou Arietta, Siegert Richard J, Guan Wei-jie, Patel AS, Gosker HR, Lee KK, et al. The development and validation of the Bronchiectasis Health Questionnaire. Eur Respir J. 2017;49(5):1601532, http://dx.doi.org/10.1183/13993003.01532-2016.
21. Gissel TN, Hvass M, Fly J, Børsting K, Birring SS, Spinou A, et al. Translation and linguistic validation of the Bronchiectasis Health Questionnaire (BHQ) into Danish. Dan Med J. 2020;67(3):A9190520.
22. Kim HK, Lee H, Kim S-H, Choi H, Lee JH, Lee JS, et al. Validation of the Korean Version of the Bronchiectasis Health Questionnaire. Tuberc Respir Dis (Seoul). 2020;83(3):228–33, http://dx.doi.org/10.4046/trd.2020.0025.
23. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine. 2000;25(24):3186–91, http://dx.doi.org/10.1097/00007632-200012150-00014.
24. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of good practice for the translation and cultural adaptation process for Patient-Reported Outcomes (PRO) measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005;8(2):94–104, http://dx.doi.org/10.1111/j.1524-4733.2005.04054.x.
25. Terwee CB, Mokkink LB, Knol DL, Ostelo RW, Bouter LM, de Vet HC. Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. Qual Life Res. 2012;21(4):651–7, http://dx.doi.org/10.1007/s11136-011-9960-1.
26. Anthoine E, Moret L, Regnault A, Sébille V, Hardouin JB. Sample size used to validate a scale: a review of publications on newly-developed patient reported outcomes measures. Health and Quality of Life Outcomes. 2014;12(1), http://dx.doi.org/10.1186/s12955-014-0176-2.
27. Hill AT, Haworth CS, Aliberti S, Barker A, Blasi F, Boersma W, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. Eur Respir J. 2017;49(6):1700051, http://dx.doi.org/10.1183/13993003.00051-2017.
28. Kovelis D, Segretti NO, Probst VS, Lareau SC, Brunetto AF, Pitta F. Validação do Modified Pulmonary Functional Status and Dyspnea Questionnaire e da escala do Medical Research Council para o uso em pacientes com doença pulmonar obstrutiva crônica no Brasil. J Bras Pneumol. 2008;34(12):1008–18, http://dx.doi.org/10.1590/S1806-37132008001200005.
29. Athanazio R, Pereira MC, Gramblicka G, Cavalcanti-Lundgren F, de Figueiredo MF, Arancibia F, et al. Latin America validation of FACED score in patients with bronchiectasis: an analysis of six cohorts. BMC Pulm Med. 2017;17(1):73, http://dx.doi.org/10.1186/s12890-017-0417-3.
30. Martinez Garcia MA, Athanazio RA, Girón R, Máiz-Carro L, de la Rosa D, Olveira C, et al. Predicting high risk of exacerbations inbronchiectasis: the E-FACED score. Int J Chron Obstruct Pulmon Dis. 2017;12:275–84, http://dx.doi.org/10.2147/COPD.S121943.
31. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index. An international derivationand validation study. Am J Respir Crit Care Med. 2014;189(5):576–85, http://dx.doi.org/10.1164/rccm.201309-1575OC.
32. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
33. De Vet HCW, Terwee CB, Mokkink LB, et al. Reliability. In: de Vet HCW, Caroline B, Mokkink LB, et al., editors. Measurement in medicine. 1st ed. New York: Cambridge University Press; 2011. p. 96–149.
34. Terwee CB, Bot SDM, de Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60(1):34–42, http://dx.doi.org/10.1016/j.jclinepi.2006.03.012. Epub 2006 Aug 24.
35. Hadi NU, Abdullah N, Sentosa I. An easy approach to exploratory factor analysis: marketing perspective. J Educ Soc Res. 2016;6(1):215–23, http://dx.doi.org/10.5901/jesr.2016.v6n1p215.
36. Williams BA, Onsman A, Brown GT. Exploratory factor analysis: a five-step guide for novices. J Emerg Prim Health Care. 2010;8(3):1–13, http://dx.doi.org/10.33151/ajp.8.3.93.
37. Polit DF. Assessing measurement in health: beyond reliability and validity. Int J Nurs Stud. 2015;52(11):1746–53, http://dx.doi.org/10.1016/j.ijnurstu.2015.07.002. Epub 2015 Jul 17.
38. Kamata Hirofumi, Asakura Takanori, Suzuki Shoji, Namkoong Ho, Yagi Kazuma, Funatsu Yohei, et al. Impact of chronic *Pseudomonas aeruginosa* infection on health-related quality of life in *Mycobacterium avium* complex lung disease. BMC Pulm Med. 2017;17:198, http://dx.doi.org/10.1186/s12890-017-0544-x.

Pulmonology 29 (2023) 50–64

PULMONOLOGY

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ORIGINAL ARTICLE

Efficacy of Radial Endobronchial Ultrasound (R-EBUS) guided transbronchial cryobiopsy for peripheral pulmonary lesions (PPL's): A systematic review and meta-analysis

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Received 27 October 2020; accepted 16 December 2020
Available online 10 January 2021

KEYWORDS
Endobronchial ultrasound;
Cryobiopsy;
Lung cancer;
Peripheral pulmonary lesion;
Lung nodule;
Biopsy

Abstract
Background: Transbronchial lung cryobiopsy (TBLC) is frequently described for the diagnosis of diffuse parenchymal lung diseases (DPLD). A few studies have reported transbronchial cryobiopsy for the diagnosis of peripheral pulmonary lesions (PPL's). We aimed to study the utility and safety of transbronchial cryobiopsy for the diagnosis of PPL's.
Methods: We performed a systematic search of the PubMed and Embase databases to extract the relevant studies. We then performed a meta-analysis to calculate the diagnostic yields of transbronchial cryobiopsy and bronchoscopic forceps biopsy.
Results: Following a systematic search, we identified nine relevant studies (300 patients undergoing cryobiopsy). All used Radial Endobronchial Ultrasound (R-EBUS) for PPL localization. The pooled diagnostic yield of transbronchial cryobiopsy was 77% (95% CI, 71%–84%) ($I\hat{2} = 38.72\%$, $p = 0.11$). The diagnostic yield of forceps biopsy was 72% (95% CI, 60%–83%) ($I\hat{2} = 78.56\%$, $p < 0.01$). The diagnostic yield of cryobiopsy and forceps biopsy was similar (RR 1.05, 95% CI 0.96–1.15), with a 5% risk difference for diagnostic yield (95% CI, −6% to 15%). There was significant heterogeneity ($I\hat{2} = 57.2\%$, $p = 0.017$), and no significant publication bias. One severe bleeding and three pneumothoraxes requiring intercostal drain (ICD) placement (major complication rate 4/122, 1.8%) were reported with transbronchial cryobiopsy.

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https://doi.org/10.1016/j.pulmoe.2020.12.006

Conclusions: R-EBUS guided transbronchial cryobiopsy is a safe and efficacious modality. The diagnostic yields of TBLC and forceps biopsy are similar. More extensive multicentre randomized trials are required for the further evaluation and standardization of transbronchial cryobiopsy for PPL's.

Introduction

Peripheral pulmonary lesions (PPL's) are a frequent indication for pulmonologist referral in clinical practice. Clinicians can incidentally find PPL's on thoracic imaging, and many are detected on CT scans performed for lung cancer screening. The diagnosis is challenging especially for small lesions and those located in proximity to major vascular structures.[1] An accurate diagnosis is essential so that treatment decisions can be optimized. Transthoracic percutaneous biopsy and bronchoscopy are the primary modalities for tissue biopsy of PPL's. The decision regarding the choice of approach for biopsy depends on the proximity of the lesion to the chest wall, availability of resources, risk of complications depending on the patient's clinical status and physician preference. Percutaneous transthoracic approaches (CT or ultrasound-guided biopsy) provide a superior diagnostic yield.[2] However, the risk of pneumothorax is higher, especially in patients with emphysema.

Bronchoscopic modalities are safer with a lower risk of pneumothorax. Endobronchial anatomy can also be evaluated. Conventional bronchoscopy for PPL's provides a low diagnostic yield.[3] Radial Endobronchial Ultrasound (R-EBUS) is a useful modality for guided bronchoscopic biopsy of PPL's. However, the material obtained with conventional forceps biopsy under R-EBUS guidance is often insufficient.[4] The overall diagnostic yield of R-EBUS for PPL's (70.6%) is not excellent and requires further improvement.[5] Various innovations have attempted to optimize the yield of bronchoscopic biopsy of PPL's. These technologies include guide sheath method, bronchoscopic navigation, fluoroscopy, cone-beam CT guidance, and robotic bronchoscopy.[6] Although the newer technologies allow a more accurate guide to the target lesion, a suboptimal diagnostic yield compared with CT guided percutaneous biopsy remains a significant limitation.

Transbronchial lung cryobiopsy (TBLC) is commonly used in the evaluation of diffuse parenchymal lung disease (DPLD)'s.[7,8] The samples obtained with TBLC are significantly larger than the conventional bronchoscopic forceps biopsy. A few studies have described the utility of R-EBUS guided transbronchial cryobiopsy for the evaluation of PPL's. Some have also compared the yield of cryobiopsy with conventional forceps biopsy. There is increasing interest in the use of bronchoscopic cryobiopsy for sampling PPL's. The advantage of the cryoprobe is the ability to obtain a more extensive tissue, and a 360°/lateral biopsy.[9] For adjacent or eccentric lesions, this ability may be particularly advantageous. Theoretically, the freezing of a larger area surrounding the tip of the cryoprobe may also be beneficial in smaller nodules. The risks with TBLC for DPLD's include pneumothorax and bleeding. In contrast to TBLC for diffuse interstitial lung diseases, the technique of cryobiopsy for PPL's has not been standardized.[10]

We carried out a systematic review of the literature to identify the studies describing the yield and safety of transbronchial cryobiopsy for PPL's. We included studies which included human subjects undergoing transbronchial cryobiopsy for PPL. Both prospective and retrospective studies were eligible for inclusion. We also performed a meta-analysis to calculate the pooled diagnostic yield of cryobiopsy and its comparison with forceps biopsy. We also summarise the complications and safety of bronchoscopic cryobiopsy for PPL's.

Methods

Search strategy and initial review

Two authors (K.M and S.PB) performed a systematic search of the two databases: PubMed and EMBASE (01.01.2004 up to 12.08.2020) to identify the original, peer-reviewed, full-length, human subject articles describing the use of transbronchial cryobiopsy for PPL's. We used the following database-specific search strategy. Free text search terms were: (cryoprobe OR cryobiopsy OR cryotherapy OR cryo OR tblc OR transbronchial lung cryobiopsy) AND (peripheral pulmonary lesion OR ppl OR solitary pulmonary nodule OR lung nodule OR pulmonary nodule OR radial ebus OR ebus OR radial endobronchial ultrasound OR endobronchial ultrasound OR guide sheath OR radial probe OR virtual bronchoscopic navigation OR vbn OR emn OR electromagnetic navigation). All the retrieved studies were imported into reference management software (EndNote). Duplicate citations were discarded. The studies were screened by title and abstract. Full texts were downloaded for review, wherever required. The reference lists of the extracted studies were also reviewed. The finally selected studies were screened independently by three authors (K.M, S.M and S.PB). Studies describing the utilization of cryobiopsy for peripheral pulmonary lesions were included. For inclusion, sufficient data for calculating the diagnostic yield of cryobiopsy for PPL were required. The following studies were excluded: (a) studies that did not report the utilization of cryobiopsy for PPL (b) studies not in English language (c) review articles, editorials, abstracts, and letters without any case description (d) case reports or series with fewer than five patients. Any disagreement between the authors was resolved after mutual discussion.

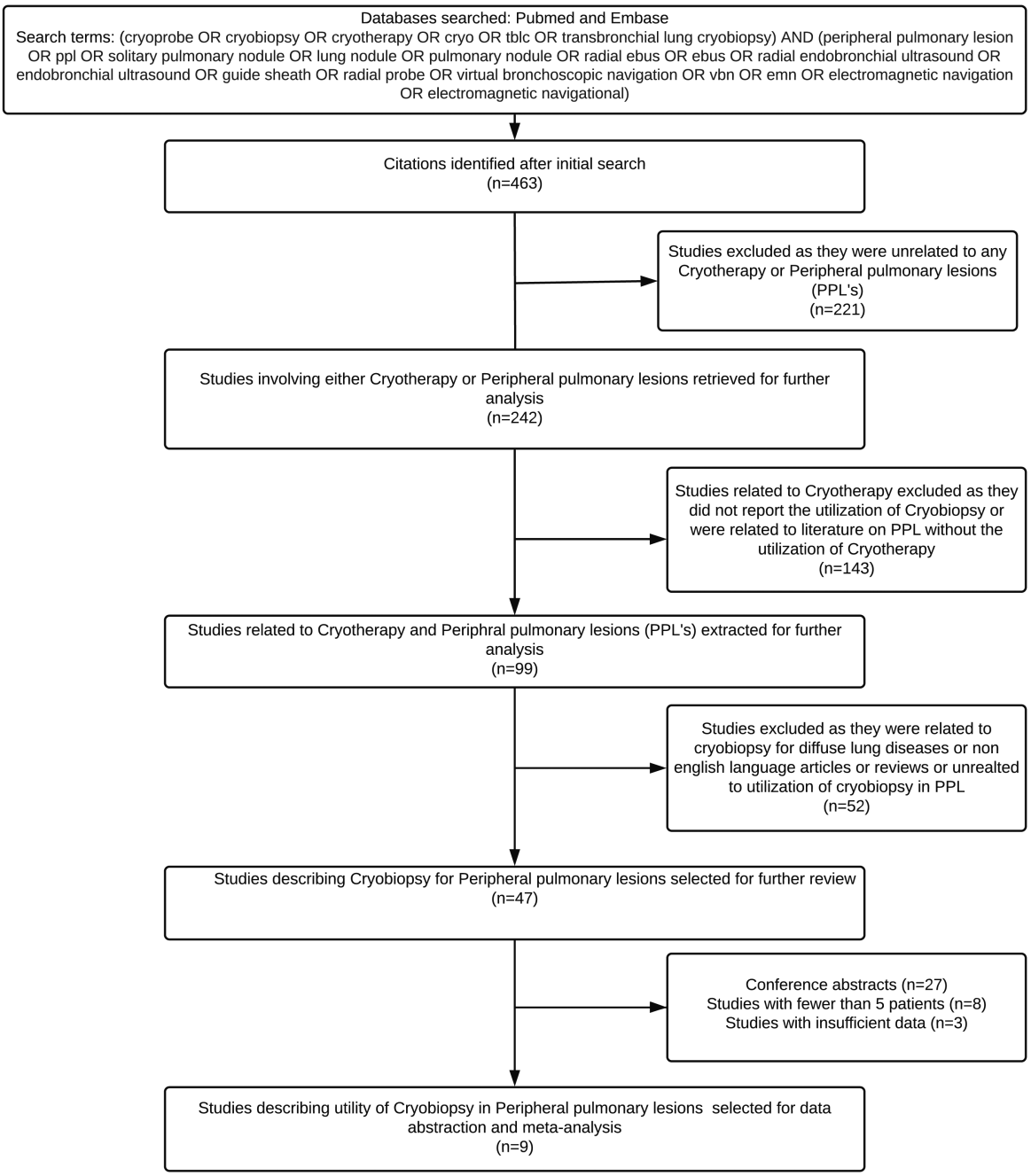

Figure 1 Figure showing the process of systematic review and selection of studies for meta-analysis.

Data abstraction

Data from the finally selected studies were abstracted on a data extraction form. The following information was retrieved after a thorough review of the full text — (a) author, (b) year, (c) number of patients, (d) gender, (e) number of centres, (f) study design, (g) age, (h) type of cryoprobe, bronchoscope and forceps used (i) anaesthesia, (j) size of target lesion (k) use of navigation, (l) use of fluoroscopy, (m) number of biopsies (n) location of the target lesion, (o) diagnostic yield of cryobiopsy, (p) diagnostic yield of forceps biopsy, (q) complications. The systematic review methodology is summarized in Fig. 1. Complications were considered minor if they included mild to moderate bleeding responding to local measures as reported by the author. Major complications included pneumothorax and severe bleeding, as described in the original study.

Assessment of study quality

Study quality was evaluated with the Methodological Index for Non-Randomized Studies (MINORS) and the Cochrane tool for Randomized studies. The MINORS tool consists of a checklist of eight items developed for non-comparative studies

and four additional items for comparative studies. Items on the MINORS tool are scored as 0 (not reported), 1 (reported but inadequate) and 2 (reported and adequate), resulting in a total score of 16 for non-comparative studies and 24 for comparative studies.[11] The Cochrane tool for RCT consists of seven questions and bias for each item is rated as ''Low risk'', ''High risk'', or ''Unclear risk'' to judge.[12] Each study was independently reviewed by two authors (KM and SPB), after which the scores were compared and decided on final scores during a consensus meeting.

Statistical analysis

Statistical analyses were performed using the STATA statistical analysis software (StataCorp 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and RevMan (Review Manager [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A proportional meta-analysis was performed to calculate the pooled diagnostic yield of forceps biopsy and transbronchial cryobiopsy. Pooled proportions, along with 95% confidence intervals were derived. A meta-analysis was also performed to compare the diagnostic yield of forceps biopsy and cryobiopsy using the pooled RR (relative risk) method. The pooled risk difference (RD) of the yield of cryobiopsy and forceps biopsy was also calculated. Complications were classified into a minor, or a major complication and summary statistics were reported.

Heterogeneity assessment

The impact of heterogeneity on the pooled estimates of the diagnostic yields and the comparative diagnostic yield was assessed using the I^2 (I-Square) test Cochran Q statistic.[13] I^2 is a statistical tool to evaluate the impact of unobserved heterogeneity. It describes the percentage of total variation seen across studies that are attributable to heterogeneity rather than chance. An I^2 value of $\geq$50% indicates significant heterogeneity. For the Cochran Q statistic, a p-value <0.1 is significant for the presence of statistical heterogeneity.

Assessment of publication bias

The funnel plot (Egger test) was used to assess for publication bias (statistically significant publication bias when $p < 0.1$).[14]

Results

The initial literature search yielded 124 articles from which nine studies (457 patients, 300 underwent cryobiopsy) were selected for data abstraction and included in the meta-analysis. The baseline study characteristics are summarized in Tables 1 and 2. The methodological quality of the studies is summarized in Table 3. Of the nine studies, four were retrospective,[9,15–17] and five were prospective studies (including one randomized controlled trial, RCT).[4,18–21] All were single-centre studies. Most studies reported a forceps biopsy group as a comparator in the same group of patients. One study reported the yield of forceps biopsy performed by the same operator in a different set of patients.[9]

Technical considerations

Artificial airways, if used, included endotracheal intubation with an endotracheal tube or rigid bronchoscopy. An artificial airway conduit (rigid bronchoscope or an endotracheal tube) was routinely used in five studies.[4,9,17,18,20] Balloon blockers were variably used. The flexible bronchoscopes used for performing cryobiopsy had an internal channel diameter from 2.0 mm to 3.2 mm. Deep sedation, general anaesthesia or total intravenous anaesthesia (TIVA) were used to optimize patient comfort in different studies. In two studies, general anaesthesia was used routinely.[4,20] Radial endobronchial ultrasound (R-EBUS) guidance with or without a guide sheath (size 1.4–1.7 mm) was used in all studies for localization of PPL before the biopsy. Fluoroscopy was used in four studies.[4,9,15,21] Guide sheaths, if used, for R-EBUS were1.95 mm SG-200C or 2.55 mm SG-201C (Olympus, Olympus Corporation, Japan). As the guide sheath was 2 cm longer than the 1050 mm long, 1.9 mm flexible cryoprobe, Herath et al. trimmed the guide sheath by three cms from the distal end for to improve performance of biopsy.[19] Electromagnetic navigation (EMN) was used in 1 study [20] and virtual bronchoscopic navigation (VBN) in 2 studies for pre-procedural planning.[16,17] Most studies used a 1.9 mm cryoprobe (ERBE, Germany) except one (used 1.2 mm cryoprobe).[4] Most of the studies used a freezing time between three to five seconds during cryobiopsy. Rapid onsite evaluation (ROSE) was used in two studies.[16,18] Schuhmann et al. reported longer procedure time with cryobiopsy as compared to forceps biopsy (5.1 ± 2.75 min, forceps biopsy and 11.6 ± 4.4 min, cryobiopsy; $p < 0.0001$). Kho et al. reported significantly increased diagnostic yield with cryobiopsy in eccentrically and adjacently orientated lesions 75.0%, compared to 48.8% with forceps biopsy ($p < 0.05$). No difference was found in the yields in concentric lesions.[9] Nasu et al. reported an increased diagnostic yield with cryobiopsy in the presence of the bronchus sign.[17]

Specimen quality

Specimen area was reported in some studies, and where comparative data was available, specimen size was larger in cryobiopsy samples as compared to forceps biopsy. The specific metric used to denote size differed across studies from an area on slide or tissue volume. On artefact comparison on both cryobiopsy and forceps biopsy, no difference was observed in the semi-quantitative scoring for tissue morphology.[4] In the context of lung cancer, a greater amount of DNA and RNA were extracted from the cryobiopsy samples, and there were higher success rates for RNA sequencing and whole-exome sequencing with the cryobiopsy samples.[21] There was good concordance for TTF-1 and p40 immunostaining between the cryobiopsy and forceps biopsy samples. Cryoprobe biopsy samples also yielded greater rates of PD-L1 expression >1% on Immunohistochemical analysis.[21]

Table 1 Baseline characteristics of studies describing the utility of transbronchial cryobiopsy for PPLs.

No.	Author/year	Country	Study design	Total number (number undergoing cryobiopsy)	Inclusion criteria	Comparison with forceps biopsy with cryobiopsy in same patients	Age (years)	Size of PPL (mm)	% Of lesions in upper lobes
1	Schuhmann et al./2014[4]	Germany	RCT	38 (31)	Solid pulmonary lesion of <40 mm	Yes	Median IQR, 68 (37–84)	29.7 (7.3)	NA
2	Hibare et al./2017[15]	India	Retrospective	55(28)	PPL requiring R-EBUS, bronchoscopically invisible	Yes	Mean (SD), 61.8 (7.2) (M), 59.3 (11.2) (F)	Size data for 41 (28 > 3 cm, 13 < 3 cm)	NA
3	Herath et al./2018[19]	New Zealand	Prospective	6 (6)	PPL 1 cm or above on CT	Yes	Mean (SD), 56.66 (13.14)	41 (19–66)	66.7
4	Taton et al./2018[20]	Belgium	Prospective	32 (29)	Age over 18 years; a CT-detected solid or nonsolid nodule with a diameter from 8 to 20 mm	Yes	Mean (SD), 68(9)	16 (3)	51.7
5	Arimura et al./2019[18]	Japan	Prospective	23 (23)	Solid lesions >2 cm away from pleura, bronchoscopically invisible	Yes	Median IQR 69.5 (46–82)	36 (10–81)	60.9
6	Kho et al./2019[9]	Malaysia	Retrospective	114 (38)	All adult patients undergoing R-EBUS-guided transbronchial biopsy	No	Median IQR 56 (47.8–64.5)	34.8 (26.3–45.1)	23 (60.5) in cry-obiopsy group46 (60.5) in the forceps group

Table 1 (*Continued*)

No.	Author/year	Country	Study design	Total number (number undergoing cryobiopsy)	Inclusion criteria	Comparison with forceps biopsy with cryobiopsy in same patients	Age (years)	Size of PPL (mm)	% Of lesions in upper lobes
7	Imabayashi et al./2019[16]	Japan	Retrospective	38 (36)	Suspected peripheral lung cancer undergoing cryobiopsy	Yes	Median IQR 66.9 (44—81)	37.2 ± 19.4	52.8
8	Nasu et al./2019[17]	Japan	Retrospective	53 (53)	A final diagnosis of lung cancer in PPL who underwent cryobiopsy	Yes	Median IQR 75 (41–90)	32 (8—85)	50.9
9	Udagawa et al./2020[21]	Japan	Prospective	121 (57)	Aged 20–80 years with suspected or diagnosed primary lung cancer by chest computed tomography scheduled to undergo TBB by bronchoscopy	Yes	Median IQR 68 (31—79)	38 (Median)	40.3

PPL: peripheral pulmonary lesion; R-EBUS: Radial Endobronchial Ultrasound; TBB: transbronchial biopsy.

Table 2 Procedural characteristics of studies included for systematic review and meta-analysis.

No.	Author/year	Modality for sampling	R-EBUS probe used	R-EBUS probe size (mm)	Anaesthesia	Artificial airway	Cryoprobe diameter (mm)	Freezing Time (s) Mean (SD)/range	No. of cryobiopsies	No. of flexible biopsies Median (Range)	Size of cryobiopsy	Size of forceps biopsy	Comments
1	Schuhmann et al./2014[4]	Radial EBUS + GS	UM-S20-20R; Olympus	1.7	GA	Yes, rigid bronchoscopy	1.2	4	3	3	11.17 mm^2 (1.25–38.59)	4.69 mm^2 (0.53–22)	7 out of 38, PPL not localized in 20 min with R-EBUS and were excluded. Duration of the cryobiopsy was significantly longer compared with forceps biopsy.
2	Hibare et al./2017[15]	Radial EBUS ± GS ± Fluoroscopy	UM-S20-17S; Olympus	1.4	NA	No	1.9	4	3	3	NA	NA	9 (14%) cases the lesion could not be located by R-EBUS
3	Herath et al./2017[19]	Radial EBUS + GS	UM-S20-20R; Olympus	1.7	Conscious sedation (5), GA (1)	Yes, GA in one patient, Five not intubated	1.9	4	1–3	NA	6.4 mm	3.4 mm	All the PPLs were visualized as concentric lesions on R- EBUS. To enable contact with the lesion, the GS was trimmed by 3 cm from the distal end
4	Taton et al./2018[20]	Radial EBUS + GS	UM-S20-17S; Olympus	1.4	GA and paralysis (Remifentanil, propofol, rocuronium)	Yes, rigid bronchoscope	1.9	7–8	2	6	5.3 ± 0.7 (mm)	1.1 ± 0.6 (mm)	The lobar location of the nodule, the bronchus sign, the nodule size, the malignant *vs* benign disease, or the technique used (nodule visualization or not with EBUS mini probe) for visualizing the nodule in addition to ENB had no statically significant impact on the diagnostic performance
5	Arimura et al./2019[18]	Radial EBUS + GS + Fluoroscopy	UM-S20-20R; Olympus	1.7	Deep sedation	Yes, intubated 7.5 mm ET	1.9	3–5	1–2	5	0.078 ± 0.008 (mean ± SEM) cm^3	0.003 ± 0.0003 (mean ± SEM) cm^3	Bronchoscopists performed the procedures with at least three years of experience

Table 2 (*Continued*)

No.	Author/year	Modality for sampling	R-EBUS probe used	R-EBUS probe size (mm)	Anaesthesia	Artificial airway	Cryoprobe diameter (mm)	Freezing Time (s) Mean (SD)/range	No. of cryobiopsies	No. of flexible biopsies Median (Range)	Size of cryobiopsy	Size of forceps biopsy	Comments
6	Kho et al./2019[9]	Radial EBUS ± GS ± Fluoroscopy	UM-S20-17S, UM-S20-20R, Olympus	1.4, 1.7	Conscious sedation or TIVA	Yes (rigid or ETT), at operator's discretion, 16/38 in cryobiopsy group and 7/76 in forceps group	1.9	3–4		5	NA	NA	ROSE during Cryo with EBUS-GS had a high sensitivity, specificity, PPV, and diagnostic accuracy for PPLs.
7	Imabayashi et al./2019[16]	Radial EBUS without sheath	UM-S20-17S; Olympus	1.4	Conscious sedation (Midazolam and Fentanyl)	No	1.9	3.3 (0.7)	1.5 ± 0.6 (1–3)	NA	12.2 mm^2 (5.6)	NA	Stamp cytology with CB facilitates the on-site confirmation of tumor inclusion and improved diagnostic yield. The EBUS probe was located within the lesion in 91.6% (33/36) cases and adjacent to the lesion in 8.3% (3/36) cases

Table 2 (*Continued*)

No.	Author/year	Modality for sampling	R-EBUS probe used	R-EBUS probe size (mm)	Anaesthesia	Artificial airway	Cryoprobe diameter (mm)	Freezing Time (s) Mean (SD)/range	No. of cryobiopsies	No. of flexible biopsies Median (Range)	Size of cryobiopsy	Size of forceps biopsy	Comments
8	Nasu et al./2019[17]	Radial EBUS + GS	UM-S20-17S, UM-S20-20R, Olympus	1.4, 1.7	Conscious/deep sedation and topical anaesthesia	Yes, intubated 8.5 mm ET	1.9	3	NA	5—6	14.1 mm^2 (range = 3.67 −40.7)	2.62 mm^2 (range = 0.737 −10.0)	Cryobiopsy with GS and positive bronchus sign were significantly associated with increased diagnostic yield of cryobiopsy (odds ratio (OR), 11.6; p = 0.044 and OR, 21.5; p = 0.034, respectively)
9	Udagawa et al./2020[21]	Radial EBUS ± GS + Fluoroscopy	NA	NA	Moderate sedation (Pethidine and Midazolam) and topical anaesthesia or GA	Yes, at anaesthesiologists discretion	1.9	3–5	2 (1–5)	5 (2–12)	15 mm^2 (1–42)	2 mm^2 (0.3–28)	Cryobiopsy yielded larger amounts of DNA (median: cryoprobe, 1.60 μg *vs* forceps, 0.58 μg, p = 0.02) and RNA (median: cryoprobe, 0.62 μg *vs* forceps, 0.17 μg, p < 0.01) extracted from samples, and tended to yield greater rates of PD-L1 expression >1% (51% *vs* 42%)

ETT: endotracheal tube; GA: general anaesthesia; GS: guide sheath; R EBUS: Radial Endobronchial Ultrasound.

Table 3 Quality assessment of the studies included in the systematic review and meta-analysis of cryobiopsy for PPL.

MINORS tool for observational studies

Serial no.	Question	Hibare et al.	Herath et al.	Taton et al.	Arimura et al.	Kho et al.	Imabayashi et al.	Nasu et al.	Udagawa H et al.
1	A clearly stated aim — the question addressed should be precise and relevant in the light of available literature	2	1	2	2	2	2	2	2
2	Inclusion of consecutive patients — all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)	2	1	2	1	0	0	0	1
3	Prospective collection of data — data were collected according to a protocol established before the beginning of the study	0	2	2	2	0	0	0	2
4	Endpoints appropriate to the aim of the study — unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.	2	1	2	2	2	2	2	2
5	Unbiased assessment of the study endpoint- blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise, the reasons for not blinding should be stated	1	1	1	1	1	1	1	1
6	Follow-up period appropriate to the aim of the study- the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events	2	2	2	2	1	1	1	2
7	A loss to follow up less than 5%- all patients should be included in the follow-up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint	2	2	2	2	1	1	1	2
8	Prospective calculation of the study size- information of the size of the detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes	0	0	0	0	0	0	0	**0**

Table 3 (*Continued*)

MINORS tool for observational studies

Serial no.	Question	Hibare et al.	Herath et al.	Taton et al.	Arimura et al.	Kho et al.	Imabayashi et al.	Nasu et al.	Udagawa H et al.
9	An adequate control group- having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data	2	2	2	2	2	2	2	2
10	Contemporary groups- control and studied group should be managed during the same time period (no historical comparison)	2	2	2	2	2	2	2	2
11	Baseline equivalence of groups- the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results	2	2	2	2	2	2	2	2
12	Adequate statistical analyses- whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk	1	0	2	2	2	2	2	2
	For every item ''Not reported (0 points)'', ''Reported but inadequate (1 point), or ''Reported and adequate (2 points)'' to judge								
	MINORS (Score/Total)	18	16	21	20	15	15	15	20

The MINORS tool consists of a checklist of eight items developed for non-comparative studies and four additional items for comparative studies. Items on the MINORS tool are scored as 0 (not reported), 1 (reported but inadequate) and 2 (reported and adequate), resulting in a total score of 16 for non-comparative studies and 24 for comparative studies.

Cochrane tool for RCT

Component	Schuhmann et al.
1. Random sequence generation	Unclear risk
2. Allocation concealment	Unclear risk
3. Blinding of participants and personnel	High risk
4. Blinding of outcome assessment	Low risk
5. Incomplete outcome data	Low risk
6. Selective reporting	Low risk
7. Other sources of bias	Low risk

For every item: ''Low risk'', ''High risk'', or ''Unclear risk'' to judge.

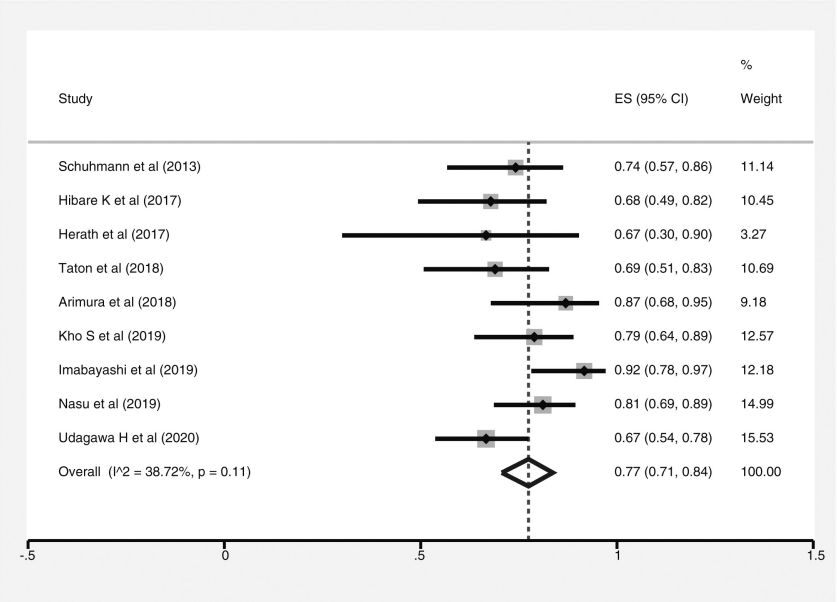

Figure 2 Figure showing the yield of individual studies and the pooled diagnostic yield of transbronchial cryobiopsy for peripheral pulmonary lesions (PPL).

Complications

Procedure-related complications reported were mainly mild bleeding. Out of the 222 patients undergoing cryobiopsy (with reported complications data), there were three pneumothorax and one episode of severe bleeding. Sixty-five patients (65/222, 29.3%) experienced minor complications in the form of mild to moderate bleeding. Most of the bleeding events were mild that settled with either a prolonged bronchoscopic suction or local adrenaline instillation.[4,9] One event of desaturation was also reported, which recovered when the procedure was stopped temporarily.[15] Post procedure pneumonia was also reported (1 case).

Meta-analysis

The pooled diagnostic yields of of transbronchial cryobiopsy and forceps biopsy were 77% (95% CI, 71%–84%)($I\hat{2}$ = 38.72%, p = 0.11) (Fig. 2), and 72% (95% CI, 60%–83%)($I\hat{2}$ = 78.56%, p < 0.01) (Fig. 3), respectively. The comparative diagnostic yields were similar (RR1.05, 95% CI 0.96–1.15) ($I\hat{2}$ = 57.2%, p = 0.017). (Fig. 4) The difference in diagnostic yield between cryobiopsy and forceps biopsy was 5% (95% CI, -6%–15%), and was not significant (Supplementary Fig. 1). There was the presence of significant heterogeneity [I^2 = 57.2%, p = 0.017]. There was no evidence of publication bias on the visual examination of the funnel plot, Eggers test (p = 0.11) (Fig. 5).

Discussion

The findings of this systematic review and meta-analysis indicate that R-EBUS guided transbronchial cryobiopsy is a safe and efficacious modality for bronchoscopic evaluation of PPL's. The overall diagnostic yield of cryobiopsy for PPL was 77% and was not inferior to standard bronchoscopic forceps biopsy performed under R-EBUS guidance.

The development of Radial EBUS technology has revolutionized the bronchoscopic approach to sample peripheral pulmonary lesions.[22] However, the yield of R-EBUS guided samples using conventional forceps is often suboptimal. This lower yield may be due to superficial sampling or crushing artefacts, and these samples may not be appropriate for immunohistochemistry or molecular analyses.[9] The use of a cryoprobe for bronchoscopic biopsy allows one to obtain significantly larger samples. Schuhmann et al.[4] reported an average tissue area of 11.17 mm^2 with cryobiopsy (4.69 mm^2 in the forceps biopsy group). In comparison, Udagawa et al.[21] found an average tissue area of 15 mm^2 (2 mm^2 in the forceps biopsy group). Cryoprobe assisted biopsy from visible endobronchial growths provides a diagnostic yield superior to conventional forceps biopsy.[23] Transbronchial lung cryobiopsy (TBLC) is commonly performed for the histological diagnosis of diffuse parenchymal lung diseases (DPLD).[8] The diagnostic yield of TBLC for DPLD's maybe comparable with video-assisted thoracoscopic surgery (VATS) lung biopsy with significant cost savings and reduced risk of mortality.[24]

The first study on the feasibility and utility of transbronchial Cryobiopsy for PPL was published by Schuhmann et al. in 2013.[4] This study is the only published RCT comparing the diagnostic yield with forceps biopsy, and multicentre studies are lacking. Since then, few studies have highlighted the safety and feasibility of performing transbronchial cryobiopsy for PPL's.

This meta-analysis has certain limitations. It included only one RCT and a relatively small number of prospective studies with uncontrolled variables. The strength of the meta-analysis is the fact that it is the only systematic review and meta-analysis on this subject. The major complication rate of cryobiopsy for PPL was low (1.8%), and this is less than that observed for TBLC for DPLD. The incidence

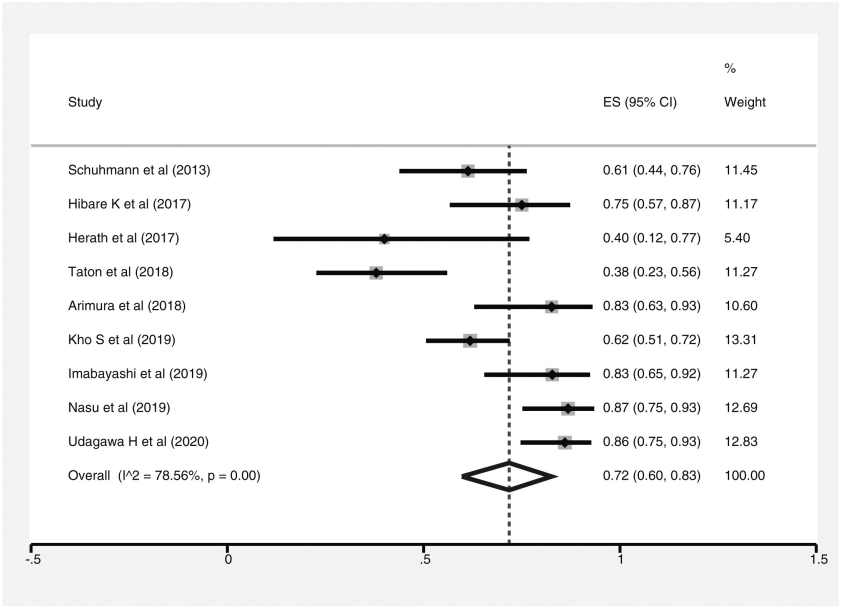

Figure 3 Figure showing the yield of individual studies and the pooled diagnostic yield of conventional transbronchial forceps biopsy for peripheral pulmonary lesions (PPL).

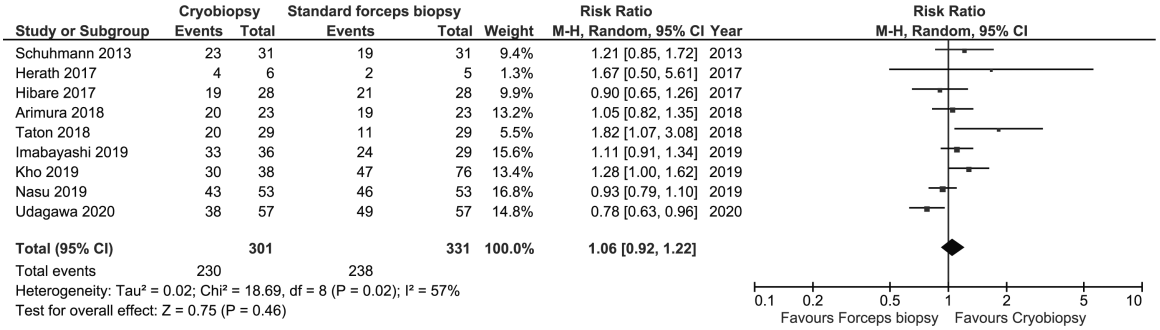

Figure 4 Forest plot showing the relative risk for the diagnostic yield of transbronchial cryobiopsy and conventional forceps biopsy for PPL.

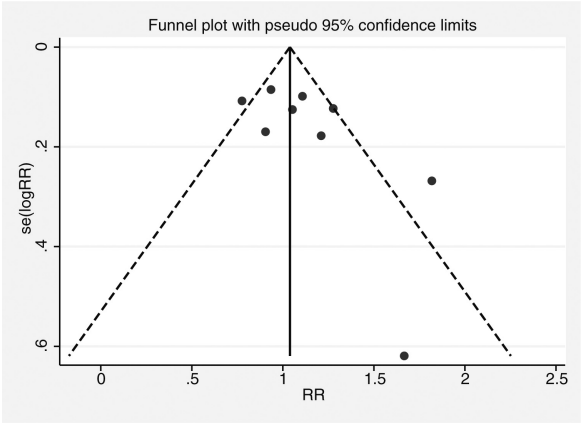

Figure 5 Funnel plot for publication bias.

of pneumothorax in TBLC for DPLD varies from 10% to 20% or even greater.[24] The risk of clinically significant bleeding may also be greater.[25] The severe bleeding rate in our meta-analysis (1/222, 0.4%) was low. Still, it is preferable that cryobiopsy for PPL's be performed after securing the airway using either endotracheal intubation or rigid bronchoscopy to handle inadvertent complications, similar to the approach in DPLD's.[10] The use of a bronchial blocker to improve the safety of the procedure is also suggested.[7] Procedural heterogeneity with varying freezing times, retrospective nature of many studies which may not have captured all complications limit the conclusions that can be drawn concerning complications. Still, the findings indicate that that cryobiopsy for PPL's maybe a safer procedure than for DPLD.

In this analysis, transbronchial cryobiopsy for PPL was not inferior to forceps biopsy. This observation is contrary to observation regarding cryobiopsy for DPLD wherein the yield of cryobiopsy is superior to forceps biopsy.[25] The possible reasons may be the operator expertise and more consistent localization of the lesion. Multicenter studies are the need of the hour to establish the utility of cryobiopsy for PPL in a real-life setting. The available studies did not employ a standardized protocol, and there were observed variations in the technique, anaesthesia methods and ancillary modal-

ities. Future studies should also focus on standardization of the various technical aspects of the procedure like the use of artificial airways and occlusion balloons. The use of a guide sheath also needs further exploration as the use of a guide sheath was not routinely possible in most cases with the larger 1.9 mm cryoprobe, as it could hinder this procedure. The 1.1 mm cryoprobe appears an exciting addition and requires further exploration.[26,27] This may allow the use of a radial EBUS in its full capacity with the maintenance of the over sheath. The more delicate probe can allow access to more distal locations and may allow sampling through a guide sheath contrary to the larger diameter cryoprobe. The use of a thinner cryoprobe may translate into possibly lower bleeding risk. These thinner cryoprobes may also be more manoeuvrable to perform upper lobe biopsies.[28] However, it is unclear whether these biopsies with smaller cryoprobes will result in diagnostic yields similar to those described with larger probes.

High SUVmax values in PET-CT were associated with an increased diagnostic yield of transthoracic biopsy of lesions in the setting of lung cancer. Further studies should also examine these factors on the yield of cryobiopsy and conventional forceps bronchoscopic biopsy of PPL.[29]

Conclusion

The results of this meta-analysis demonstrate that transbronchial cryobiopsy is a safe and efficacious option for sampling peripheral pulmonary lesions. Although we did not observe a superior yield of cryobiopsy as compared with forceps biopsy for PPL, there is a need for multicentre studies to study the utility of this modality in real-life settings. The technique of transbronchial cryobiopsy for PPL also requires standardization.

Authors' contributions

SPB: Literature search, data abstraction, prepared manuscript draft, revised the manuscript.

SM: Data abstraction, revised the manuscript, data analysis.

PT, VH, AM, RG: Revised the manuscript.

KM: Conceived the idea, literature search, data abstraction, performed meta-analysis, prepared manuscript draft, revised the manuscript.

KM is the guarantor of this paper.

Funding sources

None.

Statement of ethics

This study does not include human subjects for research as this is a meta-analysis of published studies.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgment

NA.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pulmoe.2020.12.006.

References

1. National Lung Screening Trial Research T, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395–409.
2. Han Y, Kim HJ, Kong KA, Kim SJ, Lee SH, Ryu YJ, et al. Diagnosis of small pulmonary lesions by transbronchial lung biopsy with radial endobronchial ultrasound and virtual bronchoscopic navigation versus CT-guided transthoracic needle biopsy: a systematic review and meta-analysis. PLoS One. 2018;13(1):e0191590.
3. van't Westeinde SC, Horeweg N, Vernhout RM, Groen HJM, Lammers JJ, Weenink C, et al. The role of conventional bronchoscopy in the workup of suspicious CT scan screen-detected pulmonary nodules. Chest. 2012;142(2):377–84.
4. Schuhmann M, Bostanci K, Bugalho A, Warth A, Schnabel PA, Herth FJ, et al. Endobronchial ultrasound-guided cryobiopsies in peripheral pulmonary lesions: a feasibility study. Eur Respir J. 2014;43(1):233–9.
5. Ali MS, Trick W, Mba BI, Mohananey D, Sethi J, Musani AI. Radial endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions: a systematic review and meta-analysis. Respirology. 2017;22(3):443–53.
6. Chaddha U, Kovacs SP, Manley C, Hogarth DK, Cumbo-Nacheli G, Bhavani SV, et al. Robot-assisted bronchoscopy for pulmonary lesion diagnosis: results from the initial multicenter experience. BMC Pulm Med. 2019;19(1):243.
7. Dhooria S, Agarwal R, Sehgal IS, Aggarwal AN, Goyal R, Guleria R, et al. Bronchoscopic lung cryobiopsy: an Indian association for bronchology position statement. Lung India. 2019;36(1):48–59.
8. Dhooria S, Mehta RM, Srinivasan A, Madan K, Sehgal IS, Pattabhiraman V, et al. The safety and efficacy of different methods for obtaining transbronchial lung cryobiopsy in diffuse lung diseases. Clin Respir J. 2018;12(4):1711–20.
9. Kho SS, Chan SK, Yong MC, Tie ST. Performance of transbronchial cryobiopsy in eccentrically and adjacently orientated radial endobronchial ultrasound lesions. ERJ Open Res. 2019;5(4).
10. Madan K, Mittal S, Gupta N, Hadda V, Mohan A, Guleria R. Cryoprobe transbronchial lung biopsy: how we do it? Lung India. 2018;35(6):520–2.
11. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003;73(9):712–6.
12. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med. 2015;8(1):2–10.
13. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.
14. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews

of diagnostic test accuracy was assessed. J Clin Epidemiol. 2005;58(9):882–93.
15. Hibare KR, Goyal R, Nemani C, Avinash R, Ram B, Ullas B. Radial endobronchial ultrasound for the diagnosis of bronchoscopically invisible lesions: first case series from India. Lung India. 2017;34(1):43–6.
16. Imabayashi T, Uchino J, Yoshimura A, Chihara Y, Tamiya N, Kaneko Y, et al. Safety and usefulness of cryobiopsy and stamp cytology for the diagnosis of peripheral pulmonary lesions. Cancers (Basel). 2019;11(3).
17. Nasu S, Okamoto N, Suzuki H, Shiroyama T, Tanaka A, Samejima Y, et al. Comparison of the utilities of cryobiopsy and forceps biopsy for peripheral lung cancer. Anticancer Res. 2019;39(10):5683–8.
18. Arimura K, Kondo M, Nagashima Y, Kanzaki M, Kobayashi F, Takeyama K, et al. Comparison of tumor cell numbers and 22C3 PD-L1 expression between cryobiopsy and transbronchial biopsy with endobronchial ultrasonography-guide sheath for lung cancer. Respir Res. 2019;20(1):185.
19. Herath S, Yap E. Novel hybrid cryo-radial method: an emerging alternative to CT-guided biopsy in suspected lung cancer. A prospective case series and description of technique. Respirol Case Rep. 2018;6(2):e00287.
20. Taton O, Bondue B, Gevenois PA, Remmelink M, Leduc D. Diagnostic yield of combined pulmonary cryobiopsies and electromagnetic navigation in small pulmonary nodules. Pulm Med. 2018;2018:6032974.
21. Udagawa H, Kirita K, Naito T, Nomura S, Ishibashi M, Matsuzawa R, et al. Feasibility and utility of transbronchial cryobiopsy in precision medicine for lung cancer: prospective single-arm study. Cancer Sci. 2020;111(7):2488–98.
22. Sainz Zuñiga PV, Vakil E, Molina S, Bassett RL Jr, Ost DE. Sensitivity of radial endobronchial ultrasound-guided bronchoscopy for lung cancer in patients with peripheral pulmonary lesions: an updated meta-analysis. Chest. 2020;157(4):994–1011.
23. Hetzel J, Eberhardt R, Herth FJ, Petermann C, Reichle G, Freitag L, et al. Cryobiopsy increases the diagnostic yield of endobronchial biopsy: a multicentre trial. Eur Respir J. 2012;39(3):685–90.
24. Ravaglia C, Bonifazi M, Wells AU, Tomassetti S, Gurioli C, Piciucchi S, et al. Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a comparative study versus video-assisted thoracoscopic lung biopsy and a systematic review of the literature. Respiration. 2016;91(3):215–27.
25. Dhooria S, Sehgal IS, Aggarwal AN, Behera D, Agarwal R. Diagnostic yield and safety of cryoprobe transbronchial lung biopsy in diffuse parenchymal lung diseases: systematic review and meta-analysis. Respir Care. 2016;61(5):700–12.
26. Hetzel J, Linzenbold W, Boesmueller H, Enderle M, Poletti V. Evaluation of efficacy of a new cryoprobe for transbronchial cryobiopsy: a randomized, controlled in vivo animal study. Respiration. 2020;99(3):248–56.
27. Yarmus LB, Semaan RW, Arias SA, Feller-Kopman D, Ortiz R, Bösmüller H, et al. A randomized controlled trial of a novel sheath cryoprobe for bronchoscopic lung biopsy in a porcine model. Chest. 2016;150(2):329–36.
28. Kho SS, Chai CS, Nyanti LE, Ismail AMB, Tie ST. Combination of 1.1 mm flexible cryoprobe with conventional guide sheath and therapeutic bronchoscope in biopsy of apical upper lobe solitary pulmonary nodule. BMC Pulm Med. 2020;20(1):158.
29. Doğan C, Fidan A, Cömert S, Kıral N, Salepçi B, Parmaksıza ET, et al. Can PET-CT predict diagnostic success in ultrasonography-guided transthoracic fine needle aspiration biopsies in lung cancers? Pulmonology. 2020;26(5):275–82.

Pulmonology 29 (2023) 65—76

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REVIEW

Teleconsultation in respiratory medicine — A position paper of the Portuguese Pulmonology Society

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Received 23 December 2021; accepted 6 April 2022
Available online 12 June 2022

KEYWORDS
Teleconsultation;
Respiratory medicine;
Telemedicine;
Video consultations

Abstract The COVID-19 pandemic crisis, among so many social, economic and health problems, also brought new opportunities. The potential of telemedicine to improve health outcomes had already been recognised in the last decades, but the pandemic crisis has accelerated the digital revolution. In 2020, a rapid increase in the use of remote consultations occurred due to the need to reduce attendance and overcrowding in outpatient clinics. However, the benefit of their use extends beyond the pandemic crisis, as an important tool to improve both the efficiency and capacity of future healthcare systems. This article reviews the literature regarding telemedicine and teleconsultation standards and recommendations, collects opinions of Portuguese experts in respiratory medicine and provides guidance in teleconsultation practices for Pulmonologists.

Introduction

Since its definition and first implementation initiatives at the end of the last century, the practice of telemedicine has

Abbreviations: Teleconsultation, A Portuguese Pulmonology Society postion paper.

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https://doi.org/10.1016/j.pulmoe.2022.04.007

had the potential to have a positive impact on healthcare services and health outcomes in many ways. COVID-19 and the need to reduce attendance and overcrowding in outpatient clinics led to several changes in the care and organisation of Pulmonology services. Portugal has seen a rapid increase in the use of remote consultations.

Remote consultations have proved important in reducing pressure on health services and improving access to non-COVID patients — and this is an important lesson. Although teleconsultations cannot fully replace face-to-face consultations, evidence shows that they can achieve equivalent patient outcomes while improving patient satisfaction.[1,2] Looking to the future, in a pandemic-free scenario, teleconsultations appear as a cost-effective and efficient way to enable access to routine care for chronic respiratory patients and should be incorporated, as an additional tool, in the medical care of these patients.

Nevertheless, as telemedicine and teleconsultation programmes pose unquestionable advantages in improving healthcare's efficiency, their implementation is far from optimization. Significant limitations in terms of overall guidance, both scientific and organizational, threaten their appropriate delivery. This is especially relevant in chronic respiratory diseases, as the heterogeneity of clinical conditions and patient journeys' steps demand specific guidelines.

This article reviews the literature regarding telemedicine and teleconsultation standards and recommendations, collects opinions of Portuguese experts in respiratory medicine and provides guidance in teleconsultation practices for Pulmonologists.

Methodology

A narrative non-systematic literature search of MEDLINE/Pubmed database was conducted in December 2020 using the keywords "telemedicine", "telehealth", "telemonitoring", "teleconsultation" and "video consultation". Also, other international and national societies were searched on this topic as well as documents from Portuguese authorities regarding legal issues and implementation. Other references were proposed by the authors throughout the preparation of the document and added to the final references.

Three meetings with all authors took place between January and June 2021.

The methodology applied for the elaboration of this document is shown in Fig. 1.

Telemedicine's definition and framework

Definition

Telemedicine, according to its first nomenclature reconciliation by the World Health Organization, was defined as "the delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities".[3]

More recently, from a more operational perspective, telemedicine has been seen as the "distribution of health services in conditions where distance is a critical factor, by health care providers that use information and communication technologies to exchange information useful for diagnosis where a doctor is able to perform diagnosis at distance"[4], having the potential of mediating patients' contact with specialised care consultants.[5] Although a broader concept of telehealth has been argued,[4,6,7] for the purposes of this paper, 'telemedicine' and 'telehealth' are used interchangeably. There are core elements in telemedicine that must always be respected[7]:

- its purpose of providing clinical support;
- its intention to overcome geography issues, connecting patients to healthcare professionals in different locations;
- its practice including the use of information and communication technologies;
- its goal of improving health outcomes.

Framework

In Portugal, telehealth has been perceived as a core part of digital transformation strategies in health by addressing geographic inequalities and improving access to healthcare, thus improving the health system's effectiveness and efficiency.[6] Indeed, good outcomes and promising local and regional strategies have been reported in our country.[8,9]

Furthermore, general standards for the legal practice of teleconsultations in Portugal have been established,[10] including: respecting the doctor-patient relationship, ultimately not to be replaced by teleconsultations; ensuring the independence of physicians, who shall follow this practice when a good clinical overview of the patients' condition is deemed possible; and ensuring that the physician has quality, complete, and sufficient information through teleconsultation to make a medical decision. In addition, a governmental guidance was released in 2015, focusing on teleconsultations between different healthcare institutions, with the objective of improving access to a specialised healthcare team even across long distances. That guidance falls outside the scope of this document as it applies to forms of doctor-doctor interaction where clinical cases of patients are discussed.

Telemedicine in clinical practice: teleconsultations

Telemedicine enables doctors and other healthcare providers to assist their patients beyond physical limitations as it encompasses a spectrum of diverse technologies and applications.[11]

Recently, Artificial Intelligence (AI) has been applied to medical care, not only in improving remote healthcare, in developing algorithms to match the availability of healthcare providers to patients, but even going beyond the doctor-patient relationship.[12,13] Examples of this are AI-based machine learning methods, which may even eventually replace clinical judgment.[14] Several questions and concerns have been raised, namely ethical, legal, and privacy issues.[13] These new forms of digital healthcare are beyond the scope of this paper and will not be addressed here.

The different modalities of telemedicine can be grouped in three categories (Fig. 2).[15]

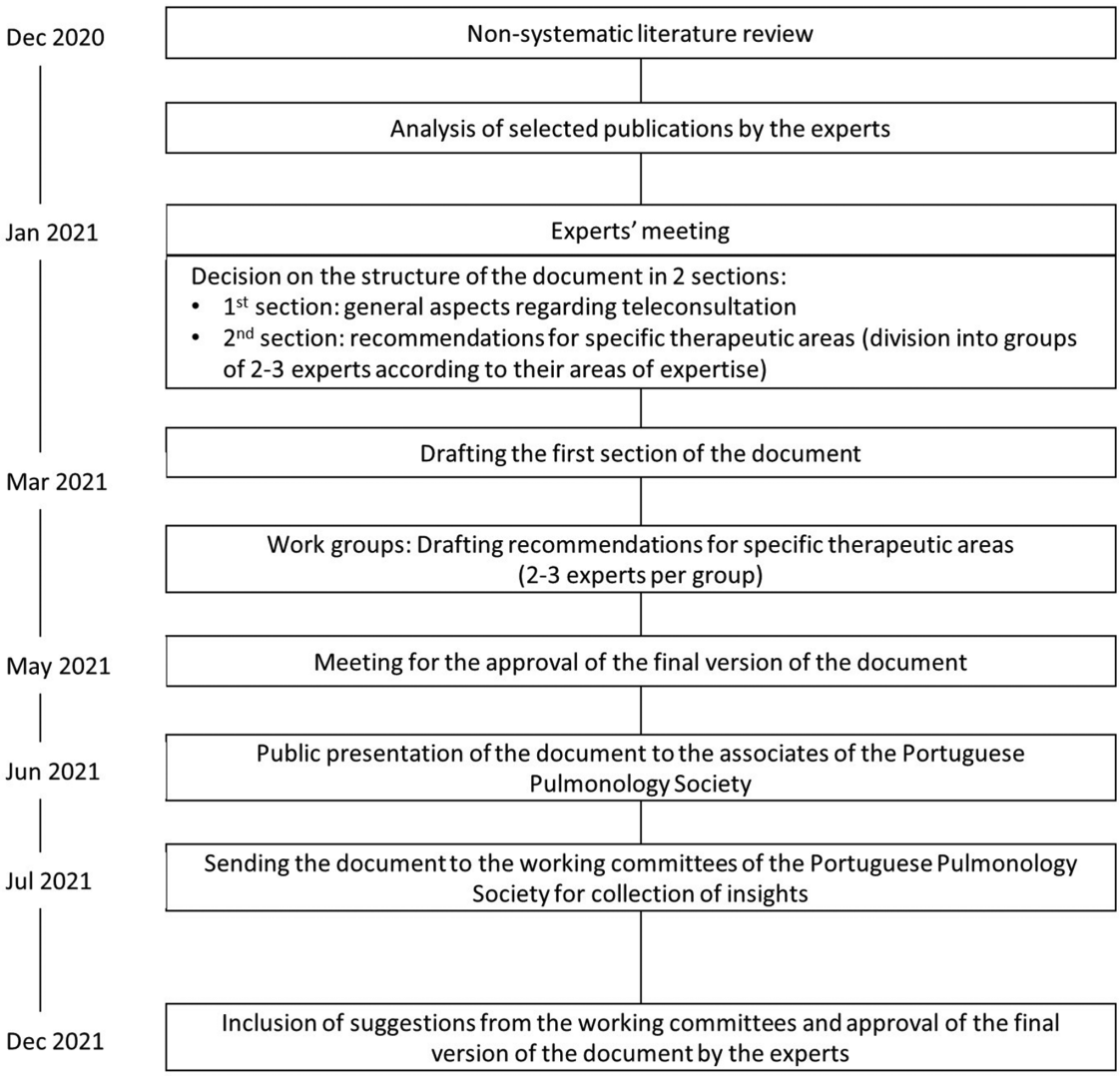

Fig. 1 Timeline and methodology used for the preparation of this document.

We will focus on teleconsultation,[16] defined as consultation in which information and communication technologies are implemented in order to overcome geographical and functional distances,[17] carried out through video and/or audio.

Teleconsultation is only a small part of telemedicine. However, teleconsultations imply that some of the other strategies are already in place. For example, in a patient with chronic respiratory failure under home non-invasive mechanical ventilation, a teleconsultation is only appropriate where telemonitoring is already happening - not only reporting adherence and ventilatory efficacy parameters, but also real-time monitoring, such as night-time oximetry and/or oxy-capnography. Home care providers have been playing a key role in this type of support, but wireless monitoring systems linked to hospital systems are now also available.

There is still a long way to go in the context of telemedicine. And this great boost that teleconsultation has had in the last year can definitely enhance the development of other potentialities of telemedicine.

It is of utmost importance to stress that the use of information and communication technologies in health should always safeguard the security of information, ensuring data privacy and confidentiality. Thus, only platforms that respect these conditions should be used.

Advantages of teleconsultation

Teleconsultations make it possible to assess, diagnose, and treat patients remotely. These take place using one of two main approaches: remote patient–doctor contact while the patient remains at home; or the patient going to a local clinic or hospital, where other healthcare providers mediate the contact with a consultant physician. The latter is indicated in clinical conditions in which a clinical and/or biometric physical evaluation is required. Both approaches encompass several advantages,[6,18–21] such as:

- increasing access to specialists regardless of their national distribution;
- improving articulation between different physicians and levels of care of the health system, namely by facilitating the communication between hospital physicians and general practitioners;

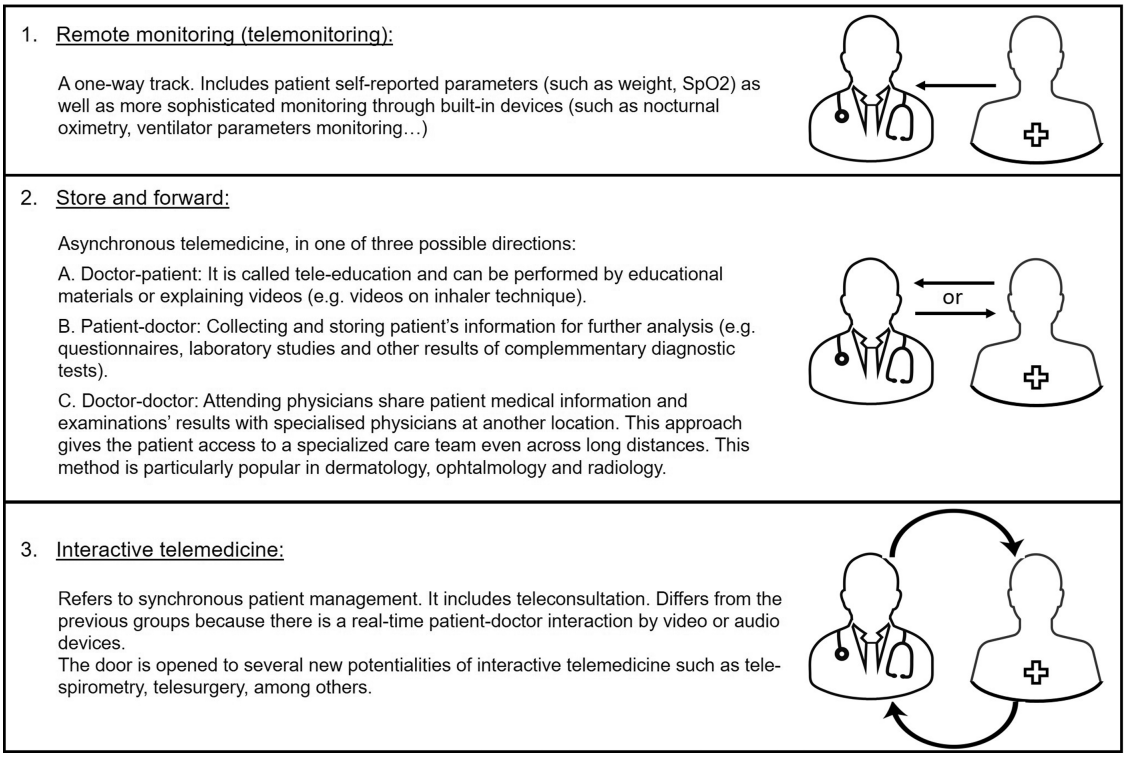

Fig. 2 Three categories of telemedicine.[15] This figure is an original image created by the authors for this publication.

- gains in care effectiveness, coupled with gains in comfort, time, and travel costs for patients;
- supporting long-term home management of specific chronic health conditions;
- reducing infections associated with healthcare services due to less crowded waiting rooms.

With regard to minimising infectious risks, critical during the pandemic of COVID-19, telehealth was established in a systematic review as very appropriate for reducing disease transmission and overall morbidity and mortality.[22] It has been argued that the pandemic led to the development of more "sophisticated" telemedicine, by simplifying processes and reducing unnecessary complexity,[23] although consensus practices remain to be established.[24]

Teleconsultation's limitations

Examples of good outcomes of telemedicine have been published, namely in Chronic Obstructive Pulmonary Disease – COPD.[25] However, teleconsultations are not suitable for all patients and for all clinical situations.[26] From a technological perspective, it is important to ensure adequate technical infrastructures (phone, computer, internet connection, as appropriate)[27] and carefully keep in mind that "technology should always be adapted to the patient and not the reverse".[25] The transition to teleconsultation, with its related bureaucratic processes, at least at the beginning, does not seem to minimize consultation time. From a clinical perspective, some conditions are not adequately managed by teleconsultation,[26–28] and some objectives of consultation may not be achieved with this modality.[27] Finally, only clinicians duly trained in teleconsultation should perform it,[29] and practices shall be standardised, compliant, and regulated.[28]

Video and audio-teleconsultations

Video consultations have shown some advantages over audio (telephone) consultations,[26] such as more personal contact between health professionals and patients,[26,30,31] although strong evidence of their effectiveness is still lacking.[24] These consultations are generally suitable for:

- younger patients ($<$ 65 years), with good digital literacy in the technological solution used;
- follow-up consultations for clinically stable patients where a full physical exam is not expected to be necessary (as video consultations allow some parts of a physical examination to be performed). First consultations and consultations due to new symptoms should only be considered in very specific and well-defined clinical circumstances;
- situations where the video is the preferred method for both clinician and patient.

On the other hand, telephone (audio) consultations tend to be shorter and have a more restricted patient disclosure of health problems than face-to-face consultations.[30] These consultations may generally be appropriate for:

- older patients ($\geq$ 65 years) and/or those with poor digital skills in complex technological solutions;
- settings where complex video call setup and/or technical infrastructures for video consultation are unattainable;
- consultations aimed at addressing simple health concerns by the patient or the physician;
- follow-up of clinically stable patients in which a physical examination is not necessary;

- situations in which a teleconsultation is deemed appropriate by both clinician and patient, and telephone is their preferred method.

Finally, there are specific situations that should exclude the possibility of a teleconsultation,[27,28] such as:

- presence of acute respiratory symptoms;
- new complications of underlying diseases;
- consultations where severe prognostic circumstances are expected to be addressed;
- or consultations where decompensation of underlying diseases cannot be correctly established.

Teleconsultations in Pulmonology's clinical practice

In the field of Pulmonology, the use of telemedicine has been proposed and reported in the management of chronic obstructive pulmonary disease (COPD), asthma, interstitial lung diseases (ILD), chronic respiratory failure (CRF), and home mechanical ventilation (HMV), among other clinical situations.[32] Even before the COVID-19 pandemic, there were some validated tools and scales for remote assessments in respiratory medicine.[33] More than 50% of pulmonologists rated the importance of telemedicine as "high" or "very high",[34,35] with potential for better care in chronic respiratory diseases such as asthma and COPD.[28]

After the COVID-19 pandemic, teleconsultation will still have a place in the future of respiratory medicine. Our view is mirrored by other publications, whose authors have recognised the incorporation of new technologies into new models of care as the key to the future success of Pulmonology.[23] Moreover, teleconsultation is seen as an important tool to improve both the efficiency and capacity of future healthcare systems,[35] and the potential for greater control and care in chronic respiratory diseases has been acknowledged.[28]

Considering teleconsultation in respiratory diseases, this document will address:

- general issues, including patient suitability and selection.
- specific issues, related to each respiratory disease.

General guidance

From a general perspective, we find that it is important to highlight some essential principles for the correct implementation of teleconsultation in respiratory diseases — Table 1.

Patient selection

Main eligibility criteria are common to the different respiratory diseases.[36] The particularities regarding specific diseases will be described below.

Inclusion Criteria

- Adults ($\geq$ 18 years) with a diagnosis of respiratory disease, with a suspected or diagnosed sleep-disordered breathing, or referred for smoking cessation;
- Verbal or written consent to perform the teleconsultation;
- Availability and familiarity with a suitable device - phone, mobile phone, tablet or computer;
- Patients already followed by the department.

Exclusion Criteria

- Current exacerbation or clinical instability requiring urgent physical examination;
- Physical or cognitive impairment that makes the teleconsultation unfeasible.

Suitability[36]

- First consultations for smoking cessation and sleep-disordered breathing may be suitable, as described below.
- Follow-up consultations and hospital discharge follow-up consultations should be considered, respecting individual plans of care for each patient according to the disease and clinical condition. Renewal of therapy plans for medication and oxygen or ventilation therapies is a clear indication for teleconsultation.
- An unscheduled consultation shall be considered if there is a need by the patient to have an additional consultation related to his/her condition. In this case, there should be an assessment of the situation through teleconsultation, and, if it is not possible to adequately resolve the problems, a face-to-face consultation should be proposed and scheduled.
- Another potential use of teleconsultation is as initial screening of acute situations for chronic respiratory patients in home care, to better decide between a home visit or a face-to-face consultation in the hospital.

Table 1 General guidance steps in teleconsultations[21,35,36].

General Guidance Steps in Teleconsultations.
1. Use of a secure platform which complies with legal data protection requirements.
2. Ensure privacy and an adequate physical, acoustic, and visual environment.
3. Introduction of healthcare staff present and verification of patient's identity.
4. Obtain verbal or written consent for the virtual consultation.
5. Check technical problems and ensure suitable two-way communication.
6. Provide a short explanation of teleconsultation (definition and rationale).
7. Proceed with teleconsultation, keeping written records of all relevant information.
8. Agree upon the ending of the consultation and schedule a follow-up consultation, if applicable.

Guidance regarding respiratory tele-rehabilitation, given its own specificities, falls outside the scope of this document and will be described elsewhere.

In this document, we discriminate the disease-specific criteria for each of the follow-up consultations in the different respiratory diseases.

However, the preparatory steps apply to all of them, and are described below.

Pre-consultation

1. Register collection of verbal or written consent in patient's medical records.
2. Schedule the appointment for a time when the patient is rested and comfortable, set a duration per call and provide any applicable questionnaires/scales, if possible
3. Define a backup plan in case the teleconsultation needs to be canceled on a short notice.

Telemedicine in Pulmonology's specific indications

Asthma[36–42]

These recommendations only apply to follow-up consultations.

1. Guidance steps

1. Introduction and confirmation of consent to perform the teleconsultation.
2. Assess asthma control by clinical assessment and through validated questionnaires (ACT - Asthma Control Test / CARAT – Control of Allergic Rhinitis and Asthma Test).
3. Assess exacerbation events since the previous consultation, including admissions and emergency visits. Detail date of occurrence, type and duration of drugs administered (specifically systemic corticosteroids).
4. Assess frequency of reliever medication use.
5. Assess environmental exposures (smoking, indoor and outdoor pollution, allergens), work-related exposures and other potential triggers.
6. Check medication withdrawal.
7. Check adherence to treatment.
8. Review inhaler technique (ideally by video call). If incorrect, reinforce education on correct inhaler technique – through detailed explanation, demonstration (if video-consultation) or through pre-recorded videos available (e.g. by sharing screen). If necessary, schedule a face-to-face visit to reinforce education on inhaler technique.
9. Assess the occurrence of adverse events to medication.
10. Measure oxygen saturation by pulse oximeter, if available.
11. Review peak expiratory flow measurements, if applicable.
12. Review the results of tests performed (laboratory studies, imaging, spirometry and others, as appropriate).
13. Assess coexistence of comorbidities that may interfere with disease control and request tests or refer to other specialities if necessary.
14. Request the appropriate tests (laboratory studies, lung function tests, imaging, as adequate).
15. Review the action plan: recognition and appropriate reaction to acute exacerbations (how and when to take medication, when to call the physician, and when to get emergency care).
16. Review the prescribed treatment and reinforce the importance of adherence to treatment.
17. Treatment adjustment, if necessary.
18. Provide instructions on the new treatment prescribed, if applicable. In case a new inhaler is prescribed, provide explanation of inhaler technique – ideally through demonstration (if video-consultation) or through pre-recorded videos available (e.g. by sharing screen). If necessary, schedule a face-to-face visit to reinforce education on inhaler technique.
19. Review non-pharmacological strategies: patient avoidance behaviours (identify triggers and remind how to avoid them) and modifiable risk factors.
20. Schedule the following consultation (teleconsultation or face-to-face appointment).

Specific tools and recommendations

- Asthma Control Test (ACT) / Control of Allergic Rhinitis and Asthma Test (CARAT)
- Peak expiratory flow meter, if applicable
- Pulse oximeter, if available
- Inhalers to explain inhaler technique (if video consultations) or pre-recorded videos on specific inhalers
- Electronic prescription system

COPD/ non-cystic fibrosis bronchiectasis[35–37,43–46]

These recommendations only apply to follow-up consultations.

1. Guidance steps

1. Introduction and confirmation of consent to perform the teleconsultation.
2. Assess symptom control by clinical assessment or through validated questionnaires as applicable:
   - Dyspnea and other symptoms through validated questionnaires (modified Medical Research Council - mMRC and/or COPD Assessment Test – CAT).
   - Cough and its characteristics
   - Sputum production, its volume and consistency / colour changes.
   - Nocturnal symptoms.
3. Assess occurrence of acute exacerbations and their severity since the previous consultation, including admissions and emergency visits. Detail date of occurrence, type and duration of drugs administered (specifically antibiotics and systemic corticosteroids).
4. Check medication withdrawal.
5. Check adherence to treatment.
6. Review inhaler technique (ideally by video call). If incorrect, reinforce education on correct inhaler technique – through detailed explanation, demonstration (if video-consultation) or through pre-recorded videos available (e.g. by sharing screen). If necessary, schedule a face-to-face visit to reinforce education on inhaler technique.
7. Assess the occurrence of adverse events to medication.
8. Measure oxygen saturation by pulse oximeter, if available.
9. Review the results of the tests performed (laboratory studies, sputum microbiological tests, imaging, spirometry and others, as appropriate).

10. Assess coexistence of comorbidities that may interfere with disease control and request tests or refer to other specialties if necessary.
11. Request the appropriate tests (laboratory studies, lung function tests, imaging, as adequate).
12. Review the action plan: recognition and appropriate reaction to acute exacerbations (how and when to take medication, when to call the physician, and when to get emergency care).
13. Check compliance (% days; hours per day) with long term oxygen therapy or non-invasive ventilation, as appropriate. In patients with non-invasive ventilation, check ventilation parameters and adjust as necessary.
14. Review the prescribed treatment and reinforce the importance of adherence to treatment.
15. Treatment adjustment, if necessary.
16. Provide instructions on the new treatment prescribed, if applicable. In case a new inhaler is prescribed, provide explanation of inhaler technique — ideally through demonstration (if video-consultation) or through pre-recorded videos available (e.g. by sharing screen). If necessary, schedule a face-to-face visit to reinforce education on inhaler technique.
17. Review modifiable risk factors and behaviours, with a special focus on smoking habits. In case of active smoking, review motivation to quit smoking.
18. Review non-pharmacological strategies and reinforce their importance. Assess present or previous enrolment in respiratory rehabilitation programs.
19. Assess family / social support.
20. Schedule the following consultation (teleconsultation or face-to-face appointment).

Specific tools and recommendations

- mMRC Questionnaire
- COPD Assessment Test (CAT) Questionnaire
- Pulse oximeter, if available
- Inhalers to explain inhaler technique (if video consultations) or pre-recorded videos on specific inhalers
- In patients with non-invasive ventilation, access to ventilator reports (adherence and ventilation parameters); to nocturnal oximetry and/or nocturnal oxi-capnography and diurnal recording of end-tidal or transcutaneous CO2
- Electronic prescription system

Lung cancer[36,47,48]

These recommendations apply to follow-up teleconsultations in patients diagnosed with lung cancer who have undergone previous curative surgery and do not require additional treatment beyond adjuvant therapy.

There are, however, some anecdotal lung cancer cases that can be considered after a long course of stability without treatment requirement, although that orientation should be validated by an accurate evaluation and decision from the multidisciplinary team meeting.

Apart from lung cancer, incidental pulmonary nodules follow-up requires serial chest CT evaluation and is guided by algorithms, posing a particular indication for teleconsultations.

1. Guidance steps

1. Introduction and confirmation of consent to perform the teleconsultation.
2. Assess symptom control by clinical assessment.
3. Assess acute events since the previous consultation, including admissions and emergency visits.
4. Characterise patient performance status through validated scales (ECOG Performance Status Scale/ Karnofsky Performance Status Scale).
5. Check medication adherence and withdrawal, if applicable.
6. Assess the occurrence of adverse events to treatment prescribed.
7. Assess compliance with the respiratory rehabilitation program defined for the patient, if applicable.
8. Measure of oxygen saturation by pulse oximetry, if available.
9. Review the results of tests performed (laboratory features, tumour markers, imaging, lung function tests, and others, as appropriate).
10. Assess coexistence of comorbidities and request tests or refer to other specialties, if necessary.
11. Request the appropriate tests (laboratory studies, tumour markers, lung function tests, imaging, as adequate).
12. Review the prescribed treatment and reinforce the importance of adherence to treatment.
13. Treatment adjustment, if necessary.
14. Review non-pharmacological strategies and modifiable risk factors, such as smoking. Promote or reinforce smoking cessation.
15. Schedule the following consultation (teleconsultation or face-to-face appointment).

Specific tools and recommendations

- ECOG Performance Status Scale/ Karnofsky Performance Status Scale
- Pulse oximeter, if available
- Electronic prescription system

Smoking cessation[36,49—53]

These recommendations apply to smokers who want to make a serious attempt to quit smoking and who have been referred to a Pulmonology clinic for assessment. First-time and follow-up consultations, unscheduled consultations, and end of follow-up consultations should be considered. We reinforce that first-time teleconsultations should be video consultations.

1. Guidance steps

First consultation

1. Introduction and confirmation of consent to perform the teleconsultation.
2. Self-declaration of tobacco consumption.

3. Assess and characterise smoking history and smoker's profile, including triggers for smoking and barriers for cessation.
4. Determine weight and height.
5. Assess motivation to quit smoking through the Visual Analogue Scale and through a validated questionnaire: Richmond test.
6. Review patient medical history (comorbidities and concomitant medication).
7. Assess nicotine dependence through a validated questionnaire: Fagerström test.
8. Assess anxiety and depression symptoms through HADS (Hospital Anxiety and Depression Scale).
9. Characterise the smoker behaviour profile.
10. Set a personalised program, discuss possible therapeutic interventions, and define the D-day to quit smoking.
11. Request appropriate tests, if necessary.
12. Provide pharmacological treatment, if necessary, and a written behavioural plan.
13. Schedule a follow-up consultation (preferably 8-15 days after D-day) and request complementary exams, if necessary.

Follow-up consultation

1. Introduction and confirmation of consent to perform the teleconsultation.
2. Self-declaration of tobacco consumption.
3. When applicable, determine if D-day was accomplished and congratulate the patient. If there is still tobacco consumption, reassess, discuss relapsing issues, encourage to set a new D-day and reinforce commitment to smoking cessation.
4. Determine weight variation.
5. Assess compliance with treatment plan. Reinforce information on how drugs work and the need to comply with the full treatment.
6. Rule out the occurrence of adverse events to medication.
7. Give advice on how to manage withdrawal symptoms: irritability, difficulty in concentrating, pain, fatigue, headache, increased appetite, insomnia, and constipation. Reinforce behavioural strategies.
8. In case of persistent high levels of anxiety or depression, consider referring for psychologic or psychiatric evaluation. If increasing appetite and weight, consider referring for nutritional support.
9. Work on relapse prevention strategies.
10. Schedule the following consultation according to the progression on the cessation process.

- Unscheduled consultation
  If there is a need to review treatments, their duration and adverse events, if there is a relapse, or in case of vital situations that require close monitoring.
- End of follow-up consultation
  At 12 months after starting treatment, if there has been abstinence for more than 6 months, no craving, and absence of significant weight gain (< 3-4 Kg) or psychological diseases or distress.

Specific tools and recommendations

- Visual Analogue Scale on motivation to quit smoking
- Richmond test
- Fagerström test
- Hospital Anxiety and Depression Scale
- Smoker behavioural profile evaluation
- Electronic prescription system

Sleep-disordered breathing[36,54–58]

First consultations and follow-up consultations should be considered for patients with sleep disorders.

Follow-up teleconsultations in sleep medicine are highly dependent on telemonitoring, not only in terms of adherence, but mainly for checking efficacy parameters. No follow-up teleconsultation should occur without the PAP device report. Other telemonitoring options may be suitable, such as nocturnal oximetry under PAP treatment.

1. Guidance steps

First consultation

1. Introduction and confirmation of consent to perform the teleconsultation.
2. Assess occupation. Seek professions with high-risk consequences in the case of sleep disorders, such as truck drivers and others.
3. Review patient medical history (medical and psychiatric comorbidities, comorbid sleep disorders, and concomitant medication).
4. Assess and characterise smoking habits and alcohol intake.
5. Detail sleep history – including sleep habits (sleep hygiene), sleep environment, timing, duration and quality of sleep, daytime naps, activities performed before initiation of sleep.
6. Assess daytime sleepiness through Epworth Sleepiness Scale.
7. Check for other symptoms associated with sleep-disordered breathing – such as snoring, witnessed apneas, gasping, non-refreshing sleep, frequent awakenings, morning headache, morning fatigue, irritability and cognitive impairment.
8. Assess body mass index (BMI).
9. Assess craniofacial patient morphology (by video call).
10. Request appropriate diagnostic tests and explain the procedure, as well the preparatory recommendations.
11. Review non-pharmacological strategies, with special focus on sleep hygiene, and reinforce their importance.
12. Treatment prescription, if applicable. Detailed explanation of treatment – its purpose, explanation of device's performance and interface selection.

Follow-up consultation / Checking the results of diagnostic tests

1. Introduction and confirmation of consent to perform the teleconsultation.
2. Check sleep diary, if applicable.
3. Review results from the sleep study performed, if applicable.

4. Treatment prescription, if applicable. Detailed explanation of treatment – its purpose, explanation of device's performance and interface selection.
5. Assess clinical response to treatment.
6. Assess daytime sleepiness through Epworth Sleepiness Scale.
7. Assess other symptoms that may be to poor efficacy of treatment, such as snoring, witnessed apneas, gasping, non-refreshing sleep, frequent awakenings, morning headache, morning fatigue, irritability and cognitive impairment.
8. In patients under PAP treatment, check adherence (through PAP devices with built-in wireless connectivity or through PAP reports prepared by the home care provider).
9. Check PAP parameters of efficacy, such as residual apnea-hypopnea index (AHI).
10. Assess the occurrence of adverse events to treatment – nasal symptoms, aerophagia, interface-related side effects, among others.
11. Review changes in sleep habits and recommendations on sleep hygiene.
12. Review PAP prescription if necessary and consider need for additional treatment.
13. Schedule nocturnal oximetry or other tests, if necessary.
14. Schedule the following consultation (teleconsultation or face-to-face appointment).

Specific tools and recommendations

- Epworth sleepiness scale
- Sleep diary
- PAP report prepared by the provider company or obtained through built-in wireless connectivity
- Electronic prescription system of home respiratory care

Home mechanical ventilation[4,36,59,60]

Follow-up teleconsultations may be considered for patients with suspected or diagnosed Nocturnal Hypoventilation Syndrome. This also applies to neuromuscular patients, depending on the speed of disease progression and clinical judgement.

Patients who require previous evaluation to start non-invasive ventilatory support are not suitable for teleconsultation. Also, patients of high complexity (e.g. Amyotrophic Lateral Sclerosis) or highly ventilator-dependent may require a face-to-face assessment, a home visit, or a scheduled hospital admission.

Considering the potential role of the caregiver, physical or cognitive impairment should not be regarded as exclusion criteria for teleconsultation.

1. Guidance steps

1. Introduction and confirmation of consent to perform the teleconsultation.
2. Review results from the diagnostic tests performed - spirometry, peak cough flow, arterial blood gases, sleep study, nocturnal oximetry and/or oxi-capnography, as appropriate.
3. Treatment prescription, if applicable. Detailed explanation of treatment – its purpose, explanation of device's performance and interface selection.
4. Assess response to treatment by clinical assessment or through validated questionnaires – Severe Respiratory Insufficiency (SRI) Questionnaire / S3-NIV Questionnaire.
5. Assess symptoms of clinical deterioration (increased daytime sleepiness, orthopnea, morning headache, dysphagia, etc.) by clinical survey, as well as a disproportionate increase in hours of ventilation or respiratory rate recorded in built-in ventilator software.
6. Measure oxygen saturation by pulse oximetry.
7. Check adherence to treatment (through ventilators with built-in wireless connectivity or through reports elaborated by the provider company).
8. Check ventilator parameters of efficacy.
9. Check nocturnal oximetry and/or oxi-capnography results to assess correction of nocturnal hypoventilation.
10. Review the prescribed treatment.
11. Verification of correct placement of the interface (nasal, oronasal, etc.). Prevent and rule out the existence of interface-related side effects (pressure ulcers, dermatitis, etc) – ideally through a video call; alternatively, make use of videos or demonstrate application of interface placement.
12. Assess the occurrence of other adverse events to treatment, such as nasal symptoms, aerophagia, among others.
13. Schedule nocturnal oximetry and/or oxi-capnography or other tests, if necessary.
14. Update of the prescription in the digital platform available, to inform the company provider of therapies for the replacement or exchange of consumables, interface and equipment.
15. Schedule the following consultation (teleconsultation or face-to-face appointment).

Specific tools and recommendations

- Questionnaires (SRI / S3-NIV)
- Pulse oximeter
- Ventilator reports prepared by the home care provider or obtained through built-in wireless connectivity. Ventilatory parameters – minimum requirements: compliance (including graph with hours of use), programmed ventilatory parameters, trend graph and / or measurement of leakage, AHI, % triggered breaths pressure, flow and alarm management
- Access to monitoring tools of ventilation efficacy – nocturnal oximetry and/or oxi-capnography
- Electronic prescription system of home respiratory care

Interstitial lung disease[36,44,61–64]

Interstitial Lung Diseases (ILDs) encompass a range of distinct diseases with substantial differences in their underlying pathophysiological mechanisms, therapeutic approach, and prognosis.

Regardless of ILD, all consultations during the diagnostic approach should be done face-to-face until the diagnosis is fully established at the Multidisciplinary Team meeting. Thereafter, diseases such as sarcoidosis or some smoking-related disorders (e.g. respiratory bronchiolitis associated

with ILD), which often have a stable clinical course and do not need any significant therapeutic intervention, are much more suitable for teleconsultation. In contrast, in all other ILDs that require complex therapeutic interventions, such as immunosuppressants and antifibrotic agents, or have a more unstable clinical course with risk of progression, patients need to be assessed in person. Therefore, the modality of the consultation will depend on the nature of the disease and the particularities of the drugs prescribed.

1. Guidance steps

1. Introduction and confirmation of consent to perform the teleconsultation.
2. Assess dyspnea through validated questionnaires (mMRC).
3. Assess disease impact (e.g. through questionnaires such as King's Brief Interstitial Lung Disease – K-BILD – health status questionnaire).
4. Assess cough through validated questionnaires (visual analogue scale - VAS, Cough Quality of Life Questionnaire).
5. Assess occurrence of acute events and their severity since the previous appointment, including admissions and emergency visits.
6. Check adherence to treatment.
7. Assess the occurrence of adverse events to medication.
8. Measure oxygen saturation by pulse oximeter, if available.
9. Review lung function tests and assess FVC and diffusion capacity evolution.
10. Review the results of other tests performed (laboratory studies, imaging, arterial blood gases, 6-min walking distance and others, as appropriate).
11. Assess coexistence of comorbidities and medications that may interfere with disease control and request complementary diagnostic tests or refer to other specialties if necessary.
12. Request the appropriate tests (laboratory studies, lung function tests, imaging, as adequate).
13. Review the action plan: how and when to take medication, strategies to minimise adverse effects, when to call the physician, and when to get emergency care.
14. Review the prescribed treatment and reinforce the importance of adherence to treatment.
15. Treatment adjustment, if necessary.
16. Provide instructions on the new treatment prescribed, if applicable.
17. Review modifiable risk factors and behaviours, with a special focus on smoking habits. In case of active smoking, review motivation to quit smoking.
18. Review non-pharmacological strategies and reinforce their importance.
19. Assess family / social support, if applicable.
20. Schedule the following consultation (teleconsultation or face-to-face appointment).

Specific tools and recommendations

- mMRC Questionnaire
- Visual Analogue Scale
- Leicester Cough Questionnaire (Chronic Cough Quality of Life Questionnaire)
- Pulse oximeter
- Electronic prescription system

Conclusions

The pandemic crisis of COVID-19, amongst so many social, economic and healthcare problems, also brought new opportunities. It has allowed other forms of contact to be explored and has accelerated the digital revolution. And great steps have been taken towards a true implementation of telemedicine.

Teleconsultation, initially performed out of a great need to not loose contact with patients, but in a very empirical way, now appears as another tool at our disposal. This document seeks to establish recommendations to standardise the practice of this telemedicine modality.

Teleconsultation is just the beginning in the digital revolution in healthcare. In a near future, it is expected that other, more complex modalities of telemedicine will also become part of daily clinical practice.

It can never be emphasized too strongly that technology should always be at the service of the patient, and not the other way around. All these emerging tools only make sense if they prove to be an added value for the patient and for the improvement of healthcare provided to patients.

Disclosure statements of all authors outside the submitted work

Prof. Dr. António Morais reports personal fees from Boehringer Ingelheim, Roche, Astra, Novartis, Sanofi and Zanbom.

Prof. Dr. António Bugalho reports personal fees from Astrazeneca, Bial, Fujifilm, Medinfar, Olympus and Pfizer.

Prof. Dr. Marta Drummond reports personal fees from Astra Zeneca, Bial, GSK, Medinfar, Mundipharma, Novartis, Sanofi and Teva.

Prof. Dr. António Jorge Ferreira reports personal fees from Bial, Boehringer Ingelheim, GSK, Mylan, Menarini and TEVA Pharma.

Dr. Ana Sofia Oliveira reports personal fees from Astra, Bial, Boehringer Ingelheim, GSK, Medinfar, Menarini, Novartis, Pfizer and Vitalaire.

Dr. Susana Sousa reports personal fees from Bial, GSK, Pfizer, Linde Healthcare Portugal and Phillips Respironics.

Prof. Dr. João Carlos Winck reports personal fees from Armstrong Medical, Breas, Philips, Nippon Gases and Vitalaire.

Prof. Dr. João Cardoso reports personal fees from Astra Zeneca, GSK, Bial, Boehringer Ingelheim, Mylan and Novartis.

Acknowledgements

Literature review and medical writing support for this article was provided by Keypoint - Consultoria Científica, Lda., and was funded by Bial.

All authors contributed to the conception of the article, interpretation of the literature review, development of the manuscript and approved the final draft.

Role of the funding source

Bial provided all necessary scientific bibliography and funded medical writing support. The authors did not receive funding for the writing of this article.

References

1. Levin K, Madsen JR, Petersen I, Wanscher CE, Hangaard J. Telemedicine diabetes consultations are cost-effective, and effects on essential diabetes treatment parameters are similar to conventional treatment: 7-year results from the Svendborg Telemedicine Diabetes Project. J Diabetes Sci Technol. 2013;7:587—95. https://doi.org/10.1177/193229681300700302.
2. Greenhalgh T, Shaw S, Wherton J, et al. Real-world implementation of video outpatient consultations at macro, meso, and micro levels: mixed-method study. J Med Internet Res. 2018;20:e150. https://doi.org/10.2196/jmir.9897.
3. WHO Group Consultation on Health Telematics. In: A Health Telematics Policy in Support of WHO's Health-For-All Strategy for Global Health Development: Report of the WHO Group Consultation on Health Telematics. Geneva; 1997. https://apps.who.int/iris/handle/10665/63857 [accessed 16 January 2021].
4. Ambrosino N, Vitacca M, Dreher M, et al. Tele-monitoring of ventilator-dependent patients: a European Respiratory Society Statement. Eur Respir J. 2016;48:648—63. https://doi.org/10.1183/13993003.01721-2015.
5. Trappenburg JCA, Niesink A, de Weert-van Oene GH, et al. Effects of telemonitoring in patients with chronic obstructive pulmonary disease. Telemed J E Health. 2008;14:138—46. https://doi.org/10.1089/tmj.2007.0037.
6. Serviços Partilhados do Ministério da Saúde. National Strategic Telehealth Plan 2019-2022. https://www.spms.min-saude.pt/wp-content/uploads/2019/11/PENTS_Tradução.pdf [accessed 16 January 2021]
7. WHO Global Observatory for eHealth. Telemedicine: opportunities and developments in Member States: report on the second global survey on eHealth 2010. Geneva. https://apps.who.int/iris/handle/10665/44497 [accessed 16 January 2021]
8. Oliveira TC, Bayer S, Gonçalves L, Barlow J. Telemedicine in Alentejo. Telemed J E Health. 2014;20:90—3. https://doi.org/10.1089/tmj.2012.0308.
9. Castela E, Ramalheiro G, Pires A, et al. Five years of teleconsultation: experience of the Cardiology Department of Coimbra Pediatric Hospital. Rev Port Cardiol. 2005;24:835—40.
10. Ordem dos Médicos. Informação jurídica — condições para exercício da telemedicina. https://ordemdosmedicos.pt/informacao-juridica-condicoes-para-exercicio-da-telemedicina /[accessed 20 January 2021]
11. Institute of Medicine of the National Academy of Sciences. Telemedicine. In: Field MJ, ed. A Guide to Assessing Telecommunications in Health Care, Washingt DC: National Academy Press; 1996.
12. Kuziemsky C, Maeder AJ, John O, et al. Role of Artificial Intelligence within the Telehealth Domain. Yearb Med Inform. 2019;28:35—40.
13. Sunarti S, Fadzlul Rahman F, Naufal M, Risky M, Febriyanto K, Masnina R. Artificial intelligence in healthcare: opportunities and risk for future. Gac Sanit. 2021;35(Suppl 1):S67—70.
14. Baker A, Perov Y, Middleton K, et al. A comparison of artificial intelligence and human doctors for the purpose of triage and diagnosis. Front Artif Intell. 2020;3:543405.
15. Piao C, Terrault N, Sarkar S. Telemedicine: an evolving field in hepatology. Hepatol Commun. 2019;3:716—21. https://doi.org/10.1002/hep4.1340.
16. Chang T, Lee J, Wu S. The telemedicine and teleconsultation system application in clinical medicine. Conf Proc IEEE Eng Med Biol Soc. 2004;2004:3392—5. https://doi.org/10.1109/IEMBS.2004.1403953.
17. Bove AA, Homko CJ, Santamore WP, Kashem M, Kerper M, Elliot DJ. Managing hypertension in urban underserved subjects using telemedicine—a clinical trial. Am Heart J. 2013;165:615—21. https://doi.org/10.1016/j.ahj.2013.01.004.
18. Manchanda S. Telemedicine—getting care to patients closer to home. Am J Respir Crit Care Med. 2020;201:26—7. https://doi.org/10.1164/rccm.2020C5.
19. European Lung Foundation. Telemedicine 2020. https://europeanlung.org/en/information-hub/factsheets/telemedicine /[accessed 19 January 2021]
20. Kolasa K, Kozinski G. How to value digital health interventions? A systematic literature review. Int J Environ Res Public Health. 2020;17:2119. https://doi.org/10.3390/ijerph17062119.
21. Wong A, Bhyat R, Srivastava S, Boissé Lomax L, Appireddy R. Patient care during the COVID-19 pandemic: use of virtual care. J Med Internet Res. 2021;23:e20621. https://doi.org/10.2196/20621.
22. Monaghesh E, Hajizadeh A. The role of telehealth during COVID-19 outbreak: a systematic review based on current evidence. BMC Public Health. 2020;20:1193. https://doi.org/10.1186/s12889-020-09301-4.
23. Izquierdo Alonso JL, Rodríguez González-Moro JM. Pneumology in the Days of COVID-19. Arch Bronconeumol. 2020;56:1—2. https://doi.org/10.1016/j.arbres.2020.05.017.
24. Ohannessian R, Duong TA, Odone A. Global telemedicine implementation and integration within health systems to fight the COVID-19 pandemic: a call to action. JMIR Public Heal Surveill. 2020;6:e18810. https://doi.org/10.2196/18810.
25. Silva F, Silva J, Belo J, Nêveda R. Telemonitorização do paciente com Doença Pulmonar Obstrutiva Crónica no Alto Minho (Portugal). In: Gonçalves L, Castelo-Branco M, Campanella N, eds. E-Saúde: Livro de Ensino Para Estudantes de Cursos de Ciências da Saúde e Para Profissionais Saúde. Covilhã, Tipogr da Univ da Beira Inter; 2018:275—80.
26. Donaghy E, Atherton H, Hammersley V, et al. Acceptability, benefits, and challenges of video consulting: a qualitative study in primary care. Br J Gen Pract. 2019;69:e586—94. https://doi.org/10.3399/bjgp19X704141.
27. Car J, Koh GC, Foong PS, Wang CJ. Video consultations in primary and specialist care during the covid-19 pandemic and beyond. BMJ. 2020;371:m3945. https://doi.org/10.1136/bmj.m3945.
28. Sociedade Brasileira de Pneumologia e Tisiologia. Posição da SBPT Sobre a Modalidade de Teleconsulta Médica Na Área Das Doenças Respiratórias. Brasília, 2019. https://sbpt.org.br/portal/posicao-sbpt-teleconsulta /[accessed 28 January 2021]
29. Oztas MO, Calikoglu E, Baz K, et al. Reliability of Web-based teledermatology consultations. J Telemed Telecare. 2004;10:25—8. https://doi.org/10.1258/135763304322764158.
30. Hewitt H, Gafaranga J, McKinstry B. Comparison of face-to-face and telephone consultations in primary care: qualitative analysis. Br J Gen Pract. 2010;60:e201—12. https://doi.org/10.3399/bjgp10X501831.
31. Rodriguez JA, Betancourt JR, Sequist TD, Ganguli I. Differences in the use of telephone and video telemedicine visits during the COVID-19 pandemic. Am J Manag Care. 2021;27:21—6. https://doi.org/10.37765/ajmc.2021.88573.
32. Ambrosino N, Fracchia C. The role of tele-medicine in patients with respiratory diseases. Expert Rev Respir Med. 2017;11:893—900. https://doi.org/10.1080/17476348.2017.1383898.
33. British Thoracic Society. Pulmonary Rehabilitation Remote Assessment. 1—5 https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/bts-pulmonary-rehab-remote-assessment.
34. Peine A, Paffenholz P, Hellmich M, et al. [Perception of the COVID-19 Pandemic among Pneumology Professionals in Germany]. Pneumologie. 2021;75:284—92. https://doi.org/10.1055/a-1240-5998.
35. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Prevention, Diagnosis and Management of

COPD: 2021 Report. https://goldcopd.org/wp-content/uploads/2020/09/GOLD-COPD-Follow-up-Telemedicine_091820_Final.pdf [accessed 1 February 2021]
36. Almonacid C, Plaza V. Guía SEPAR para la Teleconsulta de Pacientes Respiratorios. Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Ed. RESPIRA. https://issuu.com/separ/docs/guia_teleconsulta_web__1_?fr=sZDE5MzE2NjczNg [accessed 21 January 2021]
37. Health Partners Principles for Telehealth Policy 2020. https://www.lung.org/getmedia/ac136df2-5984-46b6-9503-8523f71f5425/final-principles-for-telehealth-policy-_8_27_2020-(003).pdf [accessed 18 January 2021]
38. Nathan R, Sorkness C, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004;113:59—65. https://doi.org/10.1016/j.jaci.2003.09.008.
39. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2020. http://www.ginasthma.org [accessed 10 May 2021]
40. Sociedad Española de Neumología y Cirurgía Torácica (SEPAR). Guía Espanola para el Manejo del Asma (GEMA) 5.1. https://www.gemasma.com /[accessed 10 May 2021]
41. Fonseca J, Nogueira-Silva L, Morais-Almeida M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. Allergy. 2010;65:1042—8. https://doi.org/10.1111/j.1398-9995.2009.02310.x.
42. Almonacid C, Blanco-Aparicio M, Domínguez-Ortega J, et al. Teleconsultation in the follow-up of the asthma patient. Lessons after COVID-19. Arch Bronconeumol. 2021;57:13—4. https://doi.org/10.1016/j.arbres.2020.10.005.
43. Wu F, Burt J, Chowdhury T, et al. Specialty COPD care during COVID-19: patient and clinician perspectives on remote delivery. BMJ Open Respir Res. 2021;8:e000817. https://doi.org/10.1136/bmjresp-2020-000817.
44. Bestall J, Paul E, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the medical research council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54:581—6. https://doi.org/10.1136/thx.54.7.581.
45. Ribeiro S, Cardoso C, Valério M, et al. Confirmatory evaluation of the modified medical research council questionnaire for assessment of dyspnea in patients with chronic obstructive pulmonary disease in Portugal. Acta Med Port. 2021. https://doi.org/10.20344/amp.15208.
46. Jones P, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34:648—54. https://doi.org/10.1183/09031936.00102509.
47. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649—55.
48. Royce TJ, Sanoff HK, Rewari A. Telemedicine for cancer care in the time of COVID-19. JAMA Oncol. 2020;6:1698—9. https://doi.org/10.1001/jamaoncol.2020.2684.
49. El-Bastawissi A, McAfee T, Zbikowski S, et al. The uninsured and Medicaid Oregon tobacco user experience in a real world, phone based cessation programme. Tob Control. 2003;12:45—51. https://doi.org/10.1136/tc.12.1.45.
50. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of the Fagerström Tolerance questionnaire. Br J Addict. 1991;86:1119—27. https://doi.org/10.1111/j.1360-0443.1991.tb01879.x.
51. Richmond RL, Kehoe LA, Webster IW. Multivariate models for predicting abstention following intervention to stop smoking by general practitioners. Addiction. 1993;88:1127—35. https://doi.org/10.1111/j.1360-0443.1993.tb02132.x.
52. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361—70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x.
53. Pais-Ribeiro J, Silva I, Ferreira T, Martins A, Meneses R, Baltar M. Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. Psychol Health Med. 2007;12:225—37. https://doi.org/10.1080/13548500500524088.
54. Cottrell MA, Russell TG. Telehealth for musculoskeletal physiotherapy. Musculoskelet Sci Pract. 2020;48:102193. https://doi.org/10.1016/j.msksp.2020.102193.
55. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540—5. https://doi.org/10.1093/sleep/14.6.540.
56. Sargento P, Perea V, Ladera V, Lopes P, Oliveira J. The Epworth Sleepiness Scale in Portuguese adults: from classical measurement theory to Rasch model analysis. Sleep Breath. 2015;19:693—701. https://doi.org/10.1007/s11325-014-1078-6.
57. Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012;35:287—302. https://doi.org/10.5665/sleep.1642.
58. Gay P, Weaver T, Loube D, et al. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep. 2006;29:381—401. https://doi.org/10.1093/sleep/29.3.381.
59. Windisch W, Freidel K, Schucher B, et al. The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. J Clin Epidemiol. 2003;56:752—9. https://doi.org/10.1016/s0895-4356(03)00088-x.
60. Dupuis-Lozeron E, Gex G, Pasquina P, et al. Development and validation of a simple tool for the assessment of home noninvasive ventilation: the S 3-NIV questionnaire. Eur Respir J. 2018;52:1801182. https://doi.org/10.1183/13993003.011822018.
61. Antoniou KM, Margaritopoulos GA, Tomassetti S, Bonella F, Costabel U, Poletti V. Interstitial lung disease. Eur Respir Rev. 2014;23:40—54. https://doi.org/10.1183/09059180.00009113.
62. Patel AS, Siegert RJ, Brignall K, et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. Thorax. 2012;67:804—10. https://doi.org/10.1136/thoraxjnl-2012-201581.
63. Spinou A, Birring SS. An update on measurement and monitoring of cough: what are the important study endpoints? J Thorac Dis. 2014;6:S728—34. https://doi.org/10.3978/j.issn.2072-1439.2014.10.08.
64. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58:339—43. https://doi.org/10.1136/thorax.58.4.339.

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LETTER TO THE EDITOR

Alpha-1-antitrypsin deficiency caused by a PI*ZQ0Leiria genotype- the importance of diagnosis algorithms

Dear editor

Alpha-1-antitrypsin (AAT) is the major protease inhibitor in serum whose function is the control of neutrophil elastase.[1-3]

AAT deficiency (AATD) is an autosomal codominant disorder caused by SERPINA1 mutations[4] increasing the risk of emphysema and chronic obstructive pulmonary disease (COPD). Despite most cases being connected with low AAT concentrations and PI*ZZ and PI* SZ genotypes, in rare instances, those can be correlated with rare deficiency or null variants.[4] Until now, more than 120 SERPINA1 mutations were reported and in Portugal 9.5% of patients were linked to null alleles.[2,5]

Here, we present a 46-year-old woman, former smoker (37 pack-per-year), with no family history of lung disease or occupational exposure. She was referred to our center, in 2016, with Asthma-COPD diagnosis and a mild form of AATD as indicated by a PI*MZ genotype obtained in 2012. The patient described a 4-year history of exertional dyspnea (mMRC3), wheezing and cough with frequent minimal sputum. Physical examination showed decreased breath sounds in both lungs. Patient was medicated with formoterol 24 μg, ipratropium bromide 80 μg and, aminophylline 200 mg twice a day and salbutamol 100 μg as needed with poor symptomatic control and at least one moderate to severe exacerbation per year. Chest computed (CT) tomography confirmed pulmonary hyperinflation with centrilobular and panlobular emphysema. A forced expiratory volume (FEV1)/forced vital capacity (FVC) ratio of 53% and a FEV1 of 60% of the predicted value (1.52 L) were estimated (GOLD 2, Group B). Body plethysmography showed elevation in residual volume (RV: 3.13 L; 217% of predicted) and diffusion capacity of carbon monoxide (DLCO) was moderately decreased (45% of

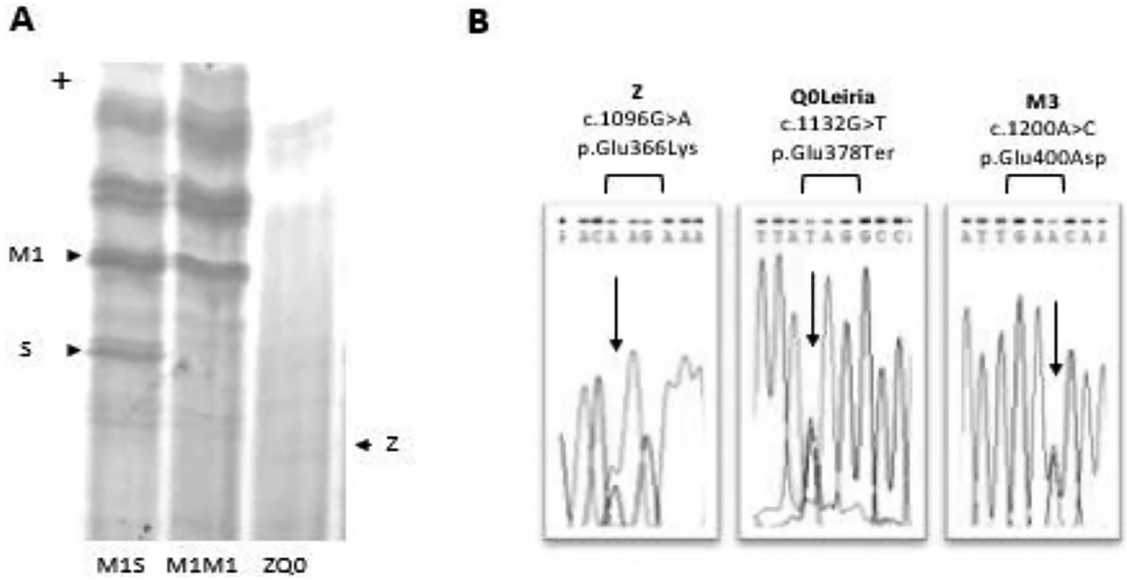

Fig. 1 Characterization of ZQ0Leiria index case. (A) Protein gel electrophoresis. Index case ZQ0 displays only a band corresponding to PI*Z allele. (B) Electropherogram of the index case for SERPINA1 (NM_000295.5) exon 5, covering the mutations that define Z, Q0Leiria and M3 alleles. The arrows show the position of the corresponding nucleotide substitutions.

https://doi.org/10.1016/j.pulmoe.2022.07.012

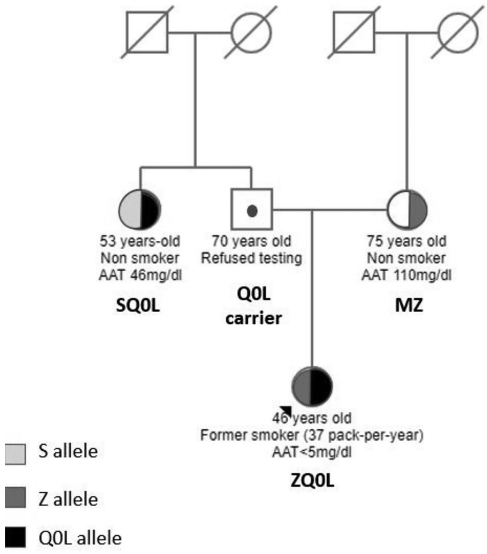

Fig. 2 Family genogram.

predicted). Arterial blood gas showed hypoxemia (pO_2 66 mmHg). AAT concentration was 5 mg/dl as measured by nephelometry. Given that patient's symptoms and AAT levels were inconsistent with a PI*MZ result, the genetic study was repeated in an independent laboratory.[3]

A PI*ZQ0 diagnosis was achieved, where the null allele was caused by novel mutation leading to the premature termination of protein sequence (NM_000295.5: c.1132G>*T*; p. Glu378Ter). This mutation found to be associated with a PI*M3 (p.Glu400Asp) background and was labeled as Q0Leiria according to AATD nomenclature (Fig. 1).

The family screening uncovered that her mother (75-year-old, nonsmoker) had a PI*MZ genotype with 110 mg/dl of AAT. No evidence of lung disease was detected (normal CT and lung function tests). Her 53-year-old aunt (non-smoker) had a PI*SQ0Leiria genotype with 46 mg/dl of AAT without respiratory symptoms or evidence of disease (normal CT and lung function tests) (Fig. 2).

Unfortunately, we lost the follow-up of this patient in 2017 and no AAT therapy could be implemented in our pulmonology department.

The Q0Leiria allele resulting from a premature termination of protein 41 codons upstream of the wildtype impairs AAT secretion as indicated by carriers low AAT concentrations and absence of a corresponding band in gels. To our knowledge this mutation is not described in the literature, nor is it present in large genomic databases.

Null mutations as Q0Leiria are not associated with AAT polymerization in the liver nor in the lung interstitium and thus, no exacerbation of pulmonary disease is expected once their clinical manifestations result exclusively from AAT loss of function. The rarity of these alleles impairs a proper evaluation of their disease risk when combined with known deficiency alleles.[6]

Although both cases analyzed in this report show AAT values bellow the protective threshold of 57 mg/dl only the smoker PI*ZQ0Leiria carrier presents her lung function seriously compromised. This confirms the importance of tobacco smoking on AATD clinical presentations. Indeed, smoke exposure is a well-known risk factor for the onset and progression of Emphysema and COPD without which severe AATD cases such the one of PI*SQ0Leira may not show symptoms of pulmonary disease.[6] Similar findings were reported for never-smokers with PI*SQ0Ourém genotypes.[7]

This report also highlights the importance of a prompt diagnosis and the need to access AAT concentration together with a detailed clinical evaluation. Without the possibility of performing the genetic test in a reference laboratory offering an algorithm of diagnosis (AAT phenotyping, genotyping and SERPINA1 sequencing) these subjects would persist misdiagnosed. The detection of Null alleles should lead to genetic counseling and a possible use of replacement therapy.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Lopes AP, Mineiro MA, Costa F, Gomes J, Santos C, Antunes C, et al. Portuguese consensus document for the management of alpha-1-antitrypsin deficiency. Pulmonology. 2018;24:1—21.
2. Seixas S. The human SERPIN repertoire and the evolution of 14q32.1 and 18q21.3 gene clusters editors. In: Geiger M, Furtmüller M, Wahlmüller F, eds. The Serpin Family Proteins with Multiple Functions in Health and Disease, Springer International Publishing; 2015:1—14.
3. Silva D, Oliveira MJ, Guimarães M, Lima R, Gomes S, Seixas S. Alpha-1- antitrypsin (SERPINA1) mutation spectrum: three novel variants and haplotype characterization of rare deficiency alleles identified in Portugal. Respir Med. 2016;116:8—18.
4. Torres-Durán M, Lopez-Campos JL, Barrecheguren M, Miravitlles M, Silvia Castillo S, et al. Alpha-1 antitrypsin deficiency: outstanding questions and future directions. Orphanet J Rare Dis. 2018;13(1):1—15.
5. Meira L, Boaventura R, Seixas S, Sucena M. Alpha-1 Antitrypsin Deficiency Detection in a Portuguese Population. COPD. 2018;15 (1):4—9.
6. O'Brien ME, Pennycooke K, Carroll TP, Shum J, Fee LT, O'Connor C, et al. The impact of smoke exposure on the clinical phenotype of alpha-1 antitrypsin deficiency in Ireland: exploiting a national registry to understand a rare disease. COPD. 2015;12 (Suppl 1):2—9.
7. Vaz Rodrigues L, Costa F, Marques P, Mendonça C, Rocha J, Seixas S. Severe α-1 antitrypsin deficiency caused by Q0(Ourém) allele: clinical features, haplotype characterization and history. Clin Genet. 2012 May;81(5):462—9.

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Received 7 February 2022; Accepted 28 July 2022
Available online 28 September 2022

Pulmonology 29 (2023) 79—82

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Sequential use of noninvasive ventilation and high flow nasal therapy after early extubation in chest trauma patients recovering from acute hypoxaemic respiratory failure

To the Editor

Post-traumatic lung injury may lead to acute respiratory distress syndrome (ARDS).[1-2] Non invasive ventilation (NIV) has been used both before and after extubation in these patients.[1-8] The sequential use of NIV and High Flow Nasal Therapy (HFNT)[9-11] may improve oxygenation while avoiding intubation, preventing reintubation, and reducing the length of invasive mechanical ventilation (iMV).[12,13] However, there is scarce evidence on the use of HFNT the trauma population at risk of weaning failure.[14]

This prospective single-center pilot study assessed feasibility and safety of early extubation.[15,16] followed by sequential use of NIV and HFNT in consecutive blunt chest trauma patients admitted to ICU between January 2nd 2017 and December 31st 2019. The study was approved by the local Ethics Committee and registered. All patients or legal representatives gave their written permission.

Patients were included for early extubation[14] if meeting all the following criteria: 1) age $\geq$18 years; 2) invasive Mechanical Ventilation (iMV) for at least 48 h; 3) pressure support ventilation (PSV) with a total applied pressure (i.e. positive end-expiratory pressure (PEEP) + inspiratory support) $\leq$20 cmH_2O and a PEEP level between 8 and 10 cmH_2O; 4) the ratio between the partial pressure of oxygen and fraction of inspired oxygen ($PaO_2/FiO_{2\ ratio}$) between 200 and 300 mmHg with FiO2 $\leq$ 0.6 and lack of ARDS; 5) $PaCO_2 \leq$ 45 mmHg and pH $\geq$7.35; 6) respiratory rate (RR) $\leq$ 30 breaths/min; 7) core temperature $<$38.5 °C; 8) Glasgow Coma Scale (GCS) $\geq$11; 9) Richmond Agitation Sedation Score (RASS) $<$3; 10) preserved cough-reflex on suctioning and need for $<$2 tracheobronchial suctioning per hour.

Patients were excluded if they met one or more of the following criteria: 1) hemodynamic instability (defined as systolic arterial pressure $<$90 mmHg despite fluid resuscitation and/or use of vasopressors); 2) life-threatening arrhythmias and/or electrocardiographic signs of ischemia; 3) sepsis; 4) secondary acute respiratory failure due to neurological disorders, status asthmaticus, chronic obstructive pulmonary disease or cardiogenic pulmonary edema; 5) tracheotomy; 6) uncontrolled vomiting; 7) RASS $\geq$3; 8) two or more organ failures; 9) body mass index (BMI) $>$ 30 kg/m; ^{2}10) documented history or suspicion of obstructive sleep apnea; 11) unstable flail chest; 12) recent upper airway or esophageal surgery; 13) pregnancy; 14) inclusion in other research protocols; 15) denied consent.

Patients underwent sequential application of NIV and HFNT as represented in Fig. 1. During NIV session full-face or oronasal masks were rotated to avoid skin breakdown.[17] Humidification was achieved through a heated humidifier. Non invasive pressure support ventilation (PSV) was set up according to the pressure level applied before extubation and was then titrated to achieve an expired tidal volume of 7—8 ml/kg, with $PaCO_2$ $<$ 45 mmHg, pH $>$7.35, and respiratory rate (RR)$<$ 30 breaths/min. PEEP was adjusted to maintain PaO_2/FiO_2 ratio $>$ 225 mmHg.

HFNT was delivered at a gas flow rate of 60 L/min and FIO_2 of 1.0, via large-bore dedicated nasal prongs at 37 °C and then adjusted according to the patient's comfort. FiO_2 was then adjusted to maintain a $SpO_2 > 92\%$.

After extubation patients received intravenous analgosedation with remifentanil (dose range of 0.02—0.08 mcg/kg/min) or dexmetedomidine (dose range 0.4—1 mcg/kg/h) in case of RASS $\geq$1 and/or Behavioural Pain Scale (BPS) $>$4. For lower BPS levels acetaminophen 1 g three time a day was given.

A weaning trial was attempted when patients reached PaO_2/FiO_2 ratio $>$ 250 mmHg. In these cases, PSV levels and PEEP were progressively decreased (by 2 cmH_2O sequential steps), until they reached a minimum threshold value of 5 and 8 cmH_2O, respectively. Then, NIV was interrupted, and patients were switched to HFNT only. Weaning from HFNT was considered successful if patients met all the following criteria: pH $>$7.35, $PaCO_2\langle$ 45 mmHg and $PaO_2\rangle$ 70 mmHg, RR $<$ 30 breaths/min, absence of dyspnea, respiratory accessory muscles recruitment, and paradoxical abdominal motion during 30-min trial with oxygen supplementation through a Venturi-mask with a FiO_2 0.35.

Reintubation was considered in the occurrence of any of the following complications during the study period: a) cardiac or respiratory arrest; b) inability to protect the airway; c) coma or psychomotor agitation with RASS $>$3 not controlled by continuous i.v. sedative infusion; d) unmanageable secretions or uncontrolled vomiting; e) life-threatening

https://doi.org/10.1016/j.pulmoe.2022.06.006

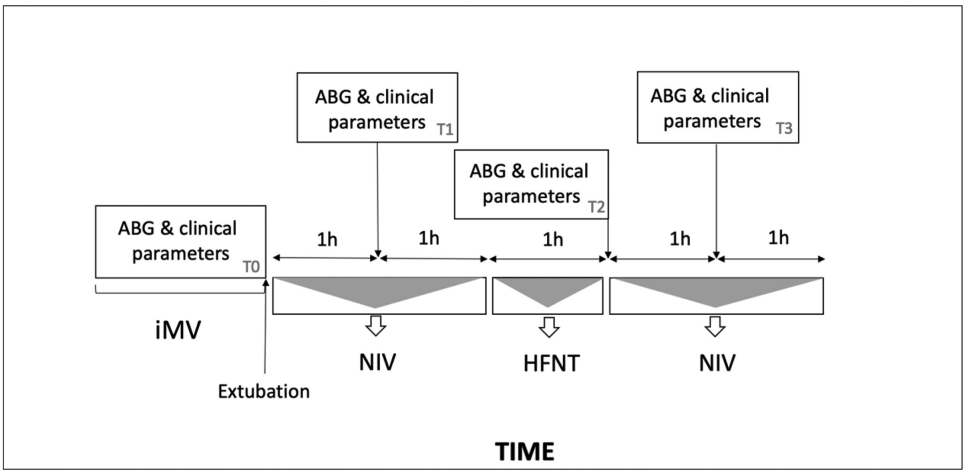

Fig. 1 Protocol flowchart and study times point. (T0), before extubation; (T1), 1 h after extubation during the first NIV cycle, (T2), 3 h after extubation during the first HFNT session; (T3) 4 h after extubation during second NIV cycle. iMV, invasive mechanical ventilation, NIV noninvasive mechanical ventilation, HFNT high flow nasal therapy.

arrhythmias or electrocardiographic signs of ischemia; f) hemodynamic instability; g) intolerance to all interface; or in the occurrence of at least two of the following criteria: h) PaO_2/FiO_2 ratio $<$ 200 mmHg; i) respiratory acidosis (pH $<$ 7.35 and $PaCO_2 >$ 50 mmHg); j) RR $>$ 40 breaths /min. Vital parameters (systemic blood pressure - SBP, heart rate - HR, respiratory rate -RR) were continuously monitored.

Continuous variables were expressed as means standard deviation (SD) or as medians (interquartile range, IQR) as appropriate, and discrete variables as counts (percentage). The analysis of the medians over the times, was carried out using the non-parametric Friedman test, considered not-normal distribution of values. Pairwise comparisons to groups were carried out using Wilcoxon signed-rank test and *P*-value adjustment with Bonferroni's method. The association between the presentation variables were first analyzed by mean of non-parametric Spearman correlation coefficient. Multiple linear regression was used to identify the variables with an important contribution to the response variability and to adjust for confounding variables with the stepwise method by Aikake Information Criterion (Aic). A *P* value $<$0.05 was considered statistically significant.

Twenty-five patients met the inclusion criteria during the study period; five patients were excluded before intervention due to respiratory and cardiovascular complications. Baseline characteristics of the study cohort at admission are shown in Table 1a. iMV was required for a mean time of 56.4 h (55.5). The protocol, ranged from 6.5 to 100.5 h (41.4 $\pm$ 28.36). Table 1b summarizes the results of blood gas analysis and clinical parameters at different time points and at the end of the study. No cases of reintubation or death were recorded. We found that there was a positive correlation between the time of iMV and the duration of the protocol, R = 0.624 (95%; CI 0.25−0.836, p. = 0.0033). Each hour of iMV was associated with an average 32 min increase in protocol time (p. 0.005).

Five patients, during HFNT needed to be switched to NIV because of PaO_2/FiO_2 ratio between 200 and 225 mmHg before reattempting HFNT. No severe adverse events were recorded. Comfort score as measured by VAS was not significantly different (p. 0.66) over time between HFNT and NIV as well as vital parameters were not different over time between HFNT and NIV. Remifentanil was never used in any patients while dexmetedomidine was used in 16 patients (mean dose range 0.8 mcg/kg/h $\pm$ 0,2).

In this prospective single-center observational pilot study of a cohort of chest trauma patients, the sequential use of NIV and HFNT following early extubation was found to be feasible and safe. None of the included patients required reintubation. Alternating the use of NIV and HFNT has proven to cause neither clinically relevant changes in respiratory parameters nor complications. This strategy may help avoid re-intubation in this patient population. However, our study has several limitations. Firstly, it lacks a control group since we did not compare the applied post-extubation protocol with other protocols or weaning practices. Secondly, we applied restrictive inclusion criteria obtaining a small, selected cohort of patients. This could explain the fact that none of the treated patients were intubated. Thirdly we did not compare dyspnea at the different study times point.

Table 1a Baseline characteristics of the patients.

Characteristics	Patients (n = 20)
Age y	51.95 (19.50)
Gender male N. (%)	15 (75.0)
BMI kg/m2	28.10 [17.50, 30.00]
Pneumothorax N.(%)	14 (70.0)
Liver contusion N.(%)	5 (25)
Spleen contusion N.(%)	4 (20)
Pelvis fracture N.(%)	5 (25)
Retroperitoneal hematoma N.(%)	1(5)
Upper or lower limbs fractures N.(%)	5 (25)
Need for chest drainage N. (%)	12 (60.0)
GCS	15.00 [6.00, 15.00]
TTSscore	12.00 (3.16)

BMI: Body Mass Index, GCS: Glasgow Coma Scale, TTSs: Thoracic Trauma Severity Score.
Data are expressed by Mean (SD), Median (IQR).

Table 1b Analysis of the medians (IQR) of each variables at different study times point. (T0), before extubation; (T1), 1 h after extubation during the first NIV cycle, (T2), 3 h after extubation during the first HFNT session; (T3) 4 h after extubation during second NIV cycle and at the end of treatment. NIV noninvasive ventilation, HFNT high flow nasal therapy.

	T0	T1	T2	T3	End of treatment	*P* value overall
Patient	20	20	20	20	20	
pH	7.44 [7.36, 7.67]	7.48 [7.36, 7.66]	7.46 [7.32, 7.66]	7.47 [7.35, 7.56]	7.45 [4.48, 7.66]	0.2
PaO_2 (mmHg)	129.00 [75.00, 170.00]	118.00 [65.00, 313.00]	100.00 [72.00, 236.00]	130.00 [101.00, 263.00]	124.50 [75.00, 238.00]	< **0.01**
$PaCO_2$ (mmHg)	42.00 [31.00, 50.00]	36.00 [23.00, 52.00]	41.50 [22.00, 60.00]	40.50 [30.00, 52.00]	39.00 [22.00, 50.00]	**0.03**
Base Excess	3.80 [−2.00, 32.00]	3.85 [−4.10, 10.10]	4.50 [−2.60, 11.90]	4.40 [−2.80, 11.30]	3.95 [0.60, 8.90]	0.87
Lactate (mEq/l)	1.00 [0.40, 2.60]	1.20 [0.60, 3.70]	1.10 [0.50, 3.00]	0.90 [0.60, 2.30]	1.00 [0.50, 2.10]	**0.02**
HCO_3 (mmol/l)	27.20 [23.00, 39.20]	26.75 [21.80, 34.10]	28.30 [22.80, 35.10]	28.15 [22.80, 34.30]	27.60 [23.70, 32.80]	0.16
FiO_2	0.53 [0.30, 0.60]	0.50 [0.35, 0.60]	0.50 [0.40, 0.60]	0.50 [0.40, 0.70]	0.50 [0.30, 0.60]	0.30
PO_2/FiO_2 ratio	239.00 [203.00, 350.00]	227.00 [163.00, 522.00]	200.00 [144.00, 393.00]	257.00 [202.00, 526.00]	265.00 [240.00, 595.00]	<**0.01**
SpO_2 (%)	100.00 [97.00, 100.00]	100.00 [98.00, 100.00]	99.70 [97.00, 100.00]	100.00 [98.90, 100.00]	100.00 [97.80, 100.00]	<**0.01**
Respiratory Rate (bpm)	14 [12.00, 18.00]	19.5 [12.00, 22.00]	18 [12.00, 26.00]	16 [12.00, 20.00]	14 [12.00, 22.00]	<**0.01**

Therefore, the preliminary results obtained have low generalizability in the reference population and should be considered as feasibility, hypothesis-generating study for further controlled trials.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Andrea Cortegiani, Giovanni Misseri, Antonino Giarratano, Giuseppe Accurso and Cesare Gregoretti declare a patent in association with the University of Palermo-Italy (No.102019000020532_Italian Ministry of Economic Development) not related to the content of this manuscript. Cesare Gregoretti received fees for lectures by Philips, and received payments by Philips for consultancies in the developing process of the EVO Ventilator and fees for lectures or consultancies from Resmed, Vivisol and AirLiquide not related to the present work.

References

1. Duggal A, Perez P, Golan E, Tremblay L, Sinuff T. Safety and efficacy of noninvasive ventilation in patients with blunt chest trauma: a systematic review. Crit. Care. 2013;17(4):R142. https://doi.org/10.1186/cc12821.
2. Chiumello D, Coppola S, Froio S, Gregoretti C, Consonni D. Noninvasive ventilation in chest trauma: systematic review and meta-analysis. Intensive Care Med. 2013;39(7):1171−80. https://doi.org/10.1007/s00134-013-2901-4.
3. Gregoretti C, Foti G, Beltrame F, et al. Pressure control ventilation and minitracheotomy in treating severe flail chest trauma. Intensive Care Med. 1995;21(12):1054−6. https://doi.org/10.1007/BF01700674.
4. Roberts S, Skinner D, Biccard B, Rodseth RN. The role of noninvasive ventilation in blunt chest trauma: systematic review and meta-analysis. Eur. J. Trauma Emerg. Surg. 2014;40(5):553−9. https://doi.org/10.1007/s00068-013-0370-7.
5. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur. Respir. J. 2017;50(2):1602426. https://doi.org/10.1183/13993003.02426-2016.
6. Hernandez G, Fernandez R, Lopez-Reina P, et al. Noninvasive ventilation reduces intubation in chest trauma-related hypoxemia. Chest. 2010;137(1):74−80.
7. Gregoretti C, Beltrame F, Lucangelo U, et al. Physiologic evaluation of non-invasive pressure support ventilation in trauma patients with acute respiratory failure. Intensive Care Med. 1998;24(8):785−90. https://doi.org/10.1007/s001340050666.
8. Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit. Care Med. 2005;33(11):2465−70. https://doi.org/10.1097/01.ccm.0000186416.44752.72.
9. Spoletini G, Cortegiani A, Gregoretti C. Physiopathological rationale of using high-flow nasal therapy in the acute and chronic setting: a narrative review. Trends Anaesth. Crit. Care. 2019;26-27:22−9.
10. Cortegiani A, Crimi C, Sanfilippo F, et al. High flow nasal therapy in immunocompromised patients with acute respiratory failure: a systematic review and meta-analysis. J. Crit. Care. 2019;50:250−6. https://doi.org/10.1016/j.jcrc.2018.12.015.

11. Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am. J. Respir. Crit. Care Med. 2014;190(3):282—8. https://doi.org/10.1164/rccm.201402-0364OC.
12. Frat J-P, Brugiere B, Ragot S, et al. Sequential application of oxygen therapy via high-flow nasal cannula and noninvasive ventilation in acute respiratory failure: an observational pilot study. Respir. Care. 2015;60(2):170—8. https://doi.org/10.4187/respcare.03075.
13. Thille AW, Muller G, Gacouin A, et al. Effect of postextubation high-flow nasal oxygen with noninvasive ventilation vs high-flow nasal oxygen alone on reintubation among patients at high risk of extubation failure: a randomized clinical trial. JAMA. 2019;322 (15):1465—75. https://doi.org/10.1001/jama.2019.14901.
14. Halub ME, Spilman SK, Gaunt KA, et al. High-flow nasal cannula therapy for patients with blunt thoracic injury: a retrospective study. Can. J. Respir. Ther. 2016;52(4):110—3.
15. Vaschetto R, Longhini F, Persona P, et al. Early extubation followed by immediate noninvasive ventilation vs. standard extubation in hypoxemic patients: a randomized clinical trial. Intensive Care Med. 2019;45(1):62—71. https://doi.org/10.1007/s00134-018 -5478-0.
16. Vaschetto R, Pecere A, Perkins GD, et al. Effects of early extubation followed by noninvasive ventilation versus standard extubation on the duration of invasive mechanical ventilation in hypoxemic non-hypercapnic patients: a systematic review and individual patient data meta-analysis of randomized controlled trials. Crit. Care. 2021;25:189. https://doi.org/10.1186/s13054-021-03595.
17. Racca F, Appendini L, Berta G, et al. Helmet ventilation for acute respiratory failure and nasal skin breakdown in neuromuscular disorders. Anesth. Analg. 2009;109(1):164—7. https://doi.org/10.1213/ane.0b013e3181a1f708.

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Received 3 March 2022; Accepted 16 June 2022
Available online 16 September 2022

Pulmonology 29 (2023) 83—84

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Should there be a tailored guided management plan for children with post-infectious bronchiolitis obliterans and bronchiectasis?

Dear editor,

Current guidelines for chronic lung diseases such as cystic fibrosis (CF), Primary Ciliary Dyskinesia (PCD) and Bronchiectasis in children recommend regular and multidisciplinary monitoring to delay long—term pulmonary complications.[1-3]

Post-infectious Bronchiolitis Obliterans (PIBO) with or without Bronchiectasis is heterogeneous with diverse clinical expression and severity,[4-6] which contributes to the lack of specific guidelines for monitorization of disease progression and precludes the design of management plans after diagnosis is established.

We aimed to describe the management plans of children with PIBO and/or Bronchiectasis in a tertiary care hospital and analyse whether the variability of care depends on the severity of the obstructive ventilatory defect as determined by FEV_1.

A retrospective chart review of children with PIBO and/or bronchiectasis followed in a tertiary care paediatric hospital was undertaken. Diagnosis was based on clinical history and thoracic computed tomography (CT) findings. All patients followed for two consecutive years (2018-19) were included. Children with otherwise etiological diagnosis like CF or PCD were excluded. The frequency (average per year) of respiratory physician visits, physiotherapy prescription (including education in the management of airway clearance), number of spirometric evaluations, anthropometric assessments and number of microbiological samples taken for bacterial culture were registered.

At our centre, spirometry is performed in cooperative patients older than 4 years of age in accordance with ERS/ATS guidelines. Analysis of height, weight, and BMI z—scores (standard scores) taken from the spirometry records and standardized using WHO reference values was completed. The best FEV_1 and FEV_1/FVC results for the calendar year were collected for all patients who performed good quality tests and averaged for analysis.

Respiratory microbiology surveillance (frequency of testing) was determined from medical record as was referral rates to physiotherapy services. The number of samples (sputum or cough swabs) analysed in a calendar year was counted and averaged.

A descriptive analysis for continuous variables was done and described as median (min and max). Linear regression analysis between average number of physician visits per year and FEV_1 z-score was performed.

During the study period, 28 children were observed (Table 1). Only four had respiratory samples collected (all with bronchiectasis). During this period, three non-residents in Portugal were observed, seven patients initiated follow-up, four were transferred and three lost to follow-up.

Fourteen (50%) had been prescribed mucus clearance devices or educated on respiratory clearance manoeuvres. Three patients with PIBO (plus bronchiectasis in two) are currently on long term oxygen (FEV_1 z-score ranged from -5.0 and -5.7).

No association between clinic visits, clearance methods or other follow-up measures described and FEV_1 z-score was found.

This study shows that patients with PIBO and/or bronchiectasis had an average of 2.7 physician appointments and performed 2/1.5 spirometries per year. Respiratory microbiology surveillance was low and only half had some record for respiratory rehabilitation or use of mucus clearance devices.

In this sample, lung function alone did not affect follow-up. However, the lack of association may be due to small sample size, presence of outliers and shared follow-up with local hospitals.

Despite the limitations and biases of our retrospective analysis, we can assume that the management plan of these children is heterogeneous, with regular physician appointments and spirometry, but low respiratory microbiology surveillance and no standard physiotherapy or nutritional consultations.

In our setting, patients with PCD, PIBO and/or bronchiectasis are managed by respiratory physicians in a general respiratory clinic without a formal multidisciplinary team. Allied health services are available on request and require a separate appointment. There are no internal or national guidelines for the management of these conditions concerning frequency of visits, lung function testing, collection of respiratory samples for bacterial culture, nutritional assessment, timing of imaging by CT or referral to respiratory physiotherapists. By comparison, at the same centre, patients with CF are seen at least every three months by a multidisciplinary team according to international recommendations.

https://doi.org/10.1016/j.pulmoe.2022.07.009

Table 1 Description of Patients' characteristics.

	Post-Infectious Bronchiolitis Obliterans n=16 (PIBO plus bronchiectasis 6)	Bronchiectasis n=12
Median age at last appointment (in years)	12.5 (7.1, 18.2)	14.1 (8.2, 17.9)
Male gender (n)	12	8
Median duration of follow-up (in years)	10.0 (2.5, 15.4)	8.1 (2.5, 14.4)
Average number of physician visits per year (range)	2.66 (1, 6)	2.67 (1, 6)
Average number of spirometries performed per year	2.00 (1, 4)	1.46 (1, 4)
Average BMI z-score	−0.69	0.36
Average FEV_1 z-score	−3.24	−0.54
Average FEV_1/FVC z-score	−2.57	−0.11

Legend: results are shown as median (min. and max.) or average (range).
PIBO: Post-Infectious Bronchiolitis Obliterans; BMI: Body Mass Index; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; z-score: standard score.

The clinical course of children with PIBO and/or bronchiectasis can be less predictable and differs from CF and PCD. While some children have serious structural and functional lung disease, others experience more subtle effects.[5-7] These heterogeneous characteristics are due to aetiology and age at diagnosis/referral to tertiary centres. Furthermore, some of these children tend to stabilize or even improve their overall status, including lung function results, over time.[5,6]

For adult patients with Chronic Obstructive Pulmonary Disease, routine follow-up is essential. It focuses on symptoms, exacerbations, objective measures of airflow limitations and identifying complications and/or comorbidities.[8] However, for children it can be on reversing the disease when possible and halting its progress.[3] Furthermore, integrated care needs to be individualized to the developmental stage of the child and the family's health literacy.

Extrapolating from standards of care for other complex chronic lung diseases could preserve lung function, reduce exacerbations, improve quality of life, prevent nutritional decline, and enhance survival for patients with PIBO and/or bronchiectasis. Since these are rare entities, there is little evidence to advise on their management. Future directions should dictate more precise standards of care tailored by severity, rate of exacerbations, decline of lung function and minimal follow-up requirements.

References

1. Villanueva G, Marceniuk G, Murphy MS, Walshaw M, Cosulich R. Guideline Committee. Diagnosis and management of cystic fibrosis: summary of NICE guidance. BMJ. 2017;359:j4574 https://doi.org/10.1136/bmj.j4574.
2. Shapiro AJ, Zariwala MA, Ferkol T, Davis SD, Sagel SD, Dell SD, et al. Genetic Disorders of Mucociliary Clearance Consortium. Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD foundation consensus recommendations based on state of the art review. Pediatr Pulmonol. 2016;51(2):115−32. https://doi.org/10.1002/ppul.23304.
3. Chang AB, Fortescue R, Grimwood K, Alexopoulou E, Bell L, Boyd J, et al. European Respiratory Society guidelines for the management of children and adolescents with bronchiectasis. Eur Respir J. 2021;58(2):2002990. https://doi.org/10.1183/13993003.02990-2020.
4. Jerkic SP, Brinkmann F, Calder A, Casey A, Dishop M, Griese M, et al. Postinfectious bronchiolitis obliterans in children: diagnostic workup and therapeutic options: a workshop report. Can Respir J. 2020;2020:5852827. https://doi.org/10.1155/2020/5852827.
5. Castro-Rodriguez JA, Giubergia V, Fischer GB, Castaños C, Sarria EE, Gonzalez R, et al. Postinfectious bronchiolitis obliterans in children: the South American contribution. Acta Paediatr. 2014;103(9):913−21. https://doi.org/10.1111/apa.12689.
6. Colom AJ, Teper AM. Post-infectious bronchiolitis obliterans. Pediatr Pulmonol. 2019;54(2):212−9. https://doi.org/10.1002/ppul.24221.
7. Bandeira T, Negreiro F, Ferreira R, Salgueiro M, Lobo L, Aguiar P, et al. Clinical, radiological, and physiological differences between obliterative bronchiolitis and problematic severe asthma in adolescents and young adults: the early origins of the overlap syndrome? Pediatr Pulmonol. 2011;46(6):573−80. https://doi.org/10.1002/ppul.21405.
8. Global Strategy for the Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Available from: http://www.goldcopd.org/ [September 2021].

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Received 5 March 2022; Accepted 18 July 2022
Available online 16 September 2022

Pulmonology 29 (2023) 85—88

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LETTER TO THE EDITOR

Idiopathic pulmonary fibrosis mortality in the Italian epicenter of COVID-19 pandemic

To the Editor,

Idiopathic pulmonary fibrosis (IPF) is a progressive, life-threatening interstitial pneumonia of unknown cause[1], affecting elderly, frail individuals with a median age at diagnosis of 66[1] and a median estimated survival of 2.5—3.5 years after diagnosis.[2-3]

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) rapidly spread worldwide and the absence of effective therapies or vaccines at the beginning of the pandemic led Governments to enforce strict measures in their efforts to limit the virus transmission.[4] On March, 9th 2020 Italy went into a full lockdown. In parallel, hospital infrastructures were redirected towards maximizing intensive care resources which resulted in routine clinical practice, including IPF outpatient clinics, being considerably reduced.[5]

The aim of our study was to assess the mortality of IPF patients included in the cohort of the tertiary outpatient IPF clinic at the "San Gerardo" Hospital, located in Monza (Lombardy, the most populated Italian region) in relation to the social and healthcare changes due to COVID-19 pandemic.

We analyzed a cohort of 212 patients recruited between May 2008 and April 2021 and alive on January 1st 2018. We recorded mortality data comparing the characteristics between patients who died in January 1st, 2018 and February 28th, 2020 (pre-pandemic and pre-lockdown period) to those who died between March 1st, 2020 and April 30th, 2021 (pandemic and post-lockdown period) using Chi-square or Fisher's exact tests for categorical variables and Mann—Whitney U test for continuous ones. Thereafter, we computed monthly average crude mortality rates for each of the

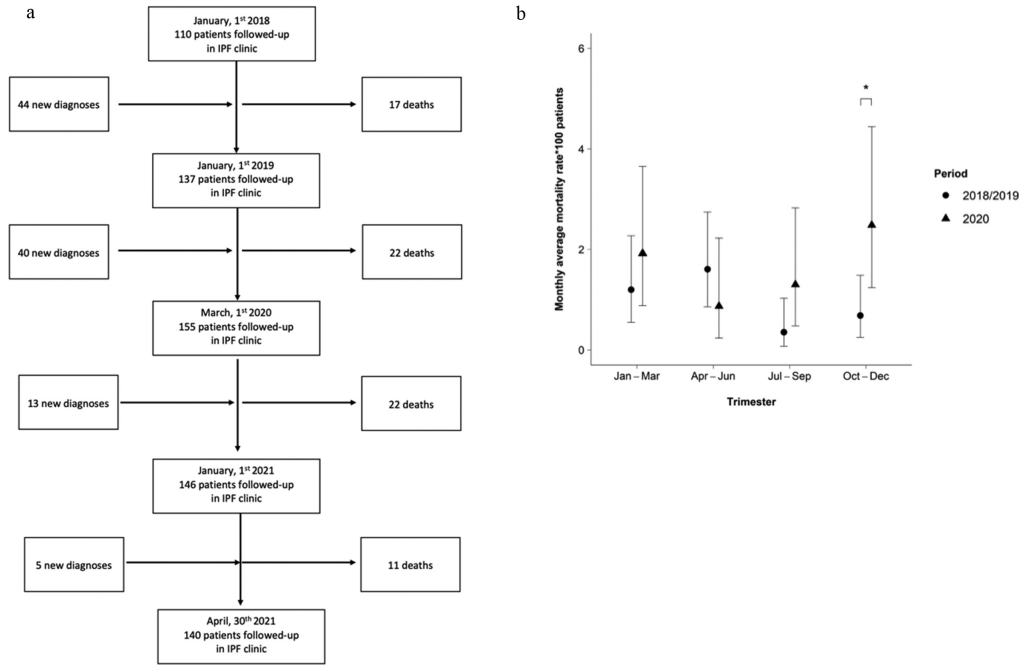

Fig. 1. **(a)** Study flow chart; **(b)** Trimestral-specific comparison of the monthly average mortality rate in 2018/2019 and in 2020 (2-sided tests) * p-value 2-sided test <0.05. IPF= idiopathic pulmonry fibrosis.

https://doi.org/10.1016/j.pulmoe.2022.04.002

Table 1 Demographics and clinical characteristics of study population.

	Death		Total	p-value
	Before March 3rd 2020	On or after March 3rd 2020		
N subjects	39	33	72	
Year of death - N(%)				
2018	17(43.59)	0(0.00)	17(23.61)	
2019	14(35.90)	0(0.00)	14(19.44)	
2020	8(20.51)	22(66.67)	30(41.67)	
2021	0(0.00)	11(33.33)	11(15.28)	
Males - N(%)	35(89.74)	30(90.91)	65(90.28)	1
Age at death - Median (Q1-Q3)	73(68 - 78)	79(72 - 82)	74(69 - 81)	0.0311
Time between last visit and death (months) - Median (Q1-Q3)	4(3 - 9)	6(3 - 9)	5(3 - 9)	0.2651
Disease duration# at death (months) - Median (Q1-Q3)	36(19 - 60)	35(25 - 58)	36(23 - 59)	0.4834
Age at diagnosis - Median (Q1-Q3)	69(65 - 75)	75(68 - 78)	71(67 - 77)	0.0588
FVC% of predicted* — Median (Q1-Q3)	67(56 — 77)	62(52 — 76)	64(52 - 77)	0.4834
DLCO% of predicted* — Median (Q1-Q3)	29(21 — 34)	26(16 — 39)	29(19 - 35)	0.2180
GAP index* — N (%)				0.9692
Stage 1	1(2,56)	1(3,03)	2(2,78)	
Stage 2	20(51,28)	16(48,48)	36(50,0)	
Stage 3	18(46,15)	16(48,48)	34(47,22)	
Antifibrotic therapy at death - N(%)				0.2118
No	12(30.77)	5(15.15)	17(23.61)	
Yes	21(53.85)	19(57.58)	40(55.56)	
Previous, but interrupted	6(15.39)	9(27.27)	15(20.83)	
Months between interruption and death - Median (Q1-Q3)	*19.0(9.4)*	*23.3(17.3)*	*21.6(14.4)*	*0.8596*
Nintedanib	*12(30,77)*	*10(30,30)*	*20(27,78)*	
Pirfenidone	*9(23,08)*	*9(27,27)*	*18(25,00)*	
Comorbidities - N(%)	29(74.36)	27(81.82)	56(77.78)	
Combined pulmonary fibrosis and emphysema	10(25.64)	6(18.18)	16(22.22)	0.4481
Obstructive sleep apnea syndrome	4(10.26)	1(3.03)	5(6.94)	0.3662
Coronary artery disease	13(33.33)	12(36.36)	25(34.72)	0.7878
Chronic Heart Failure	6(15.39)	5(15.15)	11(15.28)	0.9781
Pulmonary hypertension	11(28.21)	17(51.52)	28(38.89)	0.0432
Gastroesophageal reflux disease	11(28.21)	8(24.24)	19(26.39)	0.7038
Lung cancer (active)	1(2.56)	1(3.03)	2(2.78)	1
Type 2 diabetes	11(28.21)	10(30.30)	21(29.17)	0.8453
Hypothyroidism	2(5.13)	0(0.00)	2(2.78)	0.4965

DLCO= diffusing capacity for carbon monoxide; FVC= Forced Vital Capacity; GAP= Gender-Age-Physiology

two periods, with related exact 95% confidence intervals (95%CIs) based on a Poisson distribution, and we compared them through incidence rate ratios (IRR). Similarly, we computed trimestral-specific monthly average mortality rates for the biennium 2018-2019, and we compared them with those of 2020. Person-time at risk (in months) was computed for each subject from January, 1st 2018 or the day of IPF diagnosis, until death or the end of the period of interest. 95%CIs for IRR were based on the exact distribution of the rate of two Poisson counts, as well as 2-sided p-values. All analyses were performed using SAS version 9.4 (The SAS institute, Cary, NC) and R version 4.0.3 (R Core Team, Vienna, Austria) with the packages epitools and rateratio. test. The study received Ethics Committee approval (ASST Monza, 1538, November 14th 2019).

In the pre-lockdown period, we documented 39 deaths in our IPF cohort; in contrast, in the post-lockdown period, 33 IPF patients died (Fig. 1a). We observed a significantly younger median age at death and a trend toward younger median age at diagnosis in the pre-lockdown compared to the post-lockdown period with similar median disease duration, pulmonary function tests and severity of the disease evaluated through Gender-Age-Physiology (GAP) index (Table 1). We did not detect statistically significant differences regarding gender or antifibrotic treatment. The burden of comorbidities was similar between the two groups with the exception of pulmonary hypertension that was more common in the post-lockdown period.

We estimated that monthly average mortality rates rose from 1.03 per 100 person-months (95%CI: 0.72-1.42) during

the pre-lockdown period to 1.67 (95%CI: 1.17-2.33) post-lockdown: such increase was borderline significant, corresponding to an IRR of 1.63 (95%CI: 1.00-2.66, p=0.05). In detail, comparing the various trimestral periods, we observed a statistically significant increase in mortality in the last trimester (October/December) of 2020, as compared to the last trimester 2018: monthly average mortality rates increased from 0.68 (95%CI: 0.25-1.48) to 2.48 (1.24-4.44) per 100 person-months (IRR: 3.64, 95%CI: 1.24-12.00, p=0.008, Fig. 1b).

In the lockdown periods, patients included in our IPF cohort were regularly followed-up with telephone calls and continuously received antifibrotic treatment. Asking family members, we were able to determine that 3 out of 33 patients (9.1%) were hospitalized and died because of a confirmed diagnosis of Coronavirus disease (COVID-19) and that the great majority, 30/33 (90.9%), died at home or in long-term facilities without signs or symptoms suggestive of COVID-19.

This study showed a significant increase in mortality in our IPF cohort during the post-lockdown period that, in most of the cases, did not appear directly related to COVID-19.

In line with our results, *Marcon and colleagues* showed an excess of IPF-related deaths during the first wave of the COVID-19 pandemic.[6] However, the authors did not differentiate between deaths directly related to COVID-19 and other etiologies.

In our study, we observed a marginally significant increase in mortality during post-lockdown period compared to pre-lockdown. We believe that the increase in mortality is mainly related to the increased frailty and to limitation of access to the IPF Referral Center for a worsening of the disease during the peak of the pandemic. This is corroborated by the results of the trimestral analysis which shows an increase in the period of the COVID-19 second wave (October/December 2020), when our province (Monza-Brianza) reached the highest level of incidence of SARS-CoV-2 infection.

In our study, a number of limitations should be acknowledged. The cause of death was not confirmed for the majority of the patients. Moreover, this study was performed in a single center, limiting the generalizability of the results. Finally, given the small sample size, we were not able to run a Cox-analysis that would have been the best way to address the risk factors for mortality adjusting for possible confounders.

In conclusion, we report a statistically significant increase in mortality within our IPF cohort during the COVID-19 second wave. To the best of our knowledge, only in a minority of patients was the cause of death directly related to SARS-CoV-2 infection. In most patients, the cause of death was possibly related to the limitations to reaching the hospital and ILD-physicians of the IPF referral Center in relation to the COVID-19 pandemic in case of worsening of the disease.

Authors' contributions

FL is the guarantor of this research. PF, SC, GF, FM, LGM and FL were responsible for study concept and design. PF, SC, GF, FM and FL contributed to data acquisition. PF, SC, GF, FM, LGM and FL performed data analysis. PF, SC, GF, FM, ER, LGM and FL contributed to the drafting of this manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study received Ethics Committee approval (ASST Monza, 1538, November 14th 2019).

Consent for publication

Written informed consent was waived given the retrospective design of the study.

Conflicts of interest

The authors have no conflicts of interest to declare.

Avalilability of data and materials

Individual participant data referring to this article (i.e. text, tables and figures) will be made available upon reasonable request. The study protocol will be made available for researchers who provide a methodologically sound proposal. Proposals should be directed to paola.faverio@unimib.it

Acknowledgments

We acknowledge that this research was partially supported by the Italian Ministry of University and Research (MIUR)—Department of Excellence project PREMIA (PREcision MedIcine Approach: bringing biomarker research to clinic).

Funding sources

The authors have no funding to declare.

References

1. Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. Lancet. 2017;389(10082):1941−52. https://doi.org/10.1016/S0140-6736(17)30866-8.
2. Ley B, Collard HR, Jr King TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183(4):431−40. https://doi.org/10.1164/rccm.201006-0894CI.
3. Vancheri C, Failla M, Crimi N, Raghu G. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. Eur Respir J. 2010;35(3):496−504. https://doi.org/10.1183/09031936.00077309.
4. Koh WC, Alikhan MF, Koh D, Wong J. Containing COVID-19: Implementation of early and moderately stringent social distancing measures can prevent the need for large-scale lockdowns. Ann Glob Health. 2020; 86 (1): 88. https://doi.org/10.5334/aogh.2969.
5. Weisel KC, Morgner-Miehlke A, Petersen C, et al. Implications of SARS-CoV-2 infection and COVID-19 crisis on clinical cancer care: report of the university cancer center hamburg. Oncol Res Treat. 2020;43(6):307−13. https://doi.org/10.1159/000508272.

6. Marcon A, Schievano E, Fedeli U. Mortality associated with idiopathic pulmonary fibrosis in Northeastern Italy, 2008-2020: a multiple cause of death analysis. Int J Environ Res Public Health. 2021;18(14):7249. https://doi.org/10.3390/ijerph18147249.

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Received 12 March 2022; Accepted 1 April 2022
Available online 12 April 2022

Pulmonology 29 (2023) 89—91

PULMONOLOGY

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LETTER TO THE EDITOR

Endobronchial hamartoma — A 10-year retrospective analyses of bronchoscopy treatment

Dear editor,

Endobronchial hamartoma (EH) represents nearly 10% of all lung hamartomas, the most common benign lung tumour.[1] Although benign, hamartoma has been linked with lung cancer and very occasionally can evolve to a malignant lesion.[1,2] They are rare, slow growing, usually single tumours, often symptomatic, unlike intraparenchymal hamartomas.[2,3] Obstructive pneumonia and hemoptysis are the most frequent symptoms. However, wheezing, dyspnea and cough might be the only signs present, mimicking other conditions like asthma.[2,4] Clinical suspicion should be raised when symptoms persist, and patients offered a chest computed tomography and bronchoscopy. As EH is often symptomatic, treatment is frequently indicated.[3]

The authors intend to retrospectively analyse all cases of EH diagnosed from 2011 until mid-2021, in a tertiary hospital in Porto, Portugal. This study was approved by the hospital ethics committee (number 226/2021) on 21st September 2021. The ethics committee considered the exemption from Informed Consent to be acceptable.

During the study period, EH was diagnosed in 14 patients. Eleven patients (78.6%) were male, with a median age of 61.50 years (IQR 57.75—72.0), 71.4% were current or former smokers.

Eight patients presented respiratory symptoms that prompted endoscopic evaluation: recurrent respiratory infections (n = 4), nonresolving pneumonia (n = 2) and hemoptysis (n = 2). In the remaining six patients, EH diagnosis was incidental.

It was an incidental radiological finding in two patients who underwent thoracic/abdominal computed tomography for other reasons (chest trauma and acute cholecystitis) that revealed an endobronchial lesion. The additional four cases were incidental endoscopic findings: two patients with concurrent lung cancer (EH and neoplasm were in different lobes), one patient who underwent bronchoscopy to exclude lung metastases (rectal adenocarcinoma), and one patient with suspected airway compression by Kommerell's diverticulum.

Concerning EH location in the tracheobronchial tree, it was more frequently found in the right bronchial tree (n = 8) — Fig. 1. The lesion was often described as having smooth and regular surface, without signs of deep invasion, and sometimes with polypoid features — Fig. 2A—C.

Histological aspects provided more accurate classification of hamartomas, describing six cases of chondroid hamartoma and only one case of lipoid hamartoma, in seven cases no predominant cellular component was described (Fig. 2D).

Excluding two patients with concurrent lung cancer, eight of the 12 patients (66.7%) presented significant bronchial obstruction: main bronchus obstruction (n = 1), lobar bronchus obstruction (n = 5) and segmental bronchus obstruction (n = 2).

Ten patients needed endoscopic treatment to restore acceptable bronchial patency. Mechanical debridement plus laser photoresection were used in six cases, and only mechanical debridement was necessary in the remaining four cases. In two patients, mechanical debridement was performed through flexible bronchoscopy due to segmental

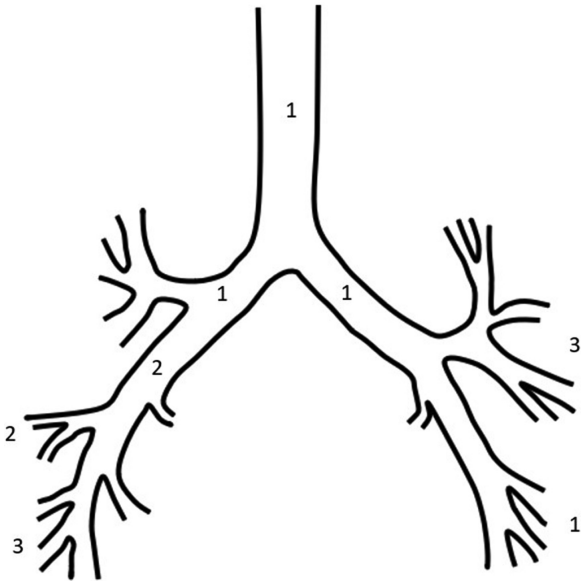

Fig. 1. Location of the 14 EHs in the tracheobronchial tree: trachea - 1; right main bronchus - 1; intermediate bronchus - 2; middle lobe bronchus - 2; right lower lobe bronchus - 3; left main bronchus - 1; left upper lobe bronchus - 3; and left lower lobe bronchus - 1.

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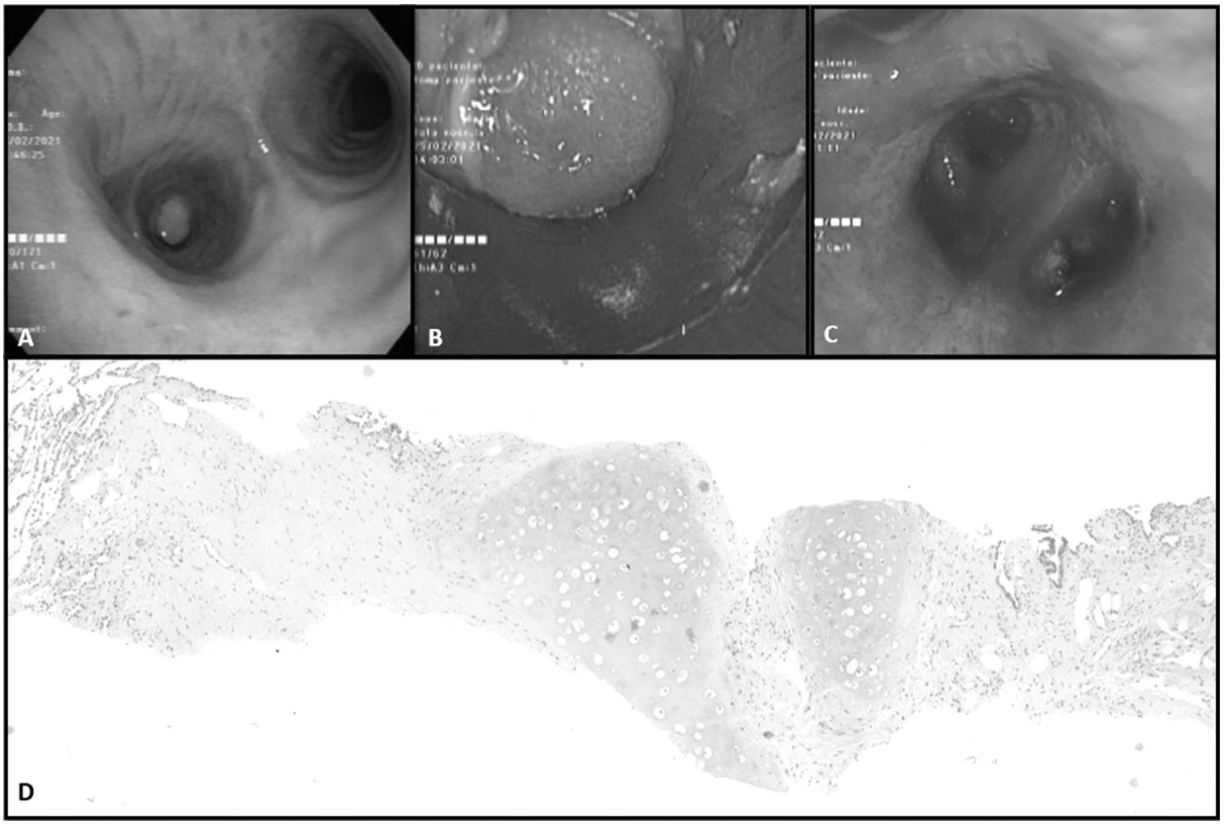

Fig. 2. An example of an endobronchial hamartoma totally occluding the intermediate bronchus (Fig. 2. A, B); and later, after treatment by rigid bronchoscopy - mechanical debridement and laser (Fig. 2. C). Endobronchial hamartoma biopsy showing endobronchial epithelium, adipose tissue and hyaline cartilage [H&E; x10] (Fig. 1.D).

lesions. All other eight patients underwent rigid bronchoscopy. Total EH resection was accomplished in half of the patients (n = 5).

One rigid bronchoscopy, performed due to total middle lobar bronchus obstruction, was complicated by pneumomediastinum and pneumothorax with no need for drainage. In this case, bronchial perforation could not be excluded, though it was not recognized during bronchoscopy. No other complications were registered.

One patient needed a second endoscopic procedure. Another patient with partial resection after mechanical debridement and laser, who maintained recurrent respiratory infections, underwent lobectomy with clinical resolution and no complications.

For the 13 patients not needing surgery, follow-up until now or until death (median time of 3.50 years (IQR 0.88-5.50)) showed no EH recurrence and no need for further endoscopic treatment.

EH management must be individualised depending on features and location of the hamartoma, symptoms, fitness and preference of the patient.[3,4]

Bronchoscopy plays an essential part in EH diagnosis, providing its precise location in the airway and biopsy.[4]

Still, bronchoscopy role in EH treatment is not less relevant, having replaced surgery as the first choice for management of EH given diagnosis confirmation and healthy lung parenchyma.[5]

EH resection is usually performed by rigid bronchoscopy, since it assures airway patency and ventilation, the use of different tools and techniques and easier control of bleeding or other complications, if necessary. Laser, electrocautery, argon plasma coagulation and cryoablation, combined with mechanical debridement, have been used in EH resection with effective results.[2]

In particular cases, flexible bronchoscopy may be preferred, as in more distal lesions, if the patient is not suitable for rigid bronchoscopy or it is not available.[2] However, the rate of recurrence associated with flexible bronchoscopy resection is superior to rigid bronchoscopy.[5]

Compared to surgery, endoscopic resection is a less invasive procedure, presents better mortality and allows sparing of healthy lung. The most frequent complication of bronchoscopy treatment is pneumothorax, still overall morbidity is low.[5]

EH presents a low recurrence rate, superior after endoscopic treatment compared to surgical treatment. Long term endoscopic surveillance guided by clinical and radiological features is advised.[5]

Altogether, the benefits of endoscopic resection seem to outweigh those of surgical treatment. Surgery is usually reserved for cases with long-standing bronchial obstruction with irreversible parenchymal damage, non-resolving symptoms or when malignancy cannot be excluded.[2]

In conclusion, endoscopic resection is the first choice in EH treatment since excellent results can be achieved in centres of expertise.

Recurrence and malignancy development, though infrequent, may occur and so, follow-up should be ensured.[2]

Conflicts of interest

The authors have no conflicts of interest to declare

References

1. Yildirim BB, Karalezli A, Er M, et al. Endobronchial hamartoma. J Bronchol Interv Pulmonol. 2011;18:355—8. https://doi.org/10.1097/LBR.0b013e318232ff0e.
2. Cosío BG, Villena V, Echave-Sustaeta J, et al. Endobronchial hamartoma. Chest. 2002;122:202—5. https://doi.org/10.1378/chest.122.1.202.
3. Bishnoi S, Asaf BB, Vijay CL, Kumar A. Surgical management of endobronchial hamartoma. Lung India. 2018;35:179—81. https://doi.org/10.4103/lungindia.lungindia_209_17.
4. Dimitrakakis G, et al. The challenge of pulmonary endobronchial chondromatous hamartomas. JBUON. 2014;19(1):60—5.
5. Abdel Hady SM, Elbastawisy SE, Hassaballa AS, Elsayed HH. Is surgical resection superior to bronchoscopic resection in patients with symptomatic endobronchial hamartoma? Interact Cardio-Vasc Thorac Surg. 2017. https://doi.org/10.1093/icvts/ivw443.

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Received 25 March 2022; Accepted 10 July 2022
Available online 15 September 2022

Pulmonology 29 (2023) 92—93

PULMONOLOGY

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LETTER TO THE EDITOR

A potentially life-threatening complication of lung metastasis thermal-ablation

Dear Editor

Pulmonary metastases are complications of multiple malignancies due to haematogenic or lymphatic spread. Most patients who develop pulmonary metastases cannot be cured; however, despite the absence of randomized controlled trials on the subject, in selected cases metastasectomy can be a therapeutic option. Apart from surgery, other treatment options include pharmacologic treatment according to the primary malignancy or various ablative techniques, such as stereotactic radiosurgery and image-guided thermal ablation.[1] Data on feasibility and potential complications of ablative techniques is lacking, despite their potential severity, as presented in this case.

The authors present a case of a 64 year-old female patient, with metastatic parathyroid carcinoma, who underwent thermal ablation of pulmonary metastasis due to hypercalcemia refractory to medical treatment with denosumab. She had previously been submitted to two lung metastasis thermal ablations, leading to improved calcium levels' control, while the oncological disease remained stable. She had no other relevant past medical history.

Eight days after this new procedure, the patient was admitted to the emergency room (ER) due to retrosternal pain and dyspnoea of one day of duration. She also complained of swallowing problems in the cervical region.

At the ER presentation, vital signs were normal: blood pressure 120/80 mmHg, respiratory rate of 18 breaths/min, heart rate of 90 beats/min, and an oxygen saturation of 93% on room air. On pulmonary auscultation, there were crackles on the right hemithorax and lung sounds were lowered on the all hemithorax, and inaudible on the right lower third. Inspection revealed a swollen neck with subcutaneous emphysema on the cervical, right chest and arm areas.

Laboratory analysis at the ER: Arterial blood gas analysis (FiO_2 50%): pH of 7.35, $PaCO_2$ of 29,1 mm Hg, PaO_2 of 72 mm Hg, and bicarbonate of 15,9 mEq/L. Ionized serum calcium levels were 1,37 mmol/L. Hemogram, urea, creatinine, and thyroid function test results were within normal limits. Chest CT revealed two pulmonary cavities on the right upper and middle lobes, a fistulous trajectory to the thoracic wall and broncho-pleural fistula. There was also pneumomediastinum and signs of right lower lobe consolidation and pleural effusion (Fig. 1).

Due to the patient stability and exuberant radiologic findings, the patient was admitted for surveillance. A diagnosis of pleuro-parenchymal fistula and pneumomediastinum after thermal lung metastasis ablation was made.

The patient started large-spectrum antibiotics and chest drainage of the right lower pleural effusion was performed. After 3 weeks of antibiotics (Piperacillin-Tazobactam) and clinical improvement, a bronchoscopy was performed that confirmed a broncho-pleural fistula. Microbiologic cultures from the pleural fluid, sputum and bronchial lavage were negative. No respiratory failure was documented. The chest tube was removed after 3 days.

After 26 days, the patient was discharged with oral antibiotic treatment with Amoxicillin-Clavunate 875/125 mg until completion of 6 weeks treatment. No surgical intervention was necessary. Due to patient's preference, limited respiratory function, technical impairments or age / comorbidities, surgery was not an option.

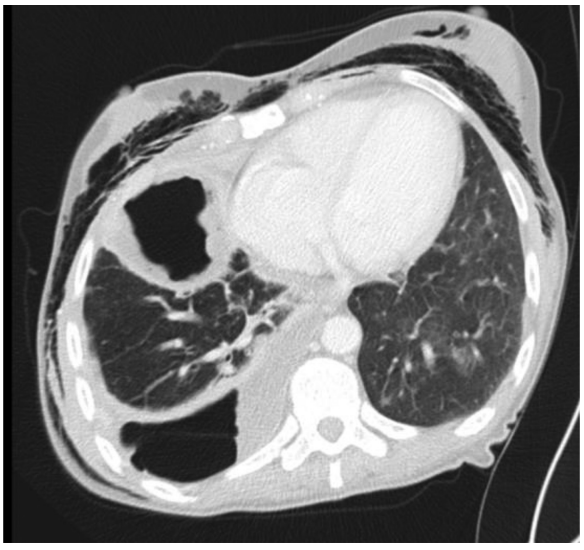

Fig. 1 Subcutaneous emphysema, right lung cavitation and hydropneumothorax at admission.

https://doi.org/10.1016/j.pulmoe.2022.06.007

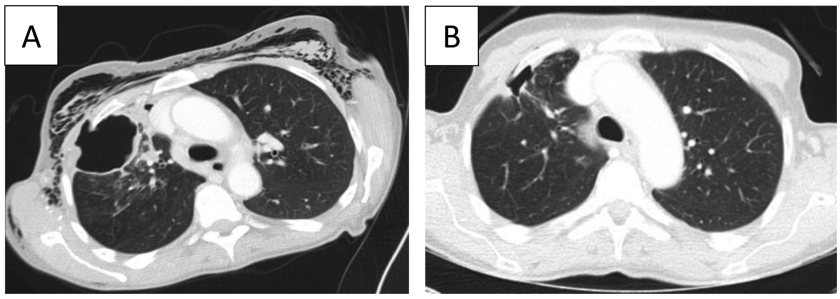

Fig. 2 Evolution of Chest CT findings. A- CT at admission with a right upper lobe (RUL) cavitary lesion with a chest wall fistula. Extensive subcutaneous emphysema. B- CT after 2 months, revealing improvement of the lung cavitation and fistula on the RUL and no subcutaneous emphysema. The metastatic lesion submitted to thermal ablation is not present.

Follow-up CT at 2 months revealed marked improvement (Fig. 2) and the patient was able to return to daily activities with no residual symptoms.

Thermal ablation techniques include radiofrequency, microwave and cryotherapy, with the first being the most commonly used. A recent review estimated that the overall survival at 5 years after the procedure ranged from 32% to 65%, due to different criteria in terms of number of metastasis, location and ECOG status of patients.[2] Chemotherapy-free survival is an important factor to take into account, with good results for thermal ablation in lung metastasis from colorectal cancer.[3]

The main complication reported is pneumothorax in up to 72% of procedures, leading to drainage in 13−47% of cases.[4] One of the strategies to reduce complications is a better recognition of the indications: absence of extra-pulmonary metastasis and <3 pulmonary metastasis appears to be related to better patient outcomes.[3−5] Other reports suggest that thermal ablation is an alternative particularly in patients with less than 5 metastasis and maximum size of 30 mm.[4]

Outcomes vary according to the primary tumor site.[2,3] A review in colo-rectal metastasis revealed a good local control and prolonged time to systemic chemetherapy.[4] Reports show that repeated ablation can improve local control.[5,6]

In this patient, endocrinology, oncology and radiology multidisciplinary assessment decided to perform thermal ablation due to persistent hypercalcemia despite denosumab, with two previous successful procedures managing to reduce serum calcium levels. The central location and size of the metastasis can explain the complication. Despite its exuberant presentation, a watchful strategy with antibiotics was preferred due to the risks associated with thoracic surgery or immediate bronchoscopy interventions. There was a progressive reduction of the cavity size and resolution of the pneumomediastinum and subcutaneous emphysema.

In conclusion, this case represents a potential fatal complication of thermal lung ablation and how a close follow-up, management and multidisciplinary discussion could prevent further complication. A careful selection of patients for thermal lung ablation is warranted.

References

1. Grippi MA. 278 contributing authors from 12 countries. Fishman's pulmonary diseases and disorders. 5th ed New York: McGraw-Hill Medical; 2015 Chapter 119 - pulmonary metastases: the role of surgical resectionISBN-13: 978-0071807289.
2. Pereira PL, Masala S. Cardiovascular and Interventional Radiological Society of Europe (CIRSE). Standards of practice: guidelines for thermal ablation of primary and secondary lung tumors. Cardiovasc. Intervent. Radiol. 2012;35(2):247−54. https://doi.org/10.1007/s00270-012-0340-1.
3. Yamakado K, Inoue Y, Takao M, Takaki H, Nakatsuka A, Uraki J, et al. Long-term results of radiofrequency ablation in colorectal lung metastases: single center experience. Oncol. Rep. 2009;22(4):885−91. https://doi.org/10.3892/or_00000513.
4. Delpla A, de Baere T, Varin E, Deschamps F, Roux C, Tselikas L. Role of thermal ablation in colorectal cancer lung metastases. Cancers (Basel). 2011;13(4):908. https://doi.org/10.3390/cancers13040908.
5. Fonck M, Perez JT, Catena V, Becouarn Y, Cany L, Brudieux E, et al. Pulmonary thermal ablation enables long chemotherapy-free survival in metastatic colorectal cancer patients. Cardiovasc. Interv. Radiol. 2018;41(11):1727−34. https://doi.org/10.1007/s00270-018-1939-7.
6. Hiraki T, Mimura H, Gobara H, Sano Y, Fujiwara H, Date H, et al. Repeat radiofrequency ablation for local progression of lung tumors: does it have a role in local tumor control? J. Vasc. Interv. Radiol. 2008;19(5):706−11. https://doi.org/10.1016/j.jvir.2007.12.441.

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Received 16 March 2022; Accepted 14 June 2022
Available online 18 July 2022

Pulmonology 29 (2023) 94—96

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LETTER TO THE EDITOR

Primary pleural lymphoma — A rare diagnosis

Dear Editor,

Primary pleural lymphoma is a rare disease, with few cases reported in literature and corresponding to 2.4% of the primary thoracic wall tumors. Diffuse large B cell lymphoma (DLBCL) is the most common subtype reported, accounting for approximately 30% of non-Hodgking's lymphomas.[1] Two types of primary pleural lymphomas were originally described in 1987, namely primary effusion lymphoma, principally associated to human immunodeficiency virus (HIV), and pyothorax-associated lymphoma, more related to human herpes virus-8 (HHV-8) infection and Ebstein-Barr virus (EBV) infection.[2,3] Pathogenesis has not yet been elucidated but may be related to chronic inflammation of pleura surface that stimulates B-cells lymphocytes uncontrolled proliferation, resulting in pleural lymphoma development. Underlying pleural disease, such as tuberculous pyothorax or pneumothorax, is one of the suggested causes. Other reported cases are associated with some degree of immunosuppression and autoimmune diseases, as vasculitis, or even previous thoracic trauma.[2,4] Clinical manifestations are unspecific, as the patient may present pleuritic chest pain, dyspnea, cough, fever, anorexia and weigh loss.[4] The diagnosis is based on histopathological evidence, using thoracic surgery or thoracoscopy.[5] The first choice of treatment is currently in discussion, but chemotherapy is the most frequently used.[4] Anthracycline-based chemotherapies combined with anti-CD20 monoclonal antibody rituximab, as cyclophosphamide, pirarubicin, vincristine and prednisolone (CHOP) can significantly improve survival, with complete response rate of 30-45%.[6] Cases of spontaneous remission are extremely rare, occurring with complete or partial resolution of the tumor without any treatment. The spontaneous remission mechanisms remain uncharacterized. A possible mechanism is the performance of pleural biopsy that generates a microtrauma and leads to an activation of pro-inflammatory state, alongside with enhanced immune recognition contributing to tumor control.[7]

The authors report a clinical case of a 52-year-old female, smoker of 40 pack-years, teacher, with exposure to asbestos in her workplace. The patient had history of osteoporosis and three episodes of pneumonia in adolescence. No history of tuberculosis (TB) or recent contacts with TB. No previous thoracic trauma. No chronic medication. She was referred to pulmonology consultation due to one-month evolution of right posterior pleuritic chest pain which was progressively worsening, with no relief factors. She had no dyspnea, cough, fever or constitutional symptoms. Chest computed tomography (CT) scan revealed macronodular pleural thickening in lower half of right hemithorax with contrast hyperenhancement, associated to moderate right pleural effusion; lymph nodes in azygos-esophageal recess, the largest one with 17 mm diameter, and centrilobular emphysema in upper lobes (Fig. 1). Blood count revealed normocytic normochromic anemia (hemoglobin 11.6 g/dL, MGV 87.3 fL, MCH 31.4 pg). Auto-immune study was normal. There was no evidence of HIV infection. Respiratory functional study was normal. Transthoracic needle aspiration biopsy of pleural nodules was performed, and histopathological exam revealed diffuse pattern of malignant neoplasm extensively occupying the pleural surface, morphologically and immunophenotypically compatible with DLBCL. Microbiology analysis of pleural biopsy was negative, namely Mycobacterium tuberculosis (MTB). EBV-encoded ribonucleic acid was also tested in the biopsy, and it was negative. Positron emission tomography (PET) scan showed slight uptake of fluor-18-fluorodesoxyglucose (FDG) in pleural nodules and pleural effusion, with no other alterations (Fig. 2). Given the diagnostic doubt and the awareness of a rare entity, a surgical biopsy was performed seven weeks later. During the surgery, there was no evidence of pleural effusion and only a 3 mm nodular area was found and biopsied, showing pleural fragments extensively occupied by malignant neoplasia. Immunohistochemical study was positive for CD20, bcl-2, bcl-6 and MUM-1, and negative for CD10. These findings agreed with DLBCL diagnosis. The patient was referred to hematology consultation and the PET scan was repeated three months later, showing total absence of uptake FDG lesions. The patient improved clinically, with no chest pain and normalization of blood count. Complete spontaneous remission of primary pleural lymphoma was admitted. The patient is currently on clinical surveillance without recurrence of the disease after one year of follow-up, confirmed by PET scan.

Pleural thickening or nodules associated with pleural effusion raised the hypothesis of an underlying neoplasm, namely pleural metastatic tumors or pleural mesothelioma, especially when exposures to asbestos is found, as in the present clinical case. Primary pleural DLBCL is a rare

https://doi.org/10.1016/j.pulmoe.2022.07.001

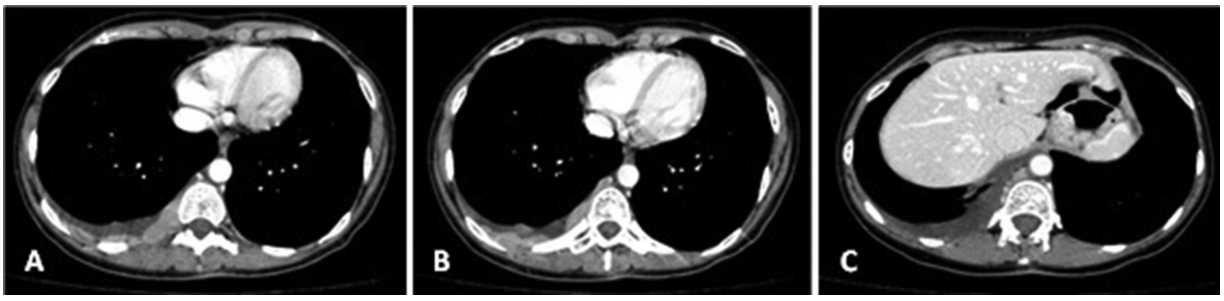

Fig. 1 (A-C). Chest CT scan showing macronodular pleural thickening in lower half of right hemithorax with contrast hyperenhancement, associated to moderate right pleural effusion.

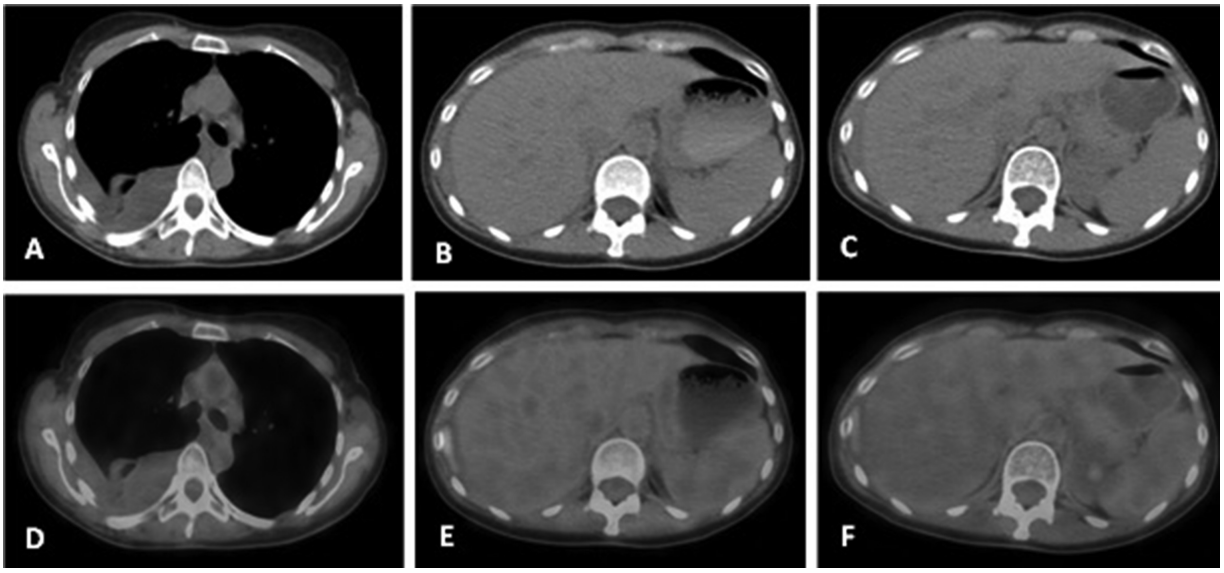

Fig. 2 (A-F). PET scan and Chest CT scan showing slight uptake of fluor-18-fluorodesoxyglucose (FDG) in pleural nodules and pleural effusion (SUV max.=1.22); small area of pleural thickening between right liver lobe and 9th right rib with more intense FDG uptake (SUV max.=4.74); no other relevant alterations.

differential diagnosis of pleural nodules, particularly when there is no previous history of pleural inflammation, such as pneumothorax or pyothorax, immunosuppression, viral infection (HIV, EBV or HHV-8) or thoracic trauma. Clinical examinations such as imaging features and laboratory examination are unspecific. Therefore, an accurate histopathological diagnosis based on thoracic surgery or thoracoscopy is essential.

In conclusion, primary pleural lymphoma is a rare entity principally associated with chronic inflammatory stimulus. Chemotherapy is the most widely used treatment, with complete remissions rates of around 35%.[2] On the other hand, spontaneous remissions are extremely rare.[7] This case highlights the importance of primary pleural lymphoma in differential diagnosis of pleural disease, reinforcing the value of an accurate histological diagnosis.

Contributions of the authors

SSG and SC prepared the manuscript. TA and PR were responsible for patient management and revised the manuscript. HMS critically revised the manuscript and approved the final version. All authors read and approved the final manuscript.

Conflicts of interest

None.

Funding

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.07.001.

References

1. King RM, Pairolero PC, Trastek VF, et al. Primary chest wall tumors: factors affecting survival. Ann Thorac Surg. 1986;41:597—601. https://doi.org/10.1016/s0003-4975(10)63067-6.
2. Sun M, Shang C, Gao J, Jiang S. Rare case of primary pleural lymphoma presenting with pleural effusion. Thoracic Cancer. 2016:145—50. https://doi.org/10.1111/1759-7714.12256.
3. Aozasa K. Pyothorax-associated lymphoma. J Clin Exp Hematop. 2006;46:5—10. https://doi.org/10.3960/jslrt.46.5.
4. Zhang Q, Ju Y, Qu T, Wang T, Liu X. Primary diffuse large B-cell lymphoma as a chest-wall mass - a case report. Medicine. 2018;97(e13291):47. https://doi.org/10.1097/MD.0000000000013291.
5. Basuthakur S, Sarkar A, Burman S, Dandale R. A rare case of pleural lymphoma. Lung India. 2008;25:160—2. https://doi.org/10.4103/0970-2113.45283.
6. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomized study of the MabThera International Trial (MInT) Group. Lancet Oncol. 2011;12:1013—22. https://doi.org/10.1016/S1470-2045(11)70235-2.
7. Snijder J, Mihyawi N, Frolov A, Ewton A, Rivero G. Spontaneous remission in diffuse large cell lymphoma: a case report. J Med Case Rep. 2019;13:28. https://doi.org/10.1186/s13256-018-1937-z.

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Available online 15 September 2022

Pulmonology 29 (2023) 97—98

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CORRESPONDENCE

Indoor environmental quality—Take me where the air is clean

Dear Editor,

We read the editorial piece by Winck et al. who solicited a call for a Portuguese national strategy addressing indoor air quality.[1] The topic explored by the authors is an emerging area of interest worthy of further consideration. We found the proposed plans put forward in the Winck et al. article[1] of great interest. Among these, air recirculation is undoubtedly one of the more feasible and straightforward methods of ameliorating indoor air quality, as already pointed out by other authors.[2] The rapid and global spread of COVID-19 seems to be associated with indoor and outdoor air pollution. Studies show that in some parts of the world, where air pollution rates are high, COVID-19 is spreading faster.[3] In this sense, depending on air quality, the diffusion trends for COVID-19 could be positively or negatively affected. It should be noted that indoor air pollution could also be generated by outdoor pollutants that are brought indoors in the processes of ventilation through the building envelope.[4] Furthermore, people living in polluted air conditions are more prone to getting sick, and viral contamination becomes easier in such environments.[5] These findings have been confirmed in a recent study, whose authors found an association between exposure to air pollution and the onset of respiratory symptoms and diseases such as allergic rhinitis, cough, asthma, and COPD.[6]

At the time of writing —April 2022— despite a reduction in new COVID-19 cases and the consequent easing of the restrictive measures, the infection risk persists in schools, hospitals, and other indoor contexts. Therefore, improving indoor air quality is crucial to overcoming the pandemic and alleviating the related health and economic consequences.

After reading the piece by Winck et al., it emerges that an increasing number of guidelines has been released in the last two years by international agencies to promote appropriate ventilation inside buildings.[4,7—9] Such measures should be extended as much as possible within medical facilities, commercial buildings, and workplaces. As highlighted in the editorial by Winck et al.,[1] Recovery and Resilience Plan supported by the European Union, is an occasion to direct financial resources towards implementing safe and healthy indoor environments in the eurozone. The European Recovery Plan[10] is a € 2.018 trillion package created to respond to the COVID-19 pandemic; this unprecedented financial support should be used to facilitate local indoor air quality policies across countries. In this sense, rehabilitative pulmonary settings should be considered privileged as they would benefit from enhanced indoor air circulation. In fact, in such settings patients and professionals are greatly exposed to droplets and air contamination.[2]

We then applaud the analysis made by Winck et al.[1] because it contributed to expanding awareness of the importance of addressing indoor air quality during the COVID-19 pandemic and beyond. Furthermore, we hope that readers will be encouraged to be proactive —within the context of their institutions and workplaces— directed at enhancing indoor air quality.

As professionals, consumers, and citizens, we can all actively contribute to obtaining a better environment to live and work in.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Winck JC, Almeida SM, Correia G, Gabriel MF, Marques G, Silva MG. A call for a national strategy for indoor air quality. Pulmonology. 2022;28(4):245—51. https://doi.org/10.1016/j.pulmoe.2022.02.003.
2. Polastri M, Pehlivan E. Preventing indoor contamination in private physiotherapy practice. Int J Ther Rehabil. 2021;28(7):1—3. https://doi.org/10.12968/ijtr.2021.0118.
3. Balboa-Castillo T, Andrade-Mayorga O, Marzuca-Nassr GN, Morales Illanes G, Ortiz M, Schiferlli I, et al. Pre-existing conditions in Latin America and factors associated with adverse outcomes of COVID-19: a review. Medwave. 2021;21(4):e8181. https://doi.org/10.5867/medwave.2021.04.8180.
4. World Health Organization.2021 WHO global air quality guidelines: particulate matter (PM2.5 and PM10). Ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. https://apps.who.int/iris/bitstream/handle/10665/345329/9789240034228-eng.pdf?sequence=1&isAllowed=y (Accessed 7 April 2022)
5. Comunian S, Dongo D, Milani C, Palestini P. Air pollution and COVID-19: the role of particulate matter in the spread and increase of COVID-19′s morbidity and mortality. Int J Environ

https://doi.org/10.1016/j.pulmoe.2022.04.006

Res Public Health. 2020;17(12):4487. https://doi.org/10.3390/ijerph17124487.
6. De Matteis S, Forastiere F, Baldacci S, Maio S, Tagliaferro S, Fasola S, et al. Issue 1 - "Update on adverse respiratory effects of outdoor air pollution". Part 1): outdoor air pollution and respiratory diseases: a general update and an Italian perspective. Pulmonology. 2022;28(4):284—96. https://doi.org/10.1016/j.pulmoe.2021.12.008.
7. REHVA. COVID-19 guidance document version 4.0. how to operate HVAC and other building service systems to prevent the spread of the coronavirus (SARS-CoV-2) disease (COVID-19) in workplaces. 2020. https://www.rehva.eu/fileadmin/user_upload/REHVA_COVID-19_guidance_document_V4_23112020.pdf (Accessed 7 April 2022)
8. ASHRAE. Epidemic Task Force. Core recommendations for reducing airborne infectious aerosol exposure. 2021. https://www.ashrae.org/file%20library/technical%20resources/covid-19/core-recommendations-for-reducing-airborne-infectious-aerosol-exposure.pdf (Accessed 7 April 2022)
9. Guo M, Xu P, Xiao T, He R, Dai M, Miller SL. Review and comparison of HVAC operation guidelines in different countries during the COVID-19 pandemic. Build Environ. 2021;187:107368. https://doi.org/10.1016/j.buildenv.2020.107368.
10. European Union. Recovery plan for Europe. 2021. https://ec.europa.eu/info/strategy/recovery-plan-europe_en (Accessed 7 April 2022)

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Received 4 April 2022; Accepted 12 April 2022
Available online 11 June 2022

Pulmonology 29 (2023) 102—103

PULMONOLOGY

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PHOTO

Large cell neuroendocrine lung carcinoma — A challenging rare tumour

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Received 7 June 2022; accepted 9 June 2022
Available online 16 September 2022

A 56-year-old white male presented with a voluminous right supraclavicular node with 2 months of evolution. He was a railroad worker, a heavy smoker and with no past medical history. The physical examination revealed a voluminous palpable, non-movable, right supraclavicular node. A cervical and thoracic CT scan was performed and revealed a voluminous heterogeneous right laterocervical mass, measuring 94 × 65 mm in greater diameter, involving the ipsilateral internal jugular vein and associated with multiple mediastinal and hilar nodes (Fig. 1 — A and B). He underwent an incisional biopsy of this right supraclavicular mass and pathology result was compatible with a large cell neuroendocrine carcinoma (LCNEC) of the lung. Immunohistochemistry was positive for neuroendocrine markers, including chromogranin A, synaptophysin (Fig. 1 - C), CD56 and Ki67, and for thyroid transcription factor-1 (TTF-1) (Fig. 1 - D). The Ki67 index was >90%. There was also evidence of right adrenal gland and multiple brain metastases. He underwent radiation therapy on the right supraclavicular mass and cranial. Following worsening of his general and neurological condition, the patient died and it was not possible to start his cytostatic treatment.

The authors report a patient with a LCNEC of the lung with an atypical presentation and no pulmonary findings on the CT scan and also with no respiratory complaints but where biopsy was fundamental to obtaining the correct histopathological diagnosis. The authors also highlight two specific and uncommon features present in these case: the majority of mediastinal LCNEC originate from the thymus[1] and pulmonary LCNEC are less likely to present with advanced stage disease.[2]

Conflicts of interest

The authors have no conflicts of interest on the manuscript subject.

https://doi.org/10.1016/j.pulmoe.2022.06.013

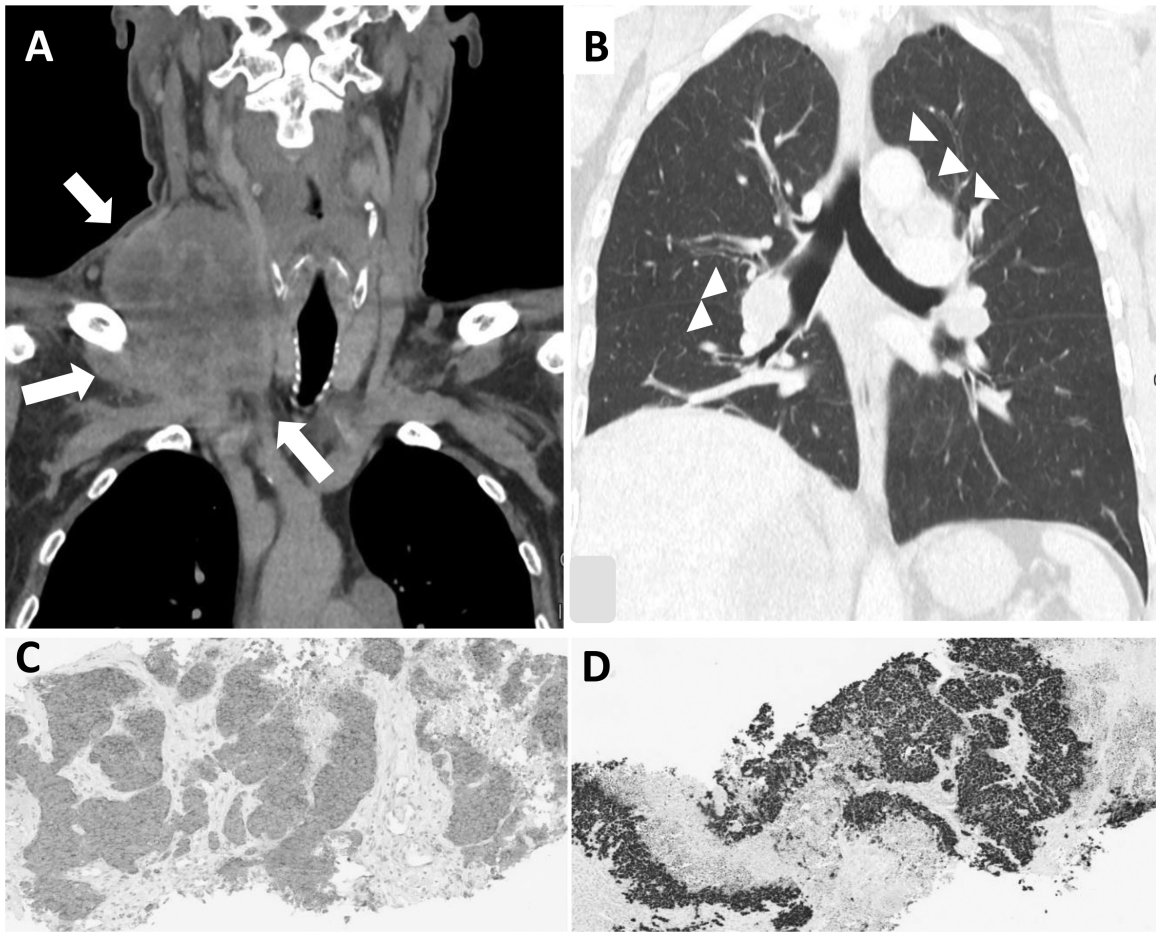

Fig. 1 Cervical (A) CT scan revealed a voluminous heterogeneous right laterocervical mass, involving the ipsilateral internal jugular vein (white arrows). Thoracic (B) CT scan revealing multiple mediastinal and hilar nodes (white arrowheads) with no pulmonary findings. Immunohistochemistry from biopsy of the right supraclavicular mass whose pathology result was compatible with a large cell neuroendocrine carcinoma of the lung: positivity for neuroendocrine markers, including synaptophysin (C) and for thyroid transcription factor-1 (TTF-1) (D).

References

1. Hidaka T, Okuzumi S, Matsuhashi A, Takahashi H, Hata K, Shimizu S, et al. Large cell neuroendocrine carcinoma of the mediastinum successfully treated with systemic chemotherapy after palliative radiotherapy. Intern Med. 2019;58(4):563—8. https://doi.org/10.2169/internalmedicine.0437-17.
2. Corbett V, Arnold S, Anthony L, Chauhan A. Management of large cell neuroendocrine carcinoma. Front Oncol. 2021;11:653162. https://doi.org/10.3389/fonc.2021.653162.